A STUDY OF MALIGNANT CERVICAL LYMPHADENOPATHY WITH UNKNOWN PRIMARY

Dissertation submitted in partial fulfillment of the regulations required for the award of

M.S. Degree in General Surgery

Branch I

DEPARTMENT OF GENERAL SURGERY

KILPAUK MEDICAL COLLEGE

The Tamil Nadu

Dr.M.G.R. Medical University

Chennai

MAY 2018

DECLARATION

I solemnly declare that the dissertation titled **"A STUDY OF MALIGNANT CERVICAL LYMPHADENOPATHY WITH UNKNOWN PRIMARY"** was done by me at Kilpauk Medical College and Hospital, Chennai during the period of January 2017 to August 2017 under the guidance and supervision of **Prof. Dr. R.KANNAN M.S.**

The dissertation is submitted to the Tamilanadu Dr.M.G.R. Medical University towards the partial fulfillment of the requirement for the award of **M.S DEGREE IN GENERAL SURGERY BRANCH- I**

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ACKNOWLEDGEMENT

I wish to thank our dean **Dr.VASANTHAMANI, MD DGO MNA MS MBA,** for having permitted me to use the resources and conduct the study in this hospital.

I am ever grateful to Professor and Head of the Department of Surgery **Prof. Dr. R.KANNAN.M.S,** for his excellent expert advice, and help in preparing this dissertation

I am greatly indebted to my unit chief **Prof. Dr.R.KANNAN M.S** for his excellent guidance and generous help in the preparation of this dissertation. Without his guidance and encouragement this work would not have been completed.

I thank all the surgical unit chiefs **Prof. Dr. RAMALAKSHMI M.S and Prof. Dr. SHANTHI M.S and Prof. ANDAL M.D. HOD PATHOLOGY DEPT.** for permitting me to carry out this study in their respective units and departments.

I also thank my Assistant Professors **Dr.S.Savitha** and **Dr.S.R.Padmanabhan** for their guidance.

Last but not the least I express my gratitude to all the patients who co-operated in this study.

ETHICAL COMMITTEE

INSTITUTIONAL ETHICS COMMITTEE
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Protocol ID. No.18/2017 Meeting held on 20/01/2017
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "**A Study of malignant Cervical Lymphadenopahy with Unknown Primary "** submitted by Dr.S.Sudha, Postgraduate in General Surgery, Govt. Royapettah Hospital ,Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

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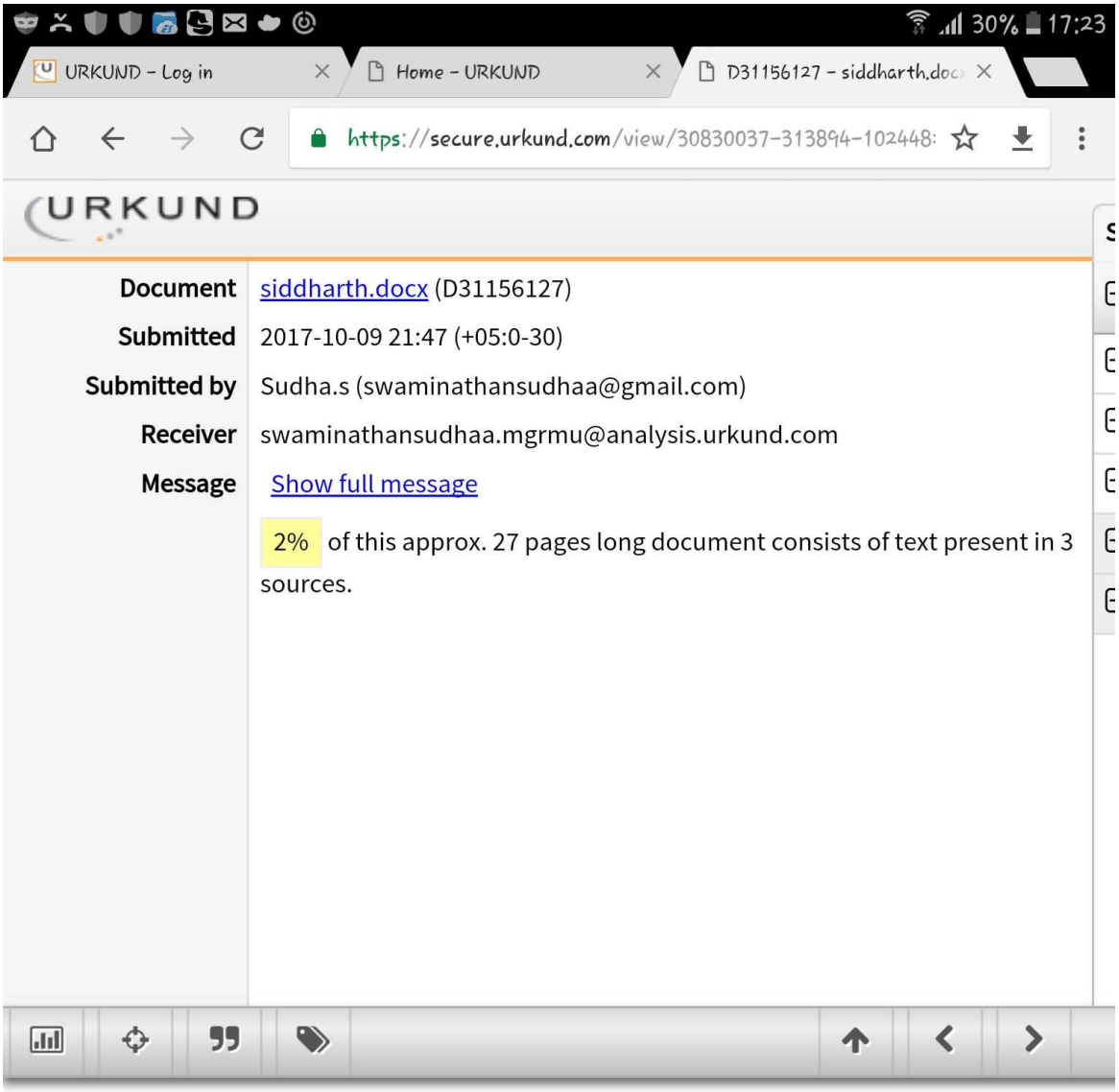

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LIST OF ABBREVATIONS USED

CT	-	Computed Tomography
MRI	-	Magnetic Resonance Imaging
PET	-	Positron Emission Tomography
FNAC	-	Fine Needle Aspiration Cytology

ABSTRACT

Background

Head and Neck cancers account for 3% of all newly discovered cancers metastatic carcinoma within cervical lymphnodes with an unknown primary tumour site accounts for 3-5% of all head and neck cancers, this highlights the need for proper systematic screening and management of secondaries neck with unknown primaries. Objectives.

The most common histopathological type common in our population and the age and sex incidence of the malignant cervical lymphadenopathy with an unknown primary, the staging of the disease, interpretation of possible site of primary based on nodal involvement and various investigations to identify the primary site and ideal treatment modality for the patients studied and reported

Methodology

Patients with malignant cervical lymhadenopathy are diagnosed in department of General Surgery at Government Royapettah hospital.43 of them are to be selected, detailed history is elicited from the patient thorough clinical examination of the patient is done and disease staged according to TNM Classification. FNAC / histopathological study of the tumour is done and age and sex incidence of disease also done

Results

The results of the study like histopathological types, age and sex incidence of diseases and topographical distribution of disease are identified and put on the tables

Conclusion

With all the available investigations the unknown primary sites were being tried to identified and treatment like neck dissection and or adiotherapy/chemotherapy were done for the patients.

Keywords:

Chest X-Rays, CT Scan, MRI Scan, PET-CT Scan, Panendoscopy, FNAC, HPE, Immunohistochemical Analysis.

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INTRODUCTION

Head and Neck cancers account for 3% of all newly discovered cancers metastatic carcinoma within cervical lymphnodes with an unknown primary tumour site accounts for 3-5% of all head and neck cancers, this highlights the need for proper systematic screening and management of secondary's neck with unknown primaries.

The control of such regional metastatic disease constitutes an important part of the process of treating head and neck cancer. The presence of an enlarged node proven histologically positive for metastasis is ominous findings and as a general rule it decreases the 5-year survival rate by at least 50%.When nodal involvement becomes multiple extends low in the neck, no patient gets cured regardless of the treatment given. When the primary site of carcinoma is known, focused therapy to primary site and cervical lymphadenopathy can be given. Without this thorough knowledge clinicians are obligated to treat the entire pharyngeal axis and larynx to cover the possible origins of the metastatic carcinoma. The occult primary treatment regimen results in a significant increase in morbidity to the patient.

AIMS OF THE STUDY

1. To analyse the histopathological type common in our population
2. To find age and sex incidence of the malignant cervical lymphadenopathy with an unknown primary.
3. To stage the disease at the time of presentation
4. To interpret the possible site of primary based on the nodal involvement.
5. To describe the various investigations used to identify the primary site.
6. To discuss the ideal treatment modality for the patients.

REVIEW OF LITERATURE

ANATOMY OF THE CERVICAL LYMPHATICS

The lymphatics has three components; the capillaries, vessels and the nodes.

Capillaries

Lymphatic capillaries are tiny thin walled vessels located in the spaces between cells which serve to drain extra cellular fluid. Lymphatic capillaries are found in all tissues; each lymphatic capillary carries lymph into a lymphatic vessel which in turn connects to a lymphnode. Lymph is ultimately returned to the venous circulation. they are more abundant in the upper respiratory and gastrointestinal tract

Vessels

Lymphatic vessels are thin walled, valved structures that carry lymph ,lined by endothelial cells and have a thin layer of smooth muscles, and adventitia that bind the vessels to the surrounding tissue, which in turn is enveloped by an outer connective tissue layer., with the lymph circulation entirely dependant on compression by surrounding muscles, lymphatic vessels that carry lymph to a lymphnode is called afferent lymph vessel, and one that carries it from a lymphnode is called the efferent lymph vessel

Nodes

A lymph node is an ovoid or kidney shaped organ of lymphatic system. Range in size from a few mm to about 1-2 cm long. Each lymphnode is surrounded by a fibrous capsule, which extends inside the node to form trabeculae. The substance of the node is divided into the outer cortex and inner medulla.. there are nearly 500 nodes in the body and of these 200 are in the Head and Neck. Nodes contain a subcapsular sinus below a prominent capsule, into which lymphatic fluid drains. This capsule is often the first site of metastatic growth. The fluid permeates the substance of the node and exists through the hilum to enter more lymphatic vessels. The nodes are located between the superficial cervical and prevertebral fascia and thus they are very amenable to surgical removal. The lymphatic fluid eventually enters the venous system at the junction of the internal jugular and subclavian veins.

All nodes are palpable when enlarged except few retrovisceral nodes and those deep to the sternomastoid muscle. Because tumours have no primary lymphatics, cancer cells presumably gain access to the lymphatic system at the periphery through clefts between lymphatic endothelial cells.

Lymphatic vessels are continuously contracting; actin like filaments are observed in lymphatic endothelial cells. Afferent lymphatics join a marginal sinus in the cortex of individual lymph nodes. When cancer cells lodge in lymph nodes, proliferation first occurs in the periphery and later in the medulla. From there anastamosing channels penetrate the body of the node to form hilar efferent channels into which the marginal sinuses drain directly. The efferent channels from a group of nodes form the lymphatic trunks that in turn form collecting trunks. The collecting trunks drain into the venous system. According to traditional view, cancer cells in the lymphatic system can gain access to the blood stream only through these terminal collecting trunks at their junctions with major blood vessels.

LYMPHATICOVENOUS COMMUNICATIONS

Many lymphaticovenous communications exist normally in body. Embryonically lymphatics originate from the buds of venous endothelium. Substances of varying sizes have been demonstrated, to pass from lymphatics to veins within the lymph nodes.

Cells that enter the lymphatics are transported to lymph nodes in the afferent vessels, and are deposited in the peripheral subcapsular sinuses of the node, subsequent process are variable, based on the existence of

lymphaticovenous anastamosis.

Cancer cells may permanently lodge in the lymph nodes,or may traverse nodes taking egress by efferent lymphatics or through the lymphaticovenous communications within nodes to become hematogenously disseminated or may completely bypass the lymph nodes to enter the blood vascular system.

Primary hematogenous spread may occur when cells have gain access to small blood vessels in the tumour stroma; such vessels develop from existing host vessels, presumably as a response to tumour angiogenesis. Blood borne tumour cells also traverse interstitial spaces, invade the lymphatics and disseminate via lymphatics.

Thus in addition to the classical route from afferent channels ,through the medulla to the efferent channels, cells may bypass medulla by means of the marginal sinus or may enter the blood stream in the node. Additionally lymph nodes may be completely bypassed through collateral channels, although this route will be enhanced by local obstruction to lymphatic flow caused by metastases or reactive lymph node hyperplasia, including sinus histiocytosis. Tumuor cells can also bypass the nearest regional nodes and proceed to more remote lymph nodes. This phenomenon of skip metastases is seen not infrequently in head and neck cancer patients.

The many oppurtunities for lymphaticovenous and interlymphatic communication prevent any discrimination between hematogenous and lymphogenous metastasis anatomically. This two way communication may account for confused patterns metastasis being confined to one or the other except perhaps in early subclinical cancer.

Reversal of lymph flow can be easily produced; retrograde flow of lymph is enhanced and filtering efficiency of lymph nodes is decreased by inflammation, fibrosis from radiation and tumour growth with in them. Tumour emboli are able to disseminate through existing anastamoses or in newly formed collateral channels.

WHY CARCINOMA FAVOUR LYMPHATIC SPREAD

A first step in the metastatic process is the detachment of cancer cells or group of cells from their primary tumours .Clusters have better chance of survival than single cells.

Single cancer cells tend to enter the blood or lymphatic systems equally, whereas cell clumps are more restricted to enter the blood vessels.

Because of intimacy with their own blood supply, sarcomas have a better chance than carcinomas of gaining early access to blood channels moreover sarcomas comparatively having lower thrombogenic activity, so they have less chance of being held up by intravascular thrombosis .

Sarcomas also preferentially separate as multicelluar units rather than as single cells. This would promote their survival in the blood stream and would tend to hinder their access to lymphatic systems.

Conversely, the greater tendency of carcinomas to release single cells would favour early direct lymphatic spread.

ANATOMY OF NECK NODES

The nodal system of the head and neck consists of two groups deep cervical chain or cervical lymphnode proper and an outlying intermediary group arranged into two circles, the ‘outer circle’ and the ‘inner circle’. The internal jugular vein which remains surrounded by nodes of the terminal group lies vertically between the outer and inner circles of the outlying group.

All the lymph follows a sequential pattern of spread from superficial to deep and from the upper to lower parts of neck. These lower confluent vessels form into a jugular trunk, which on the right side ends at the junction of the jugular vein and the brachiocephalic vein or join the right lymphatic duct. On the left side the trunk will usually join the thoracic duct as it arches behind the lower part of the carotid sheath and in front of the sub clavian artery to enter the junction of the internal jugular vein with the brachiocephalic vein

Superior deep cervical group

These nodes drain the soft palate, tonsil, posterior 1/3 ofl tongue, pyriform fossa, supraglottic larynx. The important node of this group is jugulodigastric node otherwise known as tonsillar or JD node.

It liest below and behind the angle of mandible. It is enlarged in all of tonsillar pathologies

Middle deep cervical group

This group drains the supraglottic larynx, lower pyriform sinus and post cricoid area.

Inferior deep cervical group

This group drains the thyroid, trachea and cervical oesophagus. The important node of this group is juguloomohyoid. This lies in the intermediate tendon of omohyoid and receives lymph from tongue and submental node.

Spinal accessory chain

accompanies the spinal accessory nerve in the posterior triangle and receives lymph drainage from scalp, nape of neck and from upper retropharngeal nodes.

Left scalene node

This is located at the junction of subclavian with the thoracic duct and receives drainage from thoracic duct. It is the important node to be looked for in cases of infraclavicular primaries.

Supraclavicular nodes

This receives afferents from spinal accessory chain and they are located in the posterior triangle of neck and may be involved in case of infraclavicular primaries.

SUPERFICIAL GROUP OF NODES

This is further divided into

a. inner circle of outlying group and
b. outer circle of outlying group of nodes

these nodes are situated around the skull base

Outer circle of outlying group

This forms a collar in the cervical region.

Occipital nodes

These nodes lie in the apex of posterior triangle and receives drainage from scalp and sends their efferent to deep cervical group.

Post auricular group

This group Lies superficially over the mastoid attachment of sternomastoid and they receives afferents from post auricular area, scalp

and drain into upper deep cervical group.

Pre auricular nodes

This group lies in front of the tragus and receives drainage from scalp, forhead, pinna, temple, eyelid and external auditory meatus and they ultimately drains into deep cervical group.

Parotid and facial nodes

These nodes Lie within the substance of parotid gland and drains the orbit , parotid and infratemporal fossa. It sends efferents to deep cervical group.

Buccal nodes

They Lie over the buccinator muscle near lower border of mandible. Drains cheek, lower eyelid, sends efferents to jugulodigastric node.

Submental nodes

This group of nodes numbering 3-4, lies in the submental triangle and over mylohyoid muscle. Receives their afferents from median plane structures and drains the chin and portion of lower lip, mid portion of gingival, floor of mouth, tip of tongue and nasal vestibule and send efferent to submandibular group.

Submandibular nodes

Lies in the submandibular triangle over the submandibulr gland

itself. Facial artery is in close relation with this node. This group drains the centre of forehead, nose, upper lip, floor of mouth, cheek, gums, major part of tongue and paranasal sinuses (frontal, ethmoidal, maxillary).It ultimately drains into jugulo digastric and jugulo omohyoid nodes.

INNER GROUP OF OUTLYING NODES

This nodes lie in relation to upper aerodigestive tract and drains larynx, trachea and pharynx. All nodes ultimately drain into deep cervical group.

Infra hyoid nodes

Lies in relation to throhyoid membrane and drains the hypopharynx.

Prelaryngeal nodes

It is situated in the conus elasticus of the larynx and drains the larynx and superior part of isthmus of thyroid.

Pretracheal nodes

they Situated anteriorly and in close relation with inferior thyroid veins and drains trachea and inferior part of isthmus of thyroid.

Paratracheal nodes

Trachea and oesophagus on either side of the course of recurrent laryngeal nerve and drains trachea and cervical oesophagus.

Retropharyngeal nodes

Consists of one median and two lateral groups. Receives drainage from nasopharynx, eustachian tube and adjacent vertebra.

CLASSIFICATION OF CERVICAL NODE GROUPS

Spread patterns of cancer from various primary sites in the head and neck to the cervical nodes have been documented in retrospective analyses of large group of patients undergoing neck dissections. Since the first descriptions of nodal groups, various classification systems have been described.

To address surgical management of early stage neck metastasis via neck dissection, various authours have proposed a number classification schemes. This lack of uniformity and standardization results in redundancy, misinterpretation and confusion among clinicians. The most widely accepted terminology was originally described by a group of head and neck surgeons at Memorial Sloan-Kettering Hospital. This classification uses neck levels and divides each side of the neck into 7 separate regions

- **Level I submental and sub mandibular groups : the boundaries are** - the body of the mandible, anterior belly of the contralateral digastric muscle and anterior and posterior bellies of the ipsilateral

digastric muscle two nodal subgroups are found, the submental group (Ia) is found in the submental triangle (anterior belly of digastric muscle and the hyoid bone), and the submandibular group (Ib) is found within the submandibular triangle (anterior and posterior bellies of the digastric muscle and the body of the mandible)

- **Level II upper jugular group: these** nodes are located around the upper third of the internaljugular vein, extending from the skull base down to the carotid bifurcation inferiorly it is bounded laterally by the posterior border of the strenocleidomastoid muscle and medially by the stylohyoid muscle. Two subzones are described; nodes located anterior to the spinal accessory nerve are level IIa and those nodes posterior to the nerve are called as level IIb.
- **Level III** group defines the middle jugular group nodes extending from carotid bifurcation superiorly down to the upper part of cricoid cartilage .it represents the level where omohyoid crosses the internal jugular vein The lateral border is formed by the posterior border of sternocleidomastoid muscle. The medial border is formed by the lateral border of the sternothyroid muscle.

- **Level IV** defines the lower jugular group and extends from the cricoid cartilage superiorly to the clavicle inferiorly. The lateral border is formed by the posterior border of sternocleidomastoid muscle. The medial border is formed by the lateral border of the sternothyroid.
- **Level V** nodes are located along the lower half of spinal accesory and transverse cervical artery .bordered anteriorly by the posterior border of the sternocleidomastoid muscle. Posteriorly by the anterior border of the trapezius and inferiorly by the clavicle. supraclavicular nodes are also included in this group.
- **Level VI** nodes are located in the anterior compartment. otherwise called as visceral group. These nodes surround the middle visceral structures of the neck from the level of the hyoid superiorly to the suprasternal notch inferiorly.the lateral limit on each side is the anterior border of sternocleidomastoid muscle.it contains parathyroid,the para tracheal pre tracheal and pre laryngeal lymph nodes
- **Level VII** nodes are the paratracheal nodes inferior to the suprasternal notch in the upper mediastinum.

PREDICTABLE ROUTES OF NODAL METASTASIS FROM PRIMARIES

Cancers of oral cavity have a predictable manner of spread to the cervical nodes. Depending on site of primary certain patterns of metastatic involvement are evident.

Lesions of lip, anterior buccal mucosa, anterior gingival and floor of mouth are typically metastatic to submandibular and submental group of nodes. Lesions of tongue, posterior gingival, and retromolar trigone area involves upper deep cervical chain commonly. The submandibular node is the commonest node to be involved in carcinomas of floor of mouth and jugulodigastric is the commonest node involved in cancers of tongue.

The oropharynx consisting of retromolar trigone, anterior fauces, tonsil, soft plate and base of tongue drains primarily into juguodigastric node. The commonest node to be involved in tonsillar carcinoma was jugulodigastric node. Cancers of soft palate, base of tongue and oropharyngeal wall, because of proximity to midline tended to involve bilateral jugulodigastric and rarely bilateral posterior triangle nodes (Lindberg et al).

Tumours of the nasopharnx most commonly metastasise to jugulodigastric nodes, bilaterally and in significant number of patients

posterior triangle is also involved.

Tumours of the hypopharynx and supraglottic larynx tended to metastasise to jugulodigastric nodes followed by mid and lower deep cervical chains.

Tumours of thyroid commonly involved upper or lower deep cervical group of nodes depending on site of tumour (upper pole or lower pole).

SEQUENTIAL SPREAD

Not only is the topograghic location of the involved nodes predictable for the various anatomic sites, but the sequential spread from one echelon to the other echelon is also predictable. If the first echelon of lymphatics is not involved, probability of involvement of the next echelon is low. In lateralized lesions the probability of contralateral metastasis is low when the ipsilateral side of the neck is clinically negative. The probability increases as the extent of ipsilateral metastases increases. In 1997 Molinari and colleagues used a statistical approach to predict the primary site based on the number and location of cervical metastasis. This type of information is very useful in patients who present with an unknown primary.

MECHANISM OF LYMPH NODE METASTASIS

The current hypothesis on the development of malignancies relate to

alterations in the normal mechanisms of cellular proliferation and differentiation and a failure of cell death(apoptosis). This loss of growth control of genetic mutations, including the activation of proto-oncogenes and inactivation of tumour suppressor genes. The resulting phenotypic changes provide cancer cells a growth advantage, including loss of response to normal growth controls, defects in response signals for programmed cell death, resistance to cytotoxicity, and defects in terminal differentiation.

Proposed by Fidler, the concept of tumour heterogenicity suggests that tumours are composed of heterogenous subpopulations of cells differing in immunogenecity, invasiveness, cellular growth kinetics, sensitivity to cytotoxic drugs and ability to metastasize. The local tumour environment may favour the development of more aggressive clones in the formation of metastases. Although the size of individual clones with metastasizing potential in a given tumour is significant, only a very small percentage of circulating cells lead to the development of metastatic colonies.

The events surrounding the initiation of local tumour invasion by epithelial tumours include a loss of cellular adhesion to surrounding tumour cells and basement membrane, invasion by malignant cells of the

subjacent connective tissue by the production of cellular enzymes and growth mediators, cellular attachment to extracellular membrane molecules, neovascularisation and entry or exit from the circulation through the attachment to endothelial cell ligands. A repeat of this events occurs at the metastatic sites.

In case of squamous cell carcinoma of the head and neck, malignant cells may progress from carcinoma in situ to microinvasive carcinoma, to a deeply invasive tumour with lymphatic metastasis. Interestingly a head and neck squamous cell carcinoma has the ability to manifest at both extremes of histopathological development in the same anatomic location. The critical step in the transition from carcinoma in situ to microinvasive carcinoma is the destruction of the basement membrane. This destruction is accomplished by production of specific proteolytic molecules by the tumour cells, including matrix metalloproteinases, collagenases and plasminogen activators.

Angiogenesis is the growth of new capillaries by sprouting from established vessels. In normal tissues, self-limiting angiogenesis is a part of reproduction and organogenesis in addition to wound repair and healing. Conversely, pathological angiogenesis is not auto regulated, but results from alterations in growth control mechanisms of disease process.

Various tumour derived factors (eg, prostaglandin E2,platlet-derived growth factor, transforming growth factor-beta, transforming growth factor-alpha, beta-fibroblast growth factor) are still being investigated for their propensity to facilitate endothelial cell proliferation.

Recent research looking specifically at the production of cytokines regulating immune, inflammatory and angiogenetic response in patients with laryngeal squamous cell cancer has revealed higher serum concentrations of the cytokines, interleukin-6, interleukin-8 and vascular endothelial growth factor. These agents may be important in proinflammatory and proangiogenetic responses of tumour cells.

The ability of a tumour to stimulate an angiogenic response should directly determine the capability of a tumour to metastasize and ultimately kill the host. The literature notes conflicting reports regarding microvessel density and nodal metastasis in head and neck squamous cell carcinomas. Tumour sites of varying origins with different vascularisation patterns at their primary sites may behave differently. Malignancies of head and neck especially head and neck squamous cell carcinomas are the result of a series of genetic misadventures of squamous epithelial cells leading to malignant transformation. Variable genetic susceptibility, prolonged tobacco and alcohol exposure, viruses and immune suppression all can

facilitate these genetic derangements.

Tumours invade local connective tissue by the production of proteinases and the expression of surface markers that facilitate attachment to extracellular matrix components. Tumor growth and size being limited by available nutrients from the surrounding milieu, recruitment of host capillaries leads to the formation of an intramural blood supply. Capillary lymphatic invasion by tumour cells allow malignant cell dissemination and the establishment of histologically identical tumours at distant sites.

Most recently, the expression of vascular endothelial factor-D in a mouse tumour model was found to lead to the lymphatic spread of tumour cells, tumour angiogenesis and tumour growth.

The dissemination of tumour cells beyond the primary site unfortunately remains the most significant factor in prognosis.

LYMPH NODE AND TUMOUR IMMUNITY

An early event in metastatic process is the detachment of cancer cells from the parent tumour. Because a tumour has no primary lymphatics, cancer cells presumably gain access to the lymphatic system through the clefts between the lymphatic endothelial cells at the invasive tumour periphery. Once inside the lymphatic channels, cells are carried by

the afferent lymphatics to the regional nodes where they lodge and proliferate.

The permeation theory of metastasis introduced by Handley in 1907 was based on autopsy studies of patients who had died of breast cancer and melanoma. He concluded that lymphatic metastasis originated by continuous permeation of lymphatics radiating away from the primary tumour site. The permeation concept of lymphatic metastasis was the basis for the development of in continuity (en bloc) dissection of nodes with primary cancer for head and neck.

Von Recklinghuasen noticed that metastasis could be found in the lymph glands when tumour did not involve the intervening lymphatics, and the embolic spread of metastasis is now generally accepted.

Handley's concept of permeation still applies to some clinical situations; generally recurrent cancer with obstruction of the normal lymphatic pathways leading to retrograde spread and tumors in certain sites such as large floor of mouth tumours with direct extension to the submandibular area. Previously untreated primaries even if massive seldom involve the neck by direct extension.

In the past it was believed that regional lymph nodes behave as traps against tumour cell dissemination. This 'Filter Barrier' hypothesis

proposes that regional lymph nodes serve as mechanical and biologic filters in which phagocytosis assists the more mechanical phase of particulate trapping. In various studies, it has been shown that cancer cells can traverse nodes that themselves are free of tumour, implying that the node is an ineffective barrier.

Fischer and Fischer reported that nodes were able to trap 90%of infused red blood cells and 40% of carcinoma cells. The nodes did not become saturated. Some studies have shown that nodes are potential barriers to infused tumour cells for only a limited time-approximately 3 weeks. Thereafter the tumour cells are no longer effectively retained.

In a study it has been shown that as the primary tumour increased in size the number of cells in the nodes remained constant. The authors concluded that the nodes had a reasonably constant holding capacity and that above such a threshold, all other tumour cells passed on into efferent channels and the general circulation.

Although the role of regional lymph nodes as a barrier to cancer spread and as a possible site of antitumour immune response is putative and remains to be established, majority of the workers are of the opinion that some sort of dynamic interaction does occur when tumour.

Emboli encounter lymphocytes within the nodes of head and neck cancer patients. The regional nodes are felt to be important for the initiation of systemic immunity to cancer cells, especially to weekly antigenic tumours. Patients who do not become positive for nodes at any time are thought to have immune competence that is entirely able to eliminate disseminated tumour cells in the nodes and elsewhere throughout the body. Conversely the positive lymph node may denote either a failure of the above mechanism, or a change in the biologic nature of the tumour cells, or that the number of disseminated tumour cells have exceeded the capacity of the node for cell destruction.

The existence of an enlarged node does not necessary indicate the presence of metastatic spread, especially if the node is soft. In this case it may represent no more than a coincidental infection or the mounting of an immunological reaction within the node.

However just as this is true, it has been estimated that a node smaller than 1 cm is impalpable and yet may contain $10^6 – 10^7$ tumour cells. The principal problem for the clinician is how to decide whether a node which is palpably enlarged is involved with metastasis or not. At present such a decision remains purely clinical. Some authors have recommended that any enlarged palpable node in the drainage area of a histologicaly proven

primary should be considered as metastatic until otherwise proved. Lindberg (1972) defined a clinically positive node as one which is greater than 1cm in size, spherical rather than a flat ovoid in shape and harder in consistency than a non metastatic node.

Throughout this study the above criteria of Lindberg was used to differentiate a metastatic from a non metastatic node.

THEORIES FOR THE OCCULT PRIMARY

It has been hypothesized earlier that the patient with malignant cervical lymphadenopathy but unknown primary site may in fact have no upper aerodigestive tract primary site. Rather the tumor primary developed in the neck within squamous cells remaining as remnants of brachial cleft cysts. Although this theory is intriguing, little evidence has been presented to support it and it has largely fallen out of favour.

The other theory is that these patients have exhibited spontaneous regression of the primary tumor site with persistence of cervical metastasis.

Unfortunately there is no evidence for the spontaneous regression of squamous cell carcinoma.

Current theory is that unknown primary tumours are likely to be, primary tumours that exist in the upper aerodigestive tracts or skin, but

subclinical at the time of presentation. Thus unknown primary tumours remain undetected but are presumed to be present. Anecdotal support of this theory includes the identification of some of the primary tumours during or after treatment.

HISTOLOGICAL GRADE OF THE TUMOUR AND ITS INFLUENCE

Histologically a squamuos cell carcinoma consists of an admixture of normal squamous cells and atypical anaplastic squamous cells. The more malignant the tumour, the greater is the number of atypical cells. The a typicality expresses itself in terms of variation in the size and shape of cells, hyperplasia and hyperchromatasia of the nuclei, absence of intercellular bridges, atypical mitotic figures, and keratinisation of cells.

Differentiation in a squamous cell carcinoma takes place in the direction of keratinisation, and so the degree of keratinisation represents the essential feature in the system of histological grading introduced by Broder (1921).This grading system recognizes four grades of severity according to the proportions of differentiated cells present in the tumour.

- Grade I - more than 75% of the cells are differentiated
- Grade II – between 50% to 75% of the cells are differentiated

- Grade III – between 25% to 50% of the cells are differentiated
- Grade IV – less than 25% of the cells are differentiated.

Alternatively squamous cell carcinoma can be graded as

1. Well differentiated – tumours with minimal pleomorphism, few mitoses, large number of horn pearls and abundant keratinisation.
2. Moderately differentiated – tumours where typical cells are conspicuous, few horn pearls are present and keratinisation is much less evident.
3. Poorly differentiated – tumours with much cellular and nuclear pleomorphism, negligible keratinisation and absence of horn pearls.

The relevance of histologic grade of tumour to prognosis is well established. Arthur and Farr (1972) studied the prognostic significance of histologic grade in squamous cell carcinoma of oral cavity and oropharynx and demonstrated a clear relationship between the histologic grade and metastatic nodal disease, stage of the disease and cure rate. They noted a proportionate increase in nodal involvement with increasing histologic grade of the tumour and suggested that histologic assessment should play a part in designing the therapeutic approach.Other authors have also appreciated the usefulness of histologic grading as a clue to overall prognosis.

TNM STAGING

The current classification was proposed by the American Joint Committee for Cancer Staging and end results reporting in 2017 and is being widely adopted.

In this classification, the recommended tumour (T) designation varies from one anatomic region of the head and neck to another, but the node (N) and distant metastasis (M) categories is applicable to all of the areas of the head and neck. Stage grouping based on the TNM stage is also similar throughout the head and neck.

The (N) and the (M) categories as well as the stage grouping, which are constant for all the head and neck regions are discussed first.

N –Classification of all head and neck cancers (AJCC, 2017)[1]

- Nx - nodes cannot be assessed.
- N0 - no clinical positive nodes.
- N1 – single clinically positive ipsilateral node 3cm or smaller in greatest dimension and ENE-
- N2 –Metastasis in a single ipsi lateral node larger than 3cm but not larger than 6cm in greatest dimension or
- multiple ipsilateral nodes none over 6 cms in greatest dimension and ENE-

- or in bilateral or contralateral lymphnodes none larger than 6cm in greatest dimension. ENE-

N 2a – single Ipsiolateral node larger than 3cm but not larger than 6cm in greatest dimension and ENE-.

N 2b – multiple ipsilateral node none over 6cms.

N_{2c} - metastasis in biateral or contralateral lymphnodes none larger than 6cm in greatest dimension and ENE-

- N 3 –metastasis in a lymphnode larger than 6cm in greatest dimension and ENE-
- or metstasis in any node(s) with clinically overt ENE+.

1. N3a –metastasis in a node larger than 6cms in greatest dimension and ENE-
2. N3b –metastasis in any node(s) with clinically overt ENE+

NOTES:

1. Midline nodes are considered ipsilateral nodes
2. ENE is defined as invasion of skin, infiltration of musculature, dense tethering or fixation to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk or phrenic nerve invasion with dysfunction

M - Classification of all head and neck cancers (AJCC,2017)

- Mx – metastasis not assessed
- M0 – No known metastasis
- M1 – Distant metastasis present

STAGE GROUPING OF HEAD AND NECK CANCERS (AJCC, 2017)

Stage I – T1, N0, M0

Stage II – T2, N0, M0

Stage III - T3, N0, M0

T1,2,3, N1, M0

Stage IVa – T4, N0,1, M0

T1-4, N2, M0

IVb - Any T, N3, M0

T4b, Any N, M0

IVc – Any T, Any N, M1

The T – Classification of the Oral Cavity and Oropharyngeal Tumour is Described Below (AJCC, 2017)

- Tx – primary tumour cannot be assessed
- T0 – No evidence of primary tumour
- Tis – Carcinoma in situ

- T1 – Tumour </=2cm,</=5mmdepth of invasion
- 33
- T2 – Tumour </=2cm,depth of invasion >5mm and </=10mm or
- tumour >2cm but </= 4cm and </=10mm depth of invasion
- T3 – Tumour more than 4 cms in greatest diameter or any tumour
- >10mm depth of invasion
- T4 – Tumour more than 4 cms with invasion into contiguous
- structures such as floor of mouth, skin, muscles and bone.
- T4a –moderately advanced local disease
- Tumour involving cortical bone, deep tongue musculature, maxillary sinus, skin of face
- T4b –very advanced local disease
- Tumour involving maxillary plates, pterygoid plates, skull base,encases the internal carotid artery.

RISK FACTORS FOR HEAD NECK CANCER

It has been estimated that use of tobacco and alcohol account for up to 80 percent of cases of head and neck squamous cell carcinoma. Both act throughout aerodigestive tract, contributing to the field cancerisation effect, both can induce genetic alterations, such as mutations in the p53

tumour suppressor gene. Other factors which may play a role include viral infection, occupational exposure,. radiation, dietary factors and genetic susceptibility.

- **Tobacco**-there is an increased risk of head and neck squamous cell carcinoma from a 5-to-25 fold, in heavy smokers compared to
- nonsmokers. The relative risk in current tobacco users is 6.5.the relative risk increased with the duration of smoking and gradually declined after smoking cessation
- .The age at onset (below 18 years of age) and duration of smoking (over 35 years) were high risk factors. Passive smoke exposure also a contributing factor.

- ·Epidemiologic studies have suggested that cigar smoking is associated with increased incidence of head and neck squamous cell carcinoma and smokeless tobacco with increased risk of cancer of the tongue, oral cavity and pharynx. Marijuana use may modestly increase the risk of cancer, an effect that is magnified by cigarette smoking.
- Alcohol –although it is difficult to separate the effects of smoking and alcohol, studieshave consistently shown that alcohol consumption increases risk of cancer in the upper aerodigestive tract. relative risk of developing cancer appears to be dose dependent, ranging from 5.5(alcohol intake greater than 50g/day) to 33.8(alcohol intake greater than 120g/day) .Drinking liquor associated with greater risk than drinking only wine. Moderate

alcohol intake (10 to 19g/day) has no effect among nonsmokers.

The combined effect of alcohol and smoking, with the risk of developing Head and Neck cancer being as much as 200 times greater for heavy smokers and drinkers

- **Epstein-Barr virus**-The strongest association between a virus and head and neck cancer is the Epstein-Barr virus and nasopharyngeal carcinoma. EBV is the causative agent for oral hairy leukoplakia also
- **Human papilloma virus**- HPV type-16 has been detected in 8 to 36% of head and neck cancer. It contribute by direct effects on proliferation and by increasing mutational frequency in the host cells. The prevalence of HPV infection appears to be site specific, and highest in invasive tumours of the oropharynx and oral cavity. The presence of HPV appears to confer a better prognosis.
- **Occupational exposure** – These include asbestos,, pesticide, polycyclic aromatic hydrocarbons, textile workers, wood workers, manufacturers of mustard gas,, plastic and rubber products, naphthalene refineries, ethanol, sulfuric acid mist, leather and paint workers, automobile mechanics, construction workers (cement), metal workers and bartenders (passive smoking). Formaldehyde was classified as a carcinogen in 2004 because of association with

nasopharyngeal carcinoma and possibly cancers of the nasal cavity and paranasal sinuses.

- **Radiation** – Prior radiation for either malignant or benign disease linked to head and neck cancer.
- **Diet** – Risk of nasopharyngeal carcinoma is increased in frequent consumers of preserved meats which contains high levels of added
- nitrites. Increased risk of head and neck squamous cell carcinoma has been associated with frequent intake of eggs and red meat and a low carotenoid intake.
- **Genetic factors** – First degree relatives and siblings of patients with head and neck squamous cell carcinoma are likely to develop upper aerodigestive tract cancer .
- **Others** –. Lip cancer is seen in renal transplant recipient.

MELANOMA OF UNKNOWN PRIMARY

Primary melanoma of the head and neck represents approximately 25% to 30% of all melanoma. Rarely, melanoma is identified in cervical or parotid lymph nodes without evidence of a primary tumor. Many authors theorize that metastatic melanoma in the cervical lymph node represents metastases from a primary tumor that has undergone spontaneous regression.

In working up a patient with metastatic melanoma of unknown origin, it is important to obtain a detailed history of any previous skin lesions that disappeared or were removed. Pathology slides of all previously excised “benign skin lesions” must be reviewed by an experienced dermatopathologist. As with all newonset neckmasses, an FNA is often the initial step that leads to a diagnosis of melanoma. Melanoma - specific immune histologicstaining, such as MART-1 (melanoma antigen recognized by T cells), HMB-45, or S-100, may help to confirm the histologic diagnosis. Once the histology is confirmed the, the practitioner should search for an occult melanoma primary lesion. This evaluation should include once complete dermatologic skin examination and a search for the rare occuitl visceral melanoma of the conjunctiva, mucosa of the head and neck, or gastrointestinaltract. If the thorough work-up fails to identify the primary occult melanoma, the treatment plan must focus on the cervical disease and the possibility of distant metastatic disease. The role of whole-body PET imaging in melanoma is under debate. In the initial evaluation of early stage cutaneous melanoma, PET imaging has not prove deficient. A recent study prospectively evaluated the impact of PET imaging on the detection of occult lymph node metastases and distant metastases PET scan sensitivity was 21%, and

specificity was 97% in detecting occult metastatic disease in patients with early-stage melanoma. Other researchers have suggested that PET imaging may be a valuable adjunct in staging patients with recurrent melanoma or more advanced tumors. Metastatic melanoma to cervical lymphnodes in the absence of a known primary origin remains a disease to be treated surgically. Patients presenting with jugularchain involvement require a modified radical neck dissection (levels I–V), sparing all vital structures not involved with disease. The surgeon must consider a posterior-lateral neck dissection for treatment of metastatic melanoma in level V, the postauricular, and the occipital nodal basins. Interferon alfa 2-b remains the only adjuvant therapy for melanoma approved by the US Food and Drug Administration. All patients with cervical metastasis (N1 disease or greater) are candidates. In addition, patients with regional (stage III) disease in the setting of multiple positive lymph nodes or ECS have gained increased locoregional control with the administration of postoperative hypofractionated radiotherapy (30 Gy in five fractions). Alternative systemic treatment including gene therapy and biochemotherapy, are available within the context.

Cystic metastatic disease in the neck

A cystic quality to metastatic cervical carcinoma of unknown primary origin should raise suspicion for papillary carcinoma of the thyroid gland, tonsillar SCC, and branchial cleft carcinoma. Branchial cleft carcinoma represents a primary carcinoma arisin from a congenital branchial cleft remnant and continues to be controversial. Primary occult SCC arising from Waldeyer's ring can generate cystic metastatic disease in up to 50% of patients. Therefore, strict criteria for branchial cleft carcinoma are required. The criteria for diagnosis of branchial cleft carcinoma include 1) location of the tumor along the anterior border of the sternocleidomastoid muscle, which represents the traditional course of a branchial cleft cyst; 2) histologic findings consistent with the presence of a branchial cleft cyst; 3) histologic findings consistent with the carcinoma arising within the branchial cleft cyst wall; and 4) no evidence of a primary SCC in the upper aero digestive tract for a minimum 5-year follow-up period. Given these strict criteria, the clinician cannot confirm branchial cleft carcinoma until 5 or more years of follow-up without identification of an occult primary site elsewhere. As a general rule, any adult with a cystic neck mass resembling a branchial cleft cyst warrants a thorough work-up, including imaging and

FNA biopsy to rule out malignancy. A recent report from the University of Pittsburgh describes 40 adult patients presenting with cystic neck masses. PET imaging fared no better than traditional CT scan in the identification of malignancy in these patients. The authors concluded that a thorough clinical evaluation by an experienced head and neck surgeon, in conjunction with contrast - enhanced CT and FNA biopsy, is sufficient to evaluate patients with a cystic cervical neck mass

DIAGNOSTIC EVALUATION

A complete and detailed history of the present and past illness with a thorough physical examination is mandatory to the workup of the patient.

Laboratory studies are not typically used in the workup of a patient but are used to evaluate a patient's anaesthetic risk and to provide baseline laboratory data.

Serology of Ebstein-Barr virus has been shown to correlate with the presence of nasopharyngeal carcinoma.

Chest radiograph

Chest radiograph is taken for all patients. If any suspicious lesion found in chest radiograph then CT scan is indicated. If a lung cancer is found then it is evaluated separately.

CT scan

The neck CT scan is important in the search for an occult primary site and also to evaluate the extent of nodal diseases, and to check for obvious extra capsular spread and examine for suspicious nodes in the contralateral neck. Contrast enhanced CT from the base of the skull to the level of the thoracic inlet is indicated. CT can identify tumours of the head and neck based on either anatomic distortion or specific tumour enhancement. In general tumours enhance more than any normal head and neck structures except mucosa, extraocular muscles, and blood vessels. A radiologically heterogenous appearance or the presence of central low attenuation may indicate pathologic lymphadenopathy, even in small lymph nodes.

MRI scan

MRI has multiplanar capabilities, it provides superior soft tissue contrast and it identify early evidence of dural involvement or perineural invasion .so It is useful for assessment of local spread of nasopharyngeal carcinoma and sinonasal carcinoma. MR Angiography will generate images of large arteries and veins noninvasively without the use of IV contrast. This is reserved for cases where tumour is thought to encase a major vessel.

PET scan

PET has high sensitivity, specificity and accuracy for the detection of unknown primary tumours with cervical lymphnode metastasis.. Potential clinical applications for the PET scanning include improved pretreatment staging, identification of occult primary site, estimation of treatment response and differentiation of early recurrence from scar tissue. Many incorporate this imaging modality in their diagnostic evaluation for an occult primary tumour. Tumour cells having higher metabolic rate than normal tissue; head and neck neoplasms have an increased glycolytic rate and Thus head and neck neoplasms are good candidates for metabolic imaging and can be traced using a glucose analog, 2-[fluorine-18]fluoro-2deoxy-D-glucose. (FDG).

FDG uptake reflects cellular metabolism and cellular processes such as infection., neoplasm or inflammation. They are characterized by increased metabolic activity and consequent accumulation of the FDG tracer. This accumulation which appears as hot spots on PET imaging may help to localise an unknown primary tumour.

The Danish study demonstrated that FDG PET detected a primary tumour in 24% of patients with metastatic cervical adenopathy and otherwise negative clinical and radiological evaluation.

The key limitation of PET has been the size of tumour it can detect. New PET have resolution of 5mm.and tumours of the supraglottic region and waldeyer's tonsillar ring are the most difficult to be diagnosed with FDG-PET. An additional limitation of PET scanning has been the anatomically nonspecific image produced by these scanners. Hot spots appear as general regions without good borders. whereas it may be possible to state for eg; that left side of the base of the tongue appears 'hot', so any additional information regarding the size or localization would be inaccurate.

Newer scanners that supplement PET with CT fusion techniques are becoming available. These machines can overlay the images so that the hot areas are visible as coloured halos over the CT scan image, and thus greatly facilitating the accuracy and localization of the PET technology.

Panendoscopy of the upper aerodigestive tract with biopsy samples obtained from suspicious areas should be done.

Mucosal biopsies from nasopharynx, fossa of rosenmuller, tonsils, pyriform sinus, hypopharynx, vallecula, postcricoid region and base of tongue should be done routinely for all patients with unknown primary.

Previous studies have suggested that the most common sites of primary tumour detected on panendoscopy were the nasopharynx and

hypopharynx. In a recent University of Florida study, the most common sites of primary cancer detected seen now to have shifted to include the tonsillar fossa or the base of the tongue.

Because the tonsil remains a common site of primary tumour, most clinicians advocate tonsillectomy in addition to directed biopsies in the workup of an unknown primary tumour. Questions regarding whether random tonsil biopsies or tonsillectomy should be performed in the evaluation of an unknown primary site and whether such tonsillectomy should be ipsilateral or bilateral tonsillectomy continue to be controversial.

In a 1998 study at john Hopkins hospital McQuone et al demonstrated that the detection rate of occult tonsillar carcinoma is increased by performing tonsillectomy rather than focal tonsillar biopsy. Although only 13% of tonsillar biopsy specimens were positive for squamous cell carcinoma, 39% of the patients undergoing bilateral tonsillectomy for workup of unknown primary site was found to have squamous cell carcinoma within tonsil. Furthermore one patient was found to have squamous cell carcinoma in both tonsils, strengthening the argument for bilateral tonsillectomy. Bilateral tonsillectomy does not significantly increases the morbidity associated with unilateral tonsillectomy and eliminates the asymmetry that can confound follow up

examination after a unilateral procedure.

Other Diagnostic Procedures;

Recently promising results have been reported with LASER INDUCED FLUORESCENCE IMAGING performed in parallel to pan endoscopy. Another diagnostic method to identify the site of origin with higher sensibility is FDG-SPECT, however its usefulness is still debated

MOLECULAR ASSAYS:

Some molecular assays have recently been proposed to differentiate the potential primary site. Detection of EBV with the use of insitu hybridization in metastatic lymphnodes may suggest nasopharyngeal tumour Human Papilloma virus HPV detected by polymerase chain reaction mayindicate oropharyngeal cancer.

Microsatellite Mutation Analysis of metastatc nodal tissue and samples of normal pharyngeal mucosa was also proposed.

Immunohistochemical Analysis for Cervical Lymph Node Metastasis of unknown Primary Origin

Stain/histologic feature	Suggested primary site/neoplasm
Thyroglobulin	Thyroid carcinoma
Calcitonin	Medullary carcinoma of thyroid
PSA/prostatic acid phosphatase	Prostate
Alpha feto protein	Liver, stomach, germ cell
CEA	Pancreas, breast, ovary
Estrogen/progesterone receptor	Breast
Psammoma bodies	Ovary, papillary thyroid carcinoma
Signet ring cells	stomach
Cytokeratin	Squamous cell carcinoma
Epithelial membrane antigen	Squamous cell carcinoma
MART-1	Melanoma
HMB-45	Melanoma
S-100	Melanoma

TREATMENT

Several different treatment strategies are available for management of the unknown primary site and squamous cell carcinoma metastatic to the neck.

Whether radiotherapy is sufficient treatment for control of neck disease and whether potential primary sites should be irradiated or simply followed are controversial.

Additional controversy is on whether radiation should be offered to patients pre-or postoperatively. Finally, questions have surfaced about whether the contralateral neck needs to be treated. Which treatment strategy provides best outcome remains a subject of debate in the literature.

In discussing treatment strategies, it is important first to have an understanding of prognostic factors. In all large series, lymph nodal stage has correlated with outcome. Supraclavicular lymph node metastases are more likely to be associated with disease below the clavicles, and hence, are associated with poorer survival. Histologic extracapsular spread has been noted to affect survival adversely in most large series as well. As might be expected, more primary sites were identified in patients treated with surgery than in patients treated with radiatiotherapy. Although treatment protocols may vary by institution and clinical bias, there is

consensus that advanced nodal disease and extracapsular spread necessitate more aggressive therapy.

For a few patients presenting with N1 or N2a disease, single modality therapy is a reasonable approach. Acceptable courses of treatment include neck dissection alone, radiation alone, and neck dissection plus radiation if extracapsular spread is noted on histopathologic analysis. A 1998 review from M.D. Anderson recommends that patients with N1 or small mobile N2a disease be treated with neck dissection alone and that postoperative radiation therapy be reserved for cases of extracapsular spread, multiple nodes or connective tissue invasion. The 5-year disease free survival rates were 85% in patients with a solitary node and 58% for patients with multiple nodes. Similarly, in patients who have undergone an excisional biopsy of a solitary node, the neck may be treated with radiation alone with a 95% likelihood of neck control. Thus single modality treatment in patients with N1 or N2a disease is reasonable .For patients with disease beyond N1 or N2a combined modality therapy is recommended.

Patients with more advanced disease, in contrast are triaged into an arm of treatment that includes both surgery and radiotherapy. The timing of radiotherapy is also a source of controversy. Proponents of preoperative

radiation therapy argue that surgical complications delay the initiation of radiation therapy, target tissues are theoretically better oxygenated in the preoperative state, and radioresistant primary tumours may become evident over the course of radiation therapy and can be removed with one definitive surgical procedure if radiation therapy is implemented before the planned neck dissection.

Proponents of postoperative radiation therapy argue that a neck dissection before radiotherapy allows improved delineation of disease extent and better staging through pathologic evaluation of the neck dissection specimen. Although adjuvant chemotherapy has shown mixed results, it is often recommended in cases of inoperable disease, or with distant metastases. There is some evidence that concurrent chemotherapy and radiotherapy in the postoperative setting improve locoregional control rates.

The decision to include suspected primary sites in the radiation field also remains controversial. Certainly the challenge facing the clinicians is deciding how to maximize the chance of survival while minimizing the treatment morbidity. Review of the literature reveals a trend toward treating both the ipsilateral and contralateral necks as well as potential mucosal primary sites. Certainly many of the primary sites (base of

tongue, nasopharynx, supraglottis) are known for their bilateral nodal drainage. Tong et al point out that treatment limited to the involved side of the neck alone may compromise further radiation therapy should a primary mucosal site emerge. For this reason, bilateral radiation to the neck and mucosal sites is recommended.

Debate continues to center around which portals should be included in the radiation therapy. The consensus seems to be that the oral cavity and a laryngeal strip can be excluded, but the base of the tongue, hypopharynx, and supraglottic sites should be included. The decision to include the nasopharynx should be based on whether metastases are high and posterior and whether demographic factors suggest that the patient is at high risk for a nasopharyngeal primary site. Sparing the oral cavity and of an anterior strip approximating the anterior true vocal cords may significantly decrease the morbidity of the mucosal irradiation.

Reddy et al also reported a series comparing ipsilateral radiotherapy with radiation delivered to both sides of the neck and sites of mucosal primaries. Significantly better neck control was demonstrated in the group receiving radiation to both sides of the neck and mucosal sites.

Finally, recent discussion has focused on the extent of neck dissection indicated in the patient with a cervical metastasis and unknown

primary lesion. A growing body of evidence suggest that a selective neck dissection including the involved level and contiguous levels with appropriate sacrifice of the involved structures is reasonable. Appropriate use of selective neck dissection can minimize the postoperative morbidity associated with modified and radical neck dissection without compromising neck control and survival.

Even with advances in treatment protocols, the overall survival for squamous cell carcinoma metastatic to a cervical node with an unknown primary site remains approximately 50%.The 2-,5- and 10 year disease specific survival rates have been reported to be 82%,74% and 68% respectively. Nodal stage has been shown to be significantly associated with disease specific survival.

CHEMOTHERAPY

The role of chemotherapy in head and neck cancer is expanding and its utility varies with the stage of the disease. For patients with metastatic or incurable locoregional disease chemotherapy is palliative. In contrast for patients with potentially curable locoregional head and neck cancer, chemotherapy is an integral part of multimodality approach. In such cases chemotherapy may be administered as induction therapy, concomitant with radiotherapy or with a combined approach.

Single agent chemotherapy

Several cytotoxic chemotherapy drugs have significant activity in advanced head and neck cancer when administered as a single agent. Direct comparisons of efficacy are limited by the paucity of randomized trials, and this complicates the establishment of recommendations for standard of cure. Although most patients will be treated with combination chemotherapy, occasionally single agents may be used for palliation.

The choice of agents depends in part upon the patient's clinical status and the ability to tolerate drug-specific side effects. Acceptable drugs include paclitaxel, docetaxel, methotrexate, cisplatin, carboplatin, ifosfamide and 5-Fluorouracil.

In advanced squamous cell head and neck cancer, the taxanes have emerged as perhaps the most active of all single agents.

General principles of combination chemotherapy

Many combination chemotherapy regimens have been studied for the treatment of advanced head and neck cancer. Prior to mid 1980s, the most aggressive regimens included methotrexate and generally consisted of combinations of two or four drugs, often methotrexate plus cisplatin, bleomycin, 5-FU or vincristine. These regimens have been largely replaced by three categories of drug combination:

- The combination of a platinum analog (cisplatin or carboplatin) and 5-FU.
- The combination of a platinum analog and a taxane (paclitaxel or docetaxel).
- The combination of a taxane, a platinum analog and 5-FU with or without leucovorin.

Recommendations for combination chemotherapy for advanced head and neck cancer. For metastatic or recurrent disease, any of the several regimens may be used. Since none has been proven yet to prolong survival, care must be exercised to avoid major acute or chronic toxicities and consideration should be given to single agent therapy. For patients with good performance status, appropriate combinations include cisplatin or carboplatin plus 5-FU, or platinum analog plus a taxane.

NEW THERAPIES

Monoclonal antibodies

Cetuximab- The majority of head and neck cancers over express endothelial growth factor, making them a good target for cetuximab, an anti-EGFR monoclonal antibody that inhibits receptor activity by blocking the ligand binding site. In addition to being investigated as a single agent and in combination with cytotoxic chemotherapy, cetuximab is also given

as a radiosensitiser.

Other potential agents that block the activation of EGFR are the tyrosine inhibitors such as geftinib and erlotinib.

Gene therapy

Gene therapy utilize a vector to deliver genetic material to a cell in an attempt to alter its biology via expression of the delivered gene. The majority of the effort has been aimed at modification of p53.The p53 gene is inactivated in approximately one half of squamous cell head and neck cancers.

ONYX-015 – It is an adenovirus containing a deleted E1B 55-kDa gene, which actively replicates in, and lyses p53-deficient cells.

RPR/INGN 201 – It utilizes a replication deficient adenovirus to deliver a cytomegalovirus promoter and a wild type p53 gene.

Cisplatin/epinephrine injectable gel – for patients with refractory or multiple recurrent local tumour involvement, a novel strategy is direct application of cisplatin into the tumour itself.

RADIOTHERAPY

Radiation may be given as a once daily treatment or hyper fractionated (twice daily).It may be continuous (five days per week without interruption) or given in a split course (every other week or three

weeks on with a one or two weeks break followed by three more weeks of treatment).

PROGNOSTIC FACTORS AND PATTERNS OF FAILURE:

SQUAMOUS CELL CARCINOMAS:

Several end points, including rates of survival, disease free survival, distant metastasis, loco regional control ,neck control and primary occurrence, have been used to evaluate the outcome of patients with cervical SCC metastasis from unknown primary numerous clinical and physical factors associated with these endpoints have been reported. Selection bias is unavoidable for example ipsilateral irradiation is typically administered for advanced disease or poor performance status patients, whereas surgery is performed in early stages squamous cell Carcinoma.

The majority of information available in the literature is referred to SCC. The nodal status is considered the most important prognostic factor infact the prognosis seems comparable to that observed in patients with overt primary and similar nodal stage. For patients treated with neck dissection, the prognostic factors include the number of lymphnodes, grading and extracapsular extension over the last 30 years, probably due to better pre treatment evaluation and more effective therapy, neck control and primary occurrence have improved in Head and Neck CUP patients.

The pattern of failure depends on the treatment applied. According to some authors, in early stages neck dissection alone and radiotherapy alone are equivalent and provide satisfactory nodal control after extensive radiotherapy, the predominant patterns of relapse include neck recurrence and distance metastases.

The effectiveness of radiotherapy is illustrated by the fact that the risk of emergence of a primary lesion after extensive irradiation is similar to the occurence of second tumour in a patient with overt head and neck cancer the median time to the occurrence of subsequent primary is about 21 months and the most common sites are the oral cavity, oro annasopharynx, supraglottis and lung several authors observed poor prognosis after a subsequent detection of the primary lesions in the case of cervical lymph node metastasis from SCC; Median survival of 15 months and 5 year survival of 20% after the detection of the primary other authors attributed poor outcomes to nodal relapse, but not to primary occurrence, in some series tumours arising later than 5 years after the primary treatment were classified as second primaries, whereas in others, they were considered to be site of origin the predominant site of relapse after radiotherapy includes neck, followed by distant metastasis. The crude risk of either nodal recurrence or distant metastasis is atleast two fold higher

than the risk of a developing a mucosal primary. The benefit from extensive radiotherapy to the mucosa and bilateral neck should weighed against acute and late morbidity (xerostomia, dysphagia etc.) and the difficulties in re-irradiation in the case of subsequent primary emergence. Several retrospective studies show that ipsilateral neck radiotherapy is correlated with a primary occurrence rate similar to that observed after extensive radiotherapy, for these reasons many authors perform an ipsilateral radiotherapy to the involved neck side surgery (planned neck dissection) performed after radiotherapy showed persistence of nodal disease in upto 44% of patients. Such a sequence was associated with poorer survival and with higher post operative morbidity as compared to surgery followed by radiotherapy. These outcomes may however be related to selection bias, as radiotherapy is typically attempted in patients with advanced, inoperable neck disease amichetti et al., applied local microwave hyperthermia and radiotherapy (median 70Gy to bilateral neck and potentially primary sites) in a group of 15 patients with locally advanced squamous cell neck carcinoma from unknown primary. Overall response rate was 87% but actual 5 year local control and overall survival rates were 65% and 29% respectively. Both acute and late toxicities were moderate, however long follow up and larger patients groups are needed to

evaluate the role of this approach. Patients presenting with poor performance status, very extensive nodal involvement, distant metastases or bilateral low neck involvement are usually approached with paliative irradiation. Palliative radiotherapy, independently of the radiotherapy regimen, is associated with an objective response rate of 65%, the symptomatic response rate of 57% at one year, and 25% one year survival; these results are similar to those obtained with palliative chemotherapy, which would likely be more toxic and more expensive.

UNDIFFERENTIATED AND POORLY DIFFERENTIATED CARCINOMAS:

Results are similar to those of overt undifferentiated naso pharyngeal carcinoma

ADENOCARCINOMA:

Prognosis of adenocarcinoma from unknown origin is poor, especially when level IV is involved. Due to their rarity are generally reported considering all metastatic sites.

FOLLOW UP:

Follow up examinations are scheduled on an individual basis determined by the risk of recurrence, to survey for the appearance of the primary tumour, to deal with morbidity from treatment and with

comorbidity not directly related to the cancer itself during radiation therapy periodic examinations by the head and neck surgeon my be necessary in patients experiencing difficulty with nutritional intake, airway or pain control after all treatment is completed periodic examinations by the radiation oncologist and a dentist in patients that received radiation therapy are recommended.

Thyroid function tests should be monitored if the patient received radiation to the lower neck since upto 30% of patients may develop subclinical or overt radiation induced hypothyroidism

Oncological Checks Depend on Histology:

SCC Adenocarcinoma

Clinical and fibrescopic check every two months in the first year, every 4 months for second and third year, then every six months PET once a year Additional exams at the discretion of the physician. Lymphoma and Thyroid carcinoma based on specific protocols Neck metastasis from other sited (eg, breast, prostate, colon):a follow up according to clinical and fibrescopic ENT evaluation

NECK DISSECTION

Introduction

Cancers in the head and neck region commonly metastasize to cervical lymph nodes. The term neck dissection refers to a surgical procedure in which the fibro fatty contents of the neck are removed for the treatment of cervical lymphatic metastases. Neck dissection is most commonly employed in the management of cancers of the upper aerodigestive tract. It is also used for malignancies of the skin of the head and neck area, the thyroid, and the salivary glands.

Radical neck dissection has been the standard surgical procedure for treatment of metastatic neck cancer since its description by Crile in 1906. Until only a couple of decades ago, it was widely used as an elective procedure for occult neck disease and as a therapeutic procedure for clinically manifest nodal metastases. However, in the last 2 decades, a shift toward the use of more conservative surgical procedures has occurred, arising from the realization that many non lymphatic structures in the neck, as well as certain lymph node groups, may be preserved in certain situations without compromising disease control.

The current classification of neck dissections by the American Academy of Otolaryngology / Head and Neck Surgery is based on the

following governing principles:

- Radical neck dissection is the standard basic procedure for cervical lymphadenectomy, and all other procedures represent one or more modifications of this procedure.
- When modification of the radical neck dissection involves preservation of one or more non lymphatic structures, the procedure is termed a modified radical neck dissection.
- When the modification involves one or more lymph node groups that are routinely removed in the radical neck dissection, the procedure is termed a selective neck dissection.
- When the modification involves removal of additional lymph node groups or non lymphatic structures relative to the radical neck dissection, the procedure is termed an extended radical neck dissection

This classification was developed by the Committee for Head and Neck Surgery and oncology, American Academy of Otolaryngology – Head and Neck surgery, Courtesy of the Archives of Otolaryngology – Head and Neck Surgery.

¨ Radical neck dissection

¨ Modified radical neck dissection

- Selective neck dissection
  - Supraomohyoid type
  - Lateral type
  - Posterolateral type
  - Anterior compartment type
- Extended radical neck dissection.

Radical neck dissection

Originally described by Crile in 1906, this procedure is an en bloc clearance of all fibro fatty tissue from one side of the neck, including the lymph nodes from level I through V, lymph nodes. Surrounding the tail of the parotid gland, the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle. It does not include the removal of the postauricular, suboccipital, perifacial buccinator, retropharyngeal and central compartment nodes.

Previously used for neck disease of any stage, from microscopic to bulky nodal disease, this procedure now finds its application limited to patients with advanced neck disease or with gross extracapsular spread to the spinal accessory nerve, sternomastoid muscle and the internal jugular vein.

Modified radical neck dissection

This operation involves the removal of the same lymph node groups as the radical neck dissection (levels I through V) but requires preservation of 1 or more of the 3 non lymphatic structures; the spinal accessory nerve, the internal jugular vein, and the sternomastoid muscle.

Modified neck dissection is indicated in cases with clinically palpable metastatic neck disease. Conversion to the radical neck dissection becomes necessary when gross involvement of the nerve, vein and muscle is present, although the involvement of all 3 is unusual, except in very advanced (N3) disease.

Comprehensive neck dissection is a term that frequently appears in the literature. This refers to any type of neck dissection that involves removal of lymph nodes from levels I through V and corresponds, therefore, to radical and modified radical neck dissections according to the Academy's classification.

Selective neck Dissection

This term refers to a type of neck dissection in which certain lymph node groups in the neck are preserved while others are removed. Included in this category are supraomohyoid neck dissection, lateral neck dissection, anterior compartment neck dissection, and posterolateral neck

dissection.

Supraomohyoid neck dissection

Selective removal of the level I, II and III lymph nodes is called supraomohyoid neck dissection. The operation includes the resection of soft tissue in the submental triangle, along with the submandibular triangle contents, including the submandibular gland and the fibrofatty tissue along the internal jugular vein in the upper 2 levels. The dissection contents include the fascia covering the medial aspect of the sternomastoid muscle; the muscle itself is retracted laterally and preserved. These neck contents are peeled off from the internal jugular vein and from around the accessory nerve, sparing these structures.

Supraomohyoid neck dissection is indicated for the prophylactic treatment of occult neck disease in cancers known to metastasize to this group of nodes, i.e cancers of the oral cavity. Application of this type of the neck dissection to treat clinically positive nodes remains controversial. If this operation is performed for N+ disease, including level Ic in the dissection may be prudent.

Lateral Neck dissection

Selective removal of the soft tissues containing the level, II, III and IV lymph nodes along the internal jugular vein is called lateral or

anterolateral neck dissection. The spinal accessory nerve, sternomastoid muscle, and internal jugular vein are spared in this operation.

This operation is commonly performed for the prophylactic treatment of occult disease in patients with primary cancers in the oropharynx, hypopharynx, or larynx.

Both the supraomohyoid and the lateral neck dissections may need to be performed on both sides in patients whose primary tumors are located close to or across the midline. Cancers of the central tongue, floor of the mouth, low lip, and supraglottic larynx are known to metastasize bilaterally.

Anterior compartment neck dissection

This operation involves excision of the level VI lymph nodes. The procedure is indicated for the treatment of cancers of the thyroid gland, hypopharynx, cervical trachea, cervical esophagus, and subglottic larynx. The boundaries of the dissection are the hyoid hone superiorly, the suprasternal notch inferiorly, and the carotid sheaths on either side. Hyopoparathyroidism may be a disabling complication if care is not taken to identify and preserve the parathyroid glands, and injury to the parathyroid blood supply is a risk with this procedure. Excising and reimplanting the glands into the sternomastoid or pectoralis major muscles

may be necessary. Alternatively, the dissection may be limited to one side if the lesion is not close to the midline, particularly if radiation therapy can be administered postoperatively.

Posterolateral neck dissection

Posterolateral neck dissection was initially described by Rochin in 1962 and later modified and popularized by Geopfert et al for use in patients with cutaneous malignancies of the scalp and postauricular and suboccipital regions. Unlike all other neck dissections, this operation is performed with the patient in the lateral decubitus position and consists of an en bloc removal of the lymph nodes in the suboccipital, postauricular, and upper, middle and lower jugular nodes, along with posterior triangle nodes situated superior to the accessory nerve. Although the original description included sacrifice of the accessory nerve, internal jugular vein, and a portion of the trapezius muscle, Diaz et al from the MD Anderson Cancer centre showed in 1996 that preserving these non lymphatic structures dies not increase the failure rate of this operation.

Extended neck dissection

In cases of advanced neck disease, certain lymphatic or non lymphatic structures, not routinely included in the aforementioned neck dissections, may have to be removed. Extended neck dissection is the term

used to describe these procedures. Retropharygeal lymph nodes, the hypoglossal nerve, portions of the prevertebral musculature, or the carotid artery are some of the structures that may occasionally have to be excised in order to obtain negative margins.

MATERIALS AND METHODS

During a period of 8 months from January 2017 to August 2017 datas were collected from 43 patients who were admitted to the surgical units of Kilpauk medical college hospital with a diagnosis of cervical lymphadenopathy. Children below 12 years of age were not included. All patients with known primaries were excluded from the study. Likewise patients with lymphatic malignancies were excluded. Patients with infective pathology and non specific lymphadenitis were also excluded from the study. A total of 43 patients were finally included in the study.

The workup for all the patients on admission was a follows:

History

A detailed history was obtained from all patients, attention was focused on onset of swelling, duration of swelling, rate of growth of the swelling ,associated pain, pressure and obstructive symptoms like dizziness (carotid tree involvement),shooting pain over arm (brachial plexus involvement), difficulty in breathing ,difficulty in swallowing, change in voice were elicited. History of otalgia, aural fullness, nasal congestion and epistaxis were also obtained. Social history including occupational hazards like exposure to ultraviolet light, industrial chemicals and metals were obtained. Information concerning alcohol

consumption and tobacco product usage were obtained. History of any irradiation to the head and neck in the past and past treatment of other head and neck carcinoma were elicited. Any associated illness were also noted.

Physical examination

The lymph node was taken significant if the size was more than 1cm, spherical rather than ovoid in shape, hard in consistency.

Note was made of the side and the triangle of the neck involved, the total number of palpable nodes, the groups involved, size, consistency, presence of tenderness, fixity to skin as well as deeper structures, presence of any contralateral nodes and the N stage of the nodes.

Nodes deep to the sternocleidomastoid were included in anterior cervical triangle as the classical description of the cervical triangle excludes the nodes deep to the sternomastoid muscles from either of the two triangles. Midline nodes were considered as homolateral nodes. In all instances the clinical impression of the first observer was confirmed by at least one another observer.

The physical examination was then focused on the head and neck, beginning with inspection and palpation of the skin. The scalp and external ears were inspected in detail. All zones of the neck were palpated

thoroughly in an effort to find additional lymphadenopathy or masses. The nasal vestibule, oral cavity and oropharynx were thoroughly inspected.

Because submucosal lesions are not typically evident with visual inspection, manual palpation of the oral cavity and the oropharynx were done. Special attention was paid to the base of the tongue during palpation. Special focus was given for any thyroid swelling, breast, respiratory system, abdomen, and genitalia were examined.

Chest radiograph was done for all patients. For patients with suspicious lesions on chest radiograph, CT scan of the chest was done. Bronchoscopy was done for all patients

Indirect laryngoscopy was done for all patients particularly looking for any growth or mucosal abnormalities in nasopharynx, oropharynx and larynx.

Upper gastrointestinal endoscopy was done for all patients. Ultrasound abdomen was done for all patients.

FNAC was done from the nodes. The histopathological report was expressed in three grades –Well differentiated, moderately differentiated and poorly differentiated carcinoma, adenocarcinoma and papillary carcinoma thyroid.

RESULTS OF THE STUDY

1. AGE DISTRIBUTION

Incidence of age in nodal metastasis of neck with unknown primary

Table - 1

Age in years	No of cases out of 43	Percentage %
10-20	1	2
20-30	2	5
30-40	2	5
40-50	7	16
50-60	20	46
60-70	8	19
70-80	2	5
> 80	1	2

Most cases presented around 40-70years. of them the presentation is more in 50-60 years of age

2. SEX DISTRIBUTION OF THE NODES

Sex distribution of the nodes

TABLE - 2

sex	No of cases out of 43	Percentage%
Male	37	86
Female	6	14

Out of the 43 patients with neck secondaries with unknown primary 37 (86%) patients were male, 6 (14%) patients were female.

The following were the histopathological distribution among males and females;

TABLE - 3

Histolopathology	males	Females
Poorly diff carcinoma	22	3
Mod diff carcinoma	5	1
Well diff carcinoma	8	1
Adenocarcinoma	2	1

3. TOPOGRAGHICAL DISTRIBUTION OF NODAL METASTASES

Analysis of topographical distribution of cervical node metastasis from various sites revealed the following patterns.

Of this 43 patients one patient (2.3%) presented with more than one group of nodes. it was involving the level II and level III.

One patient (2.3%) presented with bilateral nodes. and involving level II, level III and level IV.

41patients (95.34%) presented with only single group of nodes. The following pattern was noted in these patients.

Out of the 41 patients who had a single group of nodes 96% had the nodes in level II and level III.

Topographical distribution of nodes

TABLE - 4

Lymph node levels	No of patients out of	Percentage
	41	
Level I	0	0
Level II	28	68.29
Level III	11	26.82
Level IV	1	2.43
Level V	1	2.43
Level VI	0	0

Of the 41 patients who presented with single node only, most of them were in level II and level III

No patients presented with level I and level VI nodes with an unknown primary.

4. SIDE OF DISTRIBUTION OF THE NODES

TABLE - 5

Side distribution of nodes

Side of the nodes	**No of patients out of 43**	**Percentage**
Left	28	65
Right	15	35

Of the 43 patients (15patients-35%) presented with right sided nodes.28 patients (65%) presented with left sided nodes

The following are the histopathological distribution of nodes

TABLE - 6

Histopatholgy	Right	Left
Poorly diff carcinoma	7	18
Mod diff carcinoma	3	3
Well diff carcinoma	4	5
Adenocarcinoma	1	2

5. HISTOPATHOLOGICAL ANALYSIS OF THE NODAL METASTASIS

Out of the 43 patients included in the study 25 patients(58%) had poorly differentiated carcinomatous deposit .9 patients (21%) had metastatic deposit from squamous cell carcinoma.

The histopathological analyses are presented in the following

TABLE - 7

Histology	No of patients	Percentage
Poorly differentiated metastatic carcinoma	25	58
Moderately differentiated metastatic	6	14
Carcinoma		
Metastatic deposit from squamous cell	9	21

Carcinoma		
Metastatic deposit from adenocarcinoma	3	7

TREATMENT

All patients with operable nodes were treated with radical neck dissection. Those patients with extracapsular spread and multiple nodes were given radiotherapy and chemotherapy. For patients with operable bilateral nodes bilateral radical neck dissection was done in intervals.

For patients with inoperable masses chemoradiation was given. Combination chemotherapy with cisplatin (Days 1- 2) and 5-FU (for Days 1- 5) was regimen given for all the patients.

Radiotherapy was given for 33 fractions of 300cGY per day for 5 days/week. A total dose of 6600 cGy was given. Palliative radiotherapy was given for advanced disease with 10 fractions of 200cGY per day. A total of 2000 cGY was given.

During the 8 months study no subsequent primary site was identified in all the patients.

DISCUSSION

Squamous cell carcinoma of the head and neck is the most common malignancy in India. Treating a patient with malignant cervical lymphadenopathy poses a challenge to the clinician in finding out the primary site.

- The incidence of malignant cervical lymphadenopathy was 2 % of all cancers.
- The male to female ratio is 6:1 in our study, which matches with the
- world average. The higher incidence in the males could be due to increased exposure to tobacco products and occupational hazards than females.
- 81% of the patients presented between 40- 70 years. Highest incidence was seen between 50 – 60 years.
- 58% of the patients had poorly differentiated carcinoma and 21% of the patients had well differentiated squamous cell carcinoma. This is
- in contrast to the western literature where squamous cell carcinoma accounts for 30% -50% and poorly differentiated carcinoma accounts for 25%. This could imply that more aggressive cancers are seen in our part of the world. This could be due to variable disease process or the various pathogenic factors playing a part.

- 2.3% of the patients presented with bilateral nodes, which means the most probable site of primary could be in the midline structures like base of tongue, nasopharynx and supraglottis.
- In our study we also noted a higher incidence on the left side(65%), when compared to the right side(35%). Are they due to keeping the tobacco products more commonly on the left is to be evaluated by further studies.

CONCLUSION

The unknown primary tumour presents several clinical dilemmas including how to find the primary site and, if the site is never found, to direct treatment.

The incidence of patients with an unknown primary site is low overall because of the effectiveness of clinical examination coupled with pan endoscopy and directed biopsies. Modern Radiograghic technology including CT/MRI, PET scan, and recently, PET-CT may be of value in some cases. As these diagnostic methods become more refined there may eventually be no patients with an unknown primary tumour. Of course, once the primary site is identified, treatment of this patients can become much more specifically directed. We hope that in future the unknown primary site will no longer be a featured entry.

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PROFORMA

- Name Age/sex IP.No: phone No:
- Unit Address

Date of admission: Date of discharge: occupation

PRESENTING COMPLAINTS:

ANY SIGNIFICANT PRESENT HISTORY

PAST HISTORY & TREATMENT HISTORY

PHYSICAL EXAMINATION :

Level of consciousness

orientation

Hydration status

anaemia ,jaundice,clubbing,pedal edema

Vitals

- EXAMINATION OF NECK:
- Other system ex.; CVS/RS ABDOMEN CNS P/R P/V
- External genitalia
- INVESTIGATIONS:
- BLOOD ; complete hemogram

  Renal function test.,

  Serum electrolytes

  Liver function test

Chest x ray

USG NECK

FNAC

- TRU CUT BIOPSY
- CT SKULL BASE TO MEDIASTINUM
- PAN ENDOSCOPY AND TRIPLE ENDOSCOPY
- GUIDED BIOPSY
- USG ABDOMEN
- CECT ABDOMEN
- PET - CT

TYPES OF THERAPY

1. Surgery
2. Chemotherapy
3. Radiotherapy

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு :

ஆராய்ச்சி நிலையம் : பொது அறுவை சிகிச்சைத் துறை
கீழ்பாக்கம் மருத்துவக் கல்லூரி
சென்னை - 600 010.

பங்கு பெறுபவரின் பெயர் : வயது :

பங்கு பெறுபவரின் எண். :

பங்கு பெறுபவரது இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வின் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தக் காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்று அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்மந்தமாகவோ, இதைச் சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போது இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு எனது அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான முடிவுகளையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதைப் பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்குக் கூறப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் .....இடம் ..... தேதி
கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

MASTER CHART

Column 1	Column 2	Column 3	Column4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10	Column 11	Column 12	Column 13	Column 14
Name	**Age**	**Sex**	**Ip no**	**Ses**	**Smoking**	**Alcoholism**	**Familyhist**	**Neckswelling Usgneck ct neck**		**Ct neck**	**Fnac**	**Hpe**	**Treatment**
Raman	60	male	87229	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Deswan	52	male	16927	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Govindan	71	male	85664	low SES	yes	no	no	yes	done	done	done	scc	surgery /RT
Rehman	55	male	88489	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Mari	54	male	2201	low SES	yes	yes	no	yes	done	done	done	adeno	surgery /RT
Vasu	62	male	29117	low SES	yes	yes	no	yes	done	done	done	scc	chemo RT
Shane	41	male	1377	low SES	yes	no	no	yes	done	done	done	scc	surgery /RT
Rajendran	54	male	75831	low SES	yes	yes	yes	yes	done	done	done	scc	surgery /RT
Chandran	57	male	84231	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Murali	64	male	82985	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Kannan	82	male	102346	low SES	yes	no	no	yes	done	done	done	adeno	surgery /RT
Kantha	56	female	105634	low SES	no	no	no	yes	done	done	done	scc	chemo RT
Mani	45	male	98456	low SES	yes	yes	yes	yes	done	done	done	scc	chemo RT
Krishnan	56	male	78654	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Vanjikodi	55	female	97345	low SES	no	no	no	yes	done	done	done	scc	surgery /RT
Thangam	67	female	98876	low SES	no	no	no	yes	done	done	done	scc	surgery /RT
Kathirvel	52	male	87234	low SES	yes	yes	no	yes	done	done	done	scc	RT
Rajan	57	male	90867	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Siva	48	male	67543	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT

Ranjitham	56	female	45632	low SES	no	no	no	yes	done	done	done	scc	surgery /RT
Nanjamma	53	female	45670	low SES	no	no	no	yes	done	done	done	scc	surgery /RT
Saravanan	68	male	23145	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Durai	57	male	453216	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Palani	58	male	87234	low SES	yes	yes	yes	yes	done	done	done	scc	surgery /RT
Perumal	84	male	56342	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Pandu	67	male	105326	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Ahmed	45	male	42980	low SES	yes	yes	no	yes	done	done	done	adeno	surgery /RT
Shanmugam	59	male	815113	low SES	yes	no	no	yes	done	done	done	scc	chemo RT
Chandru	60	male	107744	low SES	yes	yes	no	yes	done	done	done	scc	chemo RT
Rajee	50	male	6993	low SES	yes	yes	no	yes	done	done	done	scc	surgery /RT
Hussain	65	male	99653	low SES	no	no	no	yes	done	done	done	scc	surgery /RT