"LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA"

By

Dr. LINU THOMAS

DISSERTATION SUBMITTED TO

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH,

KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY
IN
OTORHINOLARYNGOLOGY

Under the Guidance of

Dr. S.M.AZEEM.MOHIYUDDIN, MS,

PROFESSOR OF OTORHINOLARYNGOLOGY

DEPARTMENT OF OTORHINOLARYNGOLOGY,

SRI DEVARAJ URS MEDICAL COLLEGE

TAMAKA, KOLAR-563101

MAY 2018

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. S.M.AZEEM.MOHIYUDDIN**, Professor and Head of the Department of Otorhinolaryngology , Sri Devaraj Urs Medical College, Kolar, in partial fulfillment of University regulation for the award "**M.S. DEGREE IN OTORHINOLARYNGOLOGY**", the examination to be held in May 2018 by SDUAHER. This has not been submitted by me previously for the award of any degree or diploma from the university or any other university.

Date:

Place: Kolar

Dr. LINU THOMAS
Postgraduate in Otorhinolaryngology
Sri Devaraj Urs Medical College
Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA"** is a bonafide research work done by **Dr. LINU THOMAS,** under my direct guidance and supervision at Sri Devaraj Urs Medical College, Kolar**,** in partial fulfillment of the requirement for the degree of "**M.S. IN OTORHINOLARYNGOLOGY"**.

Date:
Place: Kolar

Dr. S.M.AZEEM.MOHIYUDDIN, MS
SEKHSARIA Fellowship in Head &Neck Surgery
Tata Memorial Hospital, Mumbai
Professor and Head of the Department
Department Of Otorhinolaryngology
Sri Devaraj Urs Medical College
Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE

CERTIFICATE BY THE CO-GUIDE

This is to certify that the dissertation entitled "**LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA**" is a bonafide research work done by **DR. LINU THOMAS** in partial fulfillment of the requirement for the degree of **MASTER OF SURGERY IN OTORHINOLARYNGOLOGY** as per regulations of Sri Devaraj Urs academy of higher education and research, Kolar. I have great pleasure in forwarding this to the university.

Date:

Place: Kolar

Dr. T.N.SURESH MD DNB
Professor,
Department of Pathology
Sri DevarajUrs Medical College,
Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

CERTIFICATE BY THE HEAD OF DEPARTMENT

This is to certify that the dissertation entitled "**LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA**" is a bonafide research work done by **Dr. LINU THOMAS,** under direct guidance and supervision of **Dr. S.M. AZEEM MOHIYUDDIN**, Professor, Department of Otorhinolaryngology at Sri Devaraj Urs Medical College, Kolar**,** in partial fulfillment of the requirement for the degree of "**M.S. IN OTORHINOLARYNGOLOGY"**.

Date:

Place: Kolar

Dr. S.M.AZEEM.MOHIYUDDIN, MS
SEKHSARIA Fellowship in Head &Neck Surgery
Tata Memorial Hospital, Mumbai
Professor & HOD
Department of Otorhinolaryngology
Sri Devaraj Urs Medical College
Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

ENDORSEMENT BY THE HEAD OF THE DEPARTMENT AND PRINCIPAL

This is to certify that the dissertation entitled **"LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA"** is a bonafide research work done by **Dr. LINU THOMAS** under the direct guidance and supervision of **Dr. S.M.AZEEM MOHIYUDDIN,** Professor and Head of the Department of Otorhinolaryngology, Sri Devaraj Urs Medical College, Kolar, in partial fulfillment of University regulation for the award "**M.S. DEGREE IN OTORHINOLARYNGOLOGY**".

Dr. S.M.AZEEM MOHIYUDDIN,
Professor & HOD
Department Of Otorhinolaryngology,
Sri Devaraj Urs Medical College,
Tamaka, Kolar

Date:
Place: Kolar

Dr. M. L. HARENDRA KUMAR
Principal,
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College, Tamaka, and Kolar has unanimously approved

Dr. LINU THOMAS

Post-Graduate student in the subject of OTORHINOLARYNGOLOGY

at Sri Devaraj Urs Medical College, Kolar

to take up the Dissertation work entitled

"LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA"

to be submitted to

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA,

Member Secretary

Sri Devaraj Urs Medical College,

Kolar–563 101.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

COPY RIGHT

I hereby declare that Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic/research purpose.

Date: **Dr. LINU THOMAS**

Place: Kolar

ACKNOWLEDGEMENT

Praise be to the almighty God who gave me the kind opportunity to work and study in this institution. I would like to express my deep gratitude towards Him for his gracious blessing, love, strong hold for protecting me and showing me the right path through this gratifying task.

It is with great reverence, deep sense of gratitude and respect that I would like to thank my teacher and guide , Dr. S.M.Azeem Mohiyuddin, Professor and Head of the Department of Otorhinolaryngology, Sri DevarajUrs Medical College, Tamaka, Kolar for his guidance, support, encouragement, valuable insights and constant enthusiasm during the entire period of this study and post graduation course.

I would also like to thank my co-guide Dr T.N.Suresh, Professor, Department of Pathology, Sri Devaraj Urs Medical College, Tamaka, Kolar for his guidance, support and valuable insights in preparing and completing this dissertation.

I convey my deepest regards and earnest gratitude to Dr. K.C.Prasad, Professor Department of Otorhinolaryngology, Sri DevarajUrs Medical College, Tamaka, Kolar, for his constant support and encouragement and advice during the course of this study and in completing this dissertation.

I would like to express my gratitude to Dr .R.P.Deo – visiting Professor, Dr Sagayaraj A, Dr Vinaya Babu – Associate Professors, Dr Shuaib Merchant, Dr Kouser Mohammadi, Dr Harshitha T.R, Dr Prashanth Babu– Assistant professors, Dr Sreeharsha M, Dr Abhilasha K and Dr Sumanth- Senior residents, Department of

Otorhinolaryngology for their never ending support, guidance and constant encouragement in the preparation of this dissertation and throughout my post-graduation course.

I am immensely thankful to all my PG colleagues, seniors and juniors, OT staff, Department of Anesthesia and Department of Pathology for their support in the completion of this dissertation.

Above all I would love to wholeheartedly thank to my parents Mrs.Lily kutty Thomas, my mother, who has been an infinite source of inspiration and love, Mr.P.M Thomas, my father, for all the support and encouragement. I thank them for blessing me with this opportunity and helping me during my post-graduation course.

I would also like to extend my gratitude to my wife Dr. Manna Jose for her constant love and support.

I would also like to take this opportunity to thank my dear brothers Mr Libu Thomas and Mr Liju Thomas and my dearest sister Dr Leeba Thomas, for their never ending love and care all throughout.

Last but not the least I wholeheartedly thank all my patients and their families who submitted themselves most gracefully and participated in this study.

Dr. LINU THOMAS

LIST OF ABBREVIATIONS

ABBREVATIONS	
BM	Buccal mucosa
RMT	Retromolar trigone
GBS	Gingivobuccal sulcus
FOM	Floor of mouth
AJCC	American Joint Committee against Cancer
OSCC	Oral squamous cell carcinoma
ITF	Infratemporal fossa
Ca	Carcinoma
CIS	Carcinoma in situ
HPV	Human papilloma virus
VEGF	Vascular endothelial growth factor
EGFR	Epidermal growth factor receptor
SCC	Squamous cell carcinoma
CECT	Contrast enhanced computerized tomography scan
MRI	Magnetic resonance imaging scan
USG	Ultrasonography scan
FNAC	Fine needle aspiration cytology
NACT	Neoadjuvant chemotherapy
RT	Radiotherapy
CT	Chemotherapy
HPE	Histopathological examination
NCCN	National comprehensive cancer network
LNR	Lymph node ratio

TABLE OF CONTENTS

ABSTRACT

Background:

Head & neck malignancies constitute 30%-35% of all malignancies in India. Oral cancer accounts for 30%-45% of these malignancies. Around 60-80% of these patients present with advanced disease (T3 and T4) in this hospital.

Various factors such as tumour stage, tumour site, margin status, depth of invasion and the presence of cervical lymph nodal metastasis are significant prognostic factors affecting these patients. Cervical nodal status remains one of the most significant prognostic markers in oral cavity squamous cell cancers. The presence of lymph node metastases decreases 5 year survival by approximately 50%. As such these patients are at a higher risk for recurrence. Since intensive adjuvant therapy (RT+/-CT) itself causes significant morbidity, it becomes important to accurately identify such high risk patients. Many prognostic indicators have been proposed, however, off late lymph node ratio (LNR) (total positive nodes/total number of lymph nodes dissected) has been proposed as a strong prognostic factor in OSCC patients.

Objectives:

(1) To perform composite resection in patients with Stage III and IVa oral cavity cancers and evaluate the lymph nodes for metastasis by histopathological examination.

(2) To obtain the Ratio between total number of lymph node resected and those harbouring metastasis.

(3) To correlate the depth of primary tumour with Lymph Node Ratio.

(4) To correlate the site of primary tumour with Lymph Node Ratio.

Methods:

72 patients undergoing surgery for oral cavity squamous cell carcinoma (Satge III and IVa) admitted under Department of Otorhinolaryngology and Head and Neck Surgery of R L JALAPPA HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR from December 2015 till June 2017 were included in this prospective observational study. After having taken an informed written consent and performing investigations for fitness for surgery, a composite resection of the tumor including neck dissection and reconstruction of the defect was performed. The resected specimen was evaluated by histopathological examination to look for histology, thickness and depth of tumour, pTNM staging and lymph node ratio.

Post operatively patients were assessed for locoregional control &functional outcome and the findings were documented at each follow up. All patients received adjuvant treatment as per existing guidelines.

Results:

72 patients with locally advanced (stage III and stage Iva) oral cavity squamous cell carcinoma were included in the study. 30 (42%) out of 72 patients had cervical lymph node metastasis. Out of 30 patients with pN+, 43% had N1 nodal status and 57 % patients had N2 status on histopathological examination. The average nodal yield was 20 nodes per specimen. Mean Lymph node ratio was highest in Stage IVA (0.072) than in stage III (0008). This difference in mean Lymph node ratio between stage IVA and III was statistically significant (p=<0.004). In the study there was significant positive correlation between maximum depth of tumor invasion and Lymph node ratio. (p=<0.001) i.e. with increase in maximum depth of tumor invasion, there was increase in Lymphnode ratio and vice versa. There was no significant difference in mean Lymph node ratio with

respect to site of primary tumor. After a mean follow up of 12 months with minimum follow up of 6 months, 56 patients are alive and disease free (77.8%). Of 3 patients who expired, 2 died as a result of disease process and one died due to other cause. 6 patients had local recurrence, 6 of the patients had regional recurrence and 1(had locoregional recurrence. The mean Lymph node ratio was high in subjects who expired 0.227 ± 0.287 and lower in those with Local recurrence (0.117 ± 0.09). This difference in mean Lymph node with respect to outcome at follow up was statistically significant. Lymph node ratio of 0.100 had highest sensitivity and specificity in detecting poor prognosis among subjects with SCC.

Conclusion:

Patients with higher lymph node ratio are more prone to an adverse outcome and increase in depth of invasion of tumour was associated with poor prognosis. As our study had a small sample size and limited duration of follow up, it would have been ideal to include a larger sample size and longer follow up to validate our results and assess the value of Lymph node ratio as a tool to help identify patients who are at a higher risk for disease recurrence.

Keyords: squamous cell carcinoma of oral cavity, depth of invasion, lymph node ratio

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

INTRODUCTION

INTRODUCTION

Head and neck cancer is the sixth most common malignancy across the globe but is the most common encountered malignancy in Indian population. In India, oral cavity cancer accounts for almost 50% of the head and neck cancers, thus being the most prevalent type of head and neck cancer.[1]

Treatment protocol and prognosis vary widely and are based on the stage of the disease at the time of diagnosis. Despite the fact that oral cavity is accessible for visual examination and that oral cancers and premalignant lesions have well defined clinical and diagnostic features, most patients present with locally advanced (Stage III or IV) disease requiring a wide excision of the primary tumour along with neck dissection, which can be an extensive surgery with resultant morbidity.[2]

However, in spite of aggressive surgery, the 5 year overall survival in these patients with locally advanced (Stage III and IV) disease is only about 50%. The major cause of morbidity and mortality in these patients is locoregional recurrence. Thus, it is importance to identify such patients who are at a higher risk for locoregional recurrence, and provide aggressive adjuvant therapy (radiation or chemoradiation) to prevent it.[3]

Histopathological factors commonly used to identify patients requiring adjuvant therapy are extra capsular spread, positive surgical margins, skin or bone involvement, multiple metastatic lymph nodes, nodal disease in level IV/V and perineural invasion. Among these, lymph node metastasis and surgical margin status are the most important factors affecting selection of treatment and eventual prognosis.[3]

Collective data from recent literature have shown that the depth of the tumour and site of the tumour are important factors for lymph node metastasis.[2,3,4]

Of late, lymph node ratio, ie the ratio of total metastatic node to that of total number of dissected lymph nodes, has been proposed as a significant prognostic marker, to help identify patients at higher risk of recurrence, in head and neck cancers.[5,6]

Thus by making use of standard histopathological evaluation, this study aims to correlate the primary site and depth of invasion with lymph node ratio in patients with locally advanced (stage III and stage IVa) oral cavity squamous cell carcinoma.

Therefore, by correlating lymph node ratio with the depth and site of primary tumour, this study may be helpful to identify those patients who are more likely to have locoregional recurrence and plan the extent of surgery and intensive adjuvant therapy.

OBJECTIVES

AIM

To study the relationship between lymph node ratio and the primary site and depth of tumour.

OBJECTIVES OF STUDY

(1) To perform composite resection in patients with Stage III and IVa oral cavity cancers and evaluate the lymph nodes for metastasis by histopathological examination.

(2) To obtain the Ratio between total number of lymph node resected and those harbouring metastasis.

(3) To correlate the depth of primary tumour with Lymph Node Ratio.

(4) To correlate the site of primary tumour with Lymph Node Ratio.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY OF CANCER:

The oldest description of cancer dates back to 3000-1500 BC. Carcinoma is a Greek word meaning a crab. Its latinized form is 'cancer'. Cancer is a term used to characterize abnormal growth of cells, which may result in the invasion of normal tissue or the spread to organs.

Roudolf Virchow, the "founder of cellular pathology" provided us with the pathologic basis for the study of cancer, which gave us a better understanding of the disease process. This in turn laid the foundation for the development of cancer surgery. The excised specimen could be examined & a precise diagnosis could be arrived at. More importantly, the pathologist could also report regarding the completeness of tumour excision.

It was John Hunter (1728-1793) who suggested that if a tumour had not involved surrounding tissues & was "moveable", then it could be treated by surgery[7]. He thus laid the foundation for surgical oncology.

Billroth from Germany, Hadley from London and Halsted from Baltimore, were the three surgeons, who later contributed substantially to cancer surgery. Their work led to removal of entire the tumour along with regional lymph nodes. Oral cavity cancer surgery was based on Halsted's principles i.e in which the tumour and its lymphatic drainage were removed. Later it was expanded to remove all this tissue en bloc along with intervening tissue.

Sir Henry T. Batlin, a surgeon from St. Bartholomew's Hospital, London, in 1885 A.D., performed wide excision of head and neck cancers with mandible and lymphatics of the

upper neck. He, along with Kocher, emphasized the advantage of excising metastatic neck nodes.

However, en bloc radical neck dissection was first described by George Crile in 1907 A.D. This classic report provides the basis for the technique of radical neck dissection as it is practiced today.

The first "commando" operation, as it is called now, was performed by Grant Ward in 1932 A.D. This en bloc excision of the primary within the oral cavity including portion of the mandible combined with the radical neck dissection was being performed regularly since 1942.

The term composite resection (previously known as COMMANDO operation) has been credited to Hayes Martin. It is a surgical procedure wherein the primary tumour in oral cavity/ oropharynx is removed in continuity with a segment of mandible along with a neck dissection[8].

Stephan Ariyan in 1979 A.D described the pectoralis major myocutaneous flap based on the pectoral branch of the thoracoacromial artery. This is 'the work horse' of the head and neck reconstruction surgery.

With the advent of antibacterial chemotherapy, better wound management, diagnostic tools, advances in pathology, improved surgical techniques, development in anaesthesia and transfusion techniques, the prognosis of cancer surgery improved exponentially.

ANATOMY OF THE ORAL CAVITY

The various anatomical sites within the oral cavity as described by the American Joint Committee for Cancer staging [9] are:

- Lip
- Tongue (Anterior 2/3rd)
- Floor of mouth
- Gingiva - Upper alveolus
- Lower alveolus
- Buccal mucosa
- Retromolar trigone
- Hard palate

The oral cavity extends from the skin vermilion junction of the lips to the junction of the hard and soft plate above and to the line of circumvallate papillae below and is divided into the following specific areas (Fig.1):

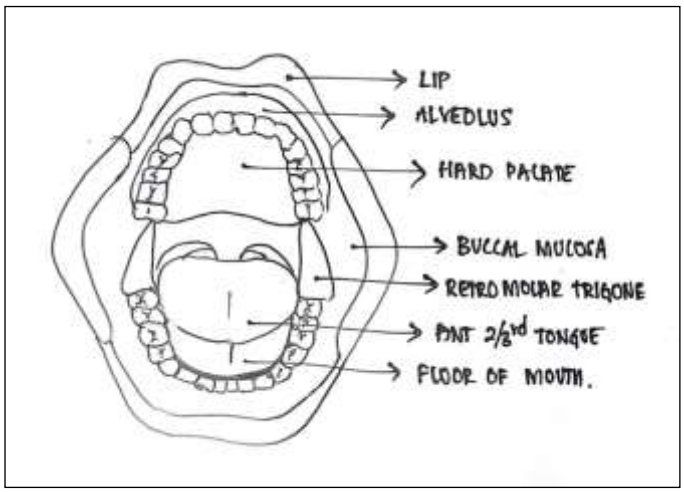


Fig 1: showing anatomical subsites of the oral cavity

Mucosal lip: The lip begins at the junction of the vermilion border with the skin and includes only the vermilion surface that is the portion of the lip that comes into contact with the opposing lip. It is well defined into an upper and lower lip, which joins at the commissures of the mouth.

Buccal mucosa: This includes all the membrane linings of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa to the alveolar ridge (upper and lower) and to the pterygomandibular raphe.

Lower alveolar ridge: This refers to the mucosa overlying the alveolar process of the mandible, which extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth. Posteriorly it extends to the ascending ramus of the mandible.

Upper alveolar ridge: This refers to the mucosa overlying the alveolar process of the maxilla, which extends from the line of attachment of mucosa in the upper gingival buccal

gutter to the junction of the hard palate. Its posterior margin is the superior end of the pterygopalatine arch.

Retromolar gingiva (Retromolar trigone): This is the area of the attached mucosa overlying the ascending ramus of the mandible from the level of the posterior surface of the last lower molar tooth to the apex superiorly, which is adjacent to the tuberosity of the maxilla.

Floor of the mouth: This is a semilunar space over the mylohyoid and hyoglossus muscles, extending from the inner surface of the lower alveolar ridge to the undersurface of the tongue. Base of the anterior pillar of the tonsil forms its posterior boundary. It is divided into two sides by the frenulum of the tongue and contains the ostia of the submandibular and sublingual salivary glands.

Hard palate: This is the cresent shaped area between the upper alveolar ridge and mucous membrane covering the palatine process of the maxillary palatine bones. It extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone.

Anterior 2/3rd of the tongue: It is the freely mobile part of the tongue that extends from the tip anteriorly to the line of circumvallate papillae posterioroly. Inferiorly it extends upto the junction of the floor of the mouth at the undersurface of the tongue. It is composed of four areas: the lateral borders, the tip, the undersurface and the dorsum.

THE BLOOD SUPPLY OF THE ORAL CAVITY:

Branches of the external carotid artery provide blood supply to the oral cavity. Lingual arteries provide blood supply to the tongue. Blood supply to the lips and the cheek mucosa is provided through the facial arteries and the internal maxillary and inferior alveolar arteries provide blood supply to the alveolar ridges.[10](Fig 2)

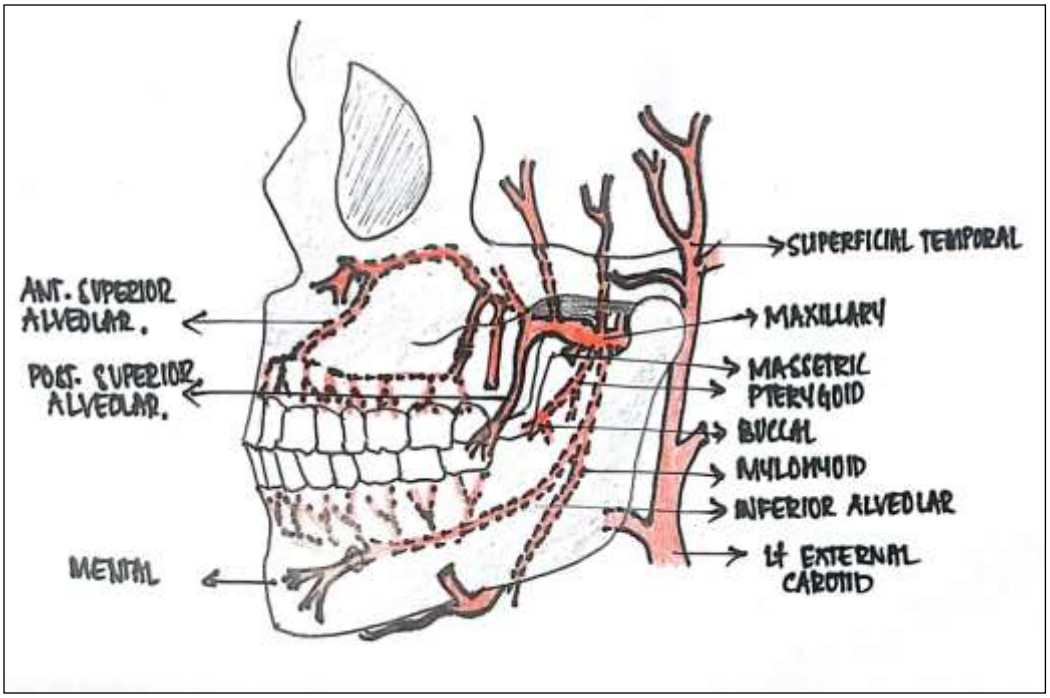


Fig 2: showing blood supply of oral cavity

THE NERVE SUPPLY OF THE ORAL CAVITY:

The sensory nerve supply to oral cavity is provided by sensory component of second and third division of trigeminal nerve, through superior and inferior alveolar and lingual nerves. Special senses of taste and secretomotor fibres to the salivary glands are provided through chorda tympani nerve traversing along the lingual nerve. Motor control of the lips and cheek is provided by the facial nerve. The hypoglossal nerve is the motor nerve for the intrinsic and extrinsic muscles of the tongue and for the movements of the medial and lateral

pterygoid muscles, and their actions are controlled by the motor components of the second and third divisions of the trigeminal nerve.[10](Fig 3)

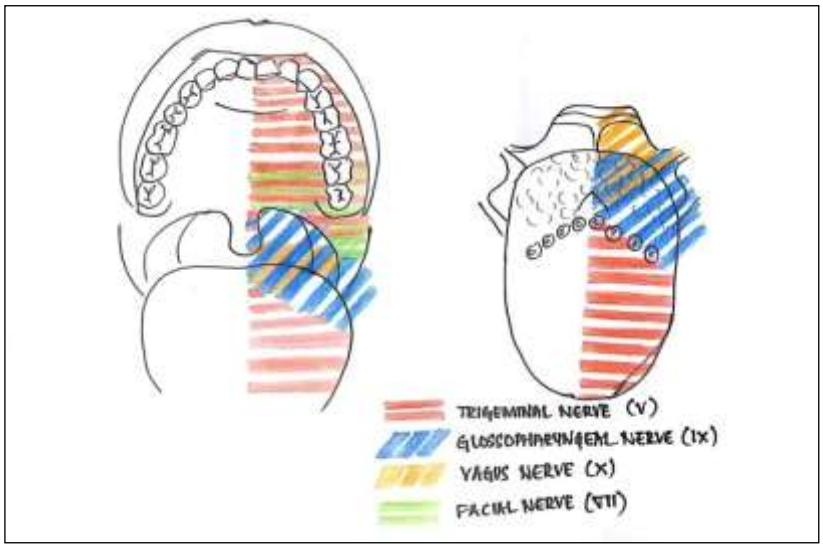


Fig 3: showing nerve supply of the oral cavity

HISTORY OF LYMPHATIC SYSTEM

Gaspero Aselli,a professor of anatomy and surgery from Italy made the first description of lymphatic systems in 1662. William Hunter, William Cruikshank, and William Hewson in London precisely described the anatomy and physiology of the lymphatics in 1786 in their monograph by Cruikshank.[11]

Sappey further described the anatomical understanding of the lymphatic system and his diagrams of lymphatic flow are still used today. During this time, Virchow and other researchers advocated that lymph nodes were a barrier to cancer spread and that cancer progressed sequentially from a primary tumor to regional lymph nodes and then to systemic sites. Radical surgical procedures, including Crile's radical neck dissection, were developed in response to this belief.

DEVELOPMENT OF LYMPHATIC SYSTEM

First evidence of lymphatic system in intrauterine life is appearance of structures known as lymph sacs which are closely related to veins in certain situation. First to appear is jugular lymph sacs which are two in number. Others are two posterior lymph sacs, one retroperitoneal lymph sac and one cisterna chyli.

According to Sabin (1916) lymph sac develop as outgrowth of endothelium of veins and lymph vessels sprout in a radiating manner and primary connections with veins are lost.[12]According to Huntington (1911) and McClure (1915) all lymph vessels are originally formed as clefts in the mesenchyme exactly as blood vessels. Lymph nodes develop as aggregation of cells in mesenchymal strands surrounded by plexuses of lymph vessels. Around each nodule vessels are transformed to lymph sinus.

LYMPH NODE GROUPS[13]

The lymph nodes are divided into various anatomical subsites and grouped into seven levels (Fig 4):

Level I: Submental IA

Submandibular IB

Level II: Upper jugular sublevels IIA and IIB (anterior and posterior to the spinal accessory nerve respectively)

Level III: Mid-jugular

Level IV: Lower jugular

Level V: Posterior triangle (spinal accessory and transverse cervical)

(upper, middle and lower corresponding to the levels that define upper, middle and lower jugular nodes)

Level VI: Prelaryngeal (Delphian)

Pretracheal

Paratracheal

Level VII: Upper mediastinal

Other groups: Sub-occipital

Retropharyngeal

Parapharyngeal

Buccinator (facial)

Preauricular

Periparotid and intraparotid.

The location of the various lymph node levels is as follows:

Level I: Contains the submental and submandibular triangles. It is bounded by the anterior belly and the posterior belly of the digastric muscle, and the hyoid bone inferiorly, and the body of the mandible superiorly.

Level II: Extends from the level of the skull base superiorly to the hyoid bone inferiorly and contains the upper jugular lymph nodes.

Level III: Contains the middle jugular lymph nodes from the hyoid bone superiorly to the level of the lower border of the cricoid cartilage inferiorly.

Level IV: Contains the lower jugular lymph nodes. It extends from the level of the cricoid cartilage superiorly upto the clavicle inferiorly.

Level V: Contains the lymph nodes in the posterior triangle, which are bounded by the anterior border of the trapezius muscle posteriorly, by the posterior border of the sternocleidomastoid muscle anteriorly, and by the clavicle inferiorly.

For descriptive purposes Level V may be further subdivided into upper, middle, and lower levels corresponding to the superior and inferior planes of the lymph nodes levels that define Levels II, III and IV.

Level VI: Contains the lymph nodes of the anterior central compartment from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side, the medial border of the carotid sheath forms the lateral boundary.

Level VII: Contains the lymph nodes inferior to the suprasternal notch in the superior mediastinum.[13]

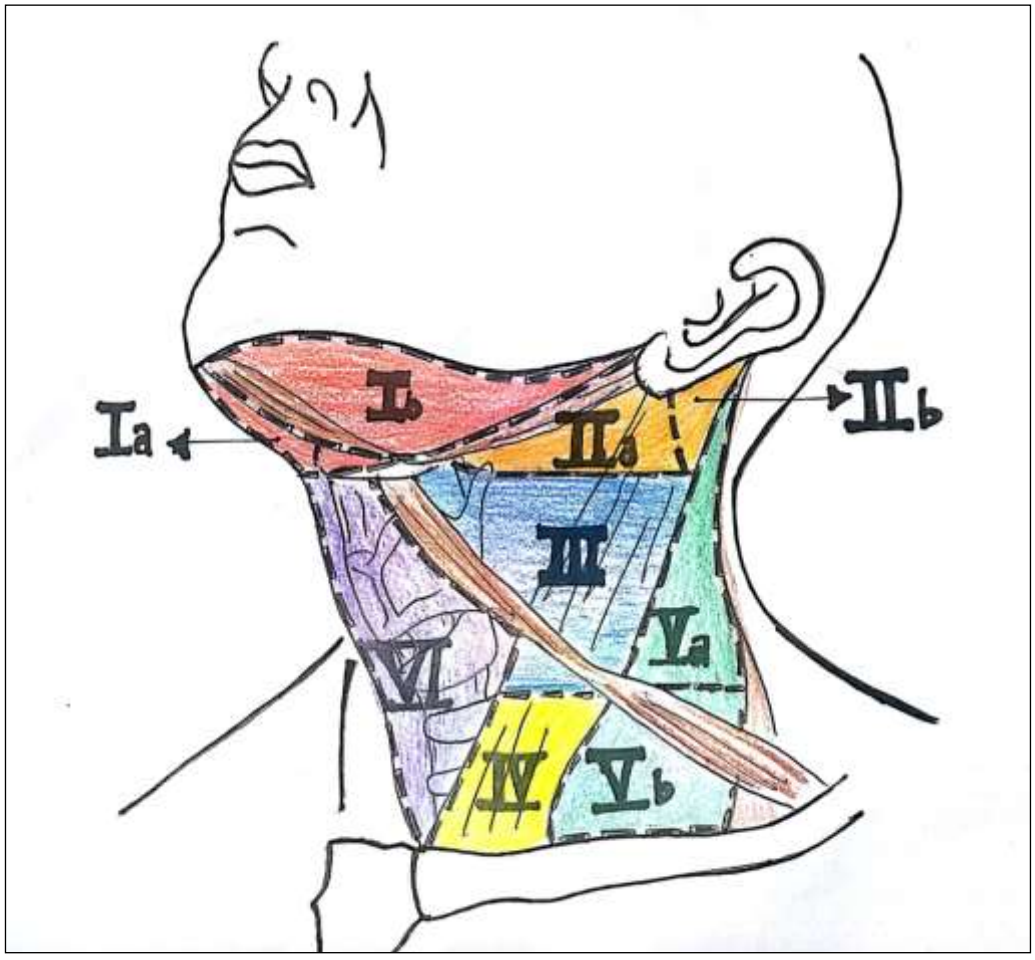


Fig 4: showing various lymph node levels

ORAL CAVITY CANCER

EPIDEMIOLOGY:

All throughout history, man has been trying to conquer malignant diseases. However it still remains a major cause for death and morbidity. It is estimated that about nine million new cancers are diagnosed every year in the world. Worldwide estimate of oral cancer detection each year is 4,05,000 cases with 2/3rd occurring in developing countries.[14]

India, Sri Lanka, Pakistan, Bangladesh, Hungary & France have the highest rates with the former 4 accounting for 30% of newly detected cases.[14] The estimated number of new cancers in India is about seven lakhs, and about 3.5 lakhs people die of cancer every year.[15]

According to the cancer registry of Kidwai Memorial Institute Of Oncology, Bangalore, Karnataka, on an average, about 5000 new cancers are registered per year[16]. Oral cancer ranks among the top three in India. Age adjusted rates of oral cancers in India is 20 per 100,000 population and accounts for over 30% of all cancers in the country.[17]

In the western world the tongue and floor of the mouth are the most common sites for primary squamous cell carcinoma in the oral cavity. However, in India the buccal mucosa and lower alveolus are the most frequently encountered primary sites.[2]

Carcinoma of buccal mucosa accounts for 40% of oral cancers in South East Asia.[18] 85% cases occur >50 years of age, except in developing countries where onset is earlier due to tobacco/ pan chewing habits. Floor of mouth cancer accounts for 18-33% of oral cancers and seen more frequently in men in 6th-7th decade. 22-39% of oral carcinomas arise in the tongue, most commonly in middle 1/3rd and in the lateral aspect.[18]

Retromolar trigone incidence in oral cancers is 6 - 7% and is more common in males. Incidence of carcinoma in Maxillary alveolus is 3.5 – 6.5% & hard palate is 1 – 3%. Oral cancers are more common in males except in hard palate carcinomas where precedence in females is more due to reverse smoking. Mandibular cancers account for 7.5 – 17.5 % of oral cancers. [18]

ETIOLOGY:

The cause of oral cancer is yet to be completely understood. Several risk factors have been implicated.

1] Smoking:

Tobacco is smoked more commonly in the form of cigarette and bidi. Some smoke a chutta (a cigar) with the burning end inside the mouth. Chemical carcinogens in the burning tobacco or repeated thermal injury are agents, which are risk factors for oral cancer. Risk increases with the amount smoked and with the total cumulative lifetime smoking years. Tobacco is smoked commonly in the form of bidi, a type of cheap cigarette made by rolling a rectangular dried piece of tendu leaf (Diospyros melanoxylon) with 0.30-0.36 gm of Saurashtra or Nipani tobacco and securing the roll with thread. The length varies from 4 cms to 7.5 cms. As compared with cigarette smoke, bidi smoke has high content of several toxic agents such as carbon monoxide, ammonia, hydrogen cyanide, phenol and carcinogenic hydrocarbons.

The other ways of smoking tobacco are clove-flavoured cigarette, various forms of pipes (wooden, clay, metal), the hookah (the Hubble bubble or water pipe), cheroots (or chuttas) and dhumtis. Tobacco may be used in raw or as processed mixtures and as a pyrolised form. The raw forms are used with lime and with areca nut (Mawa-smokeless

tobacco). Khaini is a mixture of freshly powdered tobacco and slaked lime; a quid of the mixture

It is kept for hours in the lower gingivolabial sulcus and sucked, which is risk factor for khaini cancer (squamous cell carcinoma of the lower lip). The processed forms, for example zarda, gutkha, and Manipuri tobacco are industrial products. The pyrolised (roasted) forms of tobacco (mishri, bajjar, etc) are used as dentifrice. Oral use of snuff is also practised in specific areas.[19]

2] Spirits: - Consumption of calvados {a pot distilled spirit}

3] Sepsis: - Septic and decayed teeth.

4] Sharp teeth: - Poor oral hygiene, faulty restorations, and ill-fitting dentures.

5] Spices

6] Syphilis

7] Betel quid chewing habit: - The quid consists of a betel leaf wrapped around an areca nut, which is high in tannin, quick lime and tobacco. Oral cancer develops at the site where quid is habitually kept. Smoking along with betel quid chewing enhances the risk of oral cancer by 20 to 30 times.

Fig 5: showing Betel leaves coated with slaked lime and arecnut

8] Snuff dipping and other tobacco products

Fig 6: showing various forms of tobacco consumption

9] Alcohol: Alcohol consumption has a synergistic local effect of dissolving the carcinogen in the sump area of the mouth and a systemic downward effect on the immune system. Alcoholics often have nutritional problems.[20]

10] Industrial chemicals

11] Viruses: Herpes simplex virus and the Human papilloma virus (subtype 16)

12] Immune status: - Immune deficient due to low cell mediated immunity.

13] Genetic factors: - Most sporadic tumours are the result of a multi-step process of accumulated genetic alterations. These alterations affect the epithelial cell behaviour by the loss of chromosomal heterozygosity. This in turn leads to a series of events progressing to the eventual stage of invasive squamous cell carcinoma. The corresponding genetic alterations are reflected in the clinical and microscopic pathology from hyperplasia to invasiveness of the tumour. Overexpression or underexpression of p53, p16 and other genes may predispose to

development of cancer and recurrence following treatment. Overexpression of c-erbB-2 has shown correlation with nodal disease and metastasis and worsened survival.

The syndromes that are characterized by mutagen sensitivity, including Xeroderma pigmentosum, Fanconi's anaemia and Ataxia telangiectasia, have all been associated with oral cavity cancers.[21] Other relevant genetic markers may include inducibility of cytochrome p450 enzyme system.[22]

14] Social status: - Related to social habits and to low socio-economic status

15] Sunlight exposure

16] Cirrhosis of liver

17] Diet

18] Occupation: Employment in textile industries

PRE-MALIGNANT CONDITIONS:

Definition: A morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterparts.

1) **Leukoplakia:**

Definition: It is defined as a clinical white patch in the oral mucosa that cannot be characterized clinically or pathologically as any other disease. (Fig)

Rates of malignant transformation ranges from less than 1% to 17.5%. [23]

Types of Oral Leukoplakia [23]

According to Sugar L and Banoczy J:

1) Leukoplakia simplex – White, homogeneous keratinised lesion, slightly elevated, shows lowest frequency of malignancy.

2) Leukoplakia verrucosa – White, verrucous lesion with wrinkled surface, exhibits the highest rate of association with carcinoma.

3) Leukoplakia erosiva – White, lesion with erythematous areas, erosions, fissures, exhibit the highest rate of association with carcinoma.

According to Pinoborg et al (clinical types):

1) Homogeneous: White patch with a variable appearance, smooth or wrinkled; smooth areas may have small cracks or fissures. It shows lowest frequency of malignancy.

2) Speckled or nodular: White patches with erythematous base or nodular excrescences. It shows highest rate of association with carcinoma.

According to Burkhardt (microscopic types):

1) Plain form, corresponding clinically to leukoplakia simplex.

2) Papillary endophytic, corresponding clinically to verrucous leukoplakia.

3) Papillomatous exophytic, corresponding clinically to erosive leukoplakia.

Proliferative verrucous leukoplakia:

It is high-risk type of leukoplakia. It has a tendency to be extensive or multifocal. Verrucous carcinoma evolves from this form of leukoplakia. They are associated with a high risk for malignant transformation and dysplasia .[23]

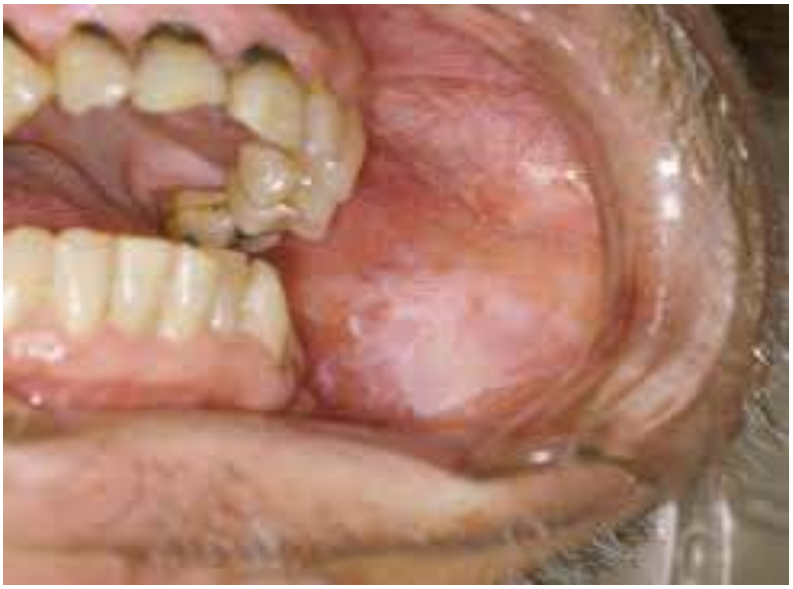


Fig 7: showing leukoplakia over left buccal mucosa

2) Erythroplakia:

These are oral mucosal lesions that appear as red, velvety plaques that cannot be clinically or pathologically ascribed to any other pre-determining condition. About 40-60% of erythroplakia exhibits either carcinoma or severe epithelial dysplasia.

Fig 8: Showing erythroplakia over left buccal mucosa

3) Melanoplakia

4) Oral submucous fibrosis

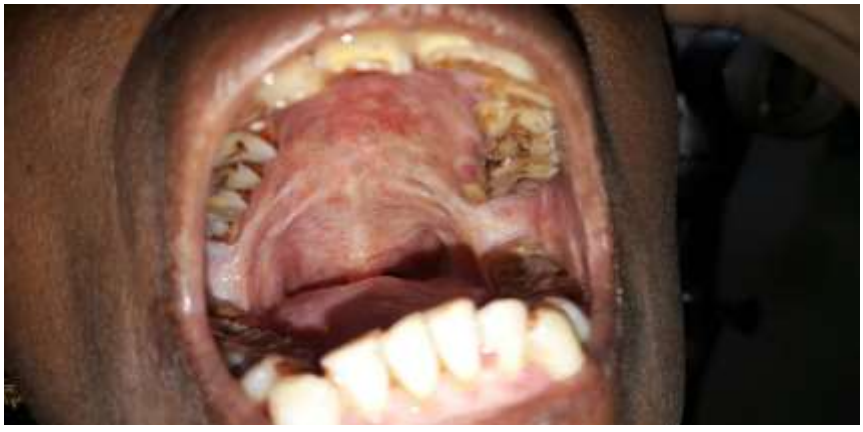


Fig 9: showing oral submucous fibrosis

5) Sideropenic dysphagia

6) Oral lichen planus: Rate of malignant transformation is about 4%. [24]

7) Discoid lupus erythematosis

8) Hyperkeratosis, oesophageal cancer

9) Dyskeratosis congenita

10) Syphilis

MALIGNANT CONDITIONS OF ORAL CAVITY [23]

1. Squamous cell carcinoma: It is the preponderant epithelial malignancy of the oral cavity.

Variants of squamous cell carcinoma:

a) Verrucous carcinoma: It is a low-grade highly well differentiated carcinoma with keratinising exophytic or warty appearance. The cellular response is usually prominent.

b) Sarcomatoid carcinomas/Pseudo sarcoma/Pseudosarcomatous squamous cell carcinomas / pleomorphic carcinoma/metaplastic carcinoma/ epidermoid carcinoma–spindle cell variant

c) Adenosquamous cell carcinoma

d) Adenoid squamous cell carcinoma

e) Basaloid squamous carcinoma

f) Basal cell carcinoma

2. Malignant oral salivary gland tumours[24]

a) Adenoid cystic carcinoma

b) Adenocarcinoma

c) Mucoepidermoid carcinoma

3. Melanoma of oral cavity

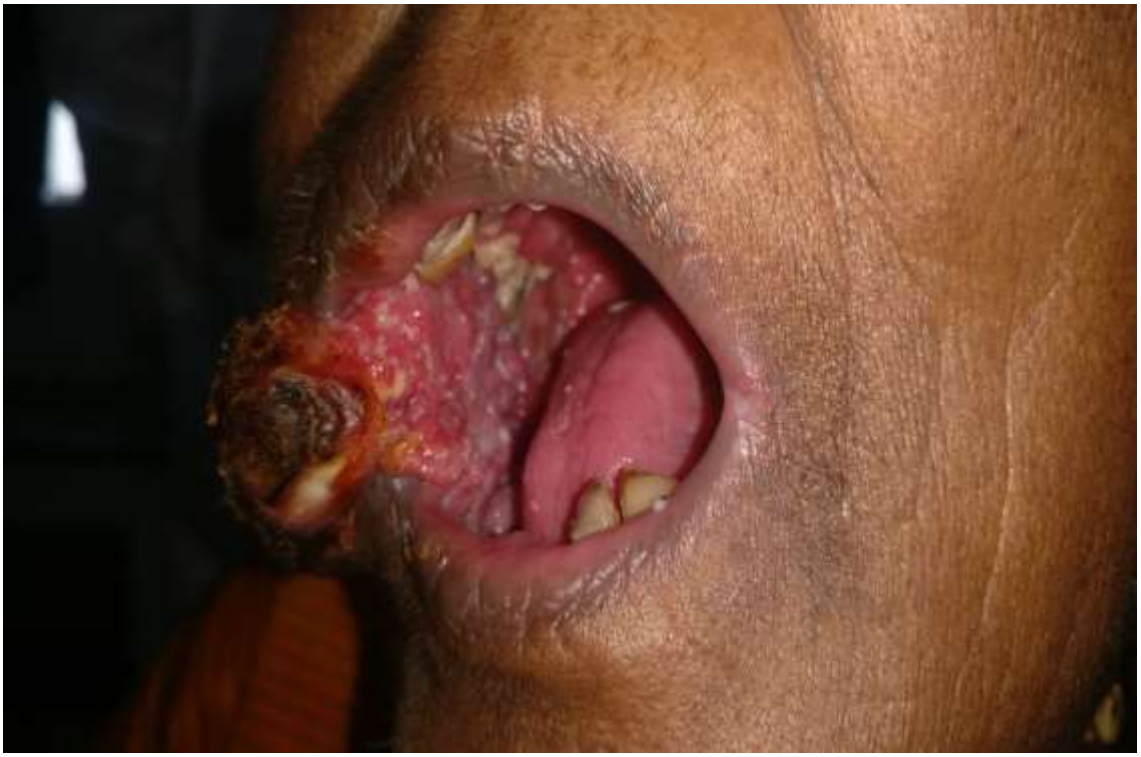


Fig 10: Showing Oral cavity Squamous cell carcinoma

TUMOUR BIOLOGY[25]

The development of a tumour involves three phases:

a) Initiation

b) Promotion

c) Progression

The initiation phase is characterized by the series of mutations that occur in sequence. For initiated cells to become tumour cells, exposures to promoting agents or conditions are required (promotion phase). The end of the promotion phase is marked by the appearance of the first neoplastic cells. Before the appearance of neoplastic cells, the abnormal cells are called preneoplastic or premalignant cells. The progression phase is characterized by invasive growth of the neoplastic cells and progression of the tumour lesion into a metastatic tumour that may eventually kill the host.

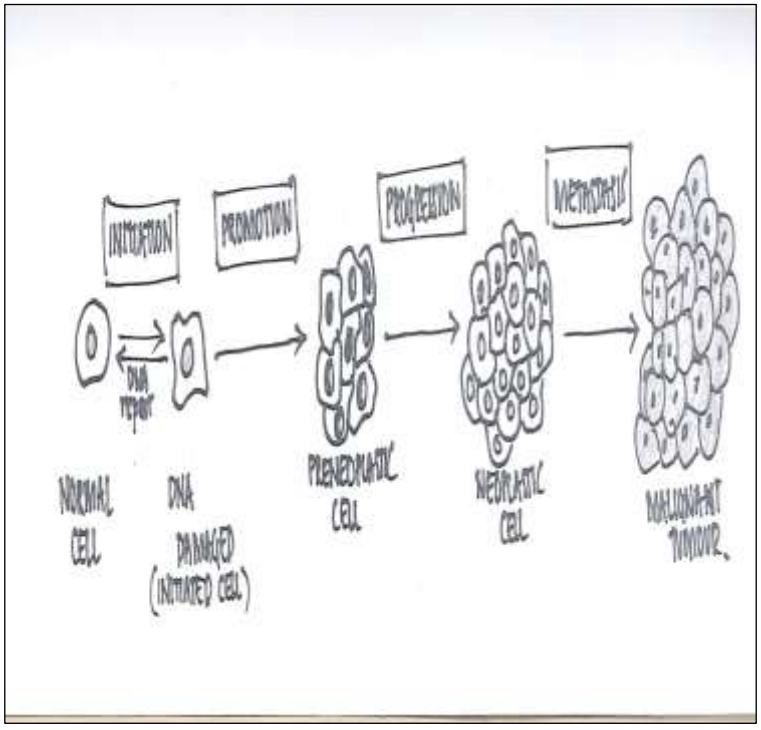


Fig 11: Showing Tumour Biology

TUMOUR ESCAPE MECHANISMS[25]

Tumour related:

a) Tumour is not immunosensitive

1) No expression of tumour-specific antigens

2) No or low expression of major histocompatibility complex molecules correlated with tumour aggressiveness and metastatic potential

3) No antigen processing or presentation (masked/modulated)

4) Resistance to immune cell-mediated killing, such as induction of apoptosis through the apoptosis-inducing molecule F_{as}

b) Tumour is not immunogenic

1) Lack of co-stimulatory molecules, therefore does not induce an immune response

2) Secretion of immunosuppressive factors that inhibit T-cell functions or defect in T cells

3) Shedding of tumour antigens that down regulate T-cell molecules

4) Induction of T-cell tolerance

5) Induction of T-cell apoptosis (programmed cell death)

B) Host related:

1) Tumour grows too fast for the immune system

2) Inherited or acquired immunodeficiency

3) Treatment (radiation, chemotherapeutic drugs) or chemical or physical carcinogens related immunosuppression

4) Deficiency in antigen presentation by antigen-presenting cells

5) Lack of access of effector cells to the tumour

6) Expression of immunodominant antigens on parental tumour that prevents stimulation with other tumour antigens

7) Age- long latent period of carcinogens

- Failure of an antitumour immune response related to age

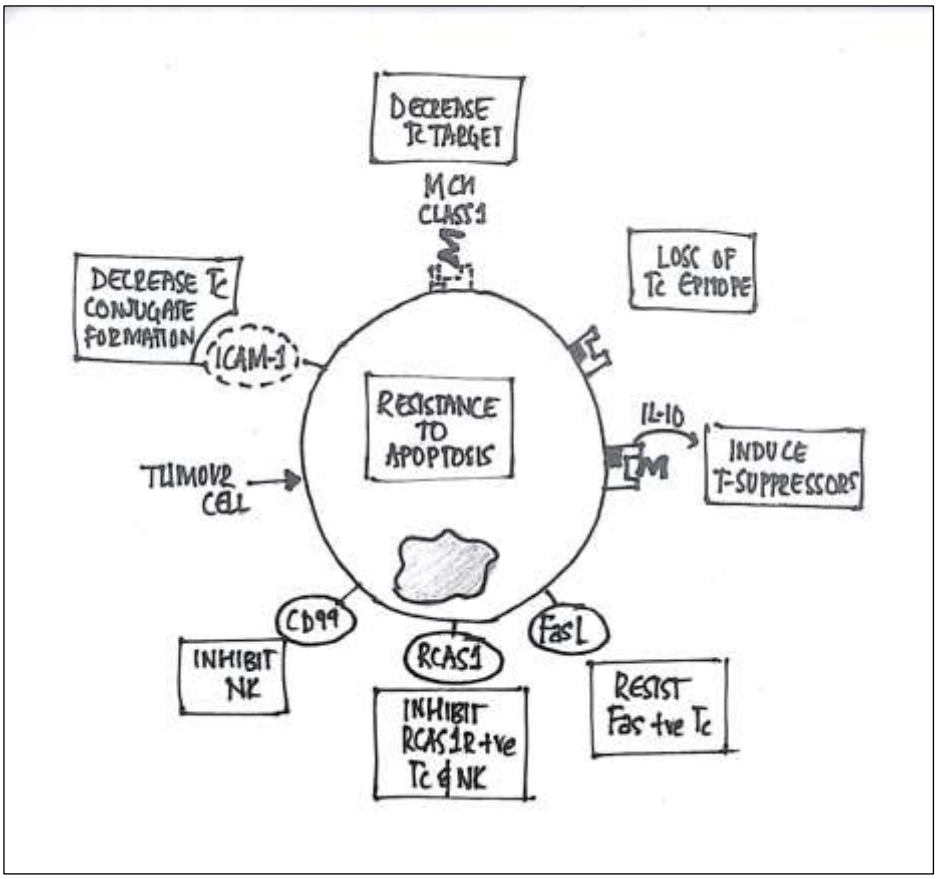


Fig 12: Showing tumour escape mechanism

CARCINOGENESIS[26]

Tumour development represents the loss of the normal signalling mechanisms involved in controlled cell growth.

Loss of cancer cell ability to undergo apoptosis (programmed cell death) allows the accumulation and clonal expansion of cells that otherwise might have died if their cell death machinery were preserved and functional. Tumour growth represents the sum of cell proliferation minus cell death. Carcinogensis involves DNA damage and the progression of mutated cells through the cell cycle called as initiation and promotion.

Around 6-10 independent genetic mutations are required for the development of malignancies in head and neck. Overexpression of mitogenic receptors, loss of tumour suppressor proteins and expression of oncogene-derived proteins that inhibits apoptosis and overexpression of proteins that derive the cell cycle, allow the unregulated cell growth.

Genetic mutation occurs as a result of DNA damages especially 9p, 3p, 11q, 8p, and 17p region. Rate of p53, p16 mutation is greater in smokers, which contributes to oral cancer and shows high incidence of recurrence after any treatment.

REGIONAL LYMPH NODES:

The involvement of the lymph nodes in metastatic deposits is always associated with a worse prognosis, approximately 50% worse than for the patients with equivalent tumours with no lymph node involvement.

It takes 10^{11} cells to produce a mass that is palpable. Due to likelihood of occult nodal metastasis, prophylactic or elective surgical neck dissection is done in oral cancer patients; particularly those involving sites that tend to metastasise early.[20]

Cancer of the lip carries a low metastatic risk and initially involves adjacent submental and submandibular nodes and then the jugular nodes. Similarly, cancers of the hard plate and alveolar ridge have a relatively lesser metastatic potential and typically involve the buccinator, submandibular, jugular and occasionally the retropharyngeal nodes.

Other oral cancers will spread primarily to submandibular and the jugular nodes and very uncommonly to the posterior triangle or to the supraclavicular nodes. Cancer of the anterior oral tongue may spread directly to lower jugular nodes. Disease in the anterior oral cavity may also spread directly to the midcervical lymph nodes.

The closer to midline the primary is, the greater the risk of bilateral cervical nodal spread. Generally, cervical lymph node involvement from oral cavity subsites follow a predictable pattern and usually spreads from the primary tumour to upper cervical nodes, then to the middle cervical nodes, and consequently to the lower cervical nodes.

PATTERN OF CERVICAL LYMPH NODE METASTASIS

The capacity for metastatic spread can be regarded as the single most important characteristic feature of a malignant tumour. The first step in the metastatic process is breach of the basement membrane at the site of primary tumour. This occurs through hydrolytic enzymes secreted by tumour like the urokinase type plasminogen activator, collagenase and stereomelysins.[27] The enzymes degrade the basement membrane proteins such as collagen IV, laminin and proteoglycans, which allow the spread of tumour cells.[28]

The lymphatic spread provides the main mode of spread beyond the primary site of origin for squamous cell carcinoma of head and neck region. The tumour cells disseminate as emboli through the lymphatic system. The tumour emboli are carried to the afferent lymphatic vessels of first level of lymph nodes. The tumour cells then localize first in the subcapsular sinus then progressively grow to replace the cortex and medulla. Eventually tumour invades the capsule of the node heralding extra capsular spread.[28] The extra capsular spread may occur in much smaller lymph nodes where tumour emboli first lodge in the capsular lymphatic sinuses and focal destruction of capsular collagen by type I Collagenase.

As the first level of lymph nodes is replaced by metastatic tumour, afferent lymph flow is deflected carrying tumour cells to the second and third level of nodes. Increasing obstruction in the lymphatics and intranodal sinuses eventually may lead to reversal of lymphatic flow and retrograde spread of tumour cells to unpredictable nodal groups.

Lympho-hematogenous spread can occur by tumour cells invading blood vessels within the lymph node or by invading small lymphatico-venous communication. Once the tumour cells arrive at draining lymph node, they can proliferate, die, remain dormant or enter the blood circulation through blood vessels in the node. The pattern of lymphatic spread follows a predictable pattern. In general, well-localized tumours spread to ipsilateral first or

second echelon lymph nodes. The tumour at or near midline may spread to both sides of neck.

The patients with clinically positive nodes in the ipsilateral neck are at risk for contralateral lymph node metastasis. This shunting occurs mainly through anastomotic channels decussating in the midline at the submental and submandibular triangles.

The Lindberg study defined the nodal groups at most risk for each primary and the pattern of subclinical microscopic metastasis follows a similar distribution.[29]Carcinoma located anteriorly within the oral cavity spreads most commonly to the submental and submandibular lymph nodes, followed by the upper jugular nodes. The posteriorly located oral carcinoma is more likely to spread to the upper jugular nodes and less frequently spread to the submandibular nodes. Shah reported a comprehensive histopathological study, which confirmed Lindberg's clinical findings.[30] The level I, II and III were at highest risk for metastasis from oral cavity cancer. Thus first echelon of lymph nodes for oral cavity lies in level I, II and III.

The incidence of lymph node metastasis that can be detected clinically is about 60%.[29] The overall incidence of occult metastasis in patients with clinically negative neck node is around 30%.[31] The relative risk of nodal metastasis depends on site, size, thickness, histological features and the immunological and biological factors of the primary tumour.[28] Poorer the differentiation the more likely the tumour metastasise early. The tumour with infiltrative margin is more likely to metastasise than those with pushing margin.

The following table describes the lymph node levels and the nodes that are at greatest risk of harbouring metastases from different primary sites.[32]

Lymph node group	Primary site
Level 1A	Floor of mouth, anterior 2/3 tongue, anterior part of mandibular ridge, lower lip.
Level 1B	Oral cavity, anterior nasal cavity, soft tissue of the mid face, submandibular gland.
Level II	Oral cavity, Anterior Nasal cavity, Nasopharynx, Oropharynx, Hypo pharynx, Supra glottic larynx, Parotid.
Level III	Oral cavity especially tongue, Nasopharynx, Oropharynx, Hypo pharynx, Supra glottic larynx, thyroid
Level IV	Hypopharynx, Thyroid, Larynx, Cervical oesophagus.
Level V	Nasopharynx, Oropharynx, Cutaneous structures of the posterior scalp and neck.
Level VI	Thyroid gland, Glottic and subglottic Larynx, apex of Pyriform fossa, Cervical oesophagus.

Table 1: Shows nodal levels that are at greatest risk of harbouring metastases from different primary sites

EVALUVATION OF CERVICAL LYMPH NODES

A proper evaluation of cervical lymph nodes is important as it influences the staging of the disease, the choice of treatment modality and functional outcome. The assessment of cervical lymph nodes depends on history, clinical examination and radiology.

History should include symptoms of upper aero digestive dysfunction. Social history should contain a detailed history regarding alcohol and tobacco consumption. Clinical examination remains the most important method of assessing regional lymph nodes. Physical examination should include careful inspection of the mucosal surface of oral cavity, Oropharynx, indirect laryngoscopy, posterior rhinoscopy and palpation of the neck.

The neck palpation should be from behind the patient using both hands for palpation. Each side of the neck should be palpated separately. The sequential examination starts first from submental and submandibular triangles. Then the neck anterior to sternocleidomastoid is palpated from above downward, till clavicle, along the supraclavicular fossa and upwards along the anterior border of Trapezius. In addition the parotid region, the posterior auricular region, the facial nodes should also be examined. Some nodes in the neck are difficult to palpate. The retropharyngeal and Para pharyngeal nodes are almost impossible to detect unless they are very large. The patients with short neck are more difficult to examine for staging. Area deep to sternomastoid should be given special attention and must be palpated by insinuating the fingers below the muscle.

The transverse process of the atlas, the carotid bifurcation and the submandibular salivary gland are some structures in the neck which may be mistaken for enlarged lymph

nodes. In addition, the lymph nodes may be enlarged due to infection causing reactive hyperplasia rather than a metastatic deposit[33].

The clinical examination of the neck has a variable reliability. Ali and co-workers, in their review of 266 specimens from radical neck dissections found a false positive rate of 20% and false negative rate of 21 %[34].

Clinically the lymph nodes bigger than 1cm in areas like submandibular and submental become palpable whereas lymph nodes in other deeper parts of the neck are palpable when they attain a size of 1.5 cm

Ultrasonography (USG) is more sensitive than clinical examination in detecting metastatic nodes. Malignant nodes show a heterogeneous appearance with a solid and cystic image, round shape, clustering and speckled calcifications on USG. This investigation will also demonstrate the relationship of metastatic nodes to major vessels in the neck[35]. In indicated cases Colour Doppler can be used.

FNAC is helpful in the assessment of palpable node in the evaluation of a patient with an unknown primary tumour. The nature of histology may help in the search for primary tumour. In the case of a clinically palpable node in the presence of proven primary disease, FNAC may not be sufficiently reliable.

Ultrasound guided FNAC (USG-FNAC) is gaining popularity because the borderline lymph nodes cannot be reliably scored on ultrasound, Computerized tomography (CT) or Magnetic resonance imaging (MRI). USG-FNAC proved to be a quick (10-20 min) and safe

(no complications) method. Although some reports of seedling of tumour cells along the needle tract are present, this is a rare finding and has never occurred with thin aspiration needle[32].

Aspiration can be obtained from the lymph nodes as small as 5 mm[36]. It has been shown that USG-FNAC has a very high specificity (100%) and sensitivity (73%)[37]. The specificity and sensitivity of USG - FNAC is better than CT or MR imaging. The sensitivity of USG- FNAC can be enhanced by P53 mutational assays[35]. Another technique to increase the accuracy of USG- FNAC is to select the sentinel node for aspiration. The sentinel node is the first site for metastases. The technique involves injecting around the primary tumour site with TC-99m labelled sulphur colloid. The localization of the sentinel node is performed by planner scintigraphy and gamma probe. Dye technique is easier to perform and is also fairly effective but not as sensitive as radioisotope study.

Computerized tomography scan (CT scan) is more accurate than clinical examination in detecting metastatic lymph nodes. It is particularly important in the necks that are difficult to examine, for restaging and for inaccessible areas such as retropharyngeal space. The rapid advances in imaging technology have enhanced the ability to identify the metastatic disease in head and neck. CT and MRI have significantly improved the accuracy of detecting occult metastasis.

C.T. Scan criteria to define a node as metastatic node includes[33]:

1. Spherical lymph nodes
2. Peripheral enhancement
3. Central necrosis (Low attenuation areas)

4. Clustering of three or more lymph nodes.

5. Scattered calcification.

6. Area of Drainage.

MRI has similar accuracy rates as CT scan. MRI differentiates nodes from surrounding tissues rather more clearly than CT scan[33]. However, limitations of CT and MRI in the assessment of small lymph node and inability to ascertain with confidence the presence or absence of metastases in any one lymph node makes CT and MRI not universally acceptable.

The metastatic nodes can be demonstrated with radio isotopes like Gallium Citrate, technetium labelled DMSA. These agents do not label normal lymph nodes. But all these investigations suffer from a low sensitivity and specificity and inability to detect nodes less than 2 cm in size by which time they are usually clinically palpable[38].

Positron Emission Tomography (PET) will assess the metabolic activity of cervical nodes using 18 fluorodeoxyglucose (18 FDG). The role of PET is confined to the detection of the occult primary and in the assessment of residual and recurrent disease following surgery and irradiation[38].

Single Photon Emission Computed Tomography (SPECT) gives three dimensional isotopic images and can detect tumour more than 4 mm in size. Immuno SPECT using TC-99 labelled monoclonal antibodies can detect tumour measuring 2 mm. These techniques depend on the uptake of radionuclide into tumour which is often related to high blood flow which explains overlap in the detection of inflammatory disease. Although the expense of PET

prohibits wide spread usage, these techniques will be used to detect occult recurrences, occult primaries or distant metastases[38]. PET has high incidence of false positive nodes, some of these can be eliminated by PET-CT i.e. superimposition of PET with CTscan. Ideally it has to be done after three months of surgery to reduce the false positive rate because of inflammatory changes following surgery.

DISTANT METASTASIS:

Distant metastasis is a rare clinical presentation, involving less than 10% of patients. The lungs are the commonest sites of distant metastases; skeletal and hepatic metastases occur less often. Mediastinal lymph node metastases are considered distant metastases.

TNM CLASSIFICATION[39]

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 2 cm or less in greatest dimension

T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumour more than 4 cm in greatest dimension

T4a Tumour invades adjacent structures (e.g. through cortical bone, into deep {extrinsic} muscles of tongue {genioglossus, hyoglossus, palatoglossus and styloglossus}, maxillary sinus and skin of face)

T4b Tumour invades masticator space, pterygoid plates, or skull base and /or encases internal carotid artery

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension

N2a Metastasis in a single ipsilateral lymph node more than 3 cm but none more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant metastasis (M)

MX Distant metastasis cannot be assessed

MO No distant metastasis

M1 Distant metastasis

Histological Grade (G)

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

Residual tumour(R)

Rx Presence of residual tumour cannot be assessed

Ro No residual tumour

R1 Microscopic residual tumour

R2 Macroscopic residual tumour

Stage grouping:

Stage 0	T0	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV A	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IV B	Any T	N3	M0
	T4b	Any N	M0
Stage IV C	Any T	Any N	M1

Table 2: showing AJCC staging of oral cavity squamous cell carcinoma

We have used the 7th edition of AJCC guidelines to stage our patients n this study, as the 8th edition will only be in effect from 2018.

THERAPEUTIC MODALITIES FOR ORAL CANCER [2, 31]

The factors that influence the choice of initial treatment are those related to the characteristics of the primary tumour (tumour factors), those related to the patients (patient's factors) and those related to the treatment delivery team (physician factors).

PHYSICIAN FACTORS: -

- Surgery
- Radiotherapy
- Chemotherapy
- Combined modality treatment
- Dental
- Rehabilitation services
- Prosthetics
- Support services
- Photodynamic therapy
- Immunotherapy
- Gene therapy

Most therapies other than surgery are not known to be effective against large tumours. Therefore, the most promising results may be obtained with therapy of non-metastatic tumours in an adjuvant setting after surgical removal of the primary tumour.

TUMOUR FACTORS:

- Site
- Size (T stage)
- Location (anterior versus posterior)
- Proximity to bone (mandible)
- Lymph node metastasis

- Previous treatment

- Histology (type, grade, depth of invasion)

PATIENT FACTORS:

- Age

- General medical condition

- Tolerance

- Occupation

- Acceptance and compliance with regards to treatment

- Life style (smoking, drinking, tobacco chewing)

- Socio-economic consideration

TREATMENT OF CERVICAL METASTASIS

The presence of cervical lymph node metastases has an adverse effect on survival. At the same time, careful and effective treatment can provide a cure in a significant number of patients with node positive neck. In the untreated neck, the patterns of spread are often predictable. Once patient has had previous radiotherapy or surgery or infection, drainage patterns are often altered. Hence, although the neck may be clinically negative (N_0) all five levels in the neck should be treated by surgery or radiotherapy. In patients with palpable neck disease (N_1, N_2, N_3), non-palpable spread may be present anywhere in the neck and correct approach for such patients is to completely encompass the disease i.e. full neck dissection. This usually involves surgery, although radiotherapy may have a place for small N_1 (less than 3 cm) node[38].

The primary goal in the treatment of patients with head and neck cancer is control of the disease. However, with increasing recognition of the substantial morbidity of radical surgical treatment, more emphasis is being placed on surgical conservatism if it does not negatively impact disease control and if it offers improved post treatment function and cosmesis. The evolution of neck dissection is representative of this trend. Radical neck dissection (RND), first described by Crile[40] in 1906, has served as the gold standard method of managing cervical metastases in patients with head and neck cancer for most of the century.

RND accomplishes en bloc removal of all cervical lymphatic contents believed to be involved with or at risk for metastatic disease from head and neck malignancy and includes removal of the sternocleidomastoid muscle, internal jugular vein, submandibular gland, and spinal accessory nerve.

This operation produces substantial postoperative morbidity from cosmetic and functional standpoints, with typical shoulder dysfunction seen after this surgery. With time, surgeons have challenged the necessity of such radical neck surgery and have explored the feasibility of modifications to it.

Evolution of neck dissection

A. 1906 - The en bloc cervical lymphadenectomy known as the RND was developed by Crile.

1. Spinal accessory and hypoglossal were preserved
2. IJV removed

B. Blair and Brown encourage the removal of the SAN.

C. 1945 - Dargent and Papillon advocate the preservation of the SAN in clinically N_0 necks.

D. 1950 - Martin popularizes the RND explaining that "Any technique that is designed to preserve the SAN should be condemned unequivocally."

E. 1963 - Suarez indicates that based on his necropsy specimens which had lymphatics only within the fibro fatty tissues, a complete cervical Lymphadenectomy could be accomplished while sparing the Sternocleidomastoid muscle, the IJV, and the SAN.

F. 1967 - 1980 Bocca and Pignataro popularize Suarez's version of neck dissection and coined the terms functional, conservative, and conservation neck dissection.

G. 1969 - 1981 Roy and Beahrs, Carenfelt and Eliasson proposed the Preservation of CN XI in clinically positive necks.

H. 1972 Lindberg's classic study indicates consistent patterns of Lymphatic drainage for carcinomas in various locations of the upper Aero-digestive tract.

I. 1990 - Shah's work confirms that of Lindberg's in a review of over 1000 neck dissection specimens.

J. 1986 - 1991 Byers, Medina, and Spiro report their results with Selective neck dissection**.**

The rationale for such modifications is based on the finding that modified radical neck dissection results in improved postoperative shoulder function and on the realization that neck recurrence is still a significant problem despite the extensiveness of radical neck dissection. Improved understanding of lymph node drainage patterns[30,41] and fascial compartments of the neck and better understanding of the indications for adjuvant postoperative radiation therapy have given further impetus to the trend away from the routine use of radical neck dissection in all patients.

CLASSIFICATION OF NECK DISSECTION

A. Comprehensive neck dissections - includes the radical neck dissection and three modifications, but always refers to a procedure in which all of groups I - V are removed.

1. Radical neck dissection

Involves the removal of all lymphatics from the inferior border of the mandible and line joining angle of the mandible to the mastoid tip, to the clavicle between the lateral border

of the sternohyoid and the anterior border of the Trapezius. The deep margin of resection is the fascial carpet of the scalene muscles and the levator scapulae. The sternocleidomastoid, the internal jugular vein, and the spinal accessory nerve are removed with the specimen. Traditionally, this was the only surgical method of treating the neck but with the development of the more limited, less morbid modifications this is no longer indicated in the N_0 neck. Many surgeons no longer advocate this approach in N+ necks unless the metastatic nodes involve the muscle, vein, or nerve.

2. Modified Radical Neck Dissection

Based on the work of Suarez as well as that of Bocca and Pignataro it indicates that an en bloc removal of the cervical lymphatics can be accomplished by stripping the fascia from the Sternocleidomastoid and internal jugular vein. No lymphatic communication was ever noted between these structures and the cervical lymphatics. These studies point out that both the spinal accessory and the hypoglossal nerve do not follow the aponeurotic compartments, but rather run across them; however, their conclusion was that if the tumor did not directly involve the nerves, they could be spared. From the above information and a desire to minimize the shoulder dysfunction associated with spinal accessory nerve sacrifice came the development of the modified radical neck dissection.

3. Type I Modified Radical Neck Dissection

Accomplishes the removal of the same regions of lymphatics as in the radical neck dissection, but the spinal accessory nerve is spared. It is used less commonly in the N_0 neck, but would be a reasonable choice with neck disease that involved the Sternocleidomastoid or jugular vein without involving the spinal accessory nerve.

4. Type II Modified Radical Neck dissection

Involves the same dissection as in the radical neck, but the spinal Accessory nerve and internal jugular vein are spared. It is indicated in N+ necks with metastatic involvement of the Sternocleidomastoid, but without involvement of the nerve and vein.

5. Type III Modified Radical Neck dissection - "Functional Neck Dissection"

It is similar to the radical neck dissection with preservation of all three above mentioned non lymphatic structures. The indications for this procedure are controversial. In Europe, this operation is popular in the treatment of hypo pharyngeal and laryngeal tumors with N_0 neck. Molinari, Lingeman, and Gavilan propose this procedure for N_1 necks when the involved nodes are mobile and no greater than 2.5 to 3cm. Bocca proposes this operation for any neck that has indications for a radical neck dissection as long as the nodes are not fixed.

B. Selective Neck Dissections

This type of dissection arose from the work of Shah, Lindberg and Byers who identified the pathways of lymphatic spread in the head and neck. Only those regions with high risk for metastasis are removed.

Types of selective neck dissection:

a. Supraomohyoid (anterolateral) neck dissection

Levels I, II, and III are removed sparing the Sternocleidomastoid, IJV, and CNXI. This is indicated in the treatment of oral cavity lesions.

b. Lateral neck dissection

Levels II, III, and IV are removed sparing the Sternocleidomastoid, IJV, and CNXI. This is indicated in tumors of the larynx, Oropharynx, and hypopharynx when the neck is N_0, although some advocate this approach with the N_1 neck with nodes limited to level II.

c. Posterolateral neck dissection

Levels II, III, IV, and V are removed sparing the Sternocleidomastoid, IJV, and CNXI. This is useful in the treatment of skin tumors with metastatic potential located in the posterior scalp or neck such as melanomas, squamous cell carcinomas, and Merkel cell carcinomas.

C. Extended neck dissections - describes any of the above dissections that include the removal of additional structures or other groups of lymph nodes.

Selective neck dissection (SND), which involves selective removal of nodal groups most at risk for metastasis with preservation of all nonlymphatic structures, has gradually gained acceptance in the clinically N_0 neck and has demonstrated regional control and survival rates similar to those of more extensive neck dissections[42].

Although SND has been accepted by many as appropriate for use in the clinically node-negative neck, its use in patients with clinically obvious (palpable) metastatic disease remains extremely controversial; however, extension of the indications for its use in this setting seems logical. In the absence of factors that would alter normal lymphatic flow in the neck, such as previous neck surgery, radiotherapy, or the presence of massive obstructive adenopathy, the rationale behind the operation, which like its more radical counterpart seeks to remove the lymph nodes involved by or at risk for involvement by head and neck cancer, remains valid.

The present classification of MRND does not classify it as types 1 and 2 but only names the non-lymphatic structures spared.

Elective neck dissection: This is the neck dissection done in N_0 cases where metastasis is expected.

Elective Selective neck dissection: This is done as a staging procedure e.g.; Supraomohyoid neck dissection.

Tumour thickness, Depth of invasion, site and Lymph node ratio

Cervical lymph nodal metastasis has a significant impact on the prognosis in patients with carcinomas of the head and neck. The presence of cervical lymph-node metastasis is considered as a strong determinant of survival in patients with squamous cell carcinoma of the oral cavity (OSCC). Lymph node metastasis reduces the survival by almost 50%. The frequency of lymphatic spread of squamous cell carcinoma is very high and even patients with no palpable lymph nodes have occult metastasis. The incidence of occult lymph-node metastasis in early-stage tumors (primary site T-categorization T1 or T2) has been reported to be between 27% and 40%.[43,44]

Level I was the most common site for nodal metastases (100%), followed by level II (32%), level III (16%), and level IV (8%).[45] Though there are multimodality treatment options, the prognosis is usually poor. The presence of occult lymph node metastasis of oral tongue followed by buccal carcinoma, is observed more often than in any other cancer of the oral cavity.[46] Literature shows an overall 5-year survival rate of 65%, even though the tumour stage distribution remained the same compared to the preceding 10-year period.[47] Survival was better related to a more aggressive treatment of the neck even in early tumor stages and to adjuvant radiotherapy in advanced tumor stages.

The presence of extra capsular spread reduces the chances of cure by 50%. As mentioned earlier the site, size, differentiation of tumor, perineural invasion, perivascular invasion, inflammatory response, and DNA content predicts aggressiveness of cervical lymph node metastasis.[48]

Tumour thickness is defined as the vertical extent of the tumour from point of maximum projection to maximum infiltration in a perpendicular fashion. It was Breslow, who established a strong link between tumor thickness (TT) and both tumor-free survival and metastasis in patients with cutaneous melanoma.[49]

Following Breslow's hypothesis, Other authors demonstrated the relationship between lymph-node involvement and tumour thickness to oral cavity malignancy.[50,51] Since then, many studies have been carried out to test this relationship. These studies have shown that tumour thickness is an important predictor for lymph-node involvement in OSCC. Many authors have also found that the thickness of the tumour correlates better with survival and involvement of the lymph nodes than does its superficial diameter.[52-54].

However later studies showed that the exophytic growth of the tumour should not be considered, as it does not represent the overcoming of tissue resistance, whereas the space left by the ulcerated tumour should be included, because it represents tissue destroyed by the downwards growth of the tumour.[55]As a result, Tumour depth was introduced as a better predictive marker for lymph node metastasis.

Tumour depth is defined as the infiltrative portion of the tumour which extend below the surface of mucosa.[55]

Primary tumour thickness and depth of invasion have been used as a predictor for lymph node metastasis in oral tongue cancer. Depth of tumour invasion is considered as an independent predictor tor cervical lymph node metastasis. Infiltration depth was defined as the maximum depth of tumour infiltration (millimetres) below the mucosal surface. In case of ulcerated or exophytic tumours, the reconstructed mucosal surface was used.[56]

In a metaanalysis by Pentenero et al, where over 50 studies were included, comparing depth of invasion and tumour thickness in predicting nodal involvement and prognosis in oral squamous cell carcinoma, depth of invasion proved to be a better predictor of cervical metastasis and overall prognosis.[57]Depth of invasion is known to be a better predictor for nodal status, because it compensates for exophytic growth or tissue destruction by the tumour.[58,59] Also studies have shown that tumour located more towards the midline ie lower

alveolus, floor of mouth and tongue, showed a higher tendency to throw cervical metastasis.[2,4,30]

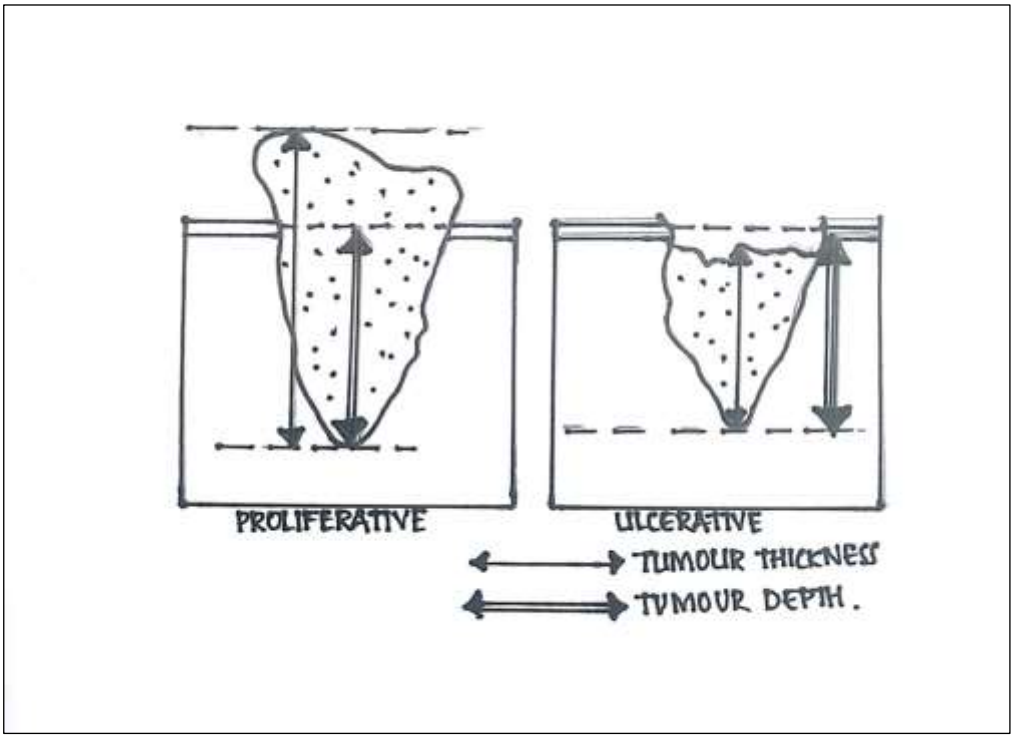


Fig 13: Showing tumour thickness and tumour depth

Therefore, Literature review shows that , cervical lymph node metastasis is the single most prognostically important factor in the management of patients with oral cavity squamous cell carcinoma and that factors such as primary site and depth of invasion of tumour are best predictors of nodal metastasis.

These patients are at a higher risk for locoregional recurrences requiring adjuvant therapy.[60] Because adjuvant therapy may induce severe toxic effects, a significant challenge is to find a reliable method to help identify such high risk patients immediately post surgery.

But identification of metastatic positive lymph nodes is based on both the quality of neck dissection (ie nodal yield- number of total nodes/neck specimen) by the surgeon and

level of scrutiny by the pathologist. As both poor neck dissection or failure to identify positive nodes could possibly downstage the disease.

Thus Lymph node ratio was introduced to address this issue. This ratio attempts to compensate for the potential bias of the sampling method by utilizing two information components, ie the regional spread of the disease (number of positive nodes) and the surgical treatment (total number of nodes removed during surgery)[5]

Lymph node ratio is defined as the total number of positive lymph nodes divided by the total nodal yield irrespective of whether patient undergoes unilateral or bilateral neck dissection.[60]

The lymph node ratio evaluates three factors that can potentially affect nodal staging: (1) tumour factors (number of positive lymph nodes), (2) surgical factors (total number of nodes removed during neck dissection) and (3) sampling factors (the efficacy of the pathological analysis).

Lymph node ratio has already been documented to be of significant prognostic importance (ie adjuvant or alternative to pN staging) in gastric[61], breast[62], prostrate[63] esophageal[64], colorectal[65] and bladder[66]cancers. In these malignancies, Lymph node ratio has been demonstrated to be an independent prognostic factor and predictor of overall survival.

However its significance in oral cavity malignancies has only been studied recently. In patients with primary oral cavity squamous cell cancer, lymph node ratio was found to be a significant indicator of overall survival, disease specific interval, regional recurrence and distant recurrence. Patients shown to be node positive with lymph node ratio <2.5% had similar outcomes to patients who were considered node negative.[67-69]

In another study, patients with oral cavity squamous cell carcinoma a lymph nodal ratio less than 6% had a higher survival rate (47% 5 year survival) when compared to patients with a nodal ratio of 6%-12.5% (37.5% 5 year survival) and patients with nodal ratio of

>12.5% (29.2% 5 year survival rate). Therefore as lymph nodal ratio increases prognosis and survival decreases.[69]

Multiple studies have shown that increasing lymph node ratio, was associated with higher risk of locoregional spread and decreased overall survival rate.[67-74]

Patients with metastatic lymph node ratio of more than 4% had a 2.7 fold increases risk of recurrences.[69-73]Increased association was seen between increasing lymph node ratio and regional and distant failure[69-71]. Thus, Lymph node ratio could play an important role in us identifying those patients who are at higher risk for local and regional recurrence and take decision so as to provide adjuvant treatment modalities.

In the current literature, there are multiple retrospective studies correlating primary site and depth of invasion of oral cavity squamous cell carcinoma to cervical lymph node metastasis and correlating lymph node ratio to that of prognosis. However there is paucity in literature regarding the correlation between primary site and depth of tumour with Lymph node ratio.

Therefore, in our prospective observational study, we aim to establish a correlation between primary site and depth of tumour in oral cavity squamous cell carcinoma to that of lymph node ratio and correlate the obtained Lymph node ratio to patient outcomes.

RECONSTRUCTION[75]

Oromandibular reconstruction continues to be one of the most challenging areas of head and neck reconstruction. Reconstruction of resulting defect can be done by the following methods:

1. Split thickness skin grafts

   Full thickness skin grafts
2. Mucous membrane flaps
3. Tongue flaps
   a. Posteriorly based lateral tongue flap
   b. Posteriorly based bilateral tongue flap
   c. Anteriorly based ventral tongue flap
4. Masseter flap
5. Nasolabial flap
6. Medial based deltopectoral flaps
7. Forehead flap
8. Sternocleidomastoid myocutaneous flap
9. Trapezius
10. Platysma myocutaneous flap
11. Pectoralis major myocutaneous flap
12. Latissimus myocutaneous flap
13. Costochondral grafts
14. Osteomyocutaneous flap- fifth rib with pectoralis major myocutaneous flap

    -Spine of scapula with trapezius

15. Free osteocutaneous groin flap
16. Free osteocutaneous fibula flap
17. Scapular Osseocutaneous flap
18. Radial forearm flap
19. Radial forearm free osteocutaneous flap
20. Free fibula and osseointegrated implants

Whenever possible, immediate single stage reconstruction is preferred over delayed reconstruction, when the former can be achieved with acceptable success rates and low morbidity. Immediate restoration of the mandible prevents the development of muscle contracture and restores mandibular form. Delayed reconstruction interferes with the radiotherapy and later healing.

The bone to mucosa relationship of the periosteum of the alveolar ridge and gingival mucosa is most difficult to duplicate and is necessary for wearing dentures. Preservation of chewing, provision of a base for dental appliances and preservation of a normal appearing lower third of the face are achieved by preservation of the buccal sulcus and the oral floor, which are all essential reasons for maintenance or restoration of the mandibular contour.

QUALITY OF LIFE:

The surgical resection of tumours involving the oral cavity has been associated with significant destruction of normal anatomy, functional deficits and suboptimal reconstruction.

Historically, disease free survival, overall survival and tumour response rates were the traditional outcome measures used to judge efficacy of treatment. Although these traditional outcomes have been helpful to clinicians, they affect some of the most basic functions of life. Despite the most aggressive treatment regimens, there has been little change in overall survival rates for patients with head and neck cancer. With this has come a greater awareness of the functional impact of surgical resection on patient's function.

Quality of life is the term used to describe the non-traditional outcome measures of functional status and psychological well-being.

Different dimensions of quality of life

1. Functional status
2. Physical complaints
3. Psychological distress
4. Social interactions

The unique attributes of the head and neck surgery and its role in speech, swallowing and deglutition as well as the cosmetic appearance allows for social interaction. Mandibular resection has always been associated with some of the functional deficits.

Different quality of life scales are used to evaluate functional status in cancer patients. They include:

1) Karnofsky Performance Scale

2) The Sickness Impact Profile

3) The University Of Washington Quality Of Life Scale

4) The Head & Neck Cancer Specific Quality Of Life Instrument[76]

1) Karnofsky Performance Scale:

The AJCC strongly recommends recording of KPS (The Karnofsky Performance Status) along with standard staging information. **David A. Karnofsky** devised KPS in 1948, which provides a uniform, reliable and objective assessment of an individual's functional status.

Karnofsky Scale: Criteria of Performance Status (PS)

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Able to carry on normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most of own needs.
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance

Diagnosis and treatment of depression also aid in symptom control and improved quality of life.

MATERIALS & METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

72 patients undergoing surgery for oral cavity squamous cell carcinoma (Stage III and IVa) admitted under Department of Otorhinolaryngology and Head and Neck Surgery of R L JALAPPA HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR from December 2015 till June 2017 were included in this prospective observational study.

SAMPLE SIZE:

Sample size of 72 cases of oral cavity cancers undergoing surgery was obtained based on the nodal ratio standard deviation in a study done in 2010.[71]

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

r = Ratio of control to cases, 1 for equal number of case and control
p^* = Average proportion exposed = proportion of exposed cases + proportion of control exposed/2
Z_β = Standard normal variate for power = for 80% power it is 0.84 and for 90% value is 1.28. Researcher has to select power for the study.
$Z_{\alpha/2}$ = Standard normal variate for level of significance as mentioned in previous section.
$p_1 - p_2$ = Effect size or different in proportion expected based on previous studies. p_1 is proportion in cases and p_2 is proportion in control.

N=Za2 (SD) 2/d2 d=5%, SD= 21.5, Za=1.96

Confidence interval= 95%

TYPE OF STUDY:

Descriptive observational Study

METHODS OF COLLECTION OF DATA:

72 Patients undergoing surgery for Oral cavity squamous cell carcinoma (Stage III and IVa) in Department of Otorhinolaryngology and Head and Neck Surgery of R L JALAPPA HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR from December 2015 – June 2017 were included in this study.

The following data were obtained for each patient:

a. History
b. Addiction habits
c. Clinical examination
d. Biopsy report
e. Radiological examination
f. Surgery details
g. Histological evaluation
h. Follow up to evaluate oncological outcome, in each group separately

A written informed consent from all the patients, after proper counselling regarding the procedure being performed and the research being done were included in the study.

INCLUSION CRITERIA

All patients diagnosed with Stage III and Stage IVa oral cavity squamous cell carcinoma undergoing surgery.

EXCLUSION CRITERIA

1. All Patients with recurrent tumour.
2. All patients with history of previous neck dissection.
3. All Patients who underwent neoadjuvant chemotherapy/radiotherapy to head and neck region.
4. All patients with N3 disease.
5. All patients in whom <10 lymph nodes were dissected.

METHOD:

72 patients with Stage III and Stage IVa oral cavity squamous cell carcinoma undergoing surgery were included in our study.

Each patient was assessed as follows:

PREOPERATIVE:

- Clinical examination
- Addiction habits
- Associated premalignant condition
- Biopsy
- Contrast enhanced CT of skull base to T4

OPERATIVE:

- Intraoperatively, all patients underwent wide excision of primary tumour along with composite neck dissection (MRND or SOHD) and appropriate reconstruction. Type of neck dissection done was based on

extent of the disease. Neck dissection specimen was tagged for different lymph node levels and send along with wide excision specimen for histopathological examination.

POST OPERATIVE: - Histopathological examination of each specimen was done for: -

- Confirmation of tumour diagnosis
- Grading of tumour
- Histology of the tumour
- Tumour thickness and Depth of tumour invasion
- Lymph node assessment and obtaining lymph node ratio; lymph node ratio is defined as total number of positive lymph nodes/ total number of dissected lymph nodes

Post operatively, all patients received adjuvant therapy when indicated, according to existing National Comprehensive Cancer Network (NCCN) guidelines.

FOLLOW UP: All operated patients were followed up for 6 to 12 months

Clinically for: - Local recurrence --- Ulceration, growth

- Regional recurrence--- Lymphadenopathy
- Distant metastasis
- Second primary cancer
- Functional integrity and cosmetic appearance
- Quality of Life

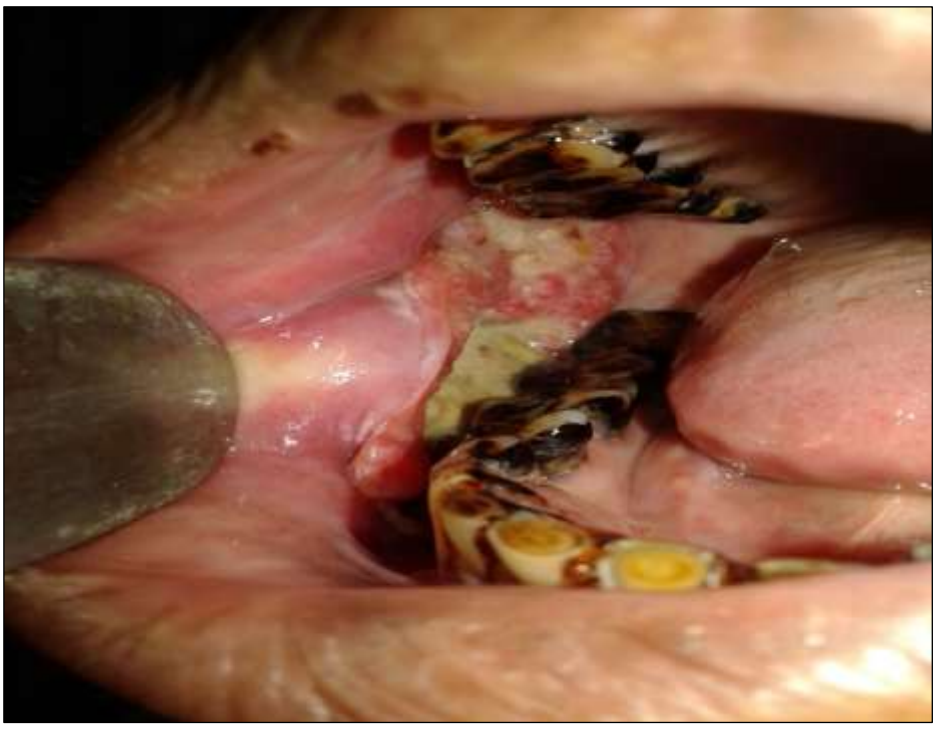


Fig 14: showing lesion involving posterior posterior buccal mucosa

Fig 15: showing lesion involving buccal mucosa and overlying skin

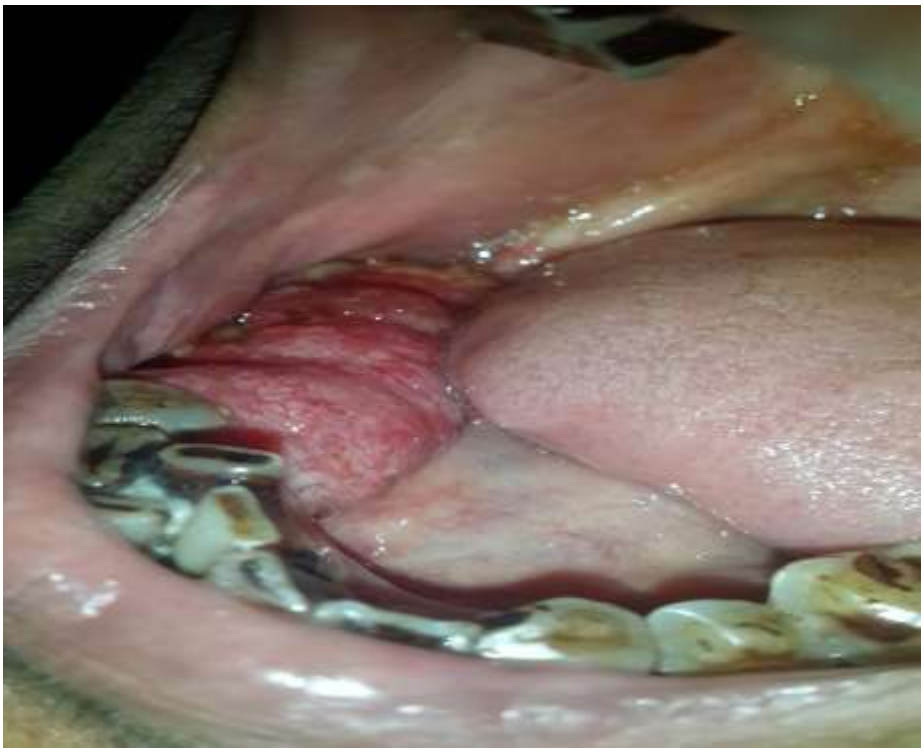


Fig 16: showing lesion involving lower alveolus

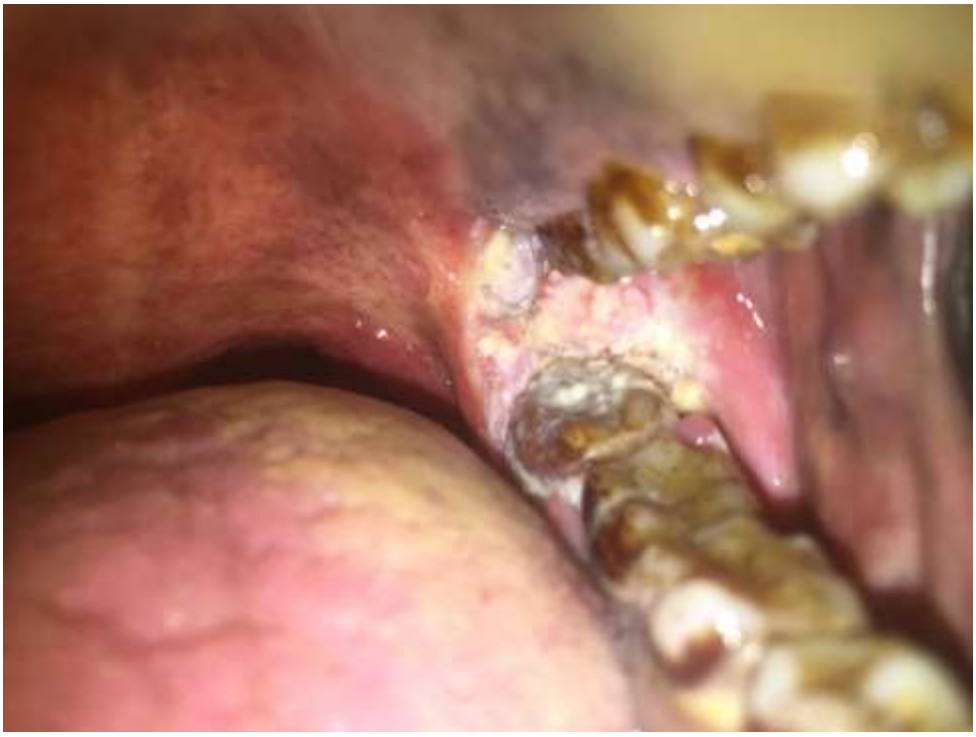


Fig 17: showing lesion involving retromolar trigone

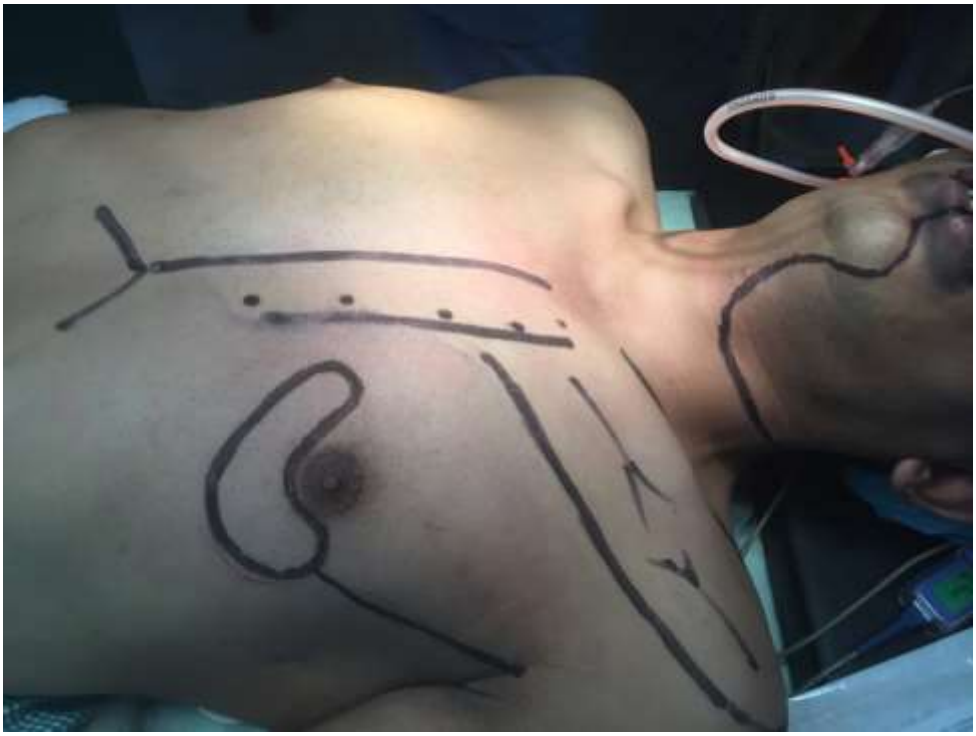


Fig 18: showing preoperative marking for neck dissection and PMMC flap

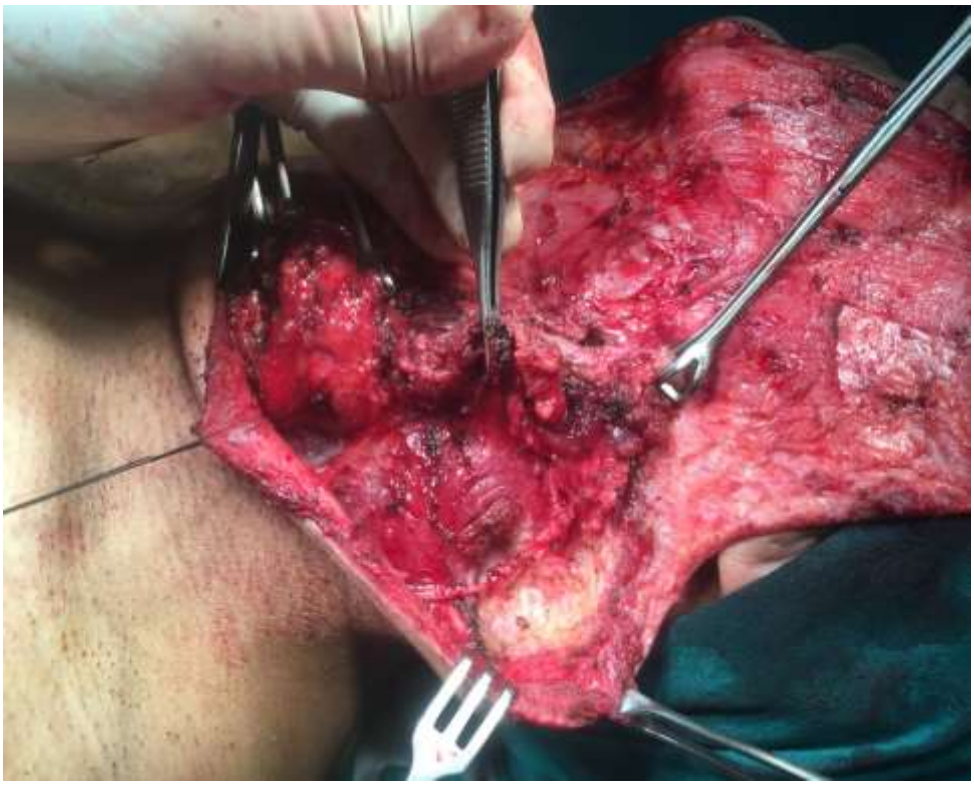


Fig 19: showing neck dissection of level V

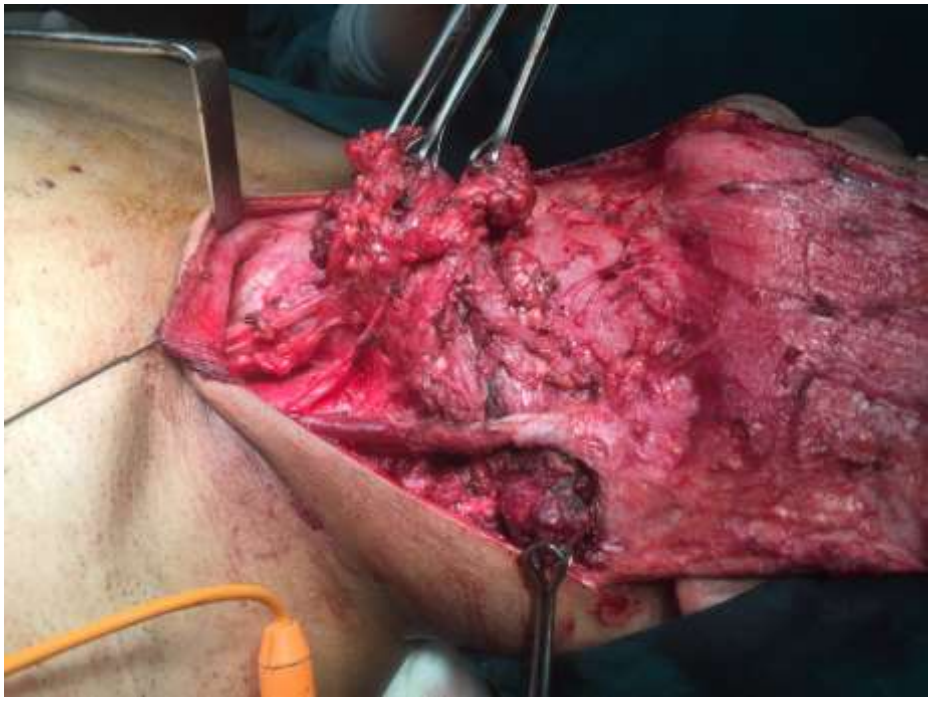


Fig 20: showing dissection of level IV

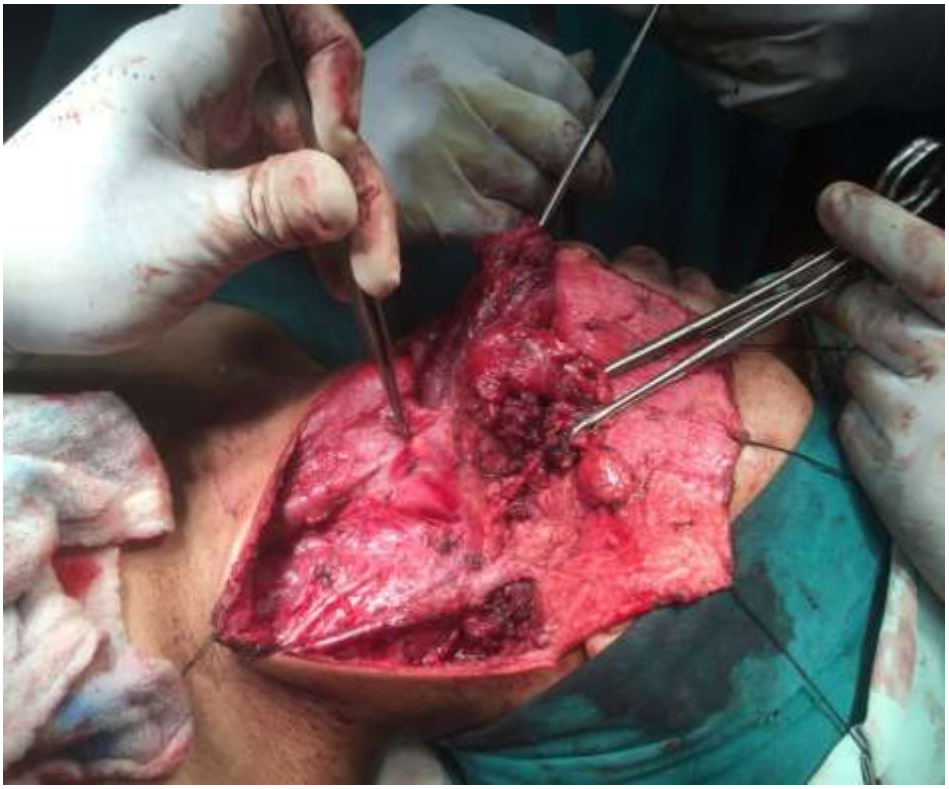


Fig 21: Showing dissection of level III and II

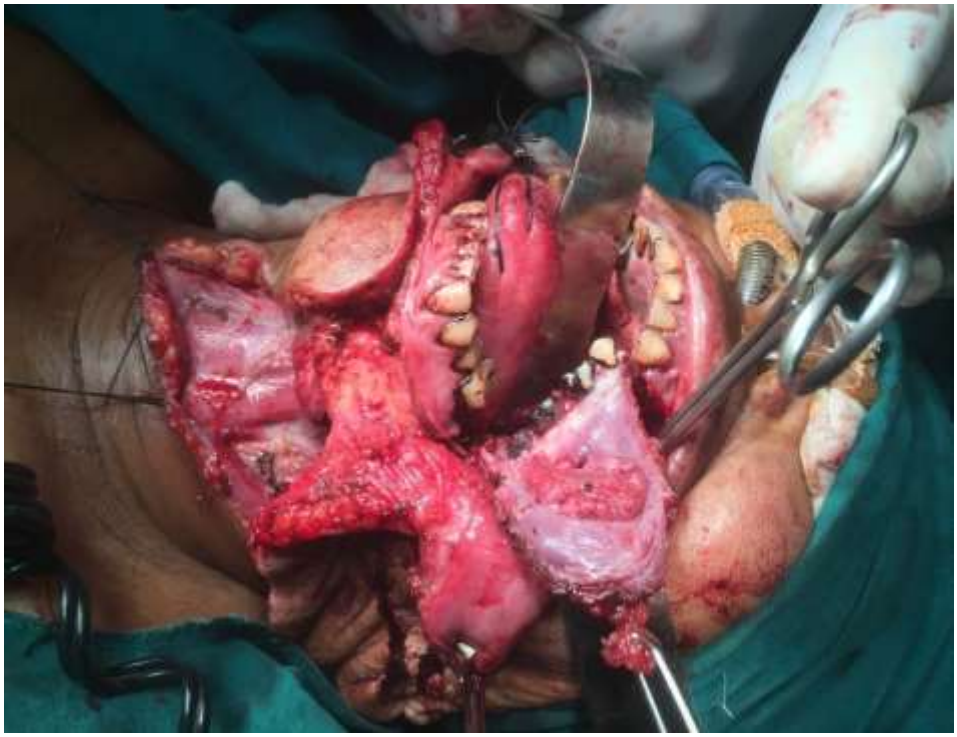


Fig 22: showing wide excision of primary tumour

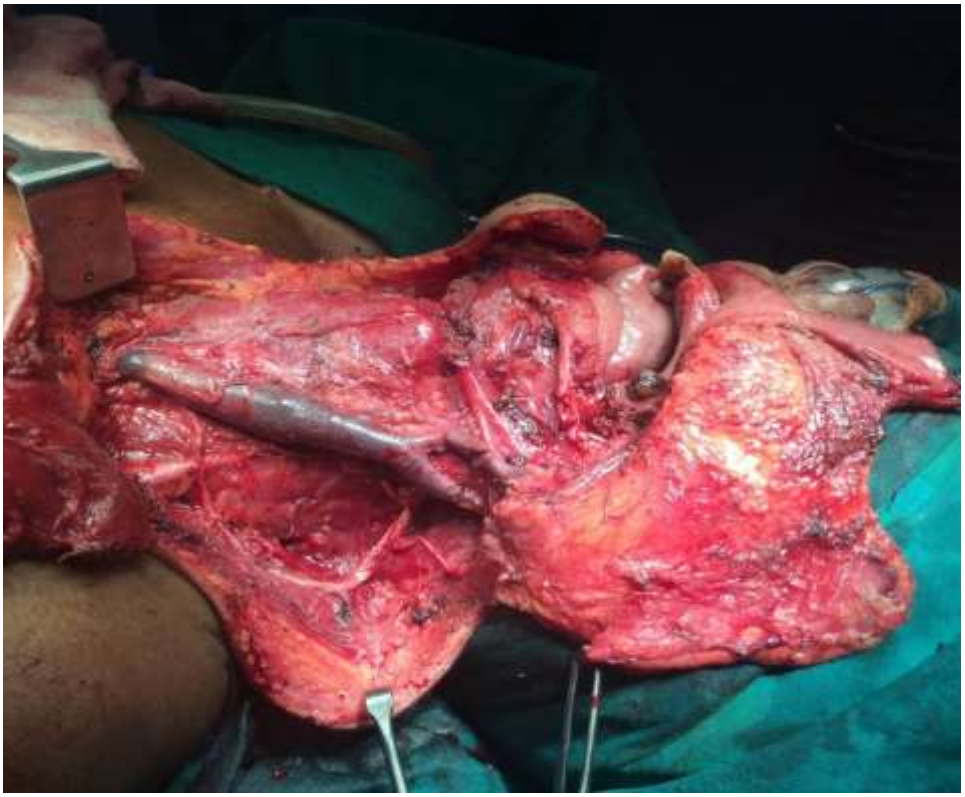


Fig 23: showing post neck dissection and wide excision of primary with hemimandibulectomy

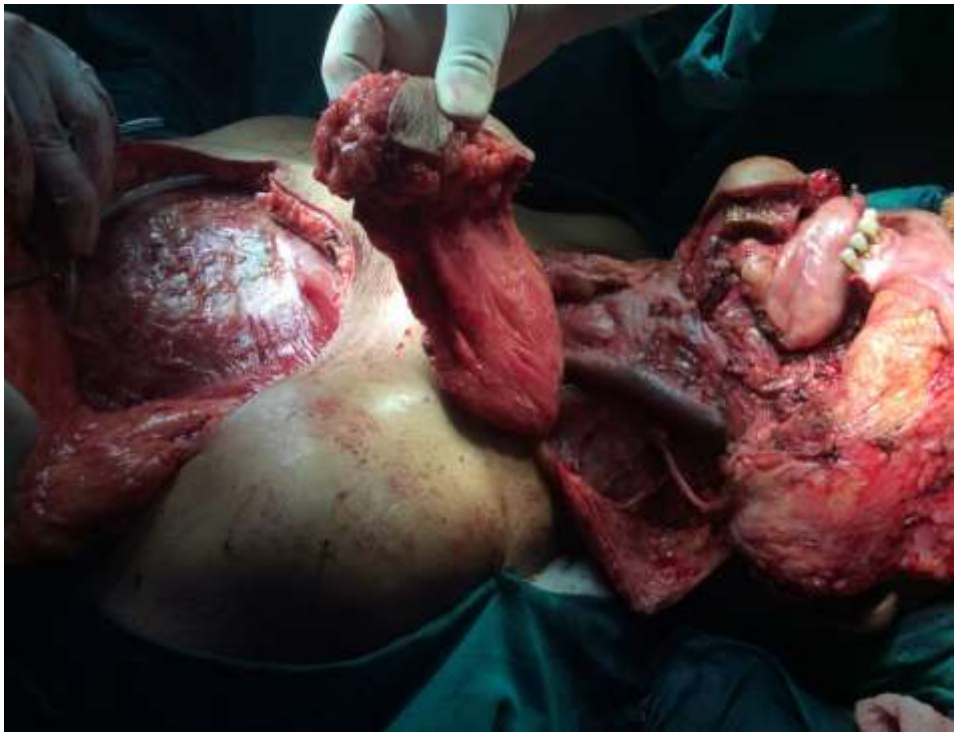


Fig 24: showing harvested PMMC flap for reconstruction

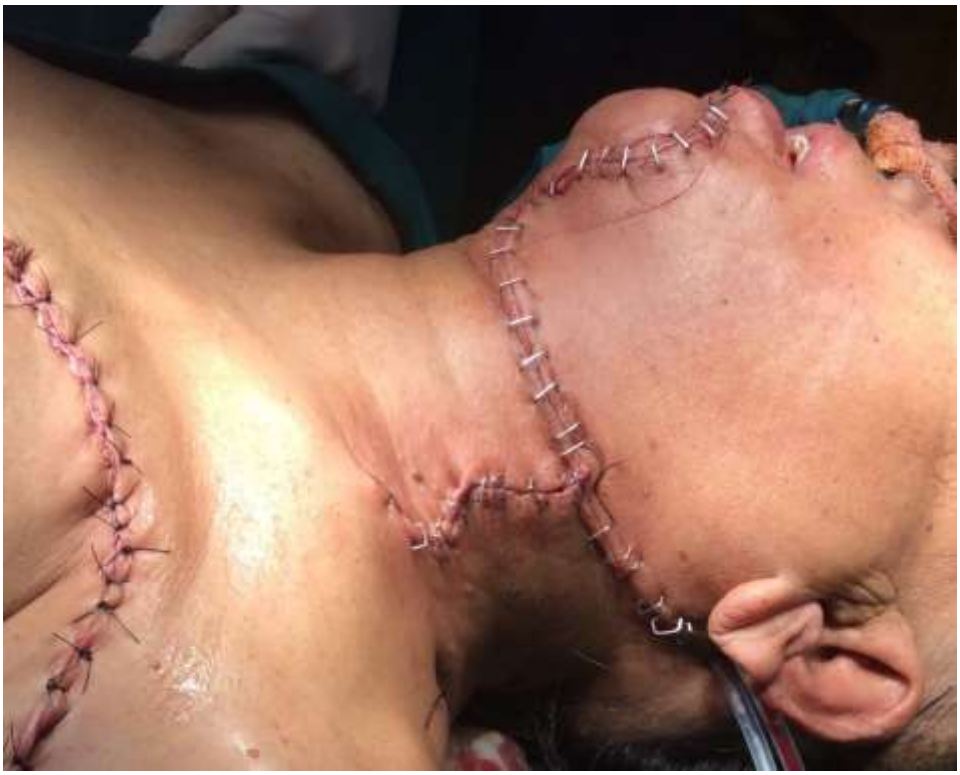


Fig25: showing closure of incision

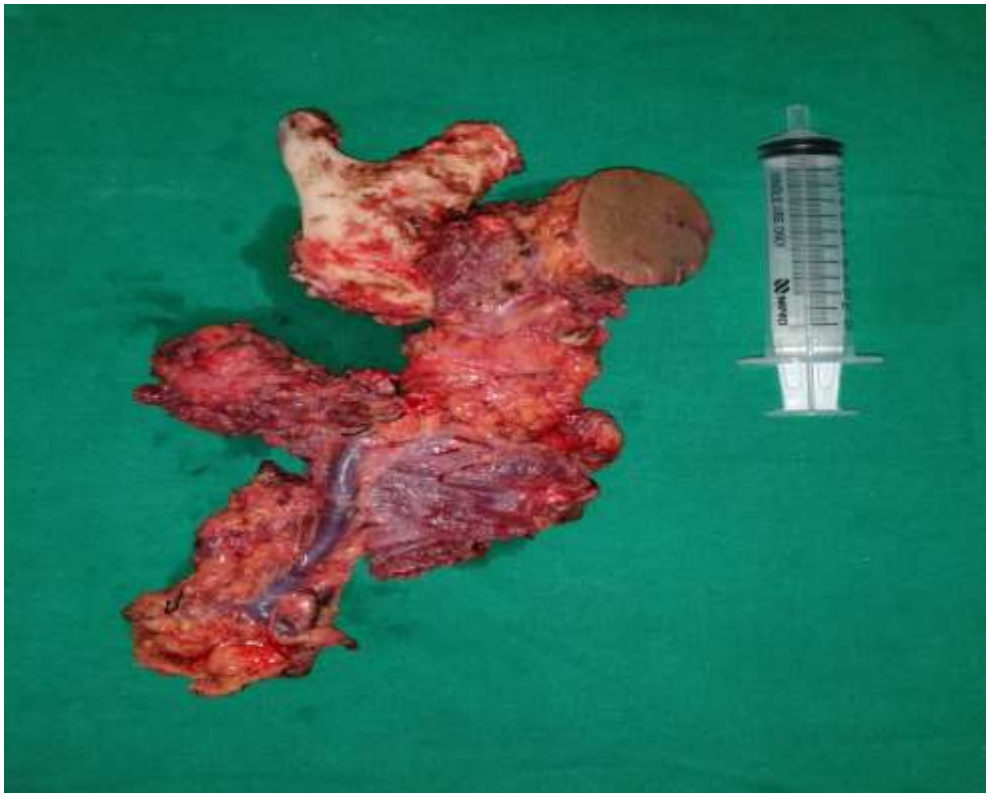


Fig 26: showing specimen of wide excision, hemimandibulectomy, overlying skin along with enbloc neck dissection

Fig 27: showing specimen of wide excision, hemimandibulectomy, overlying skin along with enbloc neck dissection. Primary lesion over gingivobuccal sulcus.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and SD. **Independent t test or Mann Whitney U test** was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. **ANOVA (Analysis of Variance) or Kruskal Wallis test** was the test of significance to identify the mean difference between more than two groups for quantitative and qualitative data respectively.

Pearson correlation was done to find the correlation between two quantitative variables.

Correlation coefficient (r)	Interpretation
0 - 0.3	**Positive Weak correlation**
0.3-0.6	**Positive Moderate correlation**
0.6-1.0	**Positive Strong correlation**
0 to (-0.3)	**Negative Weak correlation**
(-0.3) to (-0.6)	**Negative Moderate Correlation**
(-0.6) to – (1)	**Negative Strong Correlation**

Table 3: Pearson correlation

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

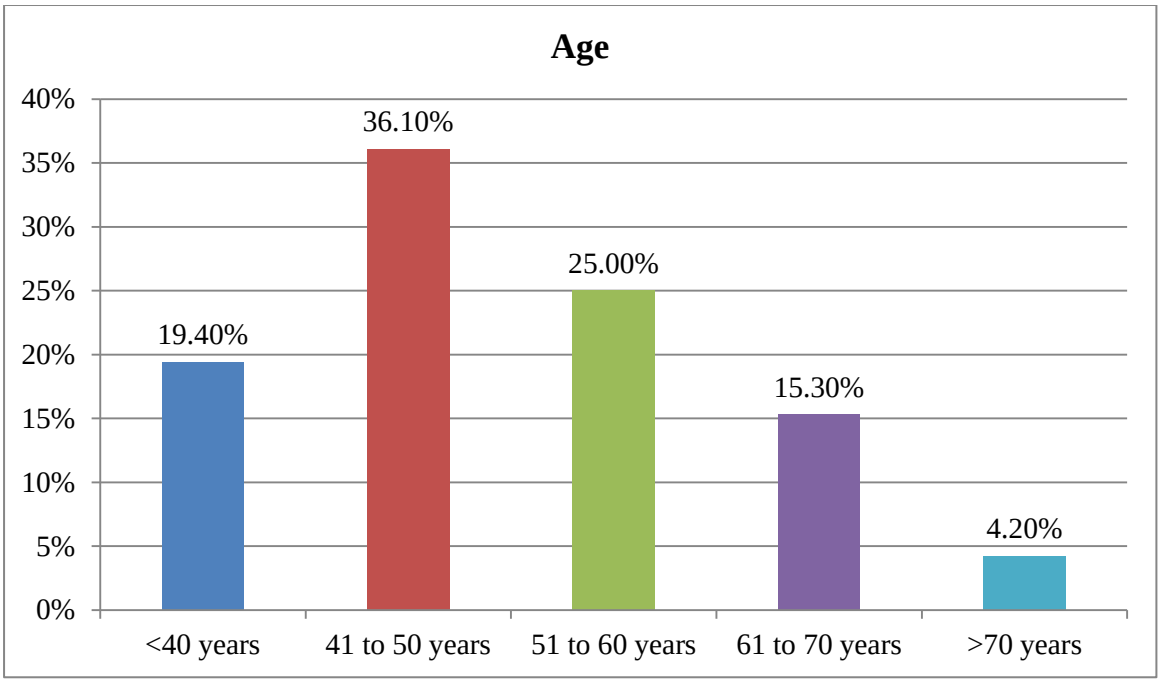
RESULTS

RESULTS:

Table 4: Age distribution of study population

		n=72	%
Age	<40 years	14	19.4%
	41 to 50 years	26	36.1%
	51 to 60 years	18	25.0%
	61 to 70 years	11	15.3%
	>70 years	3	4.2%
	Total	72	100.0%

In the study, majority of subjects were in the age group of 41 to 50 years (36.1%), 25% were in the age group 51 to 60 years, 19.4% were in the age group <40 years, 15.3% were in the age group 61 to 70 years and 4.2% were in the age group >70 years.



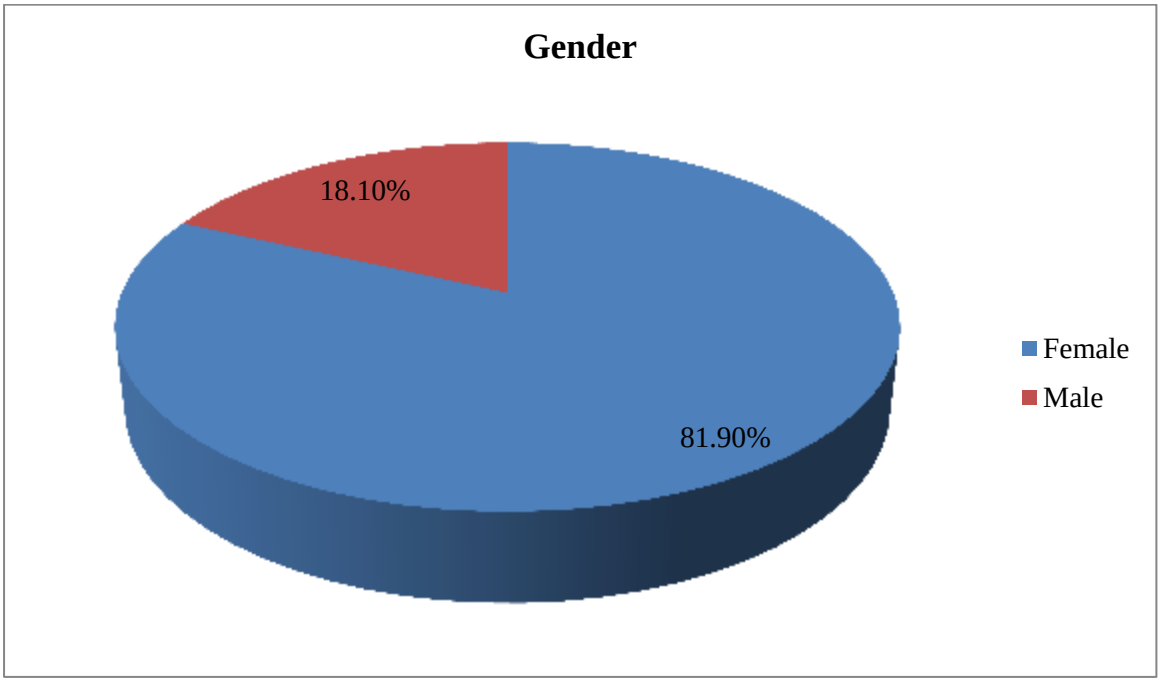
Graph 1: Bar diagram showing Age distribution of study population

Table 5: Gender distribution among subjects

		n=72	%
Gender	Female	59	81.9%
	Male	13	18.1%

In the study, majority of the patients were females (81.9%) and 18.1% were males.

Male:female ratio was 1:5.

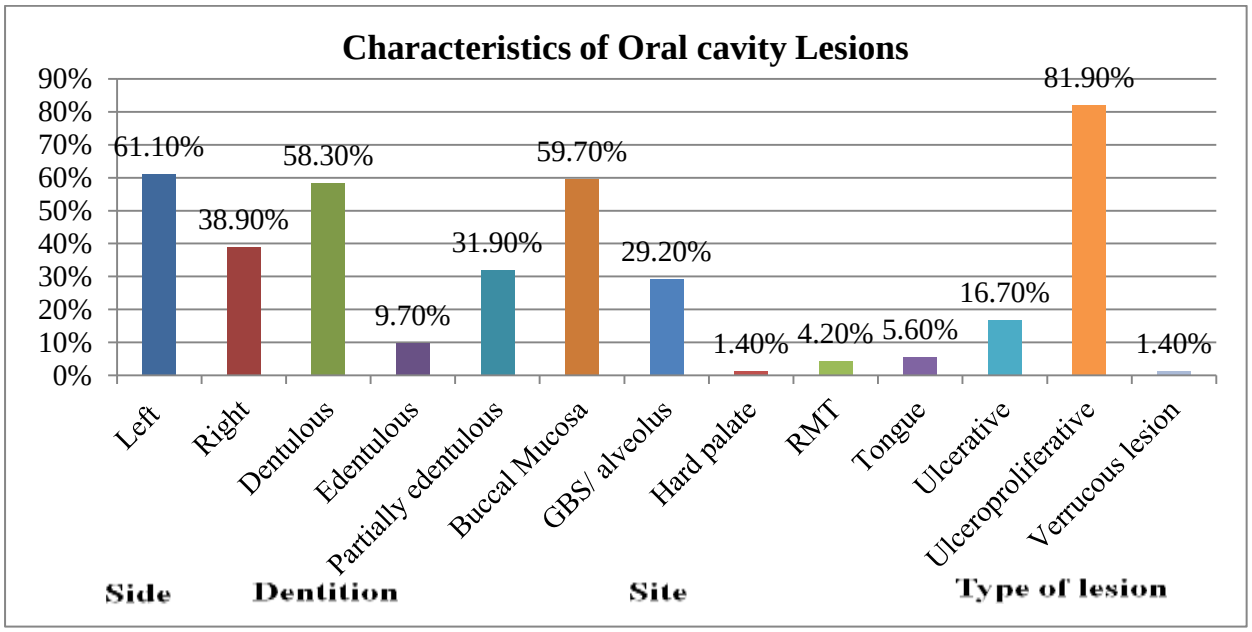


Graph 2: Pie diagram showing Gender distribution among subjects

Table 6: Characteristics of Oral cavity Lesions

		n=72	%
Side	Left	44	61.1%
	Right	28	38.9%
Dentition	Dentulous	42	58.3%
	Edentulous	7	9.7%
	Partially edentulous	23	31.9%
Site	Buccal Mucosa	43	59.7%
	GBS/ alveolus	21	29.2%
	Hard palate	1	1.4%
	RMT	3	4.2%
	Tongue	4	5.6%
Type of lesion	Ulcerative	12	16.7%
	Ulceroproliferative	59	81.9%
	Verrucous lesion	1	1.4%

In our study, 61.1% presented with disease on the left side and 38.9% on right side. 58.3% paitents were dentulous, 9.7% were edentulous and 31.9% were partially edentulous. Most common site of Oral cavity squamous cell carcinomaa was Buccal mucosa in 59.7% followed by 29.2% in GBS/alveolus and 5.6% n anterior 2/3rd of tongue. Ulceroproliferative lesion was the most common type of lesion on presentation seen in 81.9%.

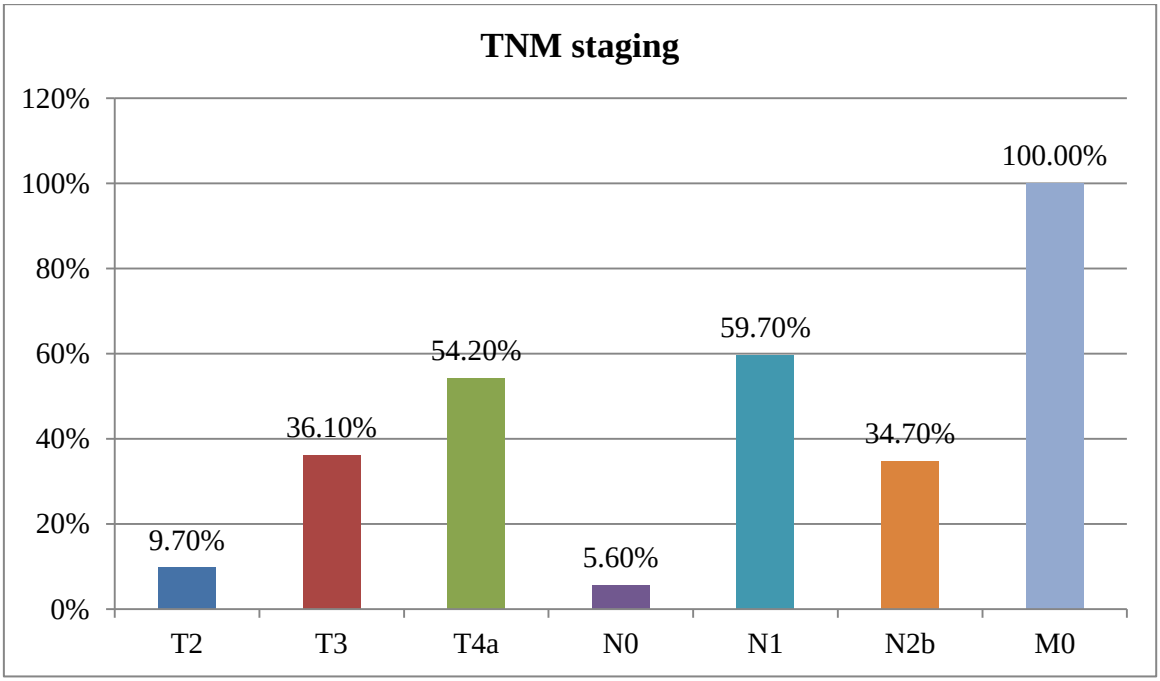


Graph 3: Bar diagram showing Characteristics of Oral cavity Lesions

Table 7: Clinical TNM staging of oral cavity lesions

		n=72	%
T	T2	7	9.7%
	T3	26	36.1%
	T4a	39	54.2%
N	N0	4	5.6%
	N1	43	59.7%
	N2b	25	34.7%
M	M0	72	100.0%

In this study, 9.7% were in T2 stage, 36.1% were in T3 stage and 54.2% were in T4a stage. 5.6% were in N0 stage, 59.7% were in N1 stage and 34.7% were in N2b stage. 100% were in M0 stage.

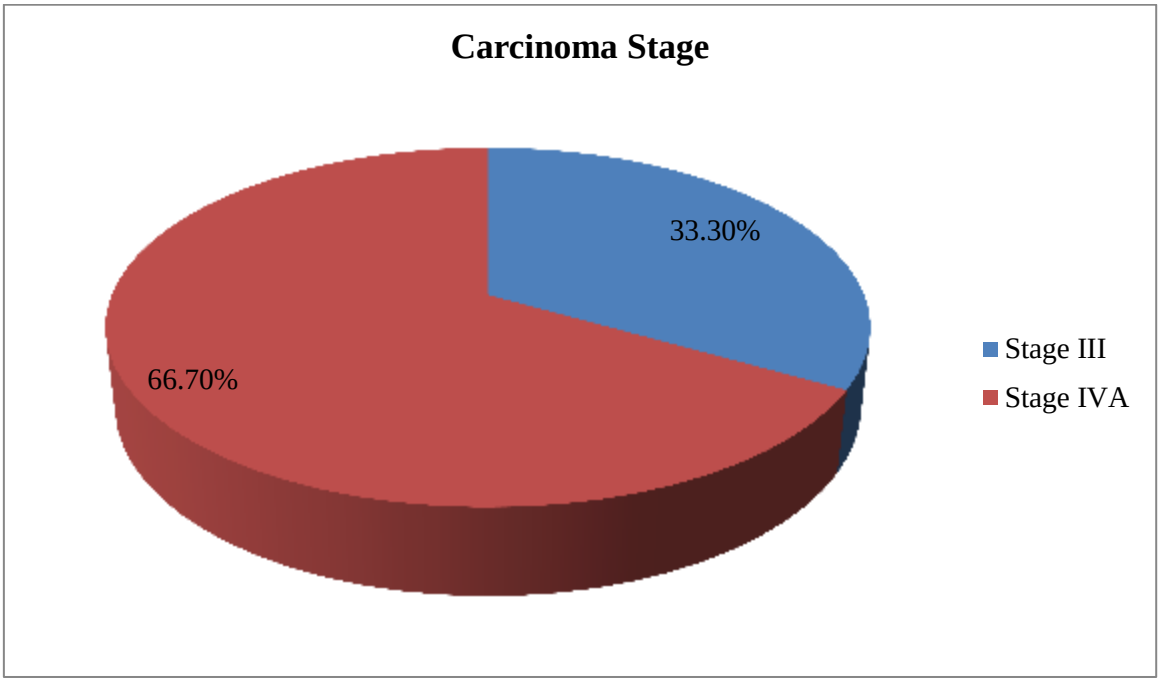


Graph 4: Bar diagram showing clinical TNM staging of oral cavity lesions

Table 8: Carcinoma stage among subjects

		n=72	%
Carcinoma Stage	Stage III	24	33.3%
	Stage IVA	48	66.7%
	Total	72	100.0%

In this study, 33.3% of the patients were in Stage III and 66.7% were in Stage IVA.

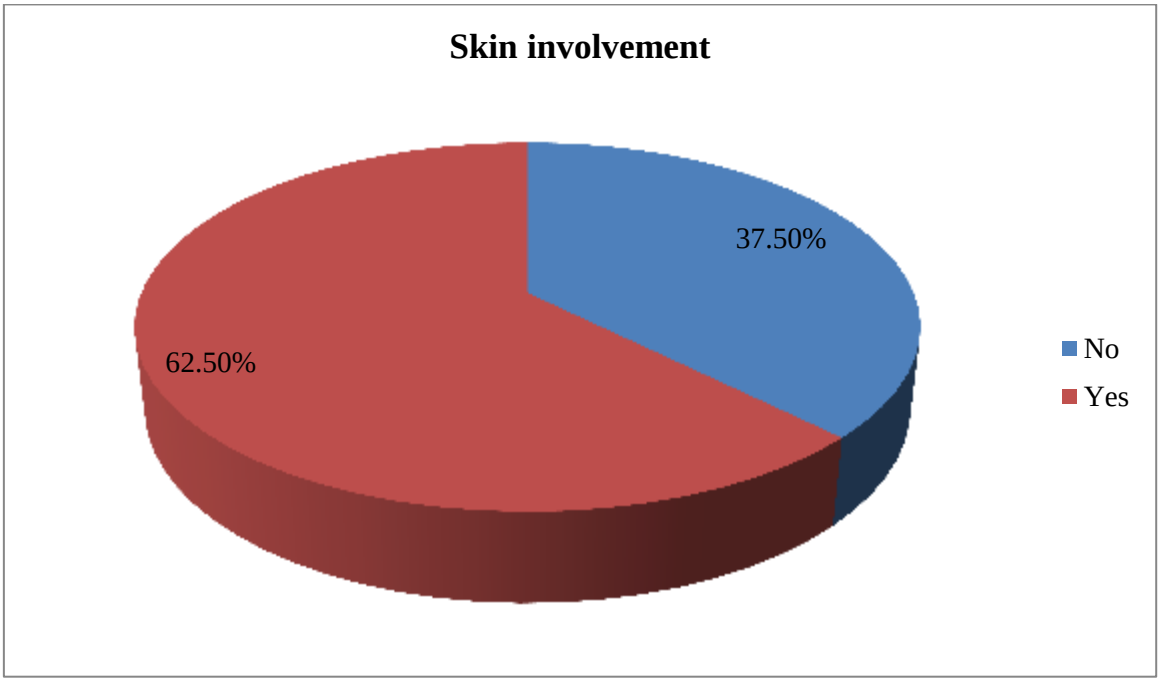


Graph 5: Pie diagram showing Carcinoma stage among subjects

Table 9: Skin Involvement among subjects with stage IV a disease

		n=48	%
Skin involvement	No	18	37.5%
	Yes	30	62.5%

Out of the 48 patients with Stage IVa disease, 30 (62.5%) patients showed skin involvement on clinical examination.

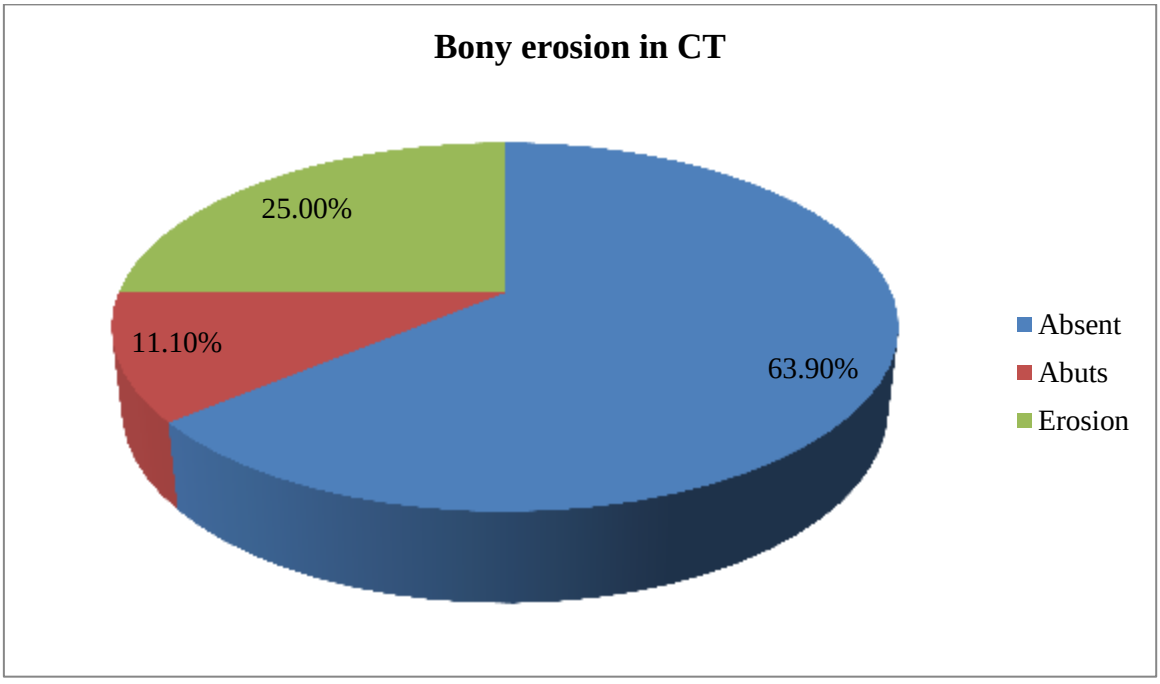


Graph 6: Pie diagram showing Skin Involvement among subjects

Table 10: Bony erosion detected in CT scan

		n=72	%
Bony erosion in CT	Absent	46	63.9%
	Abuts	8	11.1%
	Erosion	18	25.0%

In this study, 18 patients (25%) showed erosion of mandible on CT and 11.1% showed tumour abutting the mandible.

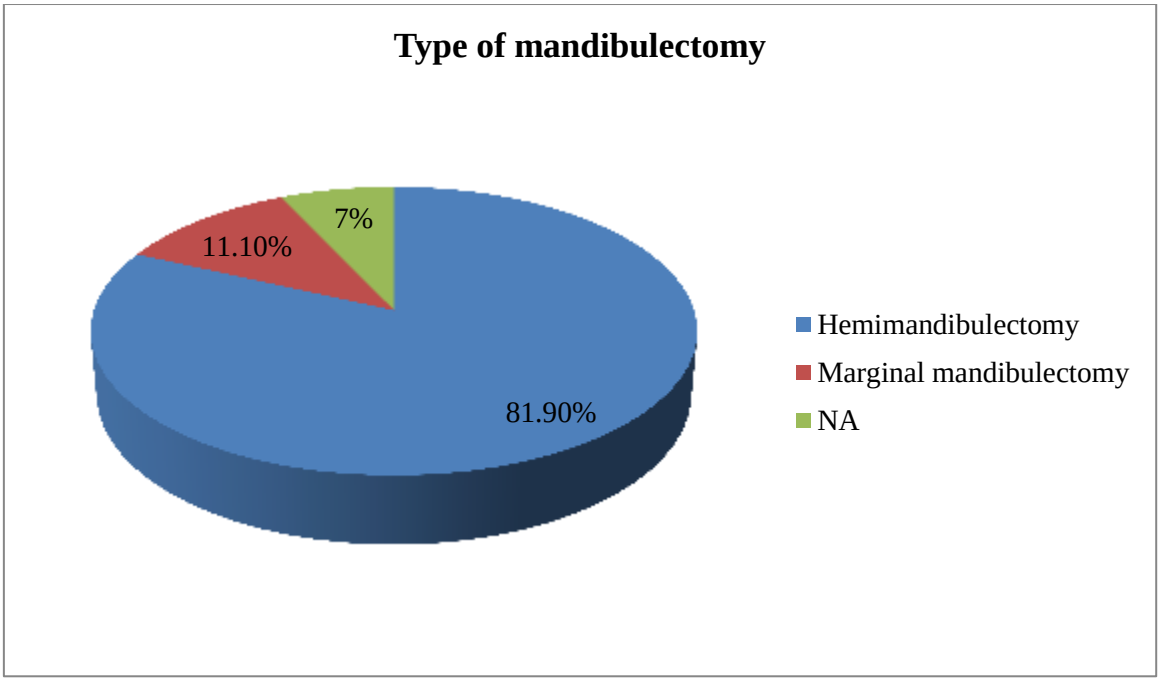


Graph 7: Pie diagram showing Bony erosion detected in CT scan

Table 11: Type of mandibulectomy among subjects

		n=72	%
Type of mandibulectomy	Hemimandibulectomy	59	81.9%
	Marginal mandibulectomy	8	11.1%
	NA	5	7%

In this study 81.9% underwent Hemimandibulectomy and 11.1% underwent Marginal mandibulectomy.

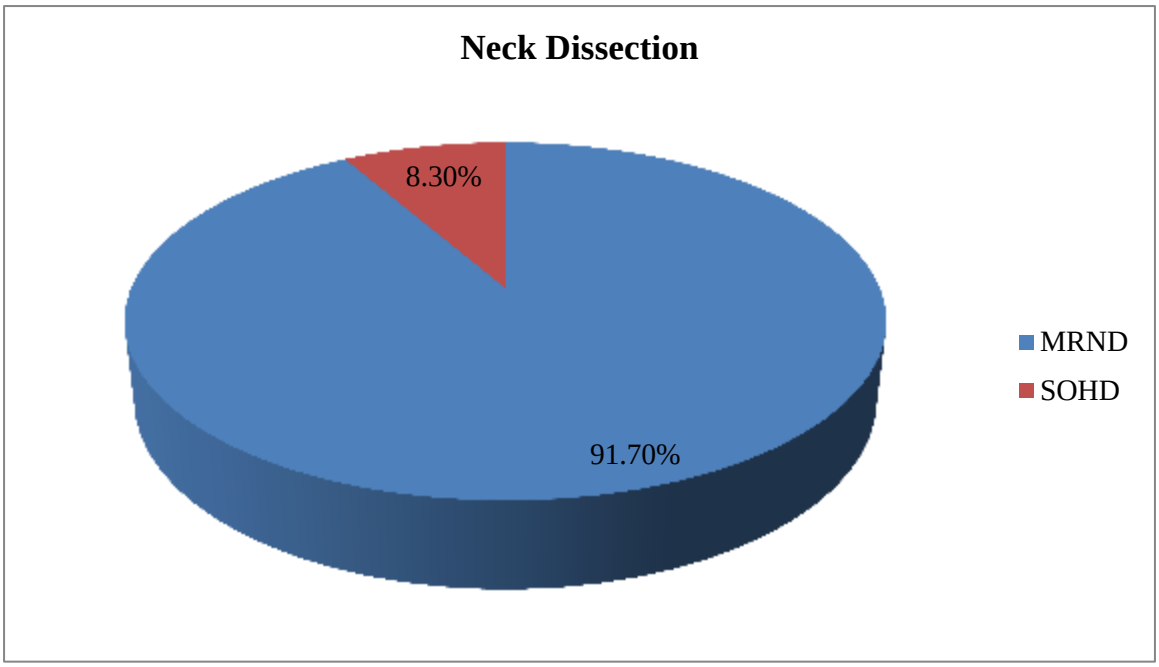


Graph 8: Pie diagram showing Type of mandibulectomy among subjects

Table 12: Type of Neck Dissection

		n=72	%
Neck Dissection	MRND	66	91.7%
	SOHD	6	8.3%

In this study, 91.7% (66) underwent modified radical neck dissection (MRND) and the remaining 8.3% underwent supraomohyoid neck dissection (SOHD).

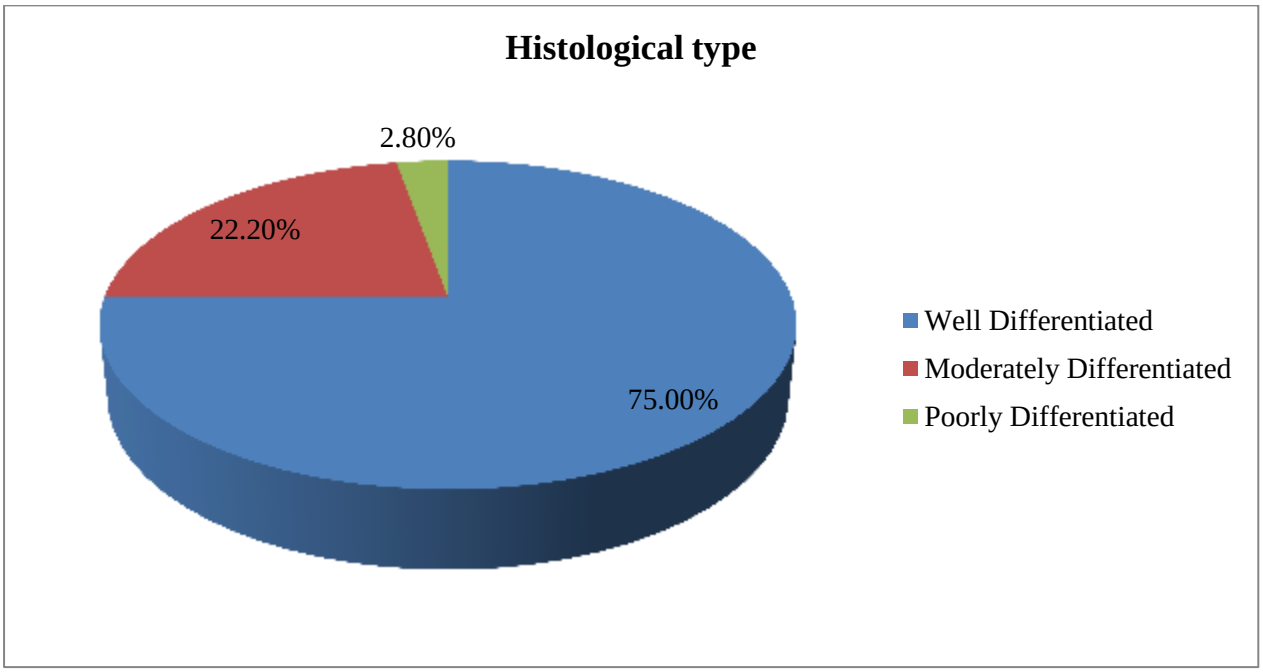


Graph 9: Pie diagram showing Neck Dissection among oral cavity SCC

Table 13: Histological type of Oral cavity Squamous cell carcinoma

		n=72	%
Histological type	Well Differentiated	54	75.0%
	Moderately Differentiated	16	22.2%
	Poorly Differentiated	2	2.8%
	Total	72	100.0%

In this study 75% were well differentiated, 22.2% were moderately differentiated and 2.8% poorly differentiated.

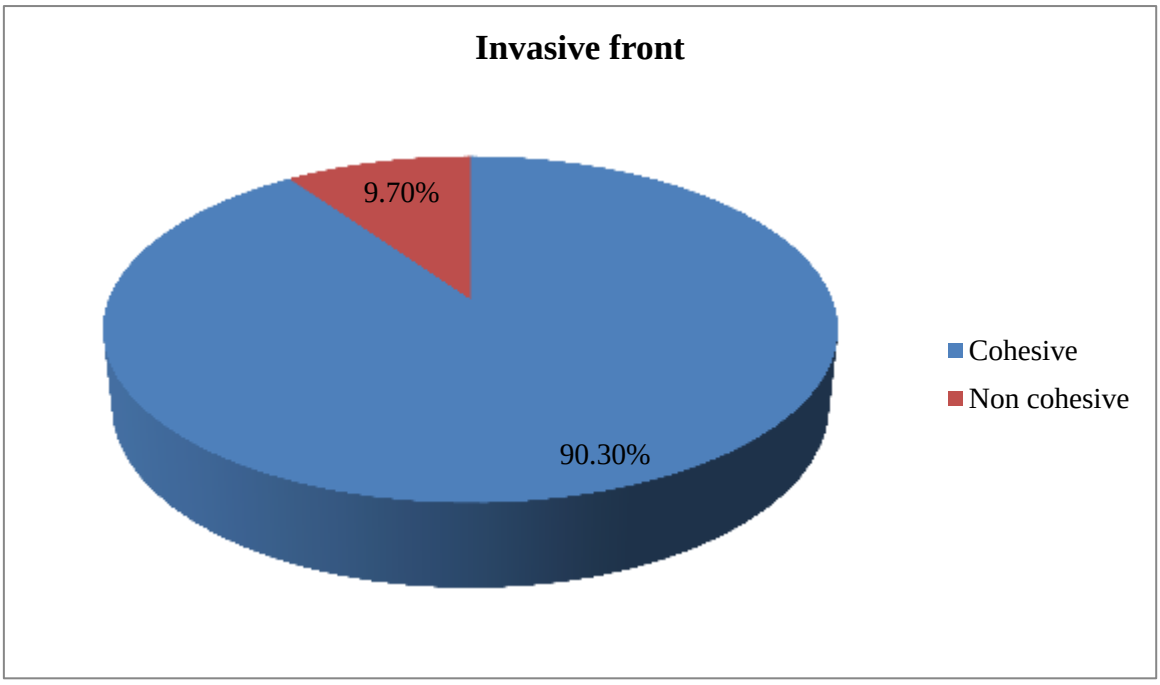


Graph 10: Pie diagram showing Histological type of Oral cavity Squamous cell carcinoma

Table 14: Invasive front of oral cavity SCC

		n=72	%
Invasive front	Cohesive	65	90.3%
	Non cohesive	7	9.7%

In this study, 90.3% had cohesive invasive front and the remaining 9.7% had non cohesive invasive front.

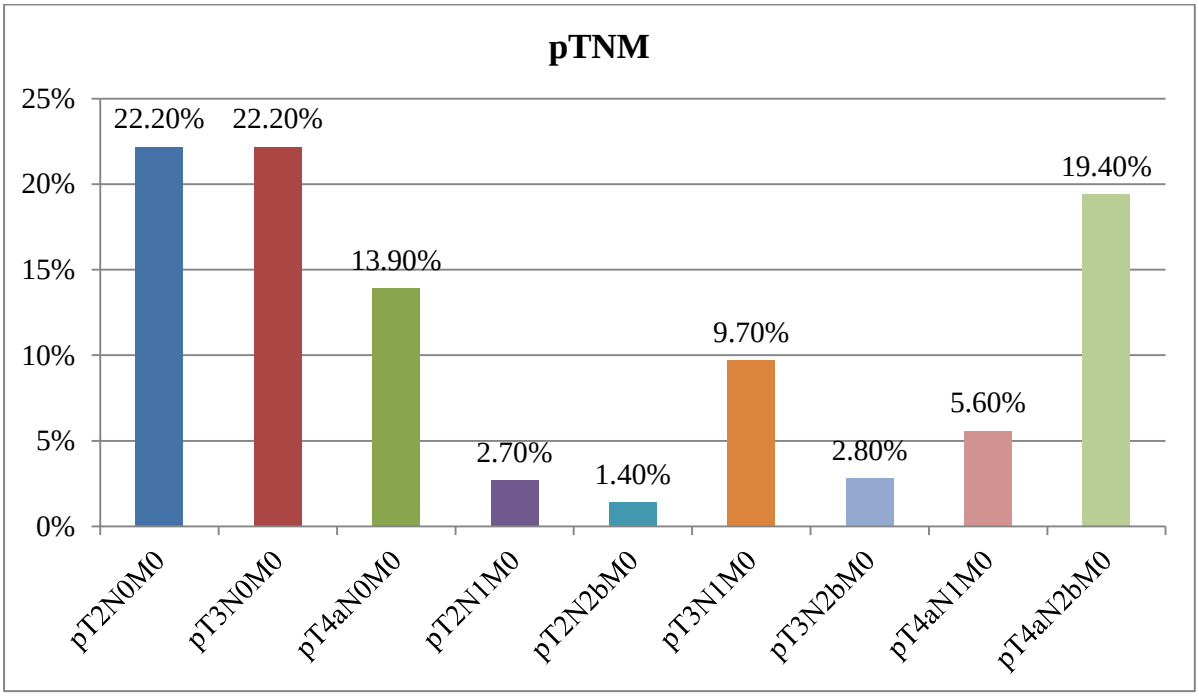


Graph 11: Pie diagram showing Invasive front of oral cavity SCC

Table 15: pTNM staging of Oral Cavity SCC

		n=72	%
pTNM	pT2N0M0	16	22.2%
	pT3N0M0	16	22.2%
	pT4aN0M0	10	13.9%
	pT2N1M0	2	2.7%
	pT2N2bM0	1	1.4%
	pT3N1M0	7	9.7%
	pT3N2bM0	2	2.8%
	pT4aN1M0	4	5.6%
	pT4aN2bM0	14	19.4%

In this study, majority had pT3N0M0 and pT2N0M0 stage 22.2%, 19.4% had pT4aN2bM0 stage. 30(41.6%) out of 42 patients had pathologically positive neck nodes.



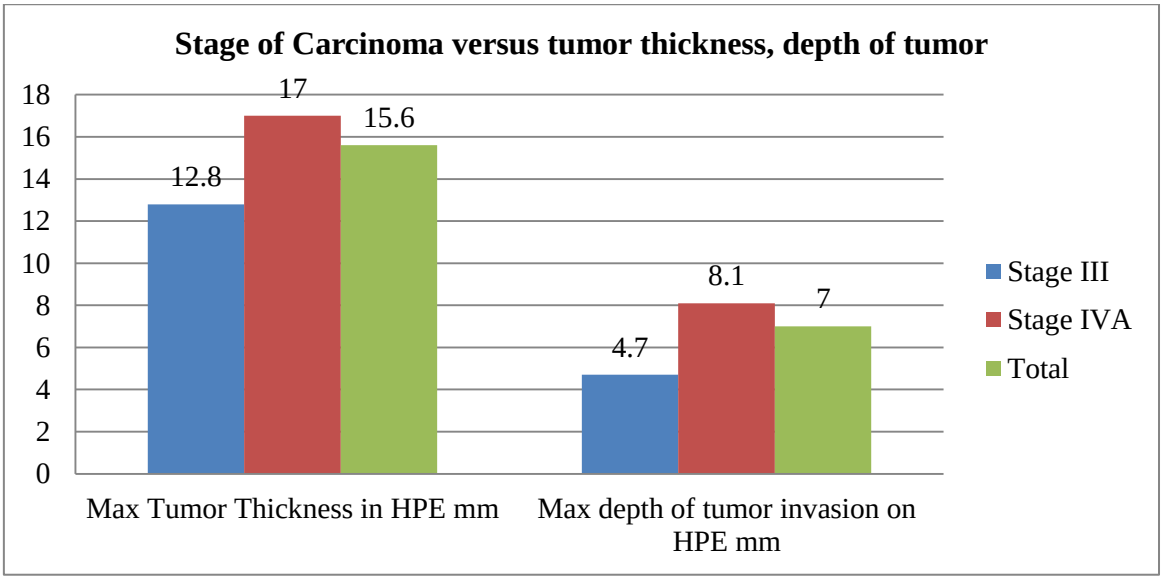
Graph 12: Bar diagram showing pTNM staging of Oral Cavity SCC

Table 16: Stage of Carcinoma versus tumor thickness, depth of tumor

	Carcinoma Stage						P value
	Stage III		Stage IVA		Total		
	Mean	SD	Mean	SD	Mean	SD	
Max Tumor Thickness in HPE mm	12.8	5.0	17.0	4.0	15.6	4.8	<0.001*
Max depth of tumor invasion on HPE mm	4.7	3.6	8.1	3.7	7.0	4.0	<0.001*

The mean tumor thickness was highest in Stage IVA than in stage III. This difference in mean tumor thickness between stage IVA and III was statistically significant.

The mean depth of tumor invasion was highest in Stage IVA than in stage III. This difference in mean max tumor thickness between stage IVA and III was statistically significant.



Graph 13: Bar diagram showing Stage of Carcinoma versus tumor thickness, depth of tumor

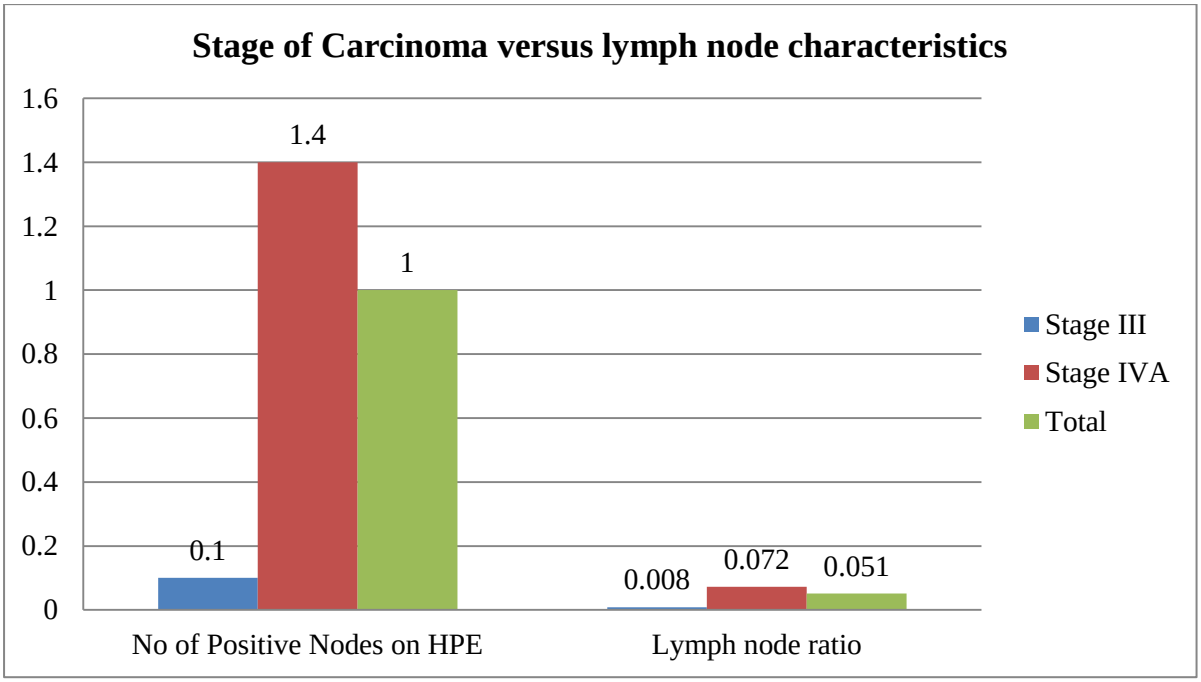
Table 17: Stage of Carcinoma versus lymph node characteristics

	Carcinoma Stage						P value
	Stage III		Stage IVA		Total		
	Mean	SD	Mean	SD	Mean	SD	
Total lymph node	19.9	3.2	19.6	2.9	19.7	3.0	0.678
No of Positive Nodes on HPE	0.1	0.3	1.4	2.0	1.0	1.7	0.003*
Lymph node ratio	0.008	0.019	0.072	0.103	0.051	0.090	0.004*

There was no significant difference in mean total lymphnode between two stages.

Mean No of Positive Nodes on HPE was highest in Stage IVA than in stage III. This difference in No of Positive Nodes on HPE between stage IVA and III was statistically significant.

Mean Lymph node ratio was highest in Stage IVA than in stage III. This difference in mean Lymph node ratio between stage IVA and III was statistically significant.

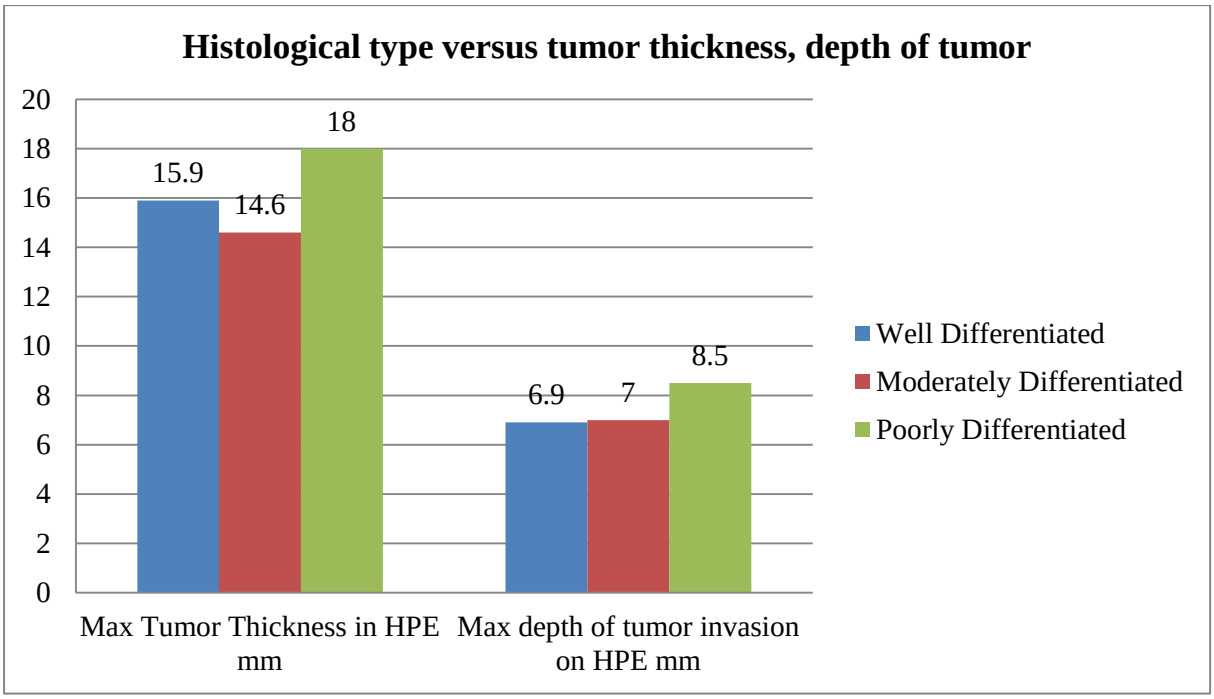


Graph 14: Bar diagram showing Stage of Carcinoma versus lymph node characteristics

Table 18: Histological type versus tumor thickness and depth of tumor

	Histological type								P value
	Well Differentiated		Moderately Differentiated		Poorly Differentiated		Total		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Max Tumor Thickness in HPE mm	15.9	4.7	14.6	5.2	18.0	2.8	15.6	4.8	0.503
Max depth of tumor invasion on HPE mm	6.9	3.8	7.0	4.5	8.5	4.9	7.0	4.0	0.859

In the study there was no significant difference in mean max tumor thickness, max depth of tumor invasion between histological types of tumor.

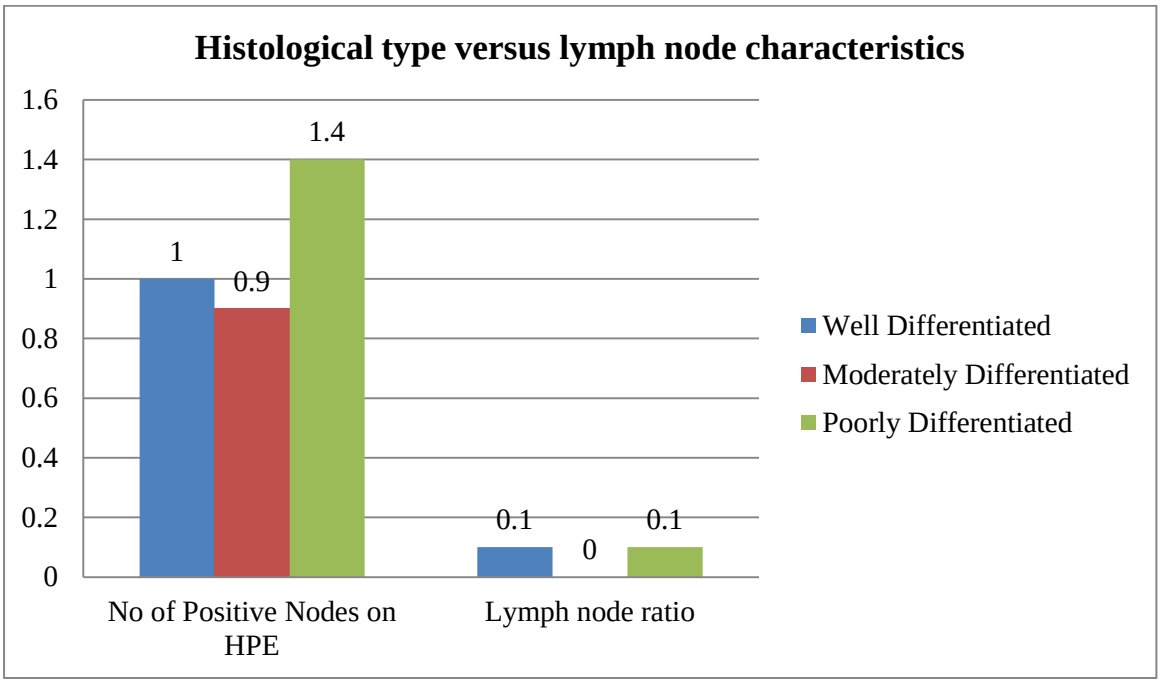


Graph 15: Bar diagram showing Histological type versus tumor thickness, depth of tumor

Table 19: Histological type versus lymph node characteristics

	Histological type								P value
	Well Differentiated		Moderately Differentiated		Poorly Differentiated		Total		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total lymph node	19.9	3.0	19.3	3.0	16.0	.0	19.7	3.0	0.155
No of Positive Nodes on HPE	1.0	1.8	.9	1.5	1.0	1.4	1.0	1.7	0.969
Lymph node ratio	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.1	0.965

In the study there was no significant difference in Total lymph nodes, No of Positive Nodes and lymph node ratio between histological types of tumor.

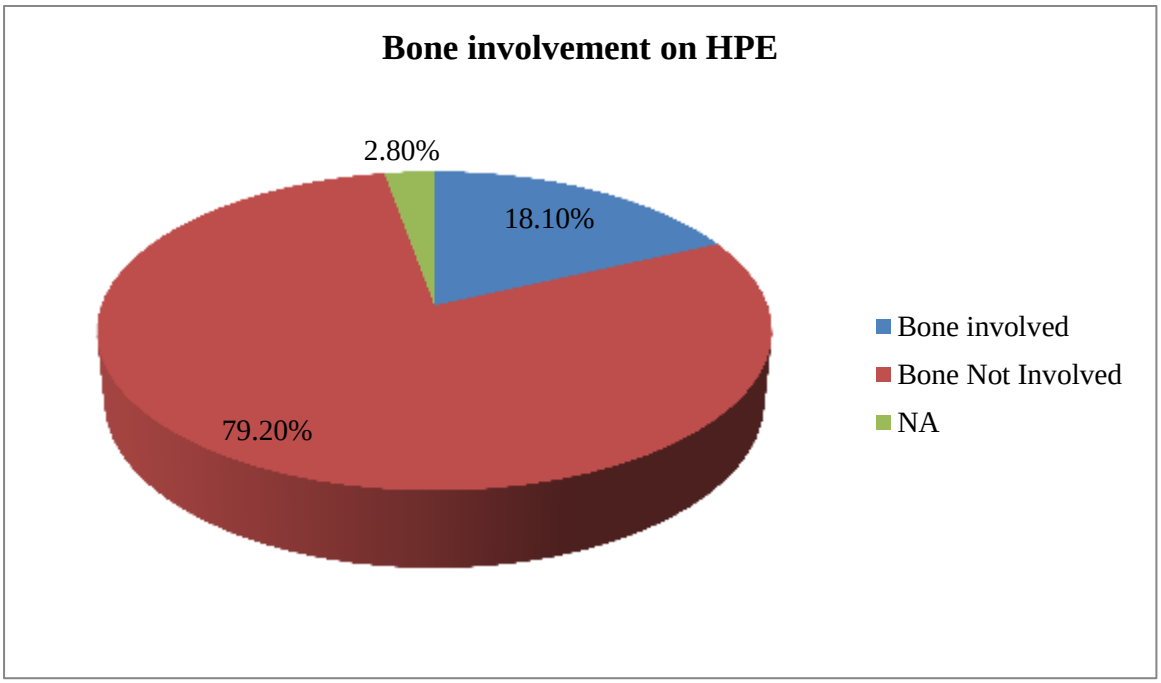


Graph 16: Bar diagram showing Histological type versus lymph node characteristics

Table 20: Bone involvement characteristics among subjects

		n=72	%
Bone involvement on HPE	Bone involved	13	18.1%
	Bone Not Involved	57	79.2%
	NA	2	2.8%
Type of bone involvement on HPE	Invasive type	13	18.1%
	NA	59	81.9%

In this study on HPE, 18.1% had bone involvement, 79.2% had no bone involvement and out of 13 subjects with bone involvement, 100% of them were invasive type. Also as mentioned previously among the 18 patients who showed erosion of mandible on CT scan, 13 (72%) showed involvement of mandible on HPE.

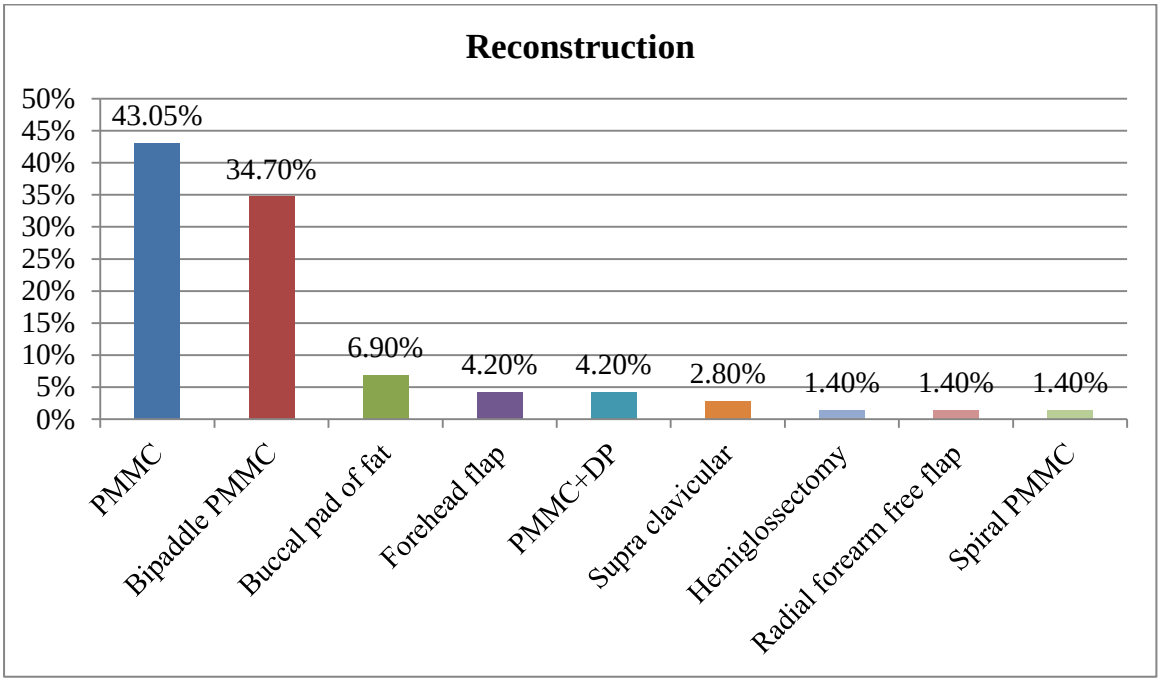


Graph 17: Bar diagram showing Bone involvement characteristics among subjects

Table 21: Reconstruction among oral cavity SCC

		n=72	%
Reconstruction	PMMC	31	43.05%
	Bipaddle PMMC	25	34.7%
	Buccal pad of fat	5	6.9%
	Forehead flap	3	4.2%
	PMMC+DP	3	4.2%
	Supra clavicular	2	2.8%
	Hemiglossectomy	1	1.4%
	Radial forearm free flap	1	1.4%
	Spiral PMMC	1	1.4%

In this study, most common reconstruction was PMMC in 43%, Bipaddle PMMC in 34.7% and others as shown in the table.

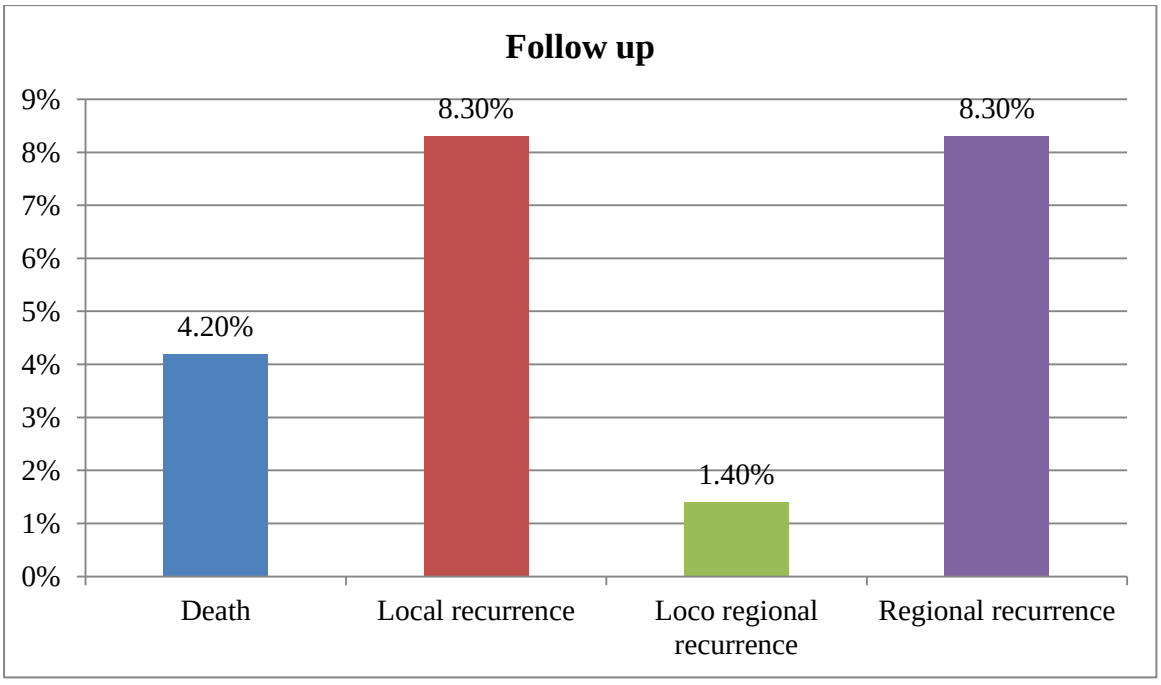


Graph 18: Bar diagram showing Reconstruction among oral cavity SCC

Table 22: Follow up findings among oral cavity SCC after a mean duration of 12 months.

		n=72	%
Follow up	Not Eventful	56	77.8%
	Death	3	4.2%
	Local recurrence	6	8.3%
	Loco regional recurrence	1	1.4%
	Regional recurrence	6	8.3%

In our study, after a mean follow up of 12 months, 77.8% of our patients were alve and doing well. 4.2% had mortality, 8.3% had Local recurrence and Regional recurrence respectively and 1.4% had Loco regional recurrence..

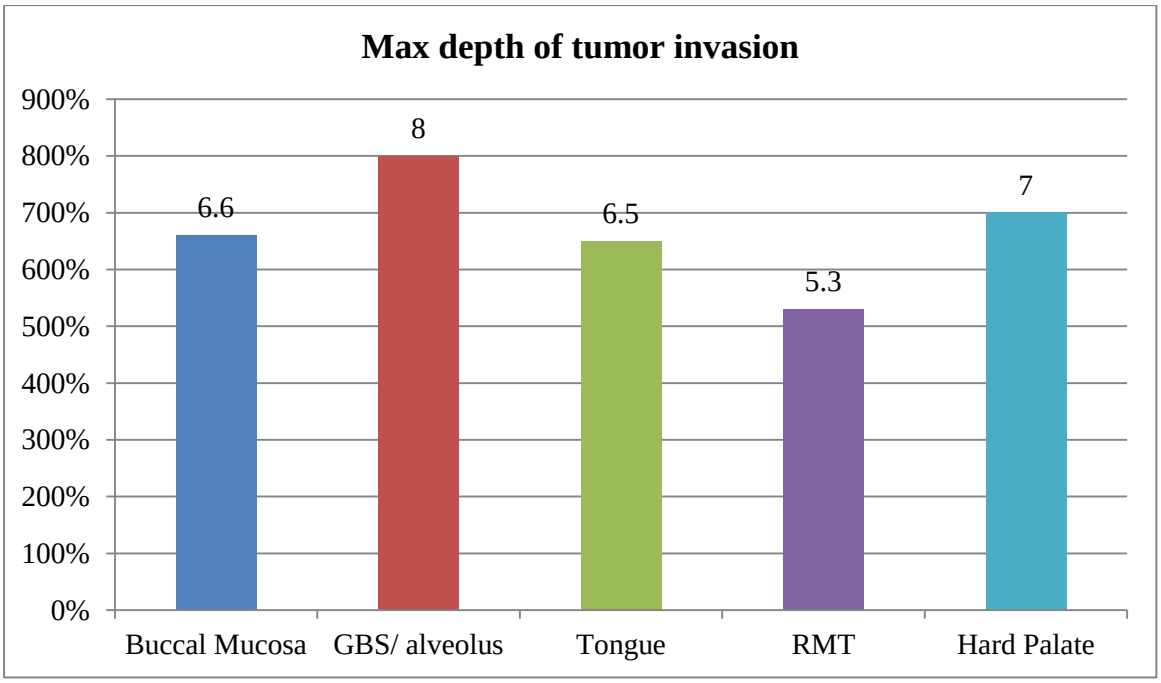


Graph 19: Bar diagram showing Follow up findings among oral cavity SCC

Table 23: Correlation between Site of tumor and Maximum depth of tumor invasion

		Max depth of tumor invasion on HPE mm	
		Mean	SD
Site	Buccal Mucosa	6.6	4.1
	GBS/ alveolus	8.0	3.7
	Tongue	6.5	5.7
	RMT	5.3	.6
	Hard Palate	7.0	.1
P value		0.660	

In ths study, mean maximum depth of tumor invasion was high in lower GBS/alveolus site and low in RMT site. However there was no significant difference in mean depth of tumor with respect to site of tumor.

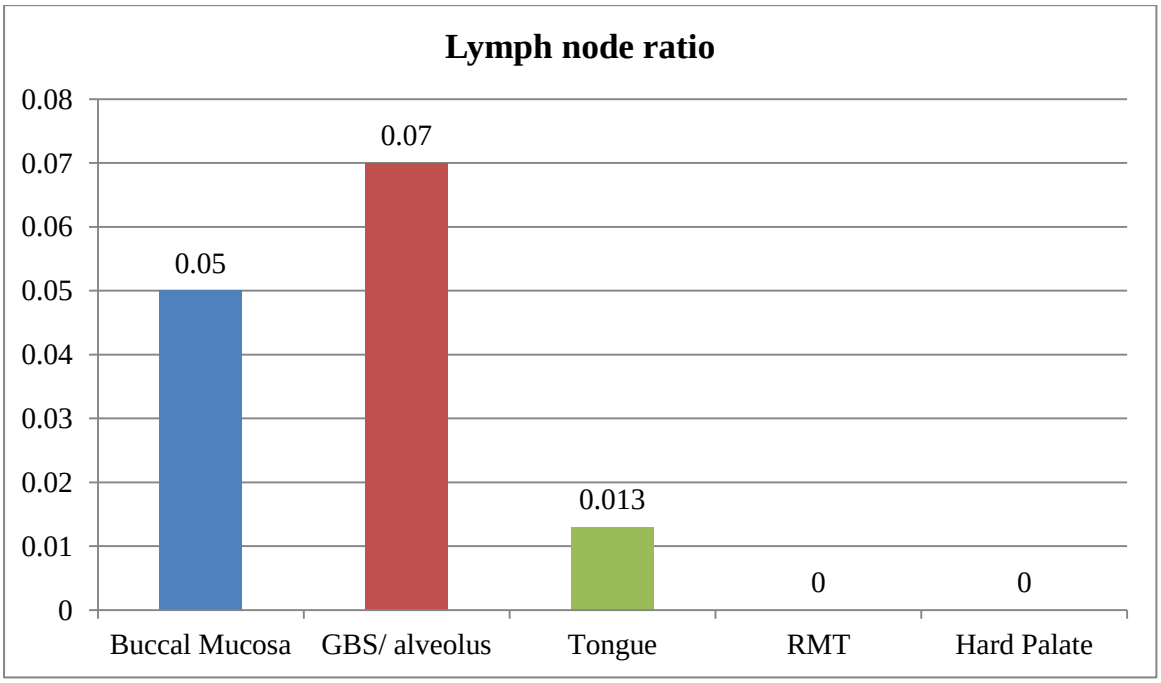


Graph 20: Bar diagram showing Correlation between Site of tumor and Maximum depth of tumor invasion

Table 24: Correlation between Site and Lymph node ratio

		Lymph node ratio	
		Mean	SD
Site	Buccal Mucosa	0.050	0.105
	GBS/ alveolus	0.070	0.067
	Tongue	0.013	0.025
	RMT	0.000	0.000
	Hard Palate	0.000	0.000
P value		0.576	

In this study, there was no significant difference in mean Lymph node ratio with respect to site of tumor. Highest lymph node ratio was seen in GBS/ alveolus site and lowest in RMT and Hard palate site.

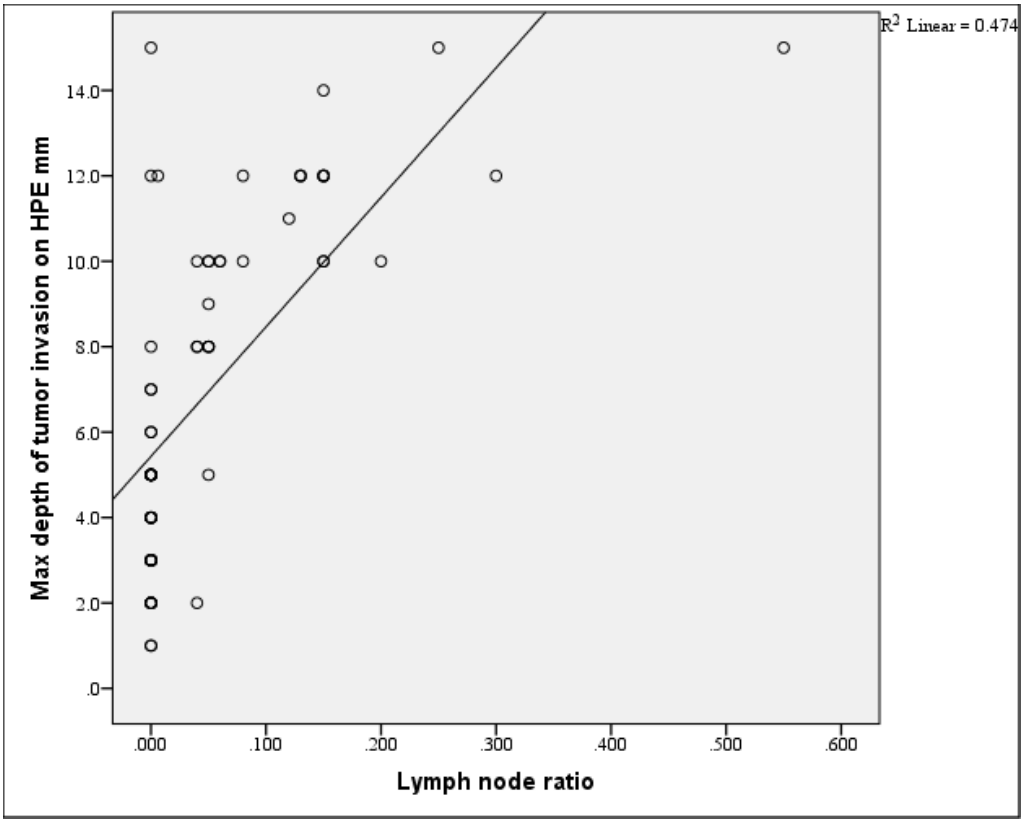


Graph 21: Bar diagram showing Correlation between Site and Lymph node ratio

Table 25: Correlation between Depth of tumor and Lymph node ratio

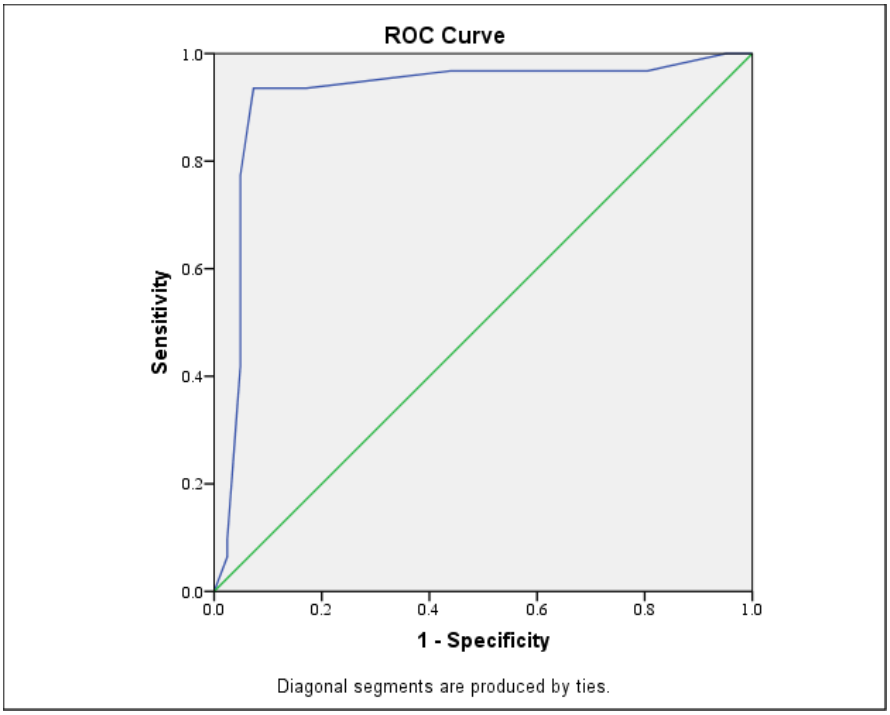
		Max depth of tumor invasion on HPE mm	Lymph node ratio
Max depth of tumor invasion on HPE mm	Pearson Correlation	1	0.688**
	P value		<0.001*
	N	72	72

In this study, there was significant positive correlation between Max depth of tumor invasion and Lymph node ratio. I.e. with increase in Max depth of tumor invasion, there was increase in Lymph node ratio and vice versa.



Graph 22: Scatter plot showing Correlation between Depth of tumor and Lymph node ratio

Table 26: ROC Curve showing cut off values of Max depth of tumor invasion with respect to Lymph node ratio



Area Under the Curve				
Test Result Variable(s): Max depth of tumor invasion on HPE mm				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.921	0.040	<0.001*	0.844	0.999

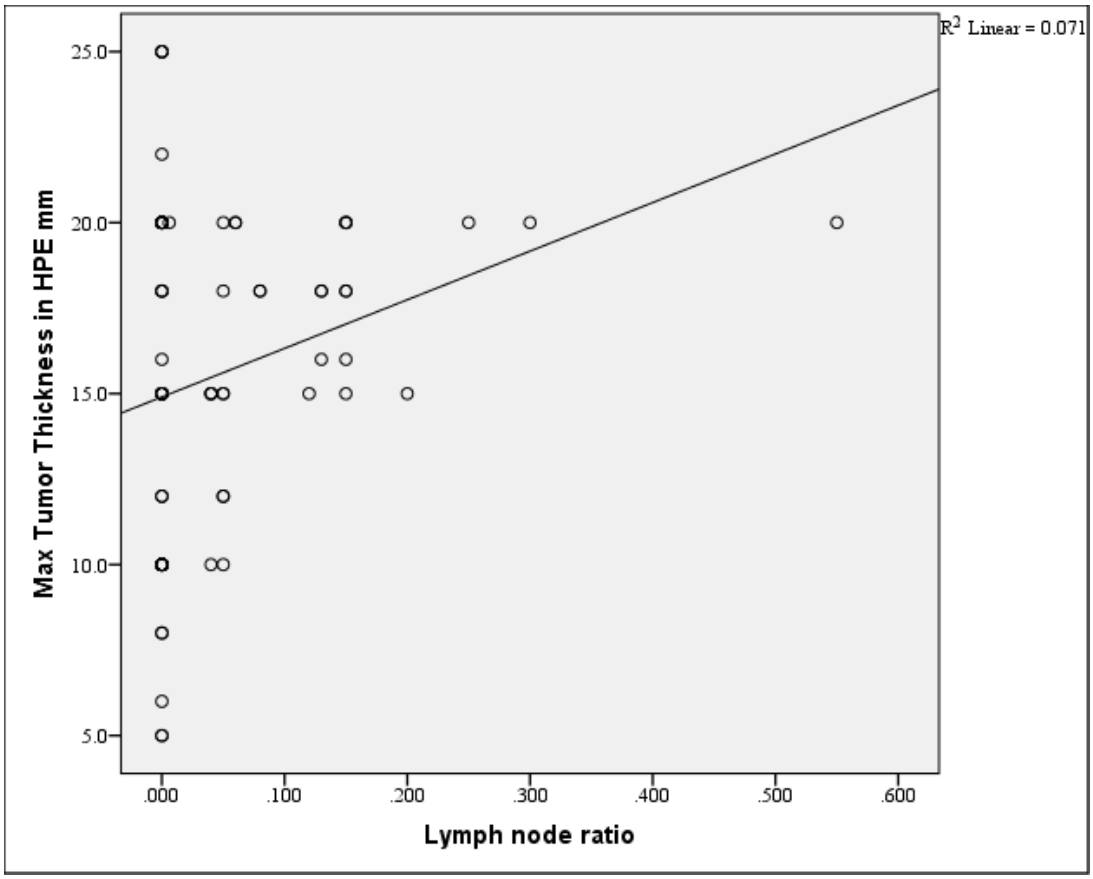
Coordinates of the Curve		
Test Result Variable(s): Max depth of tumor invasion on HPE mm		
Positive if Greater Than or Equal To[a]	Sensitivity	1 – Specificity
1.500	100%	4.9%
4.500	96.8%	56.1%
7.500	**93.5%**	**92.7%**
14.500	6.5%	97.6%
16.000	0%	100%

Max depth of tumour of 7.5 mm had highest sensitivity (93.5%) and specificity (92.7%) in detecting increased Lymph node ratio among subjects with SCC

Table 27: Correlation between Max Tumor Thickness and Lymph node ratio

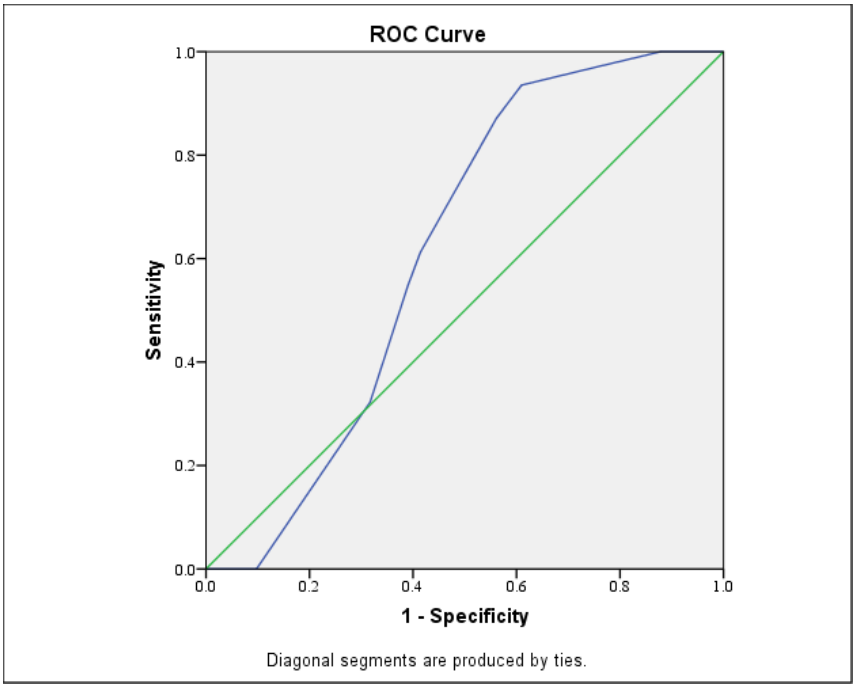
		Lymph node ratio	Max Tumor Thickness in HPE mm
Lymph node ratio	Pearson Correlation	1	0.267*
	P value		0.023*
	N	72	72

In the study there was significant positive correlation between Max Tumor Thickness and Lymph node ratio. I.e. with increase in Max Tumor Thickness, there was increase in Lymph node ratio and vice versa.



Graph 23: Scatter plot showing Correlation between Max Tumor Thickness and Lymph node ratio

Table 28: ROC Curve showing cut off values of Max Tumor Thickness with respect to Lymph node ratio



Area Under the Curve				
Test Result Variable(s): Max Tumor Thickness in HPE mm				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.616	0.067	0.095	0.485	0.746

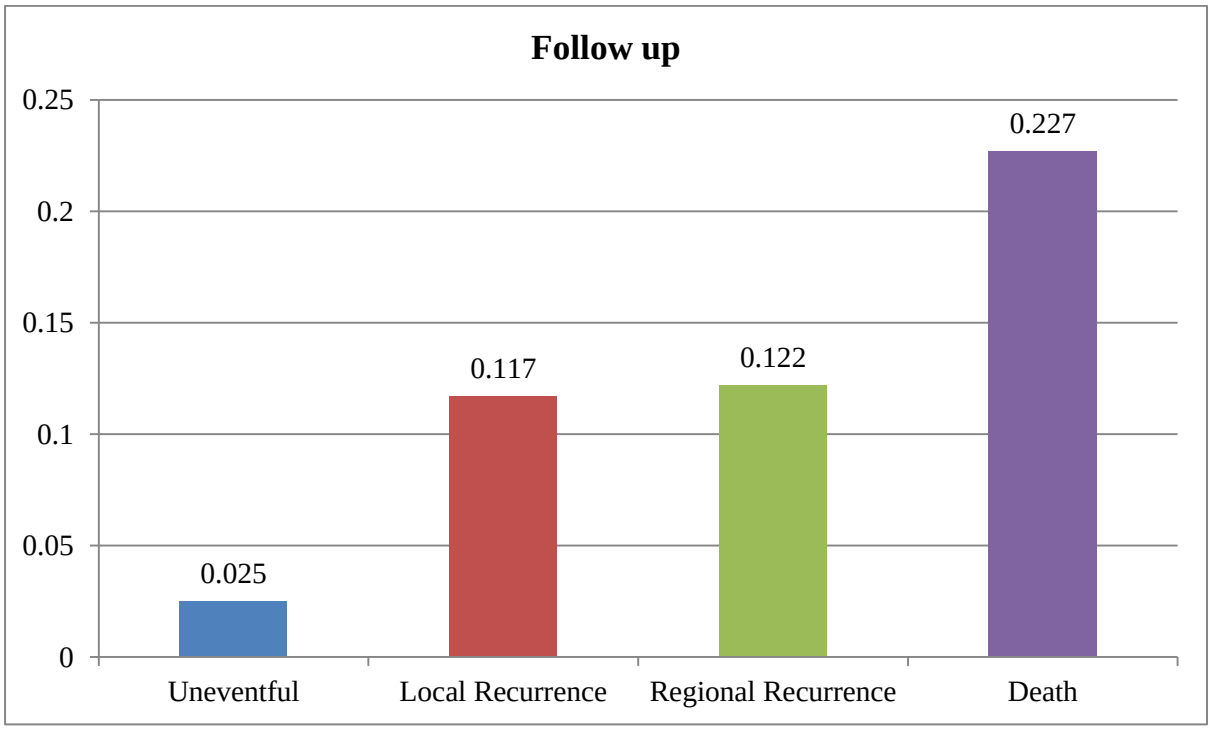
Coordinates of the Curve		
Test Result Variable(s): Max Tumor Thickness in HPE mm		
Positive if Greater Than or Equal To	Sensitivity	Specificity
4.000	100%	100%
11.000	93.5%	39%
19.000	32.3%	68.3%
21.000	0%	90.2%
26.000	0%	100%

Max Tumor Thickness of 11 mm had highest sensitivity (93.5%) and specificity (39%) in detecting increased Lymph node ratio among subjects with SCC.

Table 29: Correlation between Follow up and Lymph node ratio

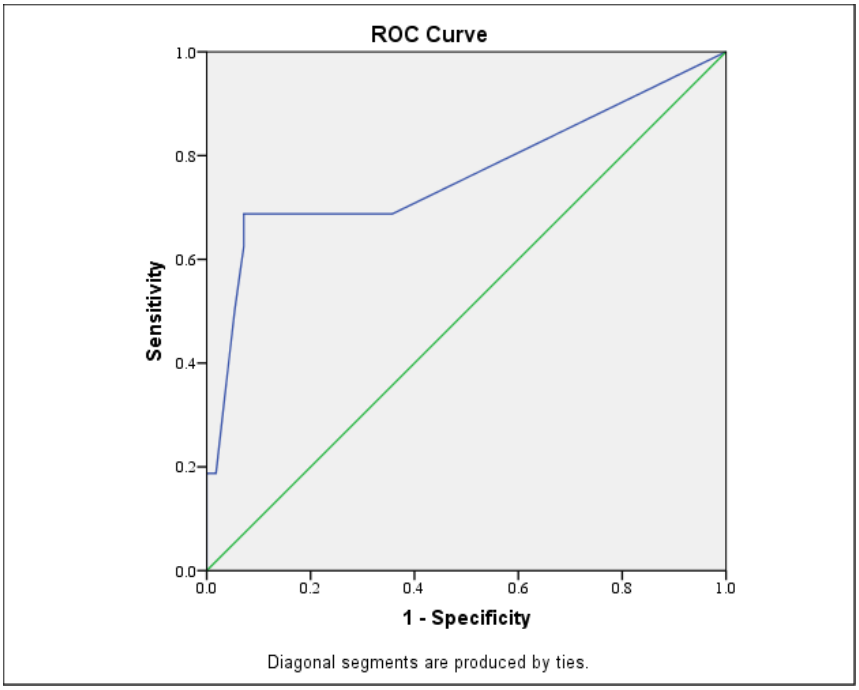
		Lymph node ratio	
		Mean	SD
Follow up	Uneventful	0.025	0.045
	Local Recurrence	0.117	0.090
	Regional Recurrence	0.122	0.112
	Death	0.227	0.287
P value		<0.001*	

In the study mean Lymph node ratio was high in subjects who died 0.227 ± 0.287 and low in those with Local recurrence (0.117 ± 0.09). This difference in mean Lymph node with respect to outcome at follow up was statistically significant.



Graph 24: Bar diagram showing Correlation between Follow up and Lymph node ratio

Table 30: ROC Curve showing cut off values of Lymph node ratio in predicting poor prognosis



Area Under the Curve				
Test Result Variable(s): Lymph node ratio				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.765	0.082	0.001*	0.603	0.926

Coordinates of the Curve		
Test Result Variable(s): Lymph node ratio		
Positive if Greater Than or Equal To[a]	Sensitivity	Specificity
0.00300	68.8%	64.3%
0.10000	**68.8%**	**92.9%**
0.22500	18.8%	100%
1.55000	0%	100%

Lymph node ratio of 0.100 had highest sensitivity and specificity in detecting poor prognosis among subjects with SCC.

DISCUSSION

DISCUSSION

Squamous cell carcinoma of the oral cavity (OSCC) is amongst the most common malignant tumours, with an estimated 2,63,900 new cases and 1,28,000 deaths per year and a significant source of morbidity.[77]

Although the overall incidence of OSCC has shown a decreasing trend in most developed countries over the past decades, it continues to be a common cancer among both male and female individuals in south–central Asia and in central and Eastern Europe.[78]

The main modality of treatment of patients with OSCC is surgical resection of the primary tumour. Neck dissection is performed either as an elective procedure or when the clinical or radiological examination shows evidence of cervical nodal metastasis.[5]

Various factors such as tumour stage, status of resected margin, depth of invasion and the presence of cervical nodal metastasis are significant prognostic factors affecting these patients.[57,79]

Cervical lymph nodal status remains one of the most significant prognostic markers in oral cavity squamous cell cancers. The presence of lymph node metastasis decreases 5 year survival by approximately 50%.[30,80] There is an increase in mortality risk associated with node positive status and patients with higher nodal disease burden have an increased risk of locoregional recurrence.[68]

As such, the probability of identifying metastasis in lymph nodes relies on the technical performance of both surgeons and pathologists.[81-83]A limited lymph node dissection could result in pathological under staging of the disease.

Mamelle et al (1994) was the first to describe the value of the number of positive nodes as a predictor of outcome for head and neck cancer patients[79].But it was only in the last 3 to 4 years that lymph node ratio (LNR) (total positive nodes/total number of lymph nodes dissected) was proposed as a strong prognostic factor in OSCC patients.[5]

This study was done at R.L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Kolar between Dec 2015- April 2017. 72 patients with locally advanced oral cavity squamous cell carcinoma (stage III and stage IVa) at presentation were included.

Majority of our patients were females, comprising of 81.9% (59/72) of the total study population. This is due to the habit of quid chewing which is more common among women, whereas men of this region have a common habit of smoking.[84] A study showing the incidence of oral cancers in India and a regional study done in Kolar, showed the incidence of oral cavity cancers to be higher among females.[84,85] In our study, maximum incidence of cases were seen in the age group between 41 to 50 years (36%). The most common oral cavity subsite to be involved was buccal mucosa (60%) followed by lower gingivobuccal sulcus (29%).

In India, buccal mucosa (BM) and lower alveolus complex, quite often extending to retromolar trigone (RMT) are common sites of primary tumour.[2] This is due to betel nut and tobacco chewing. The use of quid, which comprises of betel leaf, areca nut (areca catechu) & slaked lime (calcium hydroxide) predominantly causes malignancy in the lower gingivobuccal sulcus (GBS).[84]

In our study, most of our patients had presented with locally advanced disease, involving multiple subsites such as buccal mucosa, gingivobuccal sulcus and lower alveolus, making it difficult to pinpoint the epicentre. Such locally advanced diseases, in

our study, were grouped as lower Gingivobuccal Sulcus cancer. Such cases are common in the Indian subcontinent due to the prevalent habit of quid chewing n the local population. Hence it is also known as "Indian oral cancer".[86]

In an epidemiological study done in this region, head and neck cancer accounted for 30% of all malignancies, the most common subsite being buccal mucosa.[85] Our findings were similar to this study.[84,85]

In our study, 44% of patients presented with left sided oral cancer, which does not have any clinical importance. But the side involved by cancer mainly corresponded with the habit of placing the quid at that particular region causing repeated contact with carcinogens.[84]

Majority of our patients, 67% (48/72) presented with stage IVa disease, which can be attributed to ignorance, lack of awareness and poverty, among the people in this region .Other studies involving epidemiology, awareness and superstitions of this region have found similar findings.[15,16,84,86]

Author	Mean age of presentation	Male:female ratio	Most common site of primary	Most common stage of presentation
Gil et al (2009)	40-60 years	3.8:1	Tongue (45%)	Stage IV (39%)
Shrime et al (2009)	Not specified	1.9:1	Not specified	Stage IV (54%)
Ebrahimi et al (2011)	40-60 years	1.87:1	Floor of mouth (37%)	Not specified
S Y Kim et al (2011)	45-65 years	1.74:1	Tongue (79%)	Stage I (40%)
Patel et al (2013)	40- 50 years	1.95:1	Not specified	Stage IV (62%)
Sayed et al (2013)	40- 60 years	3.8:1	Buccal mucosa (38.9%)	Stage IV (90.6%)
Our study	41-50 years	0.2:1	Buccal mucosa (60%)	Stage IV (67%)

Table 31: Showing demographic distribution of patient population in different studies

Among the 48 patients who had Stage IVa disease, skin involvement was clinically seen in 63% (30) of cases and 37% (18) had erosion of mandible on CT scan.

All of our patients underwent wide excision of the primary tumour along with neck dissection and subsequent reconstruction.

In our study, 91.7% of patients underwent modified radical neck dissection (MRND) and 8.3% underwent supraomohyoid neck dissection (SOHD). 81.9% underwent Hemimandibulectomy and 11.1% underwent Marginal mandibulectomy. The most common reconstruction was done using PMMC in 41.7% followed by Bipaddle PMMC in 34.7%

In our institution, the oral cavity defect was reconstructed by the operating surgeons themselves, due to non-availability of facilities for microvascular surgery. Therefore, PMMC flap, which is the work horse of head and neck reconstruction, more so in rural centres, was the flap of choice for reconstruction. Most of our patients underwent hemimandibulectomy in view of advanced disease either involving or abutting the mandible, where saving the mandible is not oncologically safe.[86]

After the excision, the tumour and neck dissection specimens were subjected to histopathological examination

On HPE of the specimen 54 patients (75%) were found to have well differentiated squamous cell carcinoma and 16 patients (22.2%) had moderately differentiated squamous cell carcinoma and 2 (2.8%) showed poorly differentiated squamous cell carcinoma.

Author	**Most common histologocal differentiation of squamous cell carcinoma**
Ebrahimi et al (2011)	Moderately differentiated (53%)
Syed et al (2013)	Moderately differentiated (61%)
Our study	Well differentiated (75%)

Table 32: Showing histological differentiation of squmaous cell carcinoma among various studies

The pathological staging, down staged a significant number of patients, 16 patients (22.2%) were stage pT2N0,16 patients were stage pT3N0 (22.2%),10 patients were stage pT4N0(13.9%), 2 patients were stage pT2N1 (2.7%), 1 patient was stage pT2N2b (1.4%). 7 patients were in stage pT3N1(9.7%), 2 patient with pT3N2b (2.8%) , 4 patients (5.6%) with stage pT4aN1 and 14 (19.4%) patients with stage pT4aN2b. This down staging in HPE can be explained by the fact that the tumor tissue shrinks up to 40 % on formalin fixation and due to intrinsic tissue properties. Also most palpable lymph nodes showed reactive lymphadenitis owing to the poor oral hygiene of the rural population in this area.[84]

Out of 18 patients who had shown mandibular erosion on CT scan, 13 (72%) patients had bone involvement on histopathological examination. The small variation between CECT and HPE regarding bone involvement can be explained by the fact that demineralization of the bone or loss of teeth may be depicted as irregularity on imaging. Further, poor oral hygiene can cause gingivitis which can be seen as enhancement on CECT and occasionally very early cortical involvement may be missed by CECT.[87,88,89]

On HPE, A total of 1416 lymph nodes were evaluated, of which 70 (5%) were positive. Most of the positive nodes were found in level Ib (66%) and level II (31%). Most Other studies done have also shown a similar percentage of positive lymph nodes ranging from 3-6%.[73,83]An average number of 20 lymph nodes was obtained per specimen. This nodal yield, ie number of total lymph nodes from neck dissection specimen was comparable to other similar studies where the nodal yield ranges from 20-25.[69,73,83]

In our study, 30 (42%) out of 72 patients had cervical lymph node metastasis. Among these 30 patients, 43% had neck N1 status and 57 % patients had N2b status on histopathological examination. This was comparable to other similar studies, wherein they had obtained a range of 37-43% of patient with lymph nodes positive for metastasis[5,73]. Other similar studies have also shown majority of their pN+ patients to have pN2 disease.[5,69,71,73,83]

Author	Mean Nodal yield/specimen	Percentage of patients with positive lymph nodes	Average number of positive nodes (Total no. of positive nodes/ total no. of patients with positive nodes)	Most common pathological nodal status (pN+)
Gil et al (2009)	30	43%	2.7	pN2b (22%)
Ebrahimi et al (2011)	27	52%	3.4	pN2b (27.2%)
S Y Kim et al (2011)	25	40%	2	pN2b (18%)
Patel et al (2013)	20	46%	1	pN2b (23.2%)
Sayed et al (2013)	23	51%	3	pN2b (52.2%)
Our study	20	41.6%	2.3	pN2b (57%)

Table 33: Showing Lymph node characteristic among various studies

Mean No of Positive Nodes on HPE was highest in Stage IVA (1.4) than in stage III(0.1). This difference in No of Positive Nodes on HPE between stage IVA and III was statistically significant (p=<0.003).

Mean Lymph node ratio was highest in Stage IVA (0.072) than in stage III (0008). This difference in mean Lymph node ratio between stage IVA and III was statistically significant (p=<0.004).

The mean tumour thickness among patients with pN0 was 14.7mm, when compared to patient with pN+ which was 16.5mm. Among those patients with pN+ disease, those with N1 disease showed an mean tumour thickness of 15mm compared to those with pN2who had a mean of 18mm. Mean maximum tumor thickness was highest in Stage IVA (17.0) than compared to stage III (12.8). This difference in mean maximum tumor thickness between stage IVA and III was statistically significant (p=<0.001).

In this study there was significant positive correlation between maximum Tumor Thickness and Lymph node ratio (p=<0.023) I.e. with increase in Tumor Thickness, there was increase in Lymph node ratio and vice versa.

In our study, a maximum tumor thickness of 11 mm had the highest sensitivity (93.5%) and specificity (39%) in detecting increased Lymph node ratio among subjects with SCC. Most of the studies in literature have compared tumour thickness with cervical lymph node metastasis in early lesion, especially in tongue and floor of mouth malignancies.[50,51,57,58]

Though no studies have compared the correlation between tumour thickness and lymph node ratio, our results were similar to other studies which have shown that tumour thickness was a significant predictor for cervical lymph node metastasis.[50,51,57,58]

The mean tumour depth among patients with pN0 was 4mm, when compared to patient with pN+ which was 10.5mm. Among those patients with pN+, patients with N1 disease showed an mean tumour depth of 9mm compared to those with pN2, which had an mean of 12mm. Mean maximum depth of tumor invasion was highest in Stage IVA (8.1)in comparison to stage III (4.7). This difference in mean depth of tumour between stage IVA and III was statistically significant (p=<0.001).

In this study there was significant positive correlation between maximum depth of tumor invasion and Lymph node ratio. (p=<0.001) i.e. with increase in depth of tumor invasion, there was increase in Lymph node ratio and vice versa.

In our study, a maximum depth of tumour invasion of 7.5 mm had the highest sensitivity (93.5%) and specificity (92.7%) in detecting increased Lymph node ratio among subjects with SCC. Most studies have shown a range of depth of invasion from 2 to 5 mm to correlate with lymph node metastasis; but these studies were done in early lesions involving tongue and floor of mouth.[4,55,56,57,59]

No studies have compared the correlation of depth of invasion of tumour with lymph node ratio. But there are studies that have shown similar positive correlation between depth of tumour and nodal metastasis.[4,55,56,57,59]

In our study, there was no significant difference in mean Lymph node ratio with respect to site of primary tumor. However, highest lymph node ratio was seen in GBS/ lower alveolus site and lowest was seen in RMT and Hard palate site. Various studies in literature have quoted that lower GBS cancers are aggressive as they are in close proximity to mandible. This cancer also metastasis early to submandibular lymphnodes.[90] It is also known that tumours of tongue show a higher propensity for nodal metastasis[46,51,52,55] however in our study there was no such correlation as we had a small sample group with only 4 out 72 patients diagnosed with carcinoma of the tongue.

In our study, after a mean follow up of 12 months with minimum follow up of 6 months, 56 patients are alive and disease free (77.8%). Of the 3 patients who expired, 2 succumbed as a result of disease process and one died due to other cause. 6 patients had local recurrence, 6 of the patients had regional recurrence and 1 had locoregional recurrence. Our study has shown a more favorable outcome when compared to other similar studies, However, this could be due to our shorter follow up period in comparison.[5,69,71,73,83]

Author	Mean Lymph node ratio	Mean duration of follow up
Gil et al (2009)	0.06	67 months
Shrime et al (2009)	0.09	32 months
Ebrahimi et al (2011)	0.07	32 months
S Y Kim et al (2011)	0.06	58 months
Patel et al (2013)	0.07	50 months
Sayed et al (2013)	0.088	21 months
Our study	0.05	12 months

Table 34: Showing mean lymph node ratio and mean duration of follow up among various studies

Among the pN+ patients (n=30), patients with pN1 disease had an average lymph node ratio of 0.05 and those pN2 diseases had an average lymph node ratio of 0.18. Out of the 6 patients with local recurrence, 4 (13%) had positive lymph node metastasis with an average lymph node ratio of 0.14. All 4 had stage IVa with pN2b disease. Of the 6 patients with regional metastasis lymph node metastasis were seen in 4 (13%) cases with an average Lymph node ratio of 0.2. All 4 patients had Stage IVa with pN2b disease.

1 (3%) patient who developed locoregional recurrence also had positive metastatic lymph nodes and had a lymph node ratio of 0.25(Stage IVa, pN2b). Both patients (7%) who succumbed to disease were positive for lymph node metastasis and had stage IVa, pN2 disease with an average lymph node ratio of 0.34.

Among those patients with pN0 (n=42) disease, in our study, 2(4.7%) had local and 2 (4.7%) had regional recurrences. Both the patients with regional recurrence had stage IVa disease and one each among the 2 who had local recurrence, had stage III and Stage IVa disease respectively.

In our study, the mean Lymph node ratio was high in subjects who expired 0.227 ± 0.287 and lower in those with Local recurrence (0.117 ± 0.09). This difference in mean Lymph node with respect to outcome at follow up was statistically significant ($p<0.001$).

In our study a lymph node ratio of 0.10 had the highest sensitivity and specificity in detecting poor prognosis among subjects with SCC. Though various studies have used a wide variety of statistical methods and cut off values for lymph node ratio to show correlation with outcomes at follow up, our data was comparable to other similar studies, all which showed that higher lymph node ratio was statistically correlating with poorer outcomes.[5,69,71,73,83]

Therefore in our study, patients with higher lymph node ratio were more prone towards an adverse outcome and increase in depth of invasion of tumour was associated with poor prognosis. As our study had a small sample size and limited duration of follow up, it would be ideal to include a larger sample size and longer follow up in future studies, to validate our results and assess the value of Lymph node ratio as a tool to help identify patients who are at a higher risk for disease recurrence.

CONCLUSION

CONCLUSION

1. There is a high incidence of buccal mucosa cancers, especially among females of the age group between 40-50 years. This mainly due to prevalent quid chewing habits and lack of awareness among lower socioeconomic group in Kolar region.
2. Majority of our patients had T4a lesions. This is due to lack of awareness and low socio-economic conditions of these patients in rural population.
3. Most of the oral cancers in our series which had cervical lymph node metastases were to submandibular (level Ib) and upper deep jugular nodes (level II).
4. In our study, both Tumour thickness and Depth of tumour invasion showed a statistical correlation with the lymph node ratio. This result was similar to other studies.
5. Site of tumour did not show any statistical correlation with lymph node ratio in our study. Though the most common site of primary tumour was buccal mucosa, higher lymph node ratio was seen in gingivobuccal sulcus tumour. This can be explained by its close proximity to mandible and submandibular lymph nodes.
6. In literature, tongue malignancies have been shown to have early and aggressive lymph node metastasis, our study did not show any correlation. This could be due to our small sample size and limited representation of patients with carcinoma tongue.
7. In our study lymph node ratio also showed statistically significant correlation with follow up. I.e. Patients with higher lymph node ratio were more prone for regional and local recurrence.
8. Tumour thickness and depth of invasion are reliable criteria to predict lymph node metastasis in oral cavity squamous cell cancers during surgery and as prognostic markers.

9. Lymph node ratio is a useful tool in identifying high risk patients and provide intensive adjuvant therapy.
10. Large multi institutional prospective studies with larger sample and longer duration of follow up are required to formulate definitive protocols using Lymph node ratio as a prognostic marker for patients with oral cavity squamous cell carcinoma.

SUMMARY

SUMMARY

This study was conducted at R.L.Jalappa Hospital, Kolar. A total number of 72 patients with locally advanced (stage III and Stage IVa) oral cavity squamous cell carcinoma were included in our study. Increased incidence was seen in the 4th-6th decade of life. In our study, majority (81.9%) of the patients were females.

The most common oral cavity subsite to be involved was buccal mucosa (60%) followed by gingivobuccal sulcus (29%). Majority of our patients, 48 out of 72 presented with stage IVa disease.

In our study, since most of our patients had presented with locally advanced diseases, involving multiple subsites such buccal mucosa, gingivobuccal sulcus and lower alveolus, making it difficult to pinpoint the epicenter, all such diseases were grouped as Gingivobuccal Sulcus cancer. Such cases are common in the Indian subcontinent and hence also known as "Indian oral cancer".

Among the 48 patients who had Stage IVa disease, skin involvement was clinically seen in 63%(30) of cases and 37% (18) had erosion of mandible on CT scan. In this study, 91.7% of our patients underwent modified radical neck dissection (MRND) and 8.3% underwent supraomohyoid neck dissection (SOHD). 81.9% underwent Hemimandibulectomy and 11.1% underwent Marginal mandibulectomy. The most common reconstruction was done using PMMC in 41.7% followed by Bipaddle PMMC in 34.7%

After the excision of the tumour and neck dissection, specimen was sent for histopathological examination.

On HPE of the specimen 54 patients (75%) were found to have well differentiated squamous cell carcinoma and 16 patients (22.2%) had moderately differentiated squamous cell carcinoma and 2 (2.8%)showed poorly differentiated squamous cell carcinoma. Out of

18 patients who had shown mandibular erosion on CT scan, 13 (72%) patients had bone involvement on histopathological examination

On HPE, A total of 1416 lymph nodes were evaluated, of which 70 (5%) were positive. Most of the positive nodes were found in level Ib (66%) and level II (31%). An average number of 20 lymph nodes were obtained per specimen. In our study, 30 (42%) out of 72 patients had cervical lymph node metastasis. Among them, 43% had neck N1 status and 57 % patients had N2 status on histopathological examination.

Mean No of Positive Nodes on HPE was highest in Stage IVA(1.4) than in stage III(0.1). This difference in No of Positive Nodes on HPE between stage IVA and III was statistically significant (p=<0.003). Mean Lymph node ratio was highest in Stage IVA (0.072) than in stage III (0008). This difference in mean Lymph node ratio between stage IVA and III was statistically significant (p=<0.004).

Mean maximum tumor thickness was highest in Stage IVA (17.0) than in stage III (12.8). This difference in mean max tumor thickness between stage IVA and III was statistically significant (p=<0.001). In this study there was significant positive correlation between Max Tumor Thickness and Lymph node ratio.(p=<0.023) I.e. with increase in maximum Tumor Thickness, there was increase in Lymph node ratio and vice versa. A maximum Tumor Thickness of 11 mm had the highest sensitivity (93.5%) and specificity (39%) in detecting increased Lymph node ratio among subjects with SCC.

Mean maximum depth of tumor invasion was highest in Stage IVA (8.1) than in stage III (4.7). This difference in mean depth of tumour between stage IVA and III was statistically significant (p=<0.001). In this study there was significant positive correlation between maximum depth of tumor invasion and Lymph node ratio. (p=<0.001) i.e. with increase in maximum depth of tumor invasion, there was increase in Lymphnode ratio and vice versa. A

maximum depth of tumour invason of 7.5 mm had highest sensitivity (93.5%) and specificity (92.7%) in detecting increased Lymph node ratio among subjects with SCC

In this study there was no significant difference in mean Lymph node ratio with respect to site of tumor. However, highest lymph node ratio was seen in GBS/ lower alveolus site and lowest was seen in RMT and Hard palate site.

In our study, the mean Lymph node ratio was high in subjects who expired 0.227 ± 0.287 and low in those with Local recurrence (0.117 ± 0.09). This difference in mean Lymph node with respect to outcome at follow up was statistically significant. A lymph node ratio of 0.100 had the highest sensitivity and specificity in detecting poor prognosis among subjects with SCC.

Therefore in our study, patients with higher lymph node ratio were more prone towards an adverse outcome and increase in depth of invasion of tumour was associated with poor prognosis.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Ramesh C. Hospital Based Cancer Registry .Kidwai Memorial Institute of Oncology; 2005.

2) Shah JP ed. In: Oral cavity and oropharynx. Head and Neck Surgery, 2nd edition, New York: Mosby Wolfe, 1996:167-234.

3) Martínez-Gimeno C, Rodríguez EM, Vila CN, Varela CL. Squamous cell carcinoma of the oral cavity: a clinicopathologic scoring system for evaluating risk of cervical lymph node metastasis. Laryngoscope. 1995;105:728-33.

4) Kane SV, Gupta M, Kakade AC, D' Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity.Eur J SurgOncol.2006; 32:795-803.

5) Gil Z, Carlson DL, Boyle JO, Kraus DH, Shah JP, Shaha AR, et al.Lymph node density is a significant predictor of outcome in patients with oral cancer.Cancer. 2009;115:5700-10.

6) Chen CC, Lin JC, Chen KW. Lymph node ratio as a prognostic factor in head and neck cancer patients. Radiation Oncology. 2015;10:181.

7. Hunter, J. Lectures on the Principles of Surgery. From "Surgical Works of John Hunter" by Palmer JF, London 1835, p627.

8. Martin H, Del Valle B, Ehrlich H, Cahan WG. Neck dissection. Cancer. 1951 ;4:441-99.

9) Green FL, Page DL, Fleming ID. Head and neck sites In: The AJCC cancer staging manual 2002, 6th edition. New York: Springer Verlag, 2002; 17-31.

10) Natkinson JC, Gaze MN, Wilson JA eds. Tumours of the lip and oral cavity. In: Stell–Maran Head and Neck Surgery, 4th edition, Oxford: Butterworth Heinemann; 275-377.

11) Cruikshank,W. The anatomy of the absorbing vessels of the body. G. Nicol, London, 1786

12) Sabin,F.R.The lymphatic system in human embryos, with a consideration of the morphology of the system as a whole. Am.J.Anat.1909:9:43-91.

13) Shah JP ed, Cervical Lymph Nodes. In: Head And Neck Surgery, 2nd edition, New-York: Mosby-Wolfe,1996;355-392.

14. Ganly I, Ibrahimpasic T, Patel SG, Shah JP. Tumors of the oral cavity. In: Montgomery PQ, Evans PHR, Gullane PJ, editors. Principles and practice of Head and neck surgery and oncology. 2nd Ed. London: Informa healthcare; 2009. p. 160-71.

15. Vijaykumar KV, Sureshan V, Knowledge, attitude and screening practises of general dentists concerning oral cancer in Bangalore city. Indian J Cancer. 2012;1489-97.

16. Reddy KR. Department of epidemiology and biostatistics (hospital based cancer registry), Kidwai memorial institute of oncology. Available from :http://kidwai.kar.nic.in/statistics.htm.

17. Sankaranarayanan R, Ramdas K, Thomas G. Effect of screening on oral cancer mortality in Kerala, India: a cluster randomized controlled trial. The Lancet. 2005;365:1927-33.

18. Ganly I, Patel GN. Epidemiology and prevention of head and neck cancer. In: Watkinson JC, Gilbert RW, editor. Stell and Maran's textbook of head and neck surgery and oncology. 5th Ed. London: Hodder Arnold; 2012. p. 9-13.

19) Hoffmann D, Sanghvi LD, Wynder EL. Comparative chemical analysis of Indian bidi and American cigarette smoke. Int J Cancer. 14: 49-53.

20) Ward-Booth P ed. Surgical management of marginal tumours of the jaws and oral cavity. In: Peterson LJ, Indresano AT, Marciani RD eds. Principles of oral and maxillofacial surgery, vol.2, Philadelphia: Lippincott-Raven, 1992; 755-762.

21) German J ed. Chromosome mutation and neoplasia. New York: Alan R. Liss, 1983.

22) Guengerich FP. Roles of cytochrome P 450 enzymes in chemical carcinogenesis and cancer chemotherapy. Cancer Res. 1988; 48:2946.

23) Batsakis JG. Pathology of Tumours of the oral cavity. In: Stanley ET, Panje WR. Batsakis JG, Lindberg RD eds. Comprehensive management of Head and Neck tumours 2nd edition. Vol 2. W.B.Saunder Company, Part IV, 1999; 631 – 736.

24) HibbertJ.Oral cavity. In: Kerr AG ed. Scott- Brown's Otolaryngology and Head and Neck Surgery, vol.5, Laryngology and head and neck surgery, 6th edition, Great Britain: Butterworth Heinemann International editions, 1997,chapter 3:1-28.

25) Goedegebuure PS, Eberlein TJ. Tumour biology and tumour markers. In: Townsend CM ed. Sabiston textbook of surgery the biological basis of modern surgical practice. Book I, 16th edition, USA: Harcourt Publishers International Company, 2002; 471-485.

26) Weber RS, Duffey DC. Head and Neck. In: Townsend CM ed. Sabiston textbook of surgery the biological basis of modern surgical practice, Book I, 16th edition, USA: Harcourt publishers International Company, 2001; 533-538.

27)Enab H, Suen J eds. Management of cervical Metastasis in Head and Neck Cancer. In: Advances in Otolaryngology Head and Neck Surgery. Philadelphia: Mosby Inc, 1999; 287-313.

28) Boyd D. Invasion and metastasis. Cancer Metastasis Rev . 1996;15:77–89.

29) Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer. 1972; 29: 1146-1149.

30) Shah JP. Patterns of cervical lymph node metastases from squamous carcinoma of the upper aero-digestive tract. Am J Surg. 1990; 160: 405–409.

31) Shah JP, Lydiatt WM. Buccal mucosa, alveolus, retromolartrigone, floor of mouth, hard palate, and tongue tumours. In: Stanley ET, Panje WR, Batasakis JG, Lindberg RD eds. Comprehensive Management of Head and Neck Tumours. 2nd Edition. Vol 2, Philadelphia: WB Saunders Company 1999; 686-693.

32. Robbins KT, Clayman G, Levine PA, Medina J, Sessions RB, Shaha A, et al. Neck Dissection Classification update. ArchOtolaryngol Head And Neck Surg. 2002; 128:751-758.

33. Hibbert J. Metastatic Neck Disease. In: Kerr AG ed. Scott Brown's Otolaryngology And Head And Neck Surgery, Vol. 5,Laryngology And Head And Neck Surgery,6th Edition, Great Britan: Butterworth Heinmann International Editions,1997,Chapter 17:1-18.

34. Ali S, Tiwari RM, Snow GB. False Positive and False Negative Neck Nodes. Head Neck Surg. 1985; 8:78-82.

35. Michel WM, Vanden B, Castelijns JA, Snow GB. Diagnostic Evaluation of the Neck. In: Medina JE, Weisman RA eds. The Otolaryngology Clinics of North America-Management of Neck in Head and Neck Cancer .Part I. Philadelphia: WBC Saunders company, 1998:585-688.

36. Mc Ivor NP, Freeman JL, Saleem S. Ultrasonography and Ultrasound guided FNAC of Head and Neck Lesion – A Surgical prospective. Laryngoscope. 1994; 104: 669-674.

37. Vanden BMW, Castelijns JA, SetelHV.Occult Metastatic Neck Disease: Detection with Ultrasound And Ultra sound guided Fine Needle Asperation Cytology. Radiology. 1991; 180:457-461.

38. Watkinson JC, Gaze MN, Wilson JA. Metastatic neck Disease. In: Stell And Maran's Head and Neck Surgery, 4th Edition, India: Recd Educational And Professionals Publications Ltd, 2000: 197-214.

39)Edge S, Byrd D R, Compton C C, Fritz A G, Green FL, Trotti A Page DL. Head and neck sites In: The AJCC cancer staging manual 2010, 7th edition. New York: Springer Verlag, 2010; 41-53.

40. Crile GW. Excision of cancer of the head and neck. JAMA. 1906; 47:1780 - 1786.

41.Fisch VP, Siegel ME. Cervical lymphatic system as viewed by lymphography.AnnOtolRhinol Laryngol.1964; 73:869-882.

42. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg.1988, 10:160-167.

43. Rassekh CH, Johnson JT, Myers EN. Accuracy of intraoperative staging of the NO neck in squamous cell carcinoma. Laryngoscope.1995;105:1334-6.

44. Chan SC, Ng SH, Tzu-Chen y, Chang JT, Chen TM. False positive findings on F-18 fluro-2-deoxy-D-glucose positron emission tomography in a patient with nasopharyngeal carcinoma and extensive sinusitis. ClinNucl Med. 2005;30:62-63.

45. Shah JP, Patel GP. Head and neck surgery and oncology. New York, NY: Mosby;2003.

46. Byers RM, El-Naggar AK, Lee YY, Rao B, Fornage B, Terry NH et al. Can we detect or predict the presence of occult nodal metastasis in patients with squamous cell carcinoma of the oral tongue ? Head Neck. 1998;20:138-144.

47. Byers RM, Clayman GL, McGill D, Andrews T, Kare RP, Roberts DB, Goepfertt H. Selective neck dissections for squamous cell carcinoma of the upper digestive tract: patterns of regional failure. Head Neck.1999:21:499-505.

48. Bocca E, Pignataro O. A conservation technique in radical neck dissection. Ann OtoRhinolLaryngol.1967;76:975-87.

49. Breslow A. Tumor thickness, level of invasion and node dissection in stage I cutaneous melanoma. Ann Surg. 1975;182:572-575.

50. Mohit-Tabatabai MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg. 1986;152:351-353.

51. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg. 1986;152:345-350.

52. Asakage T, Yokose T, Mukai K, et al. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. Cancer. 1998;82:1443-1448.

53. Al-Rajhi NM, Khafaga YM, Saleem M, Al-Zahrani AM, Al-Hebshi AS, El-Husseiny GA A study comparing different approaches in managing neck nodes in early carcinoma of the tongue. Saudi Med J. 2002 ;23:1343-6.

54. Clark JR, Naranjo N, Franklin JH, de Almeida J, Gullane PJ. Established prognostic variables in N0 oral carcinoma. Otolaryngol Head Neck Surg. 2006;135:748-753.

55. Fukano H, Matsuura H, Hasegawa Y, Nakamura S. Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. Head Neck. 1997;19:205-10.

56. Melchers LJ, Schuuring E , Van Dijk BAC , De Bock GH , Witjes MJH , Van der Laan BFAM, et al. Tumour infiltration depth P4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. Oral Oncol.2012;38:337-342.

57. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck. 2005;27:1080–91.

58. O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S, et al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. Oral Oncol. 2003;39:386–90.

59. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head Neck. 1995;17:463–72.

60 Prabhu RS, Sheela H, Magliocca KR, Hall WA. Lymph node ratio influence on risk of head and neck cancer locoregional recurrence after initial surgical resection: implications for adjuvant therapy. Head Neck. 2015;108:776-782

61 Xiao LB, Yu JX, Wu WH, Xu FF, Yang SB.Superiority of metastatic lymph node ratio to the 7th edition UICC N staging in gastric cancer.World J Gastroenterol. 2011;17 :5123-30

62 Wu SG, He ZY, Li Q, Sun JY, Li FY, Lin Q,etal.Prognostic value of metastatic axillary lymph node ratio for Chinese breast cancer patients. PLoSOne. 2013;8:61410.

63 Passoni NM, Abdollah F, Suardi N, Gallina A, Bianchi M, TutoloM.Head-to-head comparison of lymph node density and number of positive lymph nodes in stratifying the outcome of patients with lymph node-positive prostate cancer submitted to radical prostatectomy and extended lymph node dissection. UrolOncol. 2014 ;32:29.

64 Ooki A, Yamashita K, Kobayashi N, Katada N, Sakuramoto S, Kikuchi S, Watanabe M Lymph node metastasis density and growth pattern as independent prognostic factors in advanced esophageal squamous cell carcinoma. World J Surg. 2007;31: 2184–2191.

65 Attaallah W, Gunal O, Manukyan M, Ozden G, Yegen C. Prognostic impact of the metastatic lymph node ratio on survival in rectal cancer. Ann Coloproctol. 2013;29: 100–105

66 Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol. 170: 35–41

67 Kunzel J, Mantsopoulous K, Psychogios G, Grundtner, Koch M. Lymph node ratio as a valuable additional predictor of outcome in selected patients with oral cavity cancer. J Oral Maxillofac Surg. 2014;117: 677-684

68 Ebrahimi A, Jonathan RC, Zhang WJ, Elliot MS, Gao K. Lymph Node ratio as an independent prognostic factor in oral squamous cell carcinoma. Head Neck. 2011; 33:1245-1251

69 Sayed SI, Sharma S, Rane P, Vaishampayan S, Talole S, Chaturvedi P, Chaukar D, Deshmukh A, Agarwal JP, D'cruz AK. Can metastatic lymph node ratio (LNR) predict survival in oral cavity cancer patients?. Journal of Surgical Oncology. 2013 ;108:256-63.

70 Susumu S , Masahito T, Keisuke S,Rahima B, TadaharuK.Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. The American Journal of Surgery.2003 ;185: 278–284.

71 Shrime MG, Clement M, Patrick JG, Gilbert RW. Impact of nodal ratio on survival in squamous cell carcinoma of the oral cavity. Head Neck. 2010;31:1129-1136

72 Suslu N, Hosal AS, Sozeri B. Prognostic value of metastatic lymph node ratio in node positive head and neck carcinomas. Am J Otolaryngol. 2010;31:315-319

73 Patel S G, Amit M, Yen T C, Liao C T, Chaturvedi P, Agarwal J P, Kowalski L P, Ebrahimi A. Lymph node density in oral cavity cancer: results of international consortium for outcomes research. British Journal of Cancer.2013;109:2087–2095.

74 Chow TL, Kwan WWY, Fung SC, HoLI.Prognostic value of lymph node density in buccal squamous cell carcinoma. Am J Otolaryngol. 2017 ;38:529-532.

75 Magee WP, Posnick JC, Williams M, McCraw JB. Cancer of the Floor of the mouth and buccal cavity. Surgical Clinics of North America Feb. 1986; 66: 31-57.

76 Terrell JE, Nanavati KA, Esclamado RM, Bishop JK, Bradford CR, Wolf GT.Head and neck cancer-specific quality of life: instrument validation. Arch Otolaryngol Head Neck Surg. 1997; 123:1125-32.

77 Shah JP, Gil Z Current concepts in management of oral cancer–surgery. Oral Oncology.2009;45: 394–401.

78 Yako-Suketomo H, MarugameT.Comparison of time trends in lip cancer incidence (1973-97) in East Asia, Europe and USA, from Cancer Incidence in Five Continents, Vols IV-VIII. Jpn J ClinOncol. 2008 ;38:456-7.

79 Mamelle G, Pampurik J, Luboinski B, Lancar R, Lusinchi A, Bosq J.Lymph node prognostic factors in head and neck squamous cell carcinomas.Am J Surg. 1994 ;168 :494-8.

80 Shingaki S, Takada M, Sasai K, et al.: Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. Am J Surg. 2003;185:278–284.

81 Bhattacharyya N. The effects of more conservative neck dissections and radiotherapy on nodal yields from the neck. Arch Otolaryngol Head Neck Surg. 1998;124: 412–416.

82 Agrama MT, Reiter D, Cunnane MF, Topham A, Keane WM. Nodal yield in neck dissection and the likelihood of metastases. Otolaryngol Head Neck Surg. 2003;128: 185–190.

83 Kim SY, Nam SY, Choi SH, Cho KJ, RohJL.Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma. Ann SurgOncol. 2011;18:2310-7.

84 Kalyani R, Das S, Bindra Singh MS, Kumar H. Cancer profile in Kolar: a ten years study. Indian J Cancer. 2010;47: 160-5.

85 Gupta P, Nandakumar A. Oral cancer scene in India. Oral Diseases. 2008;5:1-2.

86 Narendra H, Tankshali RA. Prevalence and pattern of nodal metastasis in pT4 gingivobuccal cancers and its implications for treatment. Indian journal of cancer. 2010; 47(3):328.

87 Close LG, Burns DK, Merkel M, Schaefer SD. Computed tomography in the assessment of mandibular invasion by intraoral carcinoma. Annals of Otology, Rhinology& Laryngology. 1986 ;95:383-8.

88 Momin MA, Hashimoto K,ondaK,YouT. Validity of Computed Tomography (CT) For the Assessment of Mandibular Bone Invasion by Squamous Cell Carcinoma in the Oral Cavity. JSM Dent. 2014; 2: 1021.

89 Uribe S, Rojas LA, Rosas CF. Accuracy of imaging methods for detection of bone tissue invasion in patients with oral squamous cell carcinoma. Dentomaxillofacial Radiology. 2013;42:20120346.

90 Bhat M, Rao VV, D'souza C, Aramani A, Shivaraj R. Gingivobuccal cancer: an institutional experience of 100 patients. Journal of Evolution of Medical and Dental Sciences. 2014;3:11578-85.

ANNEXURES

Study Title: Lymph Node Ratio And Its Correlation With Primary Site And Depth Of Oral Cavity Squamous Cell Carcinoma

INFORMED CONSENT FORM

I, Mr/Ms/Mrs……., have been explained in a language I can understand, that I will be included in a study which is Lymph node ratio and its correlation to primary site and depth of oral cavity squamous cell carcinoma.

I have been explained that my clinical finding, investigations, intraoperative findings, post-operative specimen and histopathological examination will be assessed and documented for the study purpose.

I have been explained that my participation in this study is entirely voluntary and I can withdraw from the study anytime and this will not affect my relation with my doctor or the treatment for my ailment.

I have understood that all my details found during the course of this study will be kept confidential and while publishing or sharing of the findings, my details will be masked.

I, in my sound mind give full consent to be added as a part of this study.

Signature of the patient:

Name:

Signature of the witness:

Name:

Date: **Place:**

LYMPH NODE RATIO AND ITS CORRELATION WITH PRIMARY SITE AND DEPTH OF ORAL CAVITY SQUAMOUS CELL CARCINOMA

PROFORMA

PERSONAL DETAIL

Name: Age: Sex: | M | F |

Address: Date: Occupation:

Telephone no.: Hospital no: | | | | | | |

E-mail ID:

PRESENTING COMPLAINT

CHIEF COMPLAINTS	YES/NO	SINCE
Presence of ulcer/mass in oral cavity		
Presence of mass/ swelling in neck		
Restricted mouth opening		
Excessive salivation		
Difficulty in swallowing		
Change in voice		
Loss of appetite		
Weight loss		
Generalized weakness		

HISTORY OF PRESENT ILLNESS

Onset: Duration: Progression:

Aggravating factors:

Relieving factors:

H/O trauma: Y/ N

H/O difficulty in swallowing: Y/ N

H/O difficulty in breathing: Y/ N

H/O change in voice: Y/ N

H/O weight loss: Y/ N

PAST HISTORY

COMORBIDITIES	YES/NO	SINCE
Hypertension		
Diabetes Mellitus		
Pulmonary Tuberculosis		
GERD		
Bronchial Asthma		

H/O previous surgery: Y/ N

Treatment History (if any): Surgery/ Radiotherapy/ Chemotherapy

FAMILY HISTORY

Contributory ☐ Not contributory ☐

PERSONAL HISTORY

Loss of appetite: Y/ N

Disturbed sleep: Y/ N

Bowel and bladder disturbances: Y/ N

Habits –

- Tobacco chewing :

Type – Betel nut ☐

Pan masala ☐

Gutka ☐

Duration - Frequency –

Side – Right/ Left/ Both Leaves overnight – Y/ N

Tobacco – Y/ N Lime – Y/ N

Stopped since –

(if stopped)

- Smoking :

Type – Filtered Cigarette

Unfiltered Cigarette ☐

Bidi ☐

Hookha ☐

Pipe ☐

Duration - Packs/Day -

Reverse smoking: Y/ N Stopped since –

(if stopped)

- Alcohol

Duration - Type -

Amount/ day - Stopped since (if stopped):

EXAMINATION:

GENERAL PHYSICAL EXAMINATION

Built: Poor ☐
Medium ☐
Well-built ☐

Nutritional status: Poor ☐
Satisfactory ☐

Temperature: Pulse: BP: RR:

Pallor: Y/ N Icterus: Y/ N Cyanosis Y/ N

Clubbing: Y/ N Lymphadenopathy: Y/ N Edema: Y/ N

LOCAL EXAMINATION

- **Oral Cavity :**

  Mouth opening: Adequate/ Trismus Grade of Trismus (if any):

  Oro-dental Hygiene: Poor/ Satisfactory Nicotine stains: Y/ N

Site: Buccal mucosa ☐

Retromolar Trigone ☐

Gingivo-buccal Sulcus ☐

Tongue ☐

Hard palate ☐

Floor of mouth ☐

Side: Right ☐ Upper ☐

Left ☐ Lower ☐

Type of Lesion:

Verrucous ☐

Ulceroproliferative ☐

Ulcerative ☐

Infiltrative ☐

Dimension:

Extent – Superior:

Inferior:

Anterior:

Posterior:

Greatest antero-posterior diameter (in cms):

Greatest Transverse diameter (in cms)

Edges:

Tender: Y/ N

Skin involvement: Y/ N

Bleeds on touch: Y/ N

Lymph nodes:

Number:

- Level/ s involved:
- Size:
- Consistency:
- Tenderness:
- Mobile/ Fixed:
- Skin over the node:

- **Nose :**

- **Ear :**

SYSTEMIC EXAMINATION:

- Cardio vascular system:
- Respiratory system:
- Abdomen:
- Central nervous system:

CLINICAL DIAGNOSIS :

INVESTIGATIONS :

Hb: RBC: TC: Platelets: DC: N: L: M: E: B:

BT: CT: HIV: Y/ N HbsAg: Y/ N RBS:

CT SCAN/USG NECK:

BIOPSY REPORT:

FNAC:

TREATMENT:

Date of surgery

Surgery done:

Excised specimen: **(Gross)**

- Site:
- Tumor size:
- Tumor thickness:
    - cms away from SUPERIOR margin:
    - cms away from INFERIOR margin:
    - cms away from ANTERIOR margin:
    - cms away from POSTERIOR margin:

Histopathological report:

Of the primary tumor:

Histological type: squamous cell carcinoma

- CONVENTIONAL
- VERUCCOUS
- PAPILLARY
- ACANTHOLYTIC

Histopathological grade:

☐ Well differentiated

☐ Moderately differentiated

☐ Poorly differentiated

Tumor Depth:

Resected Margin of Tumour:

	ANTERIOR	POSTERIOR	SUPERIOR	INFERIOR
FREE FROM TUMOUR				
INVOLVED BY THE TUMOUR				

Vascular invasion: Y/N

Nerve invasion: Y/N

Bone/ Cartilage: Y/N

Lymph node status:

Total no of lymph node:

No of positive nodes:

Level of positive nodes:

Micro-metastasis (<2mm in diameter): ☐ Present ☐ Not identified

Extra-capsular spread: ☐ Present ☐ Not identified

Lymph Node Ratio:

pTNM staging:

Follow up:

KEY TO MASTER CHART

BM: BUCCAL MUCOSA

Ca : CARCINOMA

F : FEMALE

GBS: GINGIVO BUCCAL SULCUS

L: LEFT

LN: LYMPH NODE

M: MALE

M: METASTASIS

MRND: MODIFIED RADICAL NECK DISSECTION

N: NODE

NA: NOT APPLICABLE

PMMC: PECTORALIS MAJOR MYOCUTANEOUS FLAP

DP: DELTOPECTORAL FLAP

R: RIGHT

SOHD: SUPRA OMOHYOID NECK DISSECTION

T: TUMOR

TT: TUMOUR THICKNESS

TD: DEPTH OF TUMOUR

LNR: LYMPH NODE RATIO

No	H.No	age	sex	side	dentition	site	type of lesion	Diagnosis	T	N	M	skin involvement	type of mandibulectomy	Anterior Bony margin	Ant soft tissue margin	posterior soft tissue margin	Superior soft tissue margin	inferior soft tissue margin	Bony erosion in CT	c Stage	Histological type	Invasive front	pTNM	Tumor Size	Max Tumor Thickness in HPE	Max depth of tumor invasion on HPE	Total lymph node	No Of Positive Nodes on HPE	Lymph node ratio	Bone involvement on HPE	Type of bone involvement onHPE	Follow up	Reconstruction	Neck Dissection
1	254303	55	F	R	partialy edentulous	GBS/ alveolus	ulceroproliferative	Ca Right Lower alveolus	T4a	N1	M0	yes	hemimandibulectomy	1.7cm	0.2cm	0.6cm	0.2cm	1.2cm	Absent	IVA	well differentiated	Cohesive	PT4aN1M0	6.5x2.5x1.5 cm	15	8	20	1	**0.05**	Negative	Invasive type	-	bipaddle pmmc	MRND
2	302291	45	F	R	dentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T3	N2b	M0	NO	hemimandibulectomy	1cm	2cm	4cm	1cm	1.8cm	Absent	IV A	well differentiated	Cohesive	pT3N2bM0	2.5x4.5x2cm	20	14	20	3	0.15	Negative	NA	local recurrence	pmmc	MRND
3	209944	35	F	R	dentulous	GBS/ alveolus	ulceroproliferative	Ca right lower alveolus	T4a	N2b	M0	NO	hemimandibulectomy	2cm	0.3cm	3cm	2.5cm	1.9cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	3x1x2cm	20	12	20	3	0.15	bone involved	NA	local recurrence	pmmc	MRND
4	207968	56	F	L	dentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T4a	N1	M0	NO	hemimandibulectomy	2.2cm	0.8cm	2cm	1.5cm	3.5cm	EROSION	IVA	well differentiated	Cohesive	pT3N1M0	4.5x 2.5x2cm	20	12	17	1	0.06	Negative	NA	-	pmmc	MRND
5	77216	45	F	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca Left lower alveolus	T3	N1	M0	NO	hemimandibulectom	0.2cm	0.6cm	2cm	1.5cm	3.5cm	Absent	III	well differentiated	Cohesive	pT2N0M0	3.5x3x1cm	10	4	24	0	0	Negative	NA		pmmc	MRND
6	290502	40	F	R	dentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T4a	N2b	M0	NO	hemimandibulectomy	2cm	1.2cm	3.8cm	1.4cm	1cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	4x3x0.5x2cm	20	15	20	11	0.55	bone involved	Invasive type	Death due to disease	pmmc	MRND
7	102724	75	F	L	edentulous	BM	ulceroproliferative	Ca left Buccal Mucosa	T2	N0	M0	NO	marginalmandibulectomy	1.7cm	1cm	0.3cm	0.7cm	0.5cm	Absent	III	well differentiated	Cohesive	pT2N0M0	2.2x2x1.5cm	15	2	24	0	0.04	Negative	NA	-	buccal pad of fat	SOHD
8	84111	60	F	L	edentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T3	N1	M0	NO	hemimandibulectom	4cm	0.3cm	1.8cm	4cm	1cm	Absent	III	Moderately differentiated	Noncohe	pT2N0M0	3X1x0.5cm	5	1	20	0	0	Negative	NA	-	pmmc	MRND
9	133670	60	F	L	edentulous	BM	ulceroproliferative	Ca left Buccal Mucosa	T3	N2b	M0	no	hemimandibulectom	0.8cm	0.8cm	4.5cm	0.5cm	0.9cm	Absent	IVA	well differentiated	Cohesive	pT3N1M0	5x3x2cm	20	8	20	1	/0.05	Negative	NA	-	pmmc	MRND
10	89014	45	F	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T2	N1	M0	NO	marginalmandibulect	2cm	0.5cm	0.5cm	0.5cm	1.3cm	Absent	III	Moderately differentiated	Cohesive	pT2N1M0	3x2x2cm	20	10	17	1	0.058	Negative	NA	-	buccal pad of fat	MRND
11	98125	40	M	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T4a	N1	M0	NO	hemimandibulectomy	1.5cm	2cm	2.5cm	1.5cm	2.2cm	EROSION	IVA	Moderately differentiated	Cohesive	pT4aN2bM0	3x2x1.5cm	15	10	16	3	0.2	bone involved	Invasive type	-	pmmc	MRND
12	107768	65	F	L	partialy edentulous	BM	ulceroproliferative	Ca left Buccal Mucosa	T3	N1	M0	NO	hemimandibulectomy	1.1 cm	0.8cm	0.5cm	0.2cm	1.6cm	Absent	III	well differentiated	Cohesive	pT3N1M0	5x3x1.2cm	12	8	20	1	0.05	Negative	NA	-	pmmc	MRND
13	146868	45	F	R	dentulous	GBS/ alveolus	ulceroproliferative	Ca right lower	T2	N2b	M0	NO	marginalmandibulect	1.5cm	0.9mm	1cm	1.6cm	2.7cm	Absent	IVA	poorly differentiated	Cohesive	pT2N0M0	3x4x2cm	20	5	16	0	**0**	Negative	NA	local recurrence	buccal pad of fat	MRND
14	106142	45	F	L	dentulous	RMT	ulceroproliferative	Ca left retro molar trigone	T4a	N2b	M0	Yes	hemimandibulectomy	2.5cm	0.5cm	0.8cm	0.8cm	1.6cm	Absent	IVA	well differentiated	Cohesive	pT2N0M0	2.2x1.5x1.8m	18	5	24	0	0	Negative	NA	-	bipaddle pmmc	MRND
15	76003	45	F	R	dentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T4a	N1	M0	YES	hemimandibulectomy	0.7cm	0.3cm	3cm	1cm	3.5cm	Absent	IVA	well differentiated	Cohesive	pT4aN0M0	3.2x2.4x1.5cm	15	4	16	0	0	Negative	NA	-	bipaddle pmmc	MRND
16	127365	82	F	R	edentulous	GBS/ alveolus	ulceroproliferative	Ca Right Lower alveolus	T3	N1	M0	NO	hemimandibulectomy	2.7cm	0.7cm	1cm	1.8cm	0.5cm	ABUTS	III	moderately differentiated	Cohesive	pT2N0M0	2.6x1.7x1cm	10	3	24	0	0	Negative	NA	death	pmmc	MRND
17	134922	35	M	L	dentulous	BM	ulcerative	Ca Left Buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	2cm	2cm	6.8cm	1.4cm	1.4cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	4.5x2x1.2cm	12	4	15	0	0	Negative	NA	-	bipaddle pmmc	MRND
18	192406	46	F	L	dentulous	BM	ulceroproliferative	Ca left Buccal Mucosa	T4a	N1	M0	Yes	hemimandibulectomy	2cm	2cm	0.8cm	0.2cm	0.8cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	4.5x4.5x1.5cm	15	4	21	0	0	Negative	NA	regional recurrence	bipaddle pmmc	MRND
19	132753	62	F	R	edentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T3	N2b	M0	NO	hemimandibulectomy	1.5cm	1 cm	5cm	0.7cm	2.5cm	ABUTS	III	Moderately differentiated	Cohesive	pT3N1M0	4.5x2x1.5cm	15	9	20	1	/0.05	Negative	NA	-	pmmc	MRND
20	149637	45	F	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T4a	N1	M0	YES	hemimandibulectom	2cm	2cm	1.5cm	2cm	2.2cm	Absent	IVA	well differentiated	Cohesive	pT3N1M0	4.3x4x2cm	20	10	16	1	/0.06	Negative	NA	-	bipaddle pmmc	MRND
21	154812	65	F	L	partialy edentulous	BM	ulceroproliferative	Ca left Buccal Mucosa	T3	N1	M0	NO	hemimandibulectomy	2cm	0.5cm	2cm	0.5cm	1.2cm	Absent	III	well differentiated	Cohesive	pT3N0M0	4.2x3x1cm	10	3	24	0	0	Negative	NA	-	supraclavicular	MRND
22	233148	43	F	R	dentulous	GBS/ alveolus	ulcerative	Ca right lower alveolus	T3	N1	M0	NO	hemimandibulectomy	3cm	0.3cm	1.5cm	0.8cm	0.5cm	ABUTS	III	Moderately differentiated	Cohesive	pT3N0M0	4.2x3x0.8cm	8	2	16	0	0	Negative	NA	local recurrence	pmmc	MRND
23	195419	63	F	L	partialy edentulous	BM	ulceroproliferative	Ca Left Buccal Mucosa	T4a	N1	M0	yes	hemimandibulectomy	1.2cm	1.8cm	2cm	1cm	2.7cm	Absent	IVA	Moderately differentiated	Cohesive	pT4aN0M0	3x2x2cm	20	6	19	0	0	Negative	NA	-	pmmc	MRND
24	175050	42	F	R	dentulous	BM	ulceroproliferative	Ca Right buccal mucosa	T3	N1	M0	no	hemimandibulectomy	4.56cm	0.2cm	1cm	2.5cm	3.1cm	Absent	III	well differentiated	Noncohesive	pT2N0M0	2.5x1.5x1cm	10	3	16	0	0	Negative	NA	-	pmmc	MRND
25	202488	65	M	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N1	M0	YES	hemimandibulectomy	2cm	1.2cm	1.1cm	1.5cm	1cm	Absent	IVA	well differentiated	Cohesive	pT4aN1M0	4x1.5x1.8cm	18	10	20	1	**0.05**	Negative	NA	-	bipaddle pmmc	mrnd
26	210128	70	M	R	partialy edentulous	GBS/ alveolus	ulceroproliferative	Ca right lower alveolus	T4a	N2b	M0	YES	hemimandibulectomy	1.1cm	5cm	4cm	1.5cm	2.1cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	3.5x3.5x2cm	20	12	20	3	0.15	bone involved	Invasive type	Local recurrence	bipaddle pmmc	MRND
27	137704	49	F	R	dentulous	BM	ulceroproliferative	Ca right buccal	T4a	N2b	M0	YES	hemimandibulectomy	1.5cm	2cm	2.7cm	2cm	2.2cm	Absent	IVA	well differentiated	Cohesive	pT4aN1M0	4x3x1.2cm	12	10	20	1	0.05	Negative	NA		PMMC+DP	MRND
28	172342	50	M	R	dentulous	BM	ulcerative	Ca right buccal mucosa	T4a	N2b	M0	YES	hemimandibulectomy	1 cm	1.4cm	3.5cm	2cm	2cm	Absent	IVA	Moderately differentiated	Cohesive	pT4aN2bM0	4x3x2cm	20	15	20	5	0.25	Negative	NA	locoregional recurrence	PMMC+DP	MRND
29	245886	40	M	L	dentulous	RMT	ulcerative	Ca left retro molar trigone	T4a	N0	M0	NO	hemimandibulectomy	4cm	3.5cm	2.5cm	1cm	1.7cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	2.1x0.5x2.5cm	25	5	24	0	0	Negative	NA	-	pmmc	MRND
30	242458	40	M	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T4a	N1	M0	NO	hemimandibulectomy	3cm	3cm	1cm	0.8cm	0.5cm	EROSION	IVA	well differentiated	Cohesive	pT4aN1M0	4x0.8x1.5cm	15	10	24	1	0.04	bone involved	Invasive type	-	pmmc	mrnd
31	190010	38	F	L	dentulous	GBS/ alveolus	ulcerative	Ca left lower alveolus	T4a	N1	M0	NO	hemimandibulectom	4cm	1.6cm	4cm	2cm	1cm	EROSION	IVA	well differentiated	Cohesive	pT2N1M0	3x0.5x1cm	10	8	24	1	0.04	Negative	NA	-	pmmc	mrnd
32	207968	56	F	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca Left lower alveolus	T4a	N1	M0	NO	hemimandibulectomy	2cm	1.4cm	3.5cm	2 cm	0.5cm	EROSION	IVA	well differentiated	Cohesive	pT3N1M0	4.5x1.4x1.5cm	15	8	24	1	0.04	Negative	NA	-	pmmc	mrnd
33	187119	45	F	R	dentulous	BM	ulcerative	Ca right buccal	T3	N2b	M0	NO	hemimandibulectom	2.8cm	1.5cm	2.5cm	0.2cm	1.5cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	5x3x2.2cm	22	7	20	0	0	Negative	NA	-	Spiral pmmc	MRND
34	200982	58	M	R	dentulous	GBS/ alveolus	ulceroproliferative	Ca right lower alveolus	T4a	N1	M0	NO	hemimandibulectomy	0.5cm	0.8cm	0.3cm	1.8cm	0.2cm	EROSION	IVA	well differentiated	Noncohesive	pT4aN2bM0	3x2x1.8cm	18	12	15	2	0.13	bone involved	NA	spinal Metastasis/death	pmmc	MRND
35	225949	65	M	R	partialy edentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T4a	N1	M0	YES	hemimandibulectomy	2.5cm	2cm	3.5cm	2cm	2cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	3.5x3.5x2cm	20	12	19	5	0.3	bone involved	Invasive type	regional recurrence	bipaddle pmmc	MRND
36	247143	55	F	L	dentulous	BM	verrucous lesion	Ca left buccal mucosa	T3	N2b	M0	NO	hemimandibulectomy	1.5cm	1cm	1.4cm	0.6cm	1cm	Absent	IVA	well differentiated (veruccous)	Noncohesive	pT3N0M0	4.5x3x1cm	10	3	20	0	0	Negative	NA	-	pmmc	mrnd
37	227014	35	F	R	dentulous	BM	ulceroproliferative	Ca right Buccal Mucosa	T4a	N2b	M0	yes	hemimandibulectomy	2.5cm	2cm	4cm	0.8cm	0.5cm	ABUTS	IVA	well differentiated	Cohesive	pT4aN2bM0	4x3x1.8cm	18	12	24	2	**0.08**	bone involved	Invasive type	-	bipaddle pmmc	MRND
38	305515	60	F	R	edentulous	GBS/ alveolus	ulceroproliferative	Ca Right Lower alveolus	T4a	N1	M0	Yes	hemimandibulectomy	2.4cm	2cm	1cm	1.5cm	0.5cm	EROSION	IVA	well differentiated	Cohesive	PT4aN2bM0	4.5x2.5x1.5cm	15	10	20	3	0.15	bone involved	Invasive type	-	bipaddle pmmc	MRND
39	377932	60	F	L	partialy edentulous	RMT	ulceroproliferative	Ca left retro molar trigone	T4a	N2b	M0	yes	hemimandibulectomy	1.7cm	0.2cm	0.6cm	0.2cm	1.2cm	Absent	IVA	well differentiated	Cohesive	PT4aN0M0	6.5x2.5x2cm	20	6	16	0	0	bone involved	Invasive type		bipaddle pmmc	MRND
40	388812	55	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T3	N1	M0	no	marginalmandibulectomy	1cm	2cm	4cm	1cm	1.8cm	Absent	III	well differentiated	Cohesive	pT2N0M0	2.5x1.5x0.8cm	8	2	24	0	0	Negative	NA		pmmc	MRND
41	398172	45	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N2b	M0	yes	hemimandibulectomy	2cm	0.3cm	3cm	2.5cm	1.9cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	4x1.5x1.8cm	18	10	20	3	0.15	Negative	NA		bipaddle pmmc	MRND
42	388115	35	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T2	N1	M0	no	NA		0.8cm	2cm	1.5cm	3.5cm	Absent	III	well differentiated	Cohesive	pT2N0M0	3.5x 2.5x1cm	10	2	20	0	0	NA	NA		buccal pad of fat	SOHD
43	370866	56	F	R	partialy edentulous	BM	ulceroproliferative	Ca right buccal mucosa	T2	N1	M0	no	NA		0.6cm	2cm	1.5cm	3.5cm	absent	III	well differentiated	Cohesive	pT2N0M0	3.2x3x1cm	10	3	21	0	0	NA	NA		buccal pad of fat	SOHD
44	397364	45	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	2cm	1.2cm	3.8cm	1.4cm	1cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	5.3x0.5x1.6cm	16	12	20	3	0.15	bone involved	Invasive type	regional recurrence	bipaddle pmmc	MRND
45	391792	39	M	L	dentulous	Tongue	ulceroproliferative	Ca left lateral border	T2	N1	M0	No	NA		1cm	0.3cm	0.7cm	0.5cm	Absent	III	well differentiated	Cohesive	pT2N0M0	2.2x2x1cm	10	3	22	0	0	Negative	NA		hemiglossectomy	MRND
46	389753	53	F	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T3	N1	M0	no	hemimandibulectomy	4cm	0.3cm	1.8cm	4cm	1cm	Absent	III	Moderately differentiated	Noncohesive	pT2N0M0	3X2x0.6cm	6	2	15	0	0	Negative	NA		pmmc	MRND
47	405431	60	F	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N2b	M0	yes	hemimandibulectomy	0.8cm	0.8cm	4.5cm	0.5cm	0.9cm	Absent	IVA	well differentiated	Cohesive	PT4aN0M0	3x2x2.5cm	25	5	16	0	0	Negative	NA	regional recurrence	bipaddle pmmc	MRND
48	406691	64	F	R	partialy edentulous	BM	ulceroproliferative	Ca right buccal mucosa	T4a	N2b	M0	yes	hemimandibulectomy	2cm	0.5cm	0.5cm	0.5cm	1.3cm	Absent	IVA	Moderately differentiated	Cohesive	pT4aN2bM0	5.5x1x1.8cm	18	10	24	2	0.08	Negative	NA		bipaddle pmmc	MRND
49	414178	56	F	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N2b	M0	yes	hemimandibulectomy	1.5cm	2cm	2.5cm	1.5cm	2.2cm	EROSION	IVA	Moderately differentiated	Cohesive	pT4aN0M0	5x2x1.5cm	15	5	19	0	**/0**	bone involved	Invasive type		bipaddle pmmc	MRND
50	418403	40	F	R	dentulous	BM	ulceroproliferative	Ca right buccal	T4a	N1	M0	yes	hemimandibulectom	1.1 cm	0.8cm	0.5cm	0.2cm	1.6cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	5x3x0.8cm	5	1	22	0	/0	Negative	NA		bipaddle pmmc	MRND
51	398653	54	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	1.5cm	0.9mm	2cm	1.6cm	2.7cm	Absent	IVA	poorly differentiated	Cohesive	pT4aN2bM0	5x4x1.6cm	16	12	16	2	/0.13	Negative	NA		bipaddle pmmc	MRND
52	412155	50	M	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T3	N1	M0	NO	marginalmandibulectomy	2.5cm	0.5cm	0.8cm	0.8cm	1.6cm	Absent	III	well differentiated	Cohesive	pT2N0M0	2.2x1.5x1cm	10	2	21	0	/0	Negative	NA		radial forearm free flap	MRND
53	416887	48	F	L	dentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	0.7cm	0.3cm	3cm	1cm	3.5cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	4.5x3.4x1.5cm	15	5	17	0	/0	Negative	NA		bipaddle pmmc	MRND
54	375463	32	M	L	dentulous	Tongue	ulceroproliferative	Ca left lateral border of tongue	T3	N2b	M0	no	hemimandibulectomy	2.7cm	0.7cm	1cm	1.8cm	0.5cm	ABUTS	IVA	well differentiated	Cohesive	pT3N1M0	2.6x1.7x1cm	10	5	20	1	0.05	Negative	NA		pmmc	MRND
55	421820	45	F	L	dentulous	GBS/ alveolus	ulceroproliferative	Ca Left lower alveolus	T3	N2b	M0	no	marginalmandibulectomy	2cm	2cm	6.8cm	1.4cm	1.4cm	Absent	IVA	well differentiated	Cohesive	pT2N2bM0	1.5x1x1.8cm	18	12	20	3	0.15	Negative	NA	regional recurrence	forehead flap	MRND

56	422674	35	F	L	dentulous	BM	ulcerative	Ca left buccal mucosa	T3	N0	M0	no	marginalmandibulectomy	2cm	2cm	0.8cm	0.2cm	0.8cm	Absent	III	well differentiated	Cohesive	pT3N0M0	4.5x4.5x2.0 cm	20	12	16	0	0	Negative	NA		pmmc	SOHD
57	422695	50	F	L	partialy edentulous	GBS/ alveolus	ulceroproliferative	Ca left lower alveolus	T3	N2b	M0	no	hemimandibulectomy	1.5cm	1 cm	5cm	0.7cm	2.5cm	ABUTS	IVA	Moderately differentiated	Cohesive	pT3N2bM0	4.5x2x1.5cm	15	11	17	2	0.12	Negative	NA	local recurrence	pmmc	MRND
58	430291	70	F	R	edentulous	BM	ulceroproliferative	Ca right buccal	T4a	N1	M0	yes	hemimandibulectom	2cm	2cm	1.5cm	2cm	2.2cm	Absent	IVA	well differentiated	Cohesive	pT4aN0M	4.3x4x2cm	20	5	15	0	0	Negative	NA		bipaddle pmmc	MRND
59	422635	65	F	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T3	N2b	M0	no	hemimandibulectomy	2cm	0.5cm	2cm	0.5cm	1.2cm	Absent	IVA	well differentiated	Cohesive	pT3N0M0	4x3x1.0cm	10	2	25	0	0	Negative	NA		pmmc	MRND
60	445335	50	M	R	partialy edentulous	BM	ulceroproliferative	Ca right buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	3cm	0.3cm	1.5cm	0.8cm	0.5cm	ABUTS	IVA	Moderately differentiated	Cohesive	pT4aN0M0	4x3x2cm	20	5	21	0	0	Negative	NA		bipaddle pmmc	MRND
61	438964	59	F	L	partialy edentulous	Tongue	ulcerative	Ca left lateral border of tongue	T3	N1	M0	no	hemimandibulectomy	1.2cm	1.8cm	2cm	1cm	2.7cm	Absent	III	Moderately differentiated	Cohesive	pT3N0M0	3x2x1cm	10	3	20	0	0	Negative	NA		pmmc	MRND
62	442505	50	F	L	partialy edentulous	BM	ulceroproliferative	Ca left buccal mucosa	T4a	N2b	M0	yes	hemimandibulectomy	4.56cm	0.2cm	1cm	2.5cm	3.1cm	Absent	IVA	well differentiated	Noncohesive	pT4aN0M0	2.5x1.5x1.8 cm	18	5	24	0	0	Negative	NA		bipaddle pmmc	MRND
63	442257	45	F	R	dentulous	BM	ulceroproliferative	Ca right buccal mucosa	T4a	N1	M0	yes	hemimandibulectomy	2cm	1.2cm	1.1cm	1.5cm	1cm	EROSION	IVA	well differentiated	Cohesive	pT4aN0M0	2x1.5x1.2cm	12	3	21	0	0	Negative	NA		bipaddle pmmc	MRND
64	451226	60	F	R	partialy edentulous	BM	ulceroproliferative	Ca right buccal mucosa	T3	N1	M0	no	marginalmandibulectomy	1.1cm	5cm	4cm	1.5cm	2.1cm	Absent	III	well differentiated	Cohesive	pT3N0M0	3.5x3.5x1.5 cm	15	5	19	0	0	negative	Invasive type		supraclavicular	SOHD
65	449181	37	F	R	dentulous	Tongue	ulceroproliferative	Ca right lateral	T2	N1	M0	no	NA		2cm	2.7cm	2cm	2.2cm	Absent	III	moderately diffrentiated	Cohesive	pT2N0M0	3x2x2cm	20	5	24	0	0	Negative	NA		mrnd	
66	100218	60	F	R	partialy edentulous	GBS/ alveolus	ulceroproliferative	Ca right lower alveolus	T3	N1	M0	no	hemimandibulectomy	2cm	1.4cm	3.5cm	2cm	2cm	Absent	III	Moderately differentiated	Cohesive	pT3N0M0	4.5x3x1.6cm	16	5	16	0	0	Negative	NA		forehead flap	MRND
67	102644	75	F	L	dentulous	BM	ulcerative	ca left buccal mucosa	T3	N1	M0	yes	hemimandibulectomy	4cm	3.5cm	2.5cm	1cm	1.7cm	Absent	III	well differentiated	Cohesive	pT3N0M0	2.1x0.5x1.5 cm	15	3	22	0	0	Negative	NA		pmmc	MRND
68	106142	45	F	L	dentulous	BM	ulcerative	ca left buccal mucosa	T4a	N2b	M0	yes	hemimandibulectom	3cm	3cm	1cm	0.8cm	0.5cm	EROSION	IVA	well differentiated	Cohesive	pT4aN0M	4x0.8x2cm	20	4	17	0	0	bone involved	Invasive type		bipaddle pmmc	MRND
69	102692	48	F	R	dentulous	Hard palate	ulceroproliferative	Ca right hard palate	T3	N1	M0	no		4cm	1.6cm	4cm	2cm	1cm	Absent	III	well differentiated	Cohesive	pT2N0M0	1x0.5x2.5cm	25	7	16	0	0	Negative	NA		forehead flap	MRND
70	107768	65	F	L	partialy edentulous	BM	ulcerative	Ca left buccal mucosa	T4a	N0	M0	no	hemimandibulectomy	2cm	1.4cm	3.5cm	2 cm	0.5cm	EROSION	IVA	well differentiated	Cohesive	pT3N0M0	4.5x1.4x2cm	20	8	19	0	0	Negative	NA		pmmc	MRND
71	117366	50	F	L	partialy edentulous	GBS/ alveolus	ulceroproliferative	Ca Left lower alveolus	T4a	N2b	M0	Yes	hemimandibulectomy	2.8cm	1.5cm	2.5cm	0.2cm	1.5cm	EROSION	IVA	well differentiated	Cohesive	pT4aN2bM0	5x3x1.8cm	18	12	16	2	/0.13	Negative	NA	regional recurrence	PMMC+DP	MRND
72	102915	48	F	L	partialy edentulous	GBS/ alveolus	ulcerative	Ca Left lower alveolus	T3	N1	M0	no	hemimandibulectomy	0.5cm	0.8cm	0.3cm	1.8cm	0.2cm	ABUTS	III	well differentiated	Noncohesive	pT2N0M0	3x2x1.8cm	18	4	16	0	0/16	Negative	NA		pmmc	MRND