CLINICO PATHOLOGICAL STUDY OF SECONDARIES IN NECK WITH UNKNOWN PRIMARY CANCER-PROSPECTIVE STUDY



Dissertation submitted in partial fulfillment of regulation for the

award of M.S. Degree in General Surgery

(Branch I)



The Tamilnadu Dr. M.G.R. Medical University Chennai APRIL - 2020 Coimbatore Medical College Coimbatore - 641 014 University Registration No: 221711313

CERTIFICATE

Certified that this is the bonafide dissertation done by DR. M.PRASAD and submitted in partial fulfillment of the requirements for the Degree of M.S., General Surgery, Branch I of The Tamilnadu Dr. M.G.R. Medical University, Chennai.

Date:

Unit Chief

Date:

Professor &Head Department of Surgery

Date:

Dean Coimbatore Medical College Coimbatore

DECLARATION

I, certainly declare that this dissertation titled, "Clinico Pathological study of secondaries in neck with unknown primary cancer-prospective study." The research were consistent with normal supervisory practice, and are acknowledged. I, also affirm that this bonafide work represent a genuine work of mine. The contribution of any supervisors to or part of this work was not submitted by me or any others for any award, degree or diploma to any other university board, neither in India or abroad. This is submitted to The Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Master of Surgery Degree Branch 1 (General Surgery).

Place : Dr.M.PRASAD

University Registration Number: 221711313 Date :

INSTITUTIONAL HUMAN ETHICS COMMITTEE COIMBATORE MEDICAL COLLEGE, COIMBATOR – 14

EC Reg No. ECR/892/Inst/TN/2016 Telephone No: 0422 – 2574375/76 Fax : 0422 – 2574377

CERTIFICATE OF APPROVAL

To **Dr.M.Prasad** Post Graduate, Department of General Surgery, Coimbatore Medical College & Hospital Coimbatore -18.

Dear Dr.M.Prasad

The Institutional Ethics Committee of Coimbatore Medical College, reviewed and discussed your application for approval of the proposal entitled **"Clinico Pathological study of secondaries in neck with unknown primary Cancer – Prospective Study ."**No.0122/2017.

The following members of Ethics Committee were present in the meeting held on 05.01.2018.conducted at MM - II Seminar Hall, Coimbatore Medical College Hospital Coimbatore-18

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15	Mr.V.A.Shahul Hameed, +2	Lay-Person

We approve the Proposal to be conducted in its presented form.

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ACKNOWLEDGEMENT

I express my gratitude to **Dr. B. ASOKAN, Dean** of Coimbatore Medical College Hospital for providing facilities to carry out this project work successfully.

I sincerely thank Dr. A. NIRMALA, Professor and HOD, Department of General Surgery for her constant guidance and encouragement throughout the period of this study.

I would like to express my gratitude to my **Guide and Unit Chief Prof.Dr. T. SRINIVASAN**, for his valuable guidance and support without which this project work would not have been possible.

I am extremely thankful to **Prof. Dr. LEKSHMINARAYANI**, **Prof. Dr.V.S.VENKATESAN**, **Prof.Dr. R. NARAYANAMOORTHY**, for their constant encouragement and support to carry out this study.

I would like to thank the Assistant Professors of the Department of Surgery, CMC Hospital, Dr.A.BALAMURUGAN, Dr. B. JAYALAKSHMI, Dr. A. THENMOZHI, for their voluntary and useful guidance and support.

I would also like to thank the **Supporting Staff** of Department of Surgery and **Anesthesiology**.

I extend my heartfelt thanks to all the **patients** who co-operated for this study.

LIST OF ABBREVIATIONS USED

AJCC	:	American Joint Committee on Cancer
CUP	:	Carcinoma of Unknown Primary
CECT	:	Computed Tomography
ENE	:	Extra Nodal Extension
FNAC	:	Fine Needle Aspiration Cytology
18-FDG-PET	:	18-Fluorodeoxyglucose Positron Emission Tomography
IHC	:	Immunohistochemistry
MALT	:	Mucosa Associated Lymphoid Tissue
MRND	:	Modified Radical Neck Dissection
MRI	:	Magnetic Resonance Imaging
RT	:	Radiotherapy
RND	:	Radical neck dissection
SCC	:	Squamous Cell Carcinoma

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ABSTRACT:

Background: Cancer of Unknown Primary (CUP) constitute of a heterogenous group of malignancies presenting with lymph nodes of distant metastases. Metastasis of Neck lymph node from an occult primary contribute to 5-10% of patients. With advancements in diagnostics and detection techniques incidence appears decreasing. Management of metastases from unknown origin remains a therapeutic challenge. Hence this study is done to assess the Clinicopathological patterns of presentation of neck lymph node metastases and its multimodality of managements. Methodology: All patients presenting to the department of general surgery, Coimbatore Medical College Hospital during one year period with neck node as the presentations were evaluated. After institute ethical clearance and informed written consent detailed clinical examination of the patient were done, followed by the pathological and radiological examination. Results: Total of 30 patients with FNAC confirmed malignant cervical Lymphadenopathy were included in the study. The mean age of the study participantswas 57 + 12.5 years.(60%) were squamous cell carcinoma followed by adenocarcinoma in 26.7%.90% of had stage III cancer and 10% of them had stage IV cancer. Primary site of malignancy was unidentified and patient underwent multimodality of treatment. Conclusion: The commonest histology was squamous cell carcinoma followed by Adenocarcinoma and the primary site of cancer could not be diagnosed. Males and elderly were commonly involved compared to females. Combined modality of approaches involving surgery, radiotherapy and chemotherapy were used to manage the patient with carcinoma of unknown primary.

Key words: Neck Lymph node metastasis, Carcinoma of Unknown Primary, Clincopathological pattern, treatment.

INTRODUCTION

Carcinoma of unknown primary origin is form of cancer that the patients presents with lymph nodal of distant metastases but no obvious primary origin of carcinoma was not obvious. The diagnosis was however one of the challenges and consequently depend upon the diligence exercised in the search for a primary tumour. An occult primary had been attributed to spontaneous regression of primary tumour possibly as a result of autoimmune destruction, although the exact reason was unknown.

The term carcinoma of unknown primary origin [UPC or CUP] should be used if no evidence of primary tumor was found after adequate clinical examination, fiberoptic endoscopy, imaging investigations which include fluorine 18 labelled deoxy glucose positron emission tomography[FDG-PET] ideally with CT fusion imaging [FDG]PET-CT.

Metastasis most commonly occurs to nodal levels II and III with less frequent involvement of levels I, IV,V and VI. Squamous cell carcinoma was the most common histological tumor type and poses the greatest diagnostic dilemma because of the large number of primary of upper aerodigestive regions from which nodal metastasis might originate.

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The prognosis of these patients were relatively good with overall survival rate for five years exceeding 50 percentage, irrespective of treatment modality. Isolated Supraclavicular nodal involvement was almost invariably related to malignant disease arising below the clavicles ,with likely originating cancer from Lung and Esophagus and Adenocarcinoma from Thyroid, Breast, Gastrointestinal tracts and Gynecological tracts, which appears to contribute a discrete histological and Immunohistochemical characteristics pattern.

The management of these group of patients with carcinoma of unknown primary remains to be a continuously progressing and always redefined because of the spectrum of wide variations in age at presentations, pathological type, involvement of neck nodal area, extent of lymph node involvement and the response to different therapies. In general multimodality treatment of CUP depends on the pattern of Neck lymphatic metastasis, and treatment options consists of Surgery, Radiotherapy, Chemoradiotherapy.

REVIEW OF LITERATURE

The neck extends from the base of the cranium and the inferior border of the mandible to the thoracic inlet. The superior limit of the neck is the pericraniocervical line. Inferiorly the neck blends with the thorax and upper limb at the level of the clavicle and scapula. Above and below the hyoid bone the fascial layers of the neck define a number of potential tissue 'spaces'. The tissues within these spaces are either closely applied to each other or are filled with relatively loose connective tissue. However, they offer potential routes by which unchecked infection may spread within the head and neck, and between the tissue spaces of the face and the mediastinum. They also offer convenient planes for intraoperative dissection during surgery.¹¹

The neck is grouped into 4 neck spaces or compartments.

- Vertebral compartment: contains <u>cervical vertebrae</u> and postural muscles.
- Visceral compartment: The main cervical viscera are the submandibular salivary glands, the thyroid and parathyroid glands and the cervical portions of the trachea and esophagus.
- Vascular compartments (2): on each side of the neck, contains the common carotid artery, internal jugular vein and the vagus nerve.¹²

TRIANGLES OF THE NECK:

From the front and side of the neck, it is obviously divided into anterior and posterior triangles by sternocleidomastoid. The anterior triangle may be further subdivided into submental, muscular, carotid and digastric triangles, and the posterior cervical triangle may be partitioned into occipital and supraclavicular triangles.

Anterior triangle:

The base of the anterior triangle is formed by the base of the mandible and a line from its angle to the mastoid process, and the sides are formed by the midline anteriorly and the anterior edge of sternocleidomastoid laterally.

Posterior triangle

The boundaries of the posterior triangle are the posterior border of sternocleidomastoid, the middle third of the superior surface of the clavicle, which forms the base, and the anterior margin of trapezius. The apex is the point where sternocleidomastoid and trapezius approximate to each other at the superior nuchal line. The lower portion of the posterior triangle forms the supraclavicular fossa, a very important clinical area, which lies just above and behind the clavicle at the confluence of the thoracic inlet and the aditus to the axilla and arm.¹¹



Figure 1: Triangles of neck

LYMPHATIC DRAINAGE:

Lymph nodes of the head and neck are arranged on either side of the neck in two horizontal rings and two vertical chains. The outer superficial ring is formed by the occipital, preauricular (parotid), submandibular and submental nodes and the inner deep ring is constituted by the clumps of mucosa associated lymphoid tissue (MALT) located primarily in the naso- and oro-pharynx (Waldever's ring). Superior and inferior groups of nodes related to the carotid sheath forms the vertical chain. Ultimately, all the lymphatic vessels of the head and neck drain into the deep cervical nodes, either directly or indirectly via nodes in outlying groups. Among this the most important chain of nodes are the jugular nodes (also called cervical), which run adjacent to the internal jugular vein. The other main groups are the submental, submandibular, pre- and postauricular, occipital and posterior triangle nodes. Cancers arising in the head and neck regions such as the thyroid gland, larynx, oral cavity and oropharynx, nasopharynx and paranasal sinuses spreads through these chains of lymph nodes.

Levels in Neck Nodes (Memorial Sloan—Kettering Cancer centre levelling of neck nodes)

Level I—Submental (Ia) and submandibular (Ib) lymph nodes.

Level II—Lymph nodes in upper deep cervical region. (It extends from base of skull to hyoid bone and from lateral margin of stern thyroid to posterior margin of stern mastoid muscle.)

Level III—Lymph nodes in middle cervical region (from hyoid bone to omohyoid muscle or cricothyroid membrane).

Level IV—Lymph nodes in lower cervical region (from omohyoid muscle to clavicle).

Level V—Lymph nodes in posterior triangle including supraclavicular region.

Level VI—Lymph nodes in the midline neck—pretracheal and prelaryngeal.

Level VII—Lymph nodes in the mediastinum.¹³



Figure 2: LEVELS OF CERVICAL LYMPH NODES

Boundary Level	Superior	Inferior	Anterior (Medial)	Posterior (Lateral)
IA	Symphysis of mandible	Body of Hyoid	Anterior belly of the contralateral digastric muscle	Anterior belly of the Ipsilateral digastric muscle
IB	Body of the Mandible	Posterior belly of diagastric muscle	Anterior belly of the diagastric muscle	Stylohyoid muscle
IIA	Skull Base	Horizontal plane defined by the inferior border of Hyoid bone	Stylohyoid muscle	Vertical plane defined by the spinal accessory nerve
IIB	Skull Base	Horizontal plane defined by the inferior body of Hyoid.	Vertical plane defined by the spinal accessory nerve	Lateral border of the sternocleido mastoid muscle
III	Horizontal plane defined by the inferior body of Hyoid.	Horizontal plane defined by the inferior border of Cricoid cartilage	Lateral border of the sterno hyoid muscle	Lateral border of the sternocleidomastoid muscle or sensory branches of the cervical plexus
IV	Horizontal plane defined by the inferior border of Cricoid	Clavicle	Lateral border of the sterno hyoid muscle	Lateral border of the sternocleidomastoid muscle or sensory

Table 1: Anatomical structures defining the boundaries of neck levels and sub levels

	cartilage			branches of the cervical plexus
VA	Apex of the convergence of the sternocledomastoid and trapezius muscle	Horizontal plane defined by the lower border of Cricoid cartilage	Posterior border of the sternocleido mastoid muscle or sensory branches of the cervical plexus	Anterior border of the trapezius muscle
VB	Horizontal plane defined by the lower border of cricoids cartilage	Clavicle	Posterior border of the sternocleido mastoid muscle	Anterior border of the trapezius muscle
VI	Hyoid bone	Supra sterna Notch	Common carotid artery	Common carotid artery
VII	Supra sterna notch	Innominate Artery	Sternum	Trachea, oesophagus and prevertebral fascia



Figure : 3 Memorial Sloan – Kettering Cancer Center leveling system of cervical lymph nodes (A) current modification of leveling system (B) and levels VI and VII (C)

Level	Lymph node group	Boundaries	Drainage site
1	Submental/submandibular	Mandible digastric muscle	Floor of mouth
		Digastric muscle	Anterior tongue
		Hyoid bone	Lower lip
			Mandibular alveolar ridge
II	Upper jugular chain	Skull base	Parotid
		Hyoid bone	Nasal cavity
		Stylohyoid muscle	Oral cavity
		Posterior border SCM	Nasopharynx
			Oropharynx
			Larynx
			Hypopharynx
III	Middle jugular chain	Hyoid bone	Oral cavity
		Cricoid	Nasopharynx
		Sternohyoid muscle	Oropharynx
		Posterior border SCM	Larynx
			Hypopharynx
IV	Lower jugular chain	Cricoid	Larynx
		Clavicle	Hypopharynx
		Sternohyoid muscle	Thyroid
		Posterior border SCM	Cervical esophagus
V	Posterior triangle	SCM	Nasopharynx
		Clavicle	Oropharynx
		Trapezius muscle	Posterior scalp
			Posterior neck
VI	Anterior compartment (pretracheal,	Hyoid	Thyroid
	paratracheal, Delphian node)	Suprasternal notch	Glottis
		Common carotid artery	Subglottis
			Piriform
			Cervical esophagus

Table : 2 Showing Regional lymph nodes draining at a specificprimary site



Figure : 4 Regional lymph nodes draining at a specific primary site



Figure : 5 Neck lymph node staging in secondaries

CARCINOMA:

Carcinoma is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in mortality. Although the causes of cancer are not completely understood, numerous factors are known to increase the disease's occurrence, including many that are modifiable (e.g., tobacco use and excess body weight) and those that are not modifiable (e.g., inherited genetic mutations and immune conditions). Both modifiable and non modifiable risk factors may act simultaneously or in sequence to initiate or promote cancer growth.¹⁴Neoplasm is the second leading cause of death globally after cardiovascular diseases.¹⁵With advancements in science and technology, through early identification and treatment, millions of cancer people extend their life.

Cancer cells metastasize to new areas of the body, by way of the lymph system or bloodstream. A metastatic cancer is one that has spread from the primary site of origin to different/distant site in the body. Malignant neoplasms disseminate by one of three pathways: (1) seeding within body cavities, (2) lymphatic spread, or (3) hematogenous spread. Lymphatic spread is more typical of carcinomas, whereas hematogenous spread is favored by sarcomas. However there are numerous interconnections between the lymphatic and vascular systems facilitating

all forms of cancer to disseminate through either or both systems.¹⁶ The pattern of lymph node involvement depends principally on the site of the primary neoplasm and the natural pathways of local lymphatic drainage. In some cases, the cancer cells traverse the immediate proximate nodes and gets trapped in subsequent lymph nodes, producing skip metastases. The cells may traverse all of the lymph nodes ultimately to reach the vascular compartment by way of the thoracic duct.¹⁷ A "sentinel lymph node" is the first regional lymph node that receives lymph flow from a primary tumor. It can be identified by injection of blue dyes or radiolabeled tracers near the primary tumor.¹⁸ Biopsy of sentinel lymph nodes allows determination of the extent of spread of tumor and can be used to plan further managements and prognosis of the patient. Though the enlargement of nodes near a primary neoplasm arouse concern for metastatic spread, it does not always imply cancer. The necrotic products of the neoplasm and tumor antigens often evoke immunologic responses in the nodes, such as hyperplasia of the follicles (lymphadenitis) and proliferation of macrophages in the subscapular sinuses (sinus histiocytosis). Thus, histopathologic verification of tumor within an enlarged lymph node is required.¹⁶

Most patients above 40 years of age metastasis is a common cause of neck lymph node enlargements. Regional nodes entrap the tumor cells and setup complex immunological reactions within the nodes. They first appear in the marginal sinus, from which they penetrate the medullary sinus, the medulla and then the cortex. Eventually there is total parenchymal replacement by the tumor tissue. The histological appearance of the nodes often suggests the primary tumor. Adenocarcinoma shows glandular pattern with signet ring appearance. Squamous cell carcinoma shows keratin or epithelial cells. Anaplastic carcinoma cells are extremely pleomorphic with hyper chromatic nuclei.¹⁹Neck lymph nodes are a common site of metastases for malignant tumors that originate at primary sites in the head and neck. These include squamous cell carcinomas of the upper aero digestive tract as well as metastases from salivary gland, thyroid, and skin cancers. Sometimes, primary carcinomas not originating from the head and neck region may metastasize to the neck. In evaluating a patient presenting with a malignant lymph node and no obvious primary site in the head and neck, it is essential to consider which tumors have a propensity to metastasize to the neck and how such disease should be managed. The mechanism leading to the occurrence of head and neck metastases from many of the distant primary tumors remains obscure, as there are often no obvious lymphatic pathways to explain their mode of spread. The presence of lymphatic metastases in the neck from a remote primary site has significant impact on the patient's prognosis. About 1-2% of all head and neck malignancies are accounted for by metastases from a remote primary site.²⁰

CARCINOMA OF UNKNOWN PRIMARY ORIGIN:

Neoplasms can occur in any part and in any tissue of the body. The primary cancer (the cancer that first formed) can spread to other parts of the body but cannot find where in the body the cancer first began to grow resulting in cancer of unknown primary (CUP) or occult primary tumor. Carcinoma of unknown primary (CUP) is a rare disease in which malignant cells are found in the distant part of the body but the place the primary site is not known.Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after a focused search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. Cases that initially present as CUP account for 5-10 % of head and neck cancers and approximately 75 % or more of these are squamous cell carcinomas (SCCs).²¹⁻²² When strictly defined, "true" CUP refers to metastases for which the primary tumor cannot be located after an exhaustive clinical, radiographic and surgical evaluation has been performed, the latter often including biopsies and/or resection of

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suspected primary sites. True CUP accounts for only 3–5% of head and neck cancers.²³

Most investigators limit Carcinoma of Unknown Primary to epithelial and undifferentiated cancers and do not include lymphomas, and metastatic sarcomas because these cancers have specific histologyand stage-based treatments that guide management even in the absence of a primary cancer. The emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools has challenged the "unknown" designation. Additionally, effective targeted therapies in several cancers have moved the paradigm from empiricism to considering a personalized approach to Carcinoma of unknown primary management. The reasons carcinomas present as Carcinoma of Unknown Primary remain unclear. One hypothesis states that the primary tumor either regresses after seeding the metastasis or remains so small that it is not detected. It is also possible that Carcinoma of unknown Primary falls on the continuum of cancer presentation where the primary has been contained or eliminated by the natural body defenses. Alternatively, Carcinoma of unknown primary may represent a specific malignant event that results in an increase in metastatic spread or survival relative to the primary. Whether the Carcinoma of unknown primary metastases truly

define a clone that is genetically and phenotypically unique to this diagnosis remains to be determined.²⁴

CLINICAL EVALUATION:

- In this studyof 30 patients over the period of one year with secondaries in the neck with unknown primary carcinomas were included as per inclusion criteria.
- Clinical evalution of all 30 patients were done with history taking, clinical examinations including Ecog scoring or operformance status were done.
- In this study all patient were investigated for search of primary site of carcinomas were done.
- Patients general condition was assessed and vitals were recorded.
- Neck nodular status were assessed for fixity of lymph node, consistency, surface of the skin, mobility of neck in.
- Complete blood investigations including complete blood count, blood sugars renal function tests, liver functions tests were done, to asses the renal functions and liver functions for any deviations to assess for contrast studies.
- Electrocardiogram, chest X-ray, X-ray of neck were taken to asses the status of bone changes and any alterations in lung fields.

- In this study all patients were investigated with pan endoscopy which includes Direct Laryngoscopy, Nasophyrangoscopy
 Escopagoscopy to search for the primary site of carcinomas of unknown primary.
- In this study of 30 patients were investigated with Ultrasonography of neck, Abdomen and pelvis for ascities, infilteration of surrounding structures, extend to other structures involved in the neck.¹³

In this study of 30 patients all were subjected with contrast enhanced computed tomography of neck, chest, adbomen and pelvis to diagnose the primary site or alteration in the anatomy of the regions.

EVALUATION OF A PATIENT WITH CERVICAL ADENOPATHY



Figure 6: Evaluation of patient with cervical adenopathy

DIAGNOSIS:

Fine needle aspiration cytology [FNAC] is the tool to confirm the occult secondary. If FNAC is inconclusive, only then open biopsy (incision/excision) is done to confirm. Open biopsy helps in high suspects of lymphomas or poorly differentiated carcinomas. It facilitates tissue study, immunohistochemistry, and special stains. The risk of seedling, survival and prognosis will not alter by open biopsy however other methods are adopted only when FNAC appears inadequate.²⁶

ROLE OF IMAGING STUDIES:

In this study absence of contraindications, a baseline Intravenous contrast computed tomography (CT) scan of the neck ,chest, abdomen, and pelvis is the standard of care. This helps to search for the primary tumor, evaluate the extent of disease, and select the most accessible biopsy site.

These patients were subjected to Panendoscopy involving Nasopharyngoscopy ,Direct-laryngoscopy, Esophagoscopy and Bronchoscopy. Employing panendoscopy Primary site of origin of carcinoma was not able to be diagnosed in all 30 patients involved in study.

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Posterior view of pharynx with right portion of constrictor muscle retracted laterally

HISTOLOGIC CLASSIFICATION

In this study of 30 patients According to routine light microscopy, Neck cancers of unknown primary origin are divided into four major subtypes :

- Squamous cell carcinomas
- Adenocarcinomas well to moderately differentiated
- poorly Undifferentiated carcinomas

Secondaries in neck with occult primary may be usually of squamous cell carcinoma or of nonsquamous cell carcinoma, i.e. adenocarcinoma /poorly undifferentiated tumour (lymphoma/ sarcoma/ melanoma). In upper and mid Neck region 80% are due to squamous cell carcinomas, whereas in lower cervical and supraclavicular region, 40 % can be of adenocarcinomas. Thyroid, breast, gastrointestinal tract, salivary glands are the common sites of primary in lower cervical and supraclavicular regions.²⁷

Diagnostic work-up of patients with carcinoma of unknown primary origin

- Clinical examinations
- Personal history, focusing on tumour related history
- Performance status, Respiratory system, Central nervous system, Gastrointestinal and cardiovascular system evaluation.
- Complete blood count, Renal functions tests, Liver functions tests,
- Stool for occult blood, urine routine tests, Ecg
- Clinical and fibrescopic evaluation, careful examination of surgical scars in Ear, Nose and Throat.
- Imaging studies
- Chest X ray, Thyroid and neck Ultrasonography,
- Ultrasonography of abdomen and pelvis,
- Fine needle aspiration cytology FNAC biopsy,
- Skeletal surveys,
- Examination following cytology and histopathologic diagnosis
- Contrast enhanced computed tomography of neck, chest, abdomen and pelvis,
- Magnetic resonance imaging

Physical examination including inspection and palpation of the oral cavity, base of tongue, oropharynx and nasopharynx. Direct laryngoscopy and pharyngoscopy. Biopsy of any abnormal mucosa seen or palpated. If there are no visible or palpable abnormalities, and the FNAC suggests squamous cell carcinoma or poorly differentiated malignancy, biopsy of sites of suspected primary depending on the position of the involved nodes. This usually includes biopsies of the nasopharynx, base of the tongue and pyriform sinus.

GRADING AND STAGING OF CANCER

For planning treatment and making an accurate prognosis of various treatment protocols, quantification of the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary. For this grading of the cancer establishes the estimate of its aggressiveness or level of metastasis based on the cytological differentiation of tumor cells. In order of increasing anaplasia the carcinomas may be classified as grade I, II, III, or IV. The criteria's vary with each form of carcinomas. However the difficulties in establishing clear-cut criteria have led to descriptive characterizations in some instances. The size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases determines the stage of the carcinomas.²⁴ Usually this assessment was
based on clinical and radiographic examination and in some cases surgical exploration. Currently two methods of staging are in use: the TNM system (T-primary tumor; N-lymph node involvement and Mmetastases) and the AJC (American Joint Committee) system. In the TNM system, T1, T2, T3, and T4 describe the increasing size of the primary lesion and degree of Anaplasia; N0, N1, N2, and N3 indicates progressively advancing node involvement; and M0 and M1 reflect the absence or presence of distant metastases. In the American Joint Committee on cancer method, based on the size of primary lesions and the presence of nodal spread and of distant metastases the cancers are staged from 0 to IV.



Figure : 7 Staging system of regional lymph nodes (N state) for squamous cell carcinoma of the upper aerodigestive tract, the nasopharynx.

Nodal staging in secondaries of neck

- N0-nodes not detected
- N1—single node same side < 3 cm
- N2a—single node same side 3-6 cm
- N2b—multiple nodes same side < 6 cm
- N2c—bilateral/contralateral nodes < 6 cm
- N3 node > 6 cm

AJCC CLASSIFICATION OF NECK NODES:

Table 3: AJCC CLINICAL CLASSIFICATION OF NECK NODES

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE–
N2	Metastasis in a single ipsilateral lymph node > 3 cm but not > 6 cm in greatest dimension and ENE-; or metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE-; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, ENE-
N2a	Metastasis in single ipsilateral node > 3 cm but not > 6 cm in greatest dimension and ENE-
N2b	Metastasis in multiple ipsilateral nodes, none > 6 cm in greatest dimension and ENE-
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-; or metastasis in a single ipsilat- eral node ENE+; or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE-
N3b	Metastasis in a single ipsilateral node ENE+ or multiple ipsilateral, contralateral or bilateral nodes any with ENE+

ENE- EXTRANODAL EXTENSION

PATTERNS OF CERVICAL LYMPH NODE METASTASIS FROM CARCINOMAS OF UPPER AERODIGESTIVE TRACT:

Patterns of cervical lymph node metastasis were first studied in detail by Lindberg in 1972. Later, Shah JP et al²⁸ published excellent studies on this topic. Teymoortash (2012) has reviewed the whole topic in great detail.²⁹

a) Nasal cavity and sinuses

Sino nasal squamous cell carcinomas have a metastatic rate of about 10%.²⁹ If there is an infiltration of nasal floor, columella, upper lip or floor of maxillary sinus the rate increases. The preferred metastatic areas include lymph nodes of the levels I and II, the parotid nodes and the retropharyngeal node.³⁰

b) Lips and oral cavity

The lymphatic drainage from upper lip is to level I, while buccal and parotid lymph nodes may also be affected and the cancers of lower lip usually has a low tendency for metastasis. The metastatic rate correlates with the size of the primary tumour, being about 30% for T1-T2 cancer and 60% or more for T3-T4 cancers. Anterior oral cavity drains into level I while the posterior oral cavity may drain into level II. However tongue cancers, which constitutes about 25-40% of oral cavity cancers is an exception to this. In a retrospective evaluation of 277 cases of tongue cancer, metastasis was present exclusively at levels III and IV in 15.8% cases without affecting levels I and II. The incidence of occult lymph node metastasis for T1 and T2 cancers of oral cavity is about 30-40%.³¹ A cut-off value of 4mm for tumour infiltration depth was defined as a predictor for neck metastasis in a meta-analysis of metastasized cancers of oral cavity.

c) Nasopharynx

In case of nasopharyngeal cancers, retropharyngeal lymph nodes and level II lymph nodes constitute the first site of metastasis

d) Oropharynx

In case of Oropharyngeal cancers the lymphatic drainage is effectuated mainly into lymph nodes at levels II, III and retropharyngeal lymph nodes. The cancers of posterior and lateral walls show a predilection for metastasis to retropharyngeal lymph nodes and level II.²⁹

e) Larynx

In case of carcinoma of Larynx the lymphatic drainage of supraglottic and glottis areas flows mainly to level II and III and subglottic areas into level III and IV. The involvement of pre-laryngeal Delphian lymph node in Level VI is associated with poor prognosis and higher rate of local recurrences. The metastatic frequency of laryngeal cancers varies according to tumour location and its extent.

f) Hypopharynx

Lymphatic drainage of hypopharynx mainly involves levels II and III, more rarely level IV. The Lymphatic drainage of the posterior wall of hypopharynx is first to retropharyngeal lymph nodes, followed by levels II and III. Incidence of lymph node metastasis from cancers of hypopharynx is about 65-80%, while 30-40% is of occult metastasis. Retropharyngeal metastasis occurs in about 13% of cases, mainly from cancers involving the retro-cricoid area and posterior wall of pharynx. Cancers of medial wall of pyriform sinus are reported to have an increased risk of contralateral neck metastasis.

Lymph Nodal metastasis or Secondaries to neck region, in relation to location of primary tumour, increases from anterior to posterior aspect of upper aerodigestive tract. Similarly, for tumours of larynx and pharynx, the risk of nodal metastasis increases as one progresses from centre of upper aerodigestive tract (vocal cords) towards the periphery (lateral pharyngeal wall).

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Figure : 8 The risk of nodal metastasis increases in relation to location of the primary squamous cell carcinoma of the head and neck.



The superficial lymphatic system in the head and neck. The nodes are organized into a superficial group around the head, superficial cervical nodes along the external jugular vein and deep cervical nodes along the internal jugular vein.

TREATMENT:

The treatment of Carcinoma of Unknown Primary with neck secondaries continues to evolve. The median survival duration of most patients with disseminated Carcinoma of Unknown Primary is ~6–10 months. The patient with carcinoma of unknown primary with neck secondaries, managed with multimodality approach. It combines surgery which could be Modified radical neck dissection or Radical neck dissection along with radiotherapy and chemotherapy.

Certain factors affect prognosis and treatment options.

- The number and size of lymph nodes involved.
- Treatment response or recurrence.
- Degree of anaplasia.
- Patient's age and general health.

The aim of the treatment 'true' unknown primary tumour in the head and neck is curative with the possible least morbidity to the upper aerodigestive tract. The treatment of an occult mucosal primary is often based on the natural history of mucosal squamous cell cancers of the upper aerodigestive tract. Most treatment regimens depending of the stage will therefore involve combined modality treatment, sometimes in occasions with initial stage without extra nodal spread, radiotherapy (RT), and surgery will be used as single modality treatment.⁵² The rate of emergence of the primary tumour is approximately 3 per cent per year, which is equivalent to the development of second carcinomas in the head and neck, lung and oesophagus. Therefore the primary aim of treatment is locoregional control. However, the rarity of unknown primaries (approximately 1–2 per cent of all squamous head and neck cancers) means there is a dearth of literature to guide best practice. Many of the management decisions are therefore controversial, and based on individual centre case series. Surgery on its own may be sufficient treatment for N1 involvement demonstrating no extracapsular spread, but in all other scenarios, needs to be supplemented by adjuvant (chemo) radiation. Incase of advanced neck disease combined treatment is required which could be either a combination of surgery and Radiotherapy or initial (chemo)- radiotherapy followed by planned neck dissection. Both of these approaches appear to be equally effective. ⁵³

SURGERY:

Primary is treated depending on the site, either by *wide excision (surgery*) or by *curative radiotherapy*. Then the secondaries are treated. Secondaries when *mobile*, are treated by *radical neck dissection*. When *fixed* it is *inoperable*. *Palliative external radiotherapy* is given to palliate pain and to prevent he anticipated bleeding. Sometimes *initially, external radiotherapy* is given to *downstage* the disease so that it becomes operable and later classical block dissection can be done.¹³

Types of Neck Dissection:

1. Classic radical neck dissection:

It is resection of lymph nodes (level I to V), fat, fascia, sternomastoid muscle, omohyoid muscle, internal jugular vein, external jugular vein, accessory nerve, submandibular salivary gland, lower part of parotid, prevertebral fascia—"*en-block"(Crile's' operation)*. Incision that is commonly made is *McFee* incision-Upper incision is from mastoid

process along the line of digastrics to hyoid bone point then upwards to chin. Lower incision is parallel to clavicle 2 cm above from anterior margin of Trapezius to midline.

2. Modified radical neck dissection—[MRND]

Structures preserved here are sternomastoid muscle, internal jugular vein and spinal accessory nerve.

- Modified Radical Neck Dissection type I (most important)- Only spinal accessory nerve is preserved
- Modified Radical Neck Dissection type II Accessory nerve and sternocleidomastoid are preserved.
- Modified Radical Neck Dissection type III- Accessory nerve, sternomastoid and internal jugular veins are preserved.

4. Bilateral neck dissection

Here internal jugular vein is preserved on one side. Always the side where the vein is preserved, is operated first. (If both the jugulars are ligated, cerebral congestion occurs leading to cerebral oedema which is dangerous. Jugular veins are ligated as an inevitable procedure during surgery, the patient is kept in propped-up position; antibiotics, diuretics, steroids are given, repeated CSF taps are done to control the cerebral oedema).

CHEMOTHERAPHY:

It may be used alone or as multimodality therapy.

Types

• Adjuvant chemotherapy: Chemotherapy is used before, during or after main therapeutic modality (surgery or radiotherapy). When used before it is called as anterior /induction chemotherapy. It reduces the burden, downstages the tumour, reduces the chance of micrometastasis that may occur during surgery. When used with radiotherapy (concurrent) it is used as radio sensitiser. When used after surgery/radiotherapy it is called as posterior chemotherapy.

• **Palliative chemotherapy**: It is used in advanced/ recurrent/metastatic cancers to relieve symptoms like pain/dysphagia/dyspnoea or to prevent chances of bleeding or fungation.

It may be single drug therapy like methotrexate/ bleomycin/cisplatin/5fluorouracil or multidrug combination chemotherapy. Combination chemotherapy is more beneficial which increases efficacy.

• Methotrexate – 40 mg/m2 IV weekly. It causes mucositis, bone marrow suppression with liver and kidney toxicity. Hydration and alkalisation of urine before and after therapy is beneficial to reduce toxicity.

 5 - Fluorouracil – 10-15 mg/m2 IV daily for 5 days. Complications are bone marrow suppression and gastrointestinal symptoms.

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• Bleomycin – 10-20 mg/m2 IV weekly. Pneumonitis and pulmonary fibrosis are the complications.

• Vincristine – 1-2 mg/m2 IV monthly. Neurotoxicity (sensory and motor neuropathy), constipation and alopecia are the side effects.

Cisplatin – 80-120 mg/m2 IV infusion once in 3 weeks. Complications are neurotoxicity, bone marrow suppression, renal toxicity, ototoxicity.
Adequate hydration and mannitol diuresis may be needed.

• Cyclophosphamide – 60-120 mg/m2 IV for 5 days at regular 3 weeks cycles. Alopecia, bone marrow suppression and cystitis (haemorrhagic) are the toxicities (ABC). Barbiturates should be avoided during therapy.

• Adriamycin – 60-90 mg/m2 IV. It is cardiotoxic and hence cardiac monitoring is needed while infusion.

• Paclitaxel and carboplatin as empiric chemotherapy are used in neck secondaries with occult primary.¹³

T0N1

T0N1 – no extracapsular spread. Patients presenting with N1 disease and who are subsequently confirmed following surgery as having pN1 disease without extracapsular spread may be treated with surgery alone provided the surgery has been comprehensive. This should be in the form of a modified radical neck dissection (MRND), including levels 1–5, and in

the vast majority preserving the ipsilateral sternomastoid muscle, internal jugular vein and accessory nerve. In the absence of other adjunctive therapies for the N1 neck, a MRND may be preferred as its extent and subsequent radiological assessment may avoid the need for radiation.

T0N1 – with extracapsular spread:

When extracapsular spread is found, however, then RT to at least the involved nodal levels is necessary, although it is more usual to irradiate the entire ipsilateral post-operative neck, and boost the involved levels.

T0N2a, T0N2b and T0N2c

For each of these stages comprehensive clearance of the involved lymph node levels is usually required in the form of Radical neck Dissection with possible contralateral MRND along with Radiotherapy to one or both sides of the neck

T0N3:

It may not be possible to have a curative aim in patients with this staging. Therefore, a potential role for surgery in the form of a Radical neck dissection[RND] for palliation with the aim of preventing or delaying the onset of fungation of the nodal metastasis combined with chemoradiotherapy was done.⁵³

Table 4: TREATMENT RECOMMENDATIONS FOR PATIENTWITH SECONDARIES IN NECK WITH CARCINOMA OFUNKNOWN PRIMARY.

STAGES	TREATMENT OPTIONS
N1	Modified radical neck dissection and Radiotherapy.
N2a	Radical Neck dissection then Radiotherapy.
N2b	Radiotheraphy then Radical Neck Dissection.
N2c	Bilateral Radical neck dissection and Bilateral Radiotherapy.
N3	Radical Neck Dissection combined with chemoradiotherapy

Prognostic factors in case of Neck carcinoma of Unknown primary include performance status, site and number of metastases, response to chemotherapy. Clinically, some Carcinoma of Unknown Primary diagnoses fall into a favorable prognostic subset. Others, including those with disseminated Carcinoma of Unknown Primary, do not and have a more unfavorable prognosis.

Squamous cell carcinoma

In this study of 30 patients with carcinoma of unknown primary with secondaries in neck,18[60%] patients were diagnosed to with squamous cell carcinoma[SCC]. All the patients were managed with multi modality approach. Among these patient with [SCC] 15 [83.33%] patients were in N1 stage. These patient where managed by Modified Radical Neck dissection followed by Radiotherapy. Other 3[16.6%] patients with [SCC] were in N2 stage. out of three patients in N2 stage, 2 patients are categorised under N2a stage and these patients were treated with Radical neck Dissection and Radiotherapy. One patient with [SCC] categorised under N2b, for this patient radiotherapy was given to down stage the tumour followed by Radical Neck Dissection.

Poorly differentiated carcinoma

During this study of 30 patients with secondaries in neck with carcinoma of unknown primary, 4 [13.3%]patients were diagnosed as undifferentiated carcinoma. These four patients were categorised under N1 stage and was treated with multi modality treatment of Radiotherapy and chemotherapy with follow up.^{10, 54}

Adenocarcinoma

During this study of 30 patients with neck secondaries with Carcinoma of unknown primary, Eight 8 [26.66%] patients were diagnosed with fine needle aspiration cytology as Adenocarcinomas. These 8 patients with Adenocarcinoma, were categorised under N1 stage. These eight patients were given multi-modality managements with both radiotherapy and chemotherapy and follow up.⁵



Lymph nodes dissected Levels I-V

Other structures excised Sternocleidmomastoid muscle Internal jugular vein Spinal accessory nerve Submandibular gland



Lymph nodes dissected Levels I-V

Other structures excised Sternocleidomastoid muscle Internal jugular vein Submandibular gland

Structures preserved Spinal accessory nerve

Figure : 9 Classical redical neck dissection

Figure : 9 (A) Modified radical neck dissection Type I



Lymph nodes dissected Levels I-V

Other structures excised Internal jugular vein Submandibular gland

Structures preserved Sternocleidomastoid muscle Spinal accessory nerve



Lymph nodes dissected Levels I-V

Other structures excised Submandibular gland

Structures preserved Sternocleidomastoid muscle Internal jugular vein Spinal accessory nerve

Figure : 10 Modified radical neck dissection Type II

Figure : 10 (A) Modified radical neck dissection Type III

OBJECTIVES:

- To assess the clinico-pathological patterns of presentation of cervical lymph node metastases among patients with Carcinoma of Unknown Primary in a tertiary care hospital in Coimbatore, Tamil Nadu.
- To study the various modalities of treatment for them.

METHODOLOGY

<u>STUDY DESIGN:</u> Prospective study

STUDY AREA: Coimbatore medical college hospital

STUDY SETTING: Department of General surgery, Coimbatore Medical

College Hospital.

STUDY PERIOD: January 2018- December 2018

STUDY POPULATION: All patients presenting to the department of general surgery with new neck node during the study period.

<u>SELECTION CRITERIA</u>:

INCLUSION CRITERIA:

- All patient presenting with cervical nodes as first presentation for malignancy.
- Patients without any obvious symptoms pertaining to primary site

EXCLUSION CRITERIA:

- Patient with impaired renal functions
- Patient who had allergy to contrast agents.
- Patients not willing for the study.
- Patient who were not cooperative during the study.

SAMPLE SIZE:

30 eligible patients who presented with secondaries in neck with cervical node enlargement with unknown primary at the time of initial presentation to hospital were included in the study.

SAMPLING TECHNIQUE: Universal sampling

STUDY TOOLS:

Data was obtained using a structured proforma. Detailed history was taken followed by physical examination of all the patient with cervical lymphadenopathy. After making a clinical diagnosis, further relevant investigations were carried out to confirm the diagnosis and to identify the primary site of cancer.

ETHICAL APPROVAL:

Obtained.

CONFIDENTIALITY:

Anonymity is maintained.

DATA COLLECTION PROCEDURE:

After obtaining ethical approval, informed verbal consent for the study was taken from all the participants. The purpose of the study was briefed and rapport was established. Between January 2018- December 2018, 30 patients with Cervical carcinoma of unknown primary sitepresented to the department of General surgery, Coimbatore Medical College Hospital. Based on the inclusion criteria these 30 patients were further studied in detail for their clinicopathological presentation and treatment. The demographic and clinical data (including follow-up data) of these patients were recorded. Detailed history of the patients were taken and they were further admitted to the ward for detailed clinical and pathological evaluation of the patients to confirm diagnosis and for further treatment.

Diagnostic workup and staging:

Diagnostic workup included complete medical history, physical examination, hematological examination including Complete blood count, Renal function tests, Liver functions tests, Stool for Occult blood, Urine routine tests, ECG, FNAC, Biopsy, Ultrasonograpy of Neck, Abdomen and pelvis. Endoscopic examination includes direct nasopharyngoscopy, fiber-optic laryngoscopy, esophagogastroscopy, and bronchoscopy. Imaging examination includes chest X ray, X Ray Neck Skeletal survey, Magnetic resonance imaging of the head and neck and chest regions, Contrast-enhanced Computed tomography of Neck, Chest, Abdomen and Pelvic cavity. PET scan was not done as it is not available.

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Pathologic diagnosis of metastatic lymph node was done for all the patients. Nodal staging (N1, N2, or N3) was done to all the patients according to the American Joint Committee for Cancer (AJCC) staging system.

Treatment:

The treatment strategy includes multimodality approach. It includes surgery- [Modified Radical Neck dissection], [Radical Neck dissection], Radiotherapy, Chemotherapy. For patients with Squamous cell carcinoma staged as N1 Modified Radical Neck Dissection was done followed by Radiotherapy. For Patients with N2 disease Radical neck dissection was done followed by radiotherapy. For patients FNAC diagnosed Adenocarcinoma were treated with combined modality of Radiotherapy and Chemotherapy.

Those patients FNAC diagnosed as Undifferentiated carcinoma were managed by multimodality treatment with Radiotherapy and Chemotherapy.

<u>STATISTICAL ANALYSIS</u>:

- Data entered and analysed in MS EXCEL and Descriptive statistics were used.
- Data was presented in the form of tables, figures, graphs wherever necessary.

RESULTS

During the study period, 30 patients had malignant cervical lymphadenopathy confirmed by FNAC met the inclusion criteria and were further evaluated.

Gender distribution:

These 30 patients were further categorised according to their gender, age, socio-economic status, use of alcohol/smoking/tobacco chewing, family history, any previous surgeries, duration of the disease, pathological type, staging of the disease, side of involvement and the treatment they underwent. Off the 30 patients under study 17 (56.7%) were males and 13 (43.3%) were females.

Gender	Total n= 30
Male	17 (56.7%)
Female	13 (43.3%)

Table 5: Gender distribution of the study population



Figure 11 : Gender distribution

Age distribution:

Among 30 patients, 70% were in the age group of 50 years and above followed by 30% who were below 50 years of age. Mean age of study population is 57 ± 12.5 years (SD).

Age	Total (n= 30)
<50	9 (30%)
>50	21 (70%)

 Table 6: Age distribution of the study participants



Figure 12 : Age distribution

Socio Economic Status of the study population:

Majority (76.7%) of the study subjects belonged to Below Poverty Line and only 23.3% of them were from Above Poverty Line.

Socio Economic Status	Total (n= 30)
BPL	23 (76.7%)
APL	7 (23.3%)

Table 7: Socio Economic Status of the study participants



Figure 13 : Socio Economic Status of the patients

Smoking habit of the study subjects:

Around 26.7% of the study group were smokers whereas the remaining (73.3%) were non smokers.

Smoking	Total (n= 30)
No	22 (73.3%)
Yes	8 (26.7%)

Table 8: Smoking habit among study population





Alcohol consumption among study participants:

Out of 30 patients, 26.7% of the study subjects consumed alcohol and 73.3% were non alcoholic.

Table 9: Distribution of study population based on Alcoholconsumption

Alcohol	Total (n= 30)
No	22 (73.3%)
Yes	8 (26.7%)



Figure 15 : Alcohol consumption

Tobacco chewing among patients:

Nearly half of the patients (43.3%) had the habit of chewing tobacco and 56.7% were not tobacco chewers.

Table 10: Tobacco chewin	g habit among	the study	participants
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Tobacco chewing	Total (n= 30)
No	17 (56.7%)
Yes	13 (43.3%)



Figure 16: Tobacco chewing habit

Family history of the study participants:

As Family history of Cancer plays a significant role in diagnosis, among the 30 study participants, four of them (13.3%) had family history of cancer and the remaining (86.7%) had no family history of cancer.

Table 11: Family history of cancer among the study participants

Family History	Total (n= 30)
Absent	26 (86.7%)
Present	4 (13.3%)



Figure 17: Family history of the patients

Previous surgical history of the patients

Majority (86.7%) of them dint had any past history of surgery while 13.3% of the patient had previous surgical history.

Previous Surgery	Total (n= 30)
No	26 (86.7%)
Yes	4 (13.3%)





Figure 18: Previous surgical history

Duration	Total (n= 30)
<6 months	4 (13.3%)
7-12 months	17 (56.7%)
13-18 months	5 (16.7%)
19-24 months	4 (13.3%)

 Table 13: Duration of cancer from the time of initial diagnosis



Figure 19: Duration of cancer from the time of initial diagnosis

Pathological type of the malignancy

Out of 30 patients diagnosed with malignancy, most (60%) of them had squamous cell carcinoma, 26.7% of them had adenocarcinoma, 6.7% of them had malignant melanoma and 3.3% had small cell carcinoma and 3.3% of them had epithelioid carcinoma.

Pathological type	Total (n= 30)
Squamous Cell Carcinoma	18 (60%)
Adenocarcinoma	8 (26.7%)
Undifferentiated carcinoma	4[13.3%]

 Table 14: Pathological type of malignancy



Figure 20: Pathological type of malignancy
Overall stage of the cancer:

60% of the study participants had stage III cancer and 40% of them had stage IV cancer.

Table 15: Distribution of study participants based on the overall

Overall stageTotal (n= 30)Stage III30 (100%)Stage IV-

stage of cancer

Node category of the malignancy:

Around 90% of the patient were categorised as having N1 involvement, 10% of them with N2 involvement.

Node category	Total (n= 30)
N1	27 (90%)
N2a	2 (6.7%)
N2b	1[3.33%]

 Table 16: Distribution of study participants based Node category



Figure 21 : Node category

Side of involvement of cervical lymph nodes:

50% of the study subjects had right side involvement of lymph node, 36.7% of them had left side involvement and 13.3% of the patients had bilateral involvement of cervical lymph nodes.

Involved side	Total (n= 30)
Right side	15 (50%)
Left side	11 (36.7%)
Both sides	4 (13.3%)

Table 17: Side involvement of cervical lymph nodes



Figure 22: Side of involvement of cervical lymph nodes

Treatment received by the patients:

Out of 30 patients, 50% of them had undergone surgery (MRND) & Radiotherapy. 10% of them were treated with radiotherapy and surgery (RND) and remaining 40% were treated with radiotherapy and chemotherapy.

Table 18: Distribution of Study participants based on the	e Treatment
received	

Treatment	Total (n= 30)
Radiotherapy and Surgery Modified Radical Neck dissection (MRND)	15(50%)
Radiotherapy and Radical Neck dissection (RND)	3 (10%)
Radiotherapy & Chemotherapy	12 (40%)



Figure 23: Treatment received by the patients

Scopy	Positive for primary carcinoma	Negative for carcinoma (N=30)
Direct lyrancoscopy	No	30[100%]
Esophagoscopy	No	30[100%]
Bronchoscopy	No	30[100%]
Nasophyrangoscopy	No	30[100%

Table 19 : PANENDOSCOPY

PANENDOSCOPY

In this study of 30 patients over the period of one year all the patients presenting with secondaries in the neck with carcinomas of unknown origin were investigated by pan endoscopy involving direct lyrangoscopy, video lyrangoscopy Esophagoscopy, Nasophyrangoscopy in search of primary site of carcinomas but no patients revealed any primary site of carcinomas.

DISCUSSION

Neck lymph node metastasis of unknown primary carcinoma appears to be challenging in management of these patient involved. It involves meticulous involvement of multispecialty department. Despite extensive investigations the primary could not be detected and the patients concerned had to undergo an intensive treatment with severe side effects. Therefore, primary detection is absolutely essential to focus the necessary multi modality treatment.

In the present study, 30 patients who had Neck lymph node secondaries with carcinoma of unknown primary origin was confirmed by FNAC were included. The mean age of the study participants was 57 \pm 12.5 years (SD). Off the 30 patients under study 17 (56.7%) were males and 13 (43.3%) were females. Majority (76.7%) of the study subjects belonged to Below Poverty Line. Around 26.7% of them were smokers and 26.7% of the study subjects consumed alcohol. About half of the patients (43.3%) had the habit of chewing tobacco. Nearly 13.3% of the patients had family history of cancer. For majority of them (56.7%) the duration of cancer was within 7-12 months. Squamous cell carcinoma was the major (60%) pathological type of malignancy found among the study subjects. Most of them (60%) had stage III cancer and 90% of the patient were categorized as having N1 involvement. About half of them

(50%) had right side involvement of lymph node. Those patients who were diagnosed as squamous cell carcinoma with unknown primary origin under N1 stage were managed by multi-modality approach. Surgery involving Modified Radical Neck Dissection and Radiotherapy.

Those patient with neck secondaries with carcinoma of unknown primary diagnosed by FNAC as Adenocarcinoma were total of eight[8] patients[26.6%] and Undifferentiated carcinoma were totaling to four [4] patients[13.3%]. These patients were categorized under N1 Stage and was Managed by multimodality Approach with Chemotherapy and Radiotherapy.

Those patient who were diagnosed as squamous cell carcinoma with unknown primary origin under N2 stage were 3patiens[10%] were managed by multi-modality approach. Surgery involving Radical Neck Dissection and Radiotherapy.

In this study, most (70%) of the patients were aged more than 50 years and malignancy was more common in males (56.7%) when compared to females,¹⁹ among those patients diagnosed as neck secondaries with carcinoma of unknown primary origin.⁵⁸ This shows that the Carcinoma of Unknown primary is more common in males and elderly compared to females.

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In the present study, it was found out that carcinoma of unknown primary [CUP] was more common in people living in below poverty line category. About 43.3% of the study subjects were tobacco chewers in our study.¹⁹ Nearly 26.7% of the patients were smokers in present study.⁶⁴ and.⁵⁸ This variation might be due different life style of the people living there.

In the present study reviled that 13.3% of the study participants had family history of cancer in their family. About half (56.7%) of the patients had 7-12 months of duration of cancer from the time of initiation of diagnosis. In the present study the major (60%) pathological type of malignancy was squamous cell carcinoma followed by adenocarcinoma (26.7%).⁵⁸

With respect to nodal involvement, the current study showed 90% in N1 stage and 10% in N2 stage.⁵⁸.⁶³ Out of 30 patients in our study, the primary site could not be identified.^{65 19.}

During this study all 30 patients were investigated with the panendoscopy no primary site of carcinoma was diagnosed.

In the present study the laterality of the involved necks included 50% right sided cases, 36.7% left sided cases and 13.3% bilateral cases.⁶⁴

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In this study out of 30 patients, 27(90%) of them staged N1 received multi modality management approach, Including Surgery {MRND} [RND] and Radiotherapy and Chemotherapy. Three [3]10% of patients who were in N2-level underwent Radiotherapy and Surgery - Radical neck dissection[RND] a study by Pothare AN et al .¹⁹ .⁶⁴ Non availability of PET scan being one of the limitations of the study.

CONCLUSION

Neck secondaries with occult primary appears an important clinical entity which always calls for meticulous attention, analysis and Multimodal treatment plan. Clinical symptoms in neck secondaries with carcinoma of occult primary has limited significance and clinical behavior can be highly variable. Dependence on clinical evidence alone would lead to erroneous diagnosis in a considerable number of cases. The commonest histology in our study is squamous cell carcinoma followed by Adenocarcinoma and the primary site was unidentified. Males and elderly were commonly involved compared to females. Surgery-Modified radical neck dissection[MRND],Radical neck dissection{RND},Radiotherapy and Chemotherapy are the combined plan of modalities were adopted for N1 and N2 stages. These observations suggests and justify the modes of treatment used according to the stages of the disease.

SUMMARY

Carcinoma of occult primary with secondaries to neck nodes appears to be a therapeutic challenges. Appropriate diagnostic procedures are required for proper diagnosis which is more essential for planning treatment. Clinicopathological diagnosis plays crucial role in treatment and prognosis of the patient. 30 patients presenting to surgery department of Coimbatore Medical College Hospital with neck lymph node secondaries with occult primary were studied over a period of one year for the Clincopathological diagnosis and treatment patterns. Detailed history of the patient was taken and followed by the detailed pathological and radiological evaluation was done. After diagnosis patient were started on appropriate treatment based on the clinical and pathological stage.

The study included 17 (56.7%) males and 13 (43.3%) females. The mean age of study population is 57 ± 12.5 years. 76.6% belonged to below poverty line and only 26.3% were current smokers, however majority had quit smoking in past 2 years. With respect to alcohol consumption, 26.7% were alcoholic, however nearly half 43.3% had habit of tobacco consumption. Only 4 (13.3%0 had family history of Cancer.

The mean duration of cancer from symptom to the time of initial diagnosis was 11.2 months. With respect to pathological diagnosis (60%) were squamous cell carcinoma, 26.7% of them had adenocarcinoma,

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13.3% of them had Undifferentiated carcinoma. 90% of had stage III cancer and 10% of them had stage IV cancer.

During this study all 30 patients were investigated with the panendoscopy no primary site of carcinoma was diagnosed.

Around 90% of the patient were categorized as having N1 involvement, 10% of them with N2 involvement. With respect to treatment 50% of them underwent Radiotheraphy and Surgery – {Modified Radical Neck Dissection}[MRND], 40% [12] of patients with Adenocarcinoma and Undifferentiated carcinoma were managed by multi modality approach by chemotherapy and radiotherapy. N2-10% had underwent Radiotheraphy and Surgery-{Radical Neck Dissection}[RND].

BIBLIOGRAPHY

REFERENCES:

- Stell P, Maran A, Wilson J, Gaze M, Watkinson J. Stell & Maran's head and neck surgery. 5th ed. Oxford: Butterworth-Heinemann; 2012.
- 2. Fischer J. Fisher's Mastery of Surgery. 7th ed. Wolters Kluwer; 2018.
- ESMO Guidelines Task Force. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of cancers of unknown primary site (CUP). Ann Oncol 2001;12:1057-8
- Saghatchian M, Fizazi K, Borel C, Ducreux M, Ruffie P, Le Chevalier T, et al. Carcinoma of an unknown primary site: a chemotherapy strategy based on histological differentiation – results of a prospective study. Ann Oncol 2001;12:535-40.
- Stewart JF, Tattersall MH, Woods RL et al. Unknown primary adenocarcinoma: incidence of overinvestigation and natural history. Br Med J 1979;1:1530-1533.
- 6. Muir C. Cancer of unknown primary site. Cancer 1995;75:353-356.
- Neumann G. The impact of cancer with unspecified site. Off Gesundheitswes 1988;50:13-19.
- Abbruzzese JL, Abbruzzese MC, Hess KR et al. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. J Clin Oncol 1994;12:1272-1280.
- 9. Kuttesch JF, Parham DM, Kaste SC et al. Embryonal malignancies of unknown primary origin in children. Cancer 1995;75:115-121.
- Didolkar MS, Fanous N, Elias EG et al. Metastatic carcinomas from occult primary tumours. Ann Surg 1977;186:625-630.

- 11. Brunicardi F, Andersen D, Billiar T, Dunn D, Hunter J, Kao L. Schwartz's principles of surgery. 10th ed. New York: McGraw-Hill; 2019.
- Arora, Anuj & Chugh, Anmol & Agarwal, P. & Singh, Rajdeep & Mishra, Anurag. (2015). Management of Metastatic Cervical Lymphadenopathy with Unknown Primary. New Indian Journal of Surgery. 6. 10.21088/nijs.0976.4747.6115.1.
- Calabrese L, Jereczek-Fossa B, Jassem J, Rocca A, Bruschini R. Diagnosis and management of neck metastases from an unknown primary. Acta Otorhinolaryngol Ital. 2005;25(1):2-12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2639847/#B6
- Standring S. Gray's Anatomy the anatomical basis of clinical practice. 41th ed. Spain: Elsevier; 2008:397-421
- 15. Guidera A, Dawes P, Fong A, Stringer M. Head and neck fascia and compartments: No space for spaces. Head & Neck. 2014;36(7):1058-1068.
- Townsend C, Beauchamp R, Evers B, Mattox K. Sabiston textbook of surgery. 20th ed. Saunders; 2012.
- 17. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.
- GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544. 10.1016/S0140-6736(16)31012-1
- Aster K, Kumar V, Aster J. Robbins's Basic Pathology. 9th ed. Philadelphia: Elsevier; 2013.

- 20. Chen S. Survival benefit of neck dissection for patients with breast cancer with supraclavicular lymph node metastasis. J Clin Oncol. 2010;28(Suppl):15s
- Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992, 127(4):392–399.
- 22. Pothare A, Ilamkar K. A case series of metastatic lateral cervical lymphadenopathy. International Surgery Journal. 2017;4(3):988.
- Morita S, Balch C. Textbook of complex general surgical oncology. 1st ed. McGraw-Hill Education;.
- 24. López F, Rodrigo J, Silver C, Haigentz M, Bishop J, Strojan P. Cervical lymph node metastases from remote primary tumor sites. Head & Neck. 2015;38(S1):E2374-E2385. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4991634/
- 25. Pavlidis N, Briasoulis E, Hainsworth J, Greco F. Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer. 2003;39(14):1990–2005.
- 26. Guntinas-Lichius O, Klussman J, Dinh S, Dinh M, Schmidt M, Semrau R, et al. Diagnostic work-up and outcome of cervical metastases from an unknown primary. Acta Otolaryngol.2006;126(5):536–44.
- 27. Chernock R, Lewis J. Approach to Metastatic Carcinoma of Unknown Primary in the Head and Neck: Squamous Cell Carcinoma and Beyond. Head and Neck Pathology. 2015;9(1):6-15.
- 28. Jameson J, Kasper D, Fauci A, Hauser S, Longo D, Loscalzo J et al. Harrison's principles of internal medicine. 20th ed. McGrew Hill; 2018.

- 29. Le Chevalier T, Cvitkovic E, Caille P et al. Early metastatic cancer of unknown primary origin at presentation: a clinical study of 302 consecutive autopsied patients. Arch Intern Med 1988;148:2035-2039
- 30. Wilkinson A, Maimoon S, Mahore S. FNAC in the diagnosis of lymph node malignancies: A simple and sensitive tool. Indian Journal of Medical and Paediatric Oncology. 2012;33(1):21.
- 31. DeVita V, Lawrence T, Rosenberg S. DeVita, Hellman, and Rosenberg's cancer: Principles and practice of oncology. 11th ed. Wolters Kluwer; 2018.
- Mulholland M. Greenfield's Surgery. 5th ed. Philadelphia: Wolters Kluwer Health; 2016.
- 33. PDQ Adult Treatment Editorial Board. Metastatic Squamous Neck Cancer With Occult Primary Treatment (Adult) (PDQ®): Health Professional Version. 2018 Feb 8. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65926/
- 34. Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg., 1990; 160: 405-409.
- 35. Teymoortash A, Werner JA. Current advances in diagnosis and surgical treatment of lymph node metastasis in head and neck cancer. GMS Curr Top Otorhinolaryngol Head Neck Surg., 2012; 11: Doc04
- 36. Cantu G, Bimbi G, Miceli R, Mariani L, Colombo S, Riccio S, Squadrelli M, Battisti A, Pompilio M, Rossi M. Lymph node metastasis in malignant tumours of the paranasal sinuses: prognostic value and treatment. Arch Otolaryngol Head Neck Surg., 2008; 134(2): 170-177

- 37. Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastasis" in the neck from squamous carcinoma of the oral tongue. Head neck. 1997; 19(1): 14-19
- 38. Huang SH, Hwang D, Lockwood G, Goldstein DP, O"Sullivan B. Predictive value of tumour thickness for cervical lymph node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. Cancer., 2009; 115(7): 1489-1497
- 39. Tang L, Mao Y, Liu L, Liang S, Chen Y, Sun Y, Liao X, Lin A, Liu M, Li L, Ma J. The volume to be irradiated during selective neck irradiation in nasopharyngeal carcinoma: analysis of the spread patterns in lymph nodes by magnetic resonance imaging. Cancer., 2009; 115(3): 680-688
- 40. Iyer NG, Shaha AR, Ferlito A, Thomas Robbins K, Medina JE, Silver CE, Rinaldo A, Takes RP, Suarez C, Rodrigo JP, Bradley PJ, Werner JA. Delphian node metastasis in head and neck cancers – oracle or myth? J Surg Oncol., 2010; 102(4): 354-358.
- Kamiyama R, Saikawa M, Kishimoto S. Significance of retropharyngeal lymph node dissection in hypopharyngeal cancer. Jpn J Clin Oncol., 2009; 39(10): 632-637.
- 42. Sesterhenn AM, Albert US, Barth PJ, Wagner U, Werner JA. The status of neck node metastases in breast cancer---loco-regional or distant? Breast. 2006; 15:181–186.
- 43. Tanis PJ, Nieweg OE, Valdés Olmos RA, Kroon BB. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg. 2001; 192:399–409.

- 44. Edge, S.; Byrd, DR.; Compton, CC.; Fritz, AG.; Greene, FL.; Trotti, A., editors. AJCC cancer staging manual. 7. New York, NY: Springer; 2010.
- 45. Aldridge T, Kusanale A, Colbert S, Brennan PA. Supraclavicular metastases from distant primaries: what is the role of the head and neck surgeon? Br J Oral Maxillofac Surg. 2013; 51:288–293.
- 46. Tachibana M, Dhar DK, Kinugasa S, et al. Esophageal cancer with distant lymph node metastasis: prognostic significance of metastatic lymph node ratio. J Clin Gastroenterol. 2000; 31:318–322.
- 47. Howlader, N.; Noone, AM.; Krapcho, M., et al., editors. SEER cancer statistics review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011.
- 48. Strojan P, Ferlito A, Langendijk JA, Corry J, Woolgar JA, Rinaldo A et al. Contemporary management of lymph node metastases from an unknown primary to the neck: II. A review of therapeutic options. Head Neck 2013;35:286–93
- 49. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. The Journal of Laryngology & Otology. 2016;130(S2):S170-S175.
- 50. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. ORL J Otorhinolaryngol 2001;63:214-6
- 51. Fernandez JA, Suarez C, Martinez JA, Llorente JL, Rodrigo JP, Alvarez JC. Metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary tumor: prognostic factors. Clin Otolaryngol 1998;23:158-63.

- 52. Leemans C, Tiwari R, Nauta J, Van der Waal I, Snow G. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer. 1993;71(2):452-456.
- 53. Amin M. AJCC cancer staging manual. 8th ed. New York: Springer; 2018.
- 54. Wang Y, He S, Bao Y, Cai X, Chen H, Yang X. Cervical lymph node carcinoma metastasis from unknown primary site: a retrospective analysis of 154 patients. Cancer Medicine. 2018;7(5):1852-1859.
- 55. Gorle V, Inamdar P. A clinicopathological study on cervical lymphadenopathy: an institutional experience. International Surgery Journal. 2018;5(8):2841.
- 56. Zaun G, Schuler M, Herrmann K, Tannapfel A. CUP Syndrome. Deutsches Aerzteblatt Online. 2018;115(10).Available from: <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5881077/</u>
- 57. Karthikrajan M. A CLINICOPATHOLOGICAL STUDY OF CERVICAL LYMPHADENOPATHY. Int J Modn Res Revs. 2014;2(10):354-357.
- 58. Patel M, Italiya S, Dhandha Z, Dudhat R, Kaptan K, Shah M. Study of metastasis in lymph node by fine needle aspiration cytology: our institutional experience. International Journal of Research in Medical Sciences. 2013;1(4):451.
- Hung Y, Liu S, Wang C, Wang C, Jiang R, Wu S. Treatment outcomes of unknown primary squamous cell carcinoma of the head and neck. PLOS ONE. 2018;13(10):e0205365.
- 60. Weiss D, Koopmann M, Stenner M, Savvas E, Rudack C. Clinicopathological characteristics of carcinoma from unknown primary in cervical lymph nodes. European Archives of Oto-Rhino-Laryngology. 2014;272(2):431-437.

ANNEXURE 1

PROFORMA

Name:

Age/sex:

Income/Socio Economic Status:

Family History of cancer:

History of smoking: yes/no

Tobacco Chewing: yes/no

Alcohol consumption: yes/no

Family History Of Cancer:

Signs and Symptoms:

Previous Surgery:

Duration to the time of diagnosis:

Pathological Diagnosis:

Primary Site:

Stage:

Side involved (Neck):

Nodal Staging:

Treatment:

KEY TO MASTER CHART

GENDER	FAMILY HIS	SES	SMOKING	ALCOHOL	TOBACCO CHEWING	PREV SURGERY	DURATION	РАТН	STAGE	NODE	SIDE	TREATMENT
Male-1	yes-1	above poverty line-1	yes-1	yes-1	yes-1	yes-1		1-SCC			1-right	1- surgery
female-2	no-0	below poverty line-o	no-0	no-0	no-0	no-0		2- Adenocarcinoma			2-left	2- surgety+rt
								3- Malignant Melanoma			3- bilateral	3- RT+CHEMO
								4- Small Cell Carcinoma				
								5- Epitheloid carcinoma				

GE	GENDER	FAMILY HIS	SES	SMOKING	ALCOHOL	TOBACCO CHEWING	PREV SURGERY	DURATION	PATH	STAGE	NODE	SIDE	TREATMENT
43	1	0	1	1	1	1	0	5	1	3	1	1	1
58	2	0	1	0	0	0	0	7	1	3	1	1	1
81	2	1	1	0	0	0	1	17	1	3	1	2	1
57	1	0	2	0	0	1	0	8	2	3	1	1	1
38	1	0	1	1	1	0	0	12	1	4	1	2	2
81	2	0	1	0	0	1	0	10	1	4	1	1	2
77	1	0	1	0	0	1	0	5	1	3	1	2	2
77	1	0	1	0	1	0	0	19	3	3	1	1	2
59	1	0	1	0	1	1	0	9	1	4	1	3	2
53	1	0	1	1	1	0	1	21	4	3	1	2	2
42	1	0	2	0	0	0	0	9	3	3	1	1	2
63	1	0	1	1	1	1	0	8	1	4	1	2	2
68	2	0	1	0	0	1	0	11	2	3	1	1	1
51	1	0	1	1	1	1	0	9	1	3	1	3	1
59	2	0	2	0	0	0	0	14	5	3	1	1	2
51	2	0	1	0	0	0	0	19	2	3	1	1	2
45	2	1	1	0	0	0	0	8	1	4	2	2	3
67	1	0	1	1	0	1	0	6	2	4	2	2	3
62	1	0	1	0	0	1	0	6	2	3	2	1	3
49	2	0	1	0	0	0	0	8	1	3	2	3	3
41	2	0	1	0	0	0	0	13	1	4	2	2	3
56	2	0	1	0	0	0	0	12	2	4	2	2	3
62	2	0	1	0	0	0	1	8	1	3	2	1	3
54	1	0	2	0	0	0	0	12	1	4	2	1	3
65	1	0	1	1	0	1	0	16	1	3	2	2	3
39	2	0	1	0	0	0	0	12	1	3	2	2	3
46	1	0	1	0	1	1	1	9	2	4	2	1	3
53	2	0	2	0	0	0	0	7	1	4	3	3	3
43	1	1	2	0	0	1	0	20	2	4	3	1	3
70	1	1	2	1	0	0	0	16	1	3	3	1	3

INFORMED CONSENT FORMAT

Study Volunteer ID:

Study Volunteer Name:

Coimbatore Medical College, Coimbatore – 641014 Institutional Human Ethics Committee INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS (strike off items that are not applicable)

I Dr M.PRASAD, am carrying out a study on the topic "CLINICO PATHOLOGICAL STUDY OF SECONDARIES IN NECK WITH UNKNOWN PRIMARY CANCER-PROSPECTIVE STUDY" as part of my research project being carried out under the aegis of the Department of General Surgery, Coimbatore Medical College and Hospital. My research guide is Professor Dr.T.Srinivasan, MS, Chief of unit S3, Dept. of General Surgery, Coimbatore medical college and Hospital

The justification for this study is: Neck lymph node metastases from occult primary constitute about 5%-!0% of all patients with carcinoma of un known primary site, for which diagnostic work-up remains challenging to identify the site of origin. This research were aimed to describe the clinical patterns of presentations of the cervical lymph node metastases, the pathological type of cervical

lymph node metastasis and to evaluate the type of treatment for Carcinoma of unknown primary.

The objective of this study is: To describe and to evaluate the etiology, clinical presentation, management and outcome of carcinoma of unknown primary in adult patients.

Study volunteers / participants are :All patients presenting to surgery OPD with cervical lymph node enlargement due to secondaries and patient without obvious primary malignancy.

Location: Department of General surgery, Coimbatore medical college and Hospital

We request you to kindly cooperate with us in this study. We propose to collect background information and other relevant details related to this study. We will be carrying out an **Initial interview** of 10 minutes. Data collected will be stored for a period of one and half years. We will not use the data as part of another study. A complete clinical examination will be done including visual inspection, palpation, percussion and auscultation of abdomen. Blood sample of 5 ml will be collected at one time to test the complete counts of blood along with liver, lipid and renal profiles both for routine and research study purpose. The blood sample collected at the

time of study will not be sold or shared with persons from another institution.

Benefits of the study: This study will help in developing multidisciplinary integrated approach among Surgeons, Oncologists, Pathologists and Radiologists towards the management of patients with carcinoma of unknown primary.

Risksinvolved by participating in this study: Complications related to Carcinomas.

If you are uncomfortable in answering any of our questions during the course of the interview/study, you have the right to withdraw from the interview/study at anytime. You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will NOT be paid any remuneration for the time you spend with us for this interview/study. The information provided by you will be kept in strict confidence. Under no circumstances shall be used for approved research purpose only. You will be informed about any significant new findings – including adverse events, if any, - whether directly related to you or to other participants of

this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature/left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature/Left thumb impression of the Study Volunteer/Legal Representative

Signature of the Interviewer with date:

Witness:

Contact number of PI:

Contact number of Ethics Committee Office:

PATIENT PROFORMA

NAME

AGE

SEX

OCCUPATION

ADDRESS

MARITAL STATUS

PHONE NO.

Chief Complaints :

H/O Presenting Illness:

Past history

Personal history

Family history

Treatment history

EXAMINATION:

GENERAL EXAMINATION

B.P. –

P.R. –

TEMP -

ECOG PERFORMANCE SCALE-

SYSTEMIC EXAMINATION

CNS:

CVS:

RS :

P/A:

LOCAL EXAMINATIONS:

Oral cavity

Ear, Nose, Throat

INFORMED CONSENT (IN TAMIL)

ம.பிரசாத் தனதுமுதுநிலைஅறுவைச்சிகிச்சைபட்டப்படிப்பு மருத்துவர் முழுமைப்பெறுவதற்காகமேற்கொள்ளும் CLINICO PATHOLOGICAL STUDY OF SECONDARIES IN NECK WITH UNKNOWN PRIMARY CANCER-**PROSPECTIVE STUDY** ஆய்வினைப்பற்றிஎனக்குஎன் தாய்மொழியில் விளக்கப்பட்டது. விருப்பத்துடன் கலந்துகொள்கிறேன். இந்தஆய்வில் (µ)(µ) எனினும் இந்தநேரத்திலும் எந்தகாரணமுமின்றி இந்த ஆய்விலிருந்து விலகிக்கொள்ள முழு உரிமையுள்ளது. இதனால் எனதுநலனில் எந்தபாதிப்பும் ஏற்படாதுஎன்றுஉறுதியளிக்கப்படுகிறது. இந்தஆய்வின் அறிக்கையில் என்னுடையதனிப்பட்டவிவரங்கள் அனைத்தும் ரகசியமாய் பாதுகாக்கப்படும் என்றுஎனக்குஉறுதியளிக்கப்பட்டிருகிறது. மேறகூறியஉறுதிமொழியின் யாவும் பின்பற்றப்படும் பட்சத்தில் சான் இந்துஆய்வுக்கட்டுரைக்குஎன்னுடையவிவரங்களை அளிக்கமுன்வருகிறேன். என்னுடையஒப்புதலைதந்து இந்தஆய்வறிக்கையில் இதற்குமுழுமனமுடன் பங்கேற்கிறேன்.

இப்படிக்கு

(கையொப்பம்)

Name of Participant

Sign of Participant

Name of Investigator (Signed)

Date