“EVALUATION OF TUMOUR VOLUME AS A PROGNOSTIC FACTOR IN LOCOREGIONAL OUTCOME OF LOWER GINGIVOBUCCAL CANCERS”

By

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DISSERTATION SUBMITTED TO

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

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY IN

OTORHINOLARYNGOLOGY

Under the Guidance of

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to be submitted to

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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 Devaraj Urs 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 and Dr.Naba Kumar Singh Associate Professor, Department of Radiology, 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 Devaraj Urs Medical College, Tamaka, Kolar, for his encouragement and advice during the course of this study.

I would like to convey immense gratitude and respect to Dr Sagayaraj A, Associtae Professor Department of Otorhinolaryngology, Sri Devaraj Urs Medical College, Kolar for his constant guidance, encouragement and support during the course of the study and in completing the dissertation.

I would like to express my gratitude to Dr .R.P.Deo – visiting Professor, Dr Kouser Mohammadi, Dr Abhilasha K, Dr Harshitha T.R, Dr Prashanth Babu – Assistant professors, Dr Sreeharsha M, Dr Sumanth, Dr Linu Thomas, Dr Balan Ashok Kumar, Dr Manna, Dr Shashank, Dr Indu Varsha, Dr Swpanthi, Dr Prathyusha , Dr Anjali- Senior Residents 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 Dr Aishwaraya, Dr Harshitha Narayanaswamy, Dr Harshitha, Dr Vishwashanthi, Dr Shreenidhi, Dr Niveditha and my beloved 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.Manjula Subramani, my mother, who has been an infinite source of inspiration and love. I would like to thank my uncle Mr.Kenche Gowda, my brother Manjunath Gowda and all my cousins. I thank them for blessing me with this opportunity and helping me during my post-graduation course.

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

Dr. BRINDHA.H.S

ABSTRACT

BACKGROUND

Head and neck cancers are the sixth most prevalent cancer across the globe but are the most common group of malignancies in India. Oral cavity cancer accounts for almost 50% of the head and neck cancers in India. 60% to 80% of these patients present with advanced disease as compared to 40% in developed countries.

Treatment protocol and prognosis vary widely and are based on the TNM staging of the disease at the time of diagnosis. Till 2017 Tumour (T) -classified by a subjective and two-dimensional measurement. From 2018 Depth of invasion has been incorporated in T-classification. T-classification fails to define the true three-dimensional volume which is more reliable tumour load.

The five years overall survival in these patients with locally advanced lesions is only about 50%. Therefore, it is important to identify patients who are at a higher risk for locoregional recurrence, so that aggressive treatment can be given to them. Large volume tumours have a necrotic core which does not respond to radiotherapy. Surgical resection of such tumours and adjuvant radiotherapy is also challenging due to close proximity to important structures and wide field Radiotherapy.

OBJECTIVES

(1) To determine tumour volume by pre-operative imaging of the tumour, clinical measurement and by histopathological examination of the resected specimen in patients with squamous cell carcinoma of buccal mucosa and lower gingivobuccal sulcus.

(2) To document the number and site of metastatic lymph nodes in the above patients by histopathological examination.

(3) To follow up the above patients for a minimum period of 6 months following treatment and correlate tumour volume with the locoregional outcome.

METHODS

We conducted this study at R L Jalappa Hospital and research in Kolar to document the tumour volume in oral cancers clinically staged T2 and above and treated with curative intent. However, tumours found to T4 on histopathology (skin and bone involvement) were excluded as skin or bone involvement can make a tumour aggressive irrespective of its size or volume.

We aimed to correlate the tumour volume with oncological outcomes like involvement of regional lymph nodes and recurrences. Tumour volume was calculated by measurements taken radiologically, clinically and by histopathology. Tumour volume was calculated as a product of greatest dimensions in length, breadth and thickness of tumour.

RESULTS : - In our study, majority of the patients had pathological T2 (68%) tumours, the rest had T3 tumours (32%). We observed that cervical lymph node metastasis was found in 13 out of 51 patients with T2 disease (25%) and 8 out of 24 patients in T3 disease (33.3%) The average tumour volume of T2 tumours clinically was 12.4cm^3, radiologically was 10.5cm^3 and on histopathology it was 7.1cm^3. the average tumour volume of T3 tumours on radiology was 22.6cm^3, clinically 24.2cm^3, histopathology it was 14.4cm^3. In our study, in patients who had recurrences the average tumour volume was found to be more than 15cm3 on clinical examination and was 12.7cm^3 on radiology and was more than 8cm^3 on histopathology. Among 6 recurrences in our study patients with low tumour volume i.e. 2 patients had close margins of resection (less than 5mm after formalin fixation), however they had depth of invasion more than 6mm. The tumour volume was higher in patients who had recurrence as compared to patients who are alive and disease free.

Depth of invasion of more than 5mm was a bad prognostic factor in our study. All 6 patients who recurred in our study had depth of invasion more than 6mm. According to the recent AJCC staging system, Depth of more than 5mm is considered locally aggressive disease and depth of more than 10mm is considered advanced disease. Depth of invasion is more representative than tumour thickness as a prognostic factor because it indicates tumour aggressiveness and penetration into surrounding tissue.

In our study, tumour volume correlated with lymph node metastasis and recurrence. Thickness of the tumour also had a positive correlation with lymph node metastasis, as tumour thickness is indirectly contributing to tumour volume. Depth of invasion more than 5mm was a poor prognostic factor. Close margins of resection (<5mm after formalin fixation) was found to be another bad prognostic factor. Our findings showing positive correlation of tumour volume with staging, lymph node metastasis and recurrence was similar to other studies particularly in Brazil and other parts of India where larger tumour volume correlated with disease aggressiveness and lymph node metastasis.

CONCLUSION

Tumour volume is a reliable indicator of tumour load and therefore has a significant impact on prognosis in oral cancers, when adverse factors like skin and bone involvement are excluded Tumours with larger volume have a higher chance of recurrence. Tumours with larger volume have higher frequency of lymph node metastasis. Tumour thickness has also correlated with lymph node metastasis, as tumour thickness also contributes to tumour volume. Depth of invasion of more than 5mm is a poor prognostic factor. Close margin of resection (<5mm after formalin fixation) is a bad prognostic factor.

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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
LN	Lymph node
TV	Tumour Volume
TT	Tumour Thickness
DOI	Depth of Invasion

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INTRODUCTION

Head and neck cancer are the sixth most prevalent cancer across the globe but is the most common group of malignancies in India. Oral cavity cancer accounts for almost 50% of the head and neck cancers in India. 60% to 80% of these patients present with advanced disease as compared to 40% in developed countries.[1] Head and Neck cancers have emerged as a major public health problem in India due to addictions and change in life style.[2]

Treatment protocol and prognosis vary widely and are based on the TNM staging of the disease at the time of diagnosis. Till 2017 Tumour (T) - classified by a subjective and two-dimensional measurement. From 2018 Depth of invasion has been incorporated in T-classification. T-classification fails to define the true three-dimensional volume which is more reliable of Tumour load.[3]

The five years overall survival in these patients with locally advanced lesions is only about 50%. The major cause of morbidity and mortality in these patients is locoregional recurrence. Therefore, it is important to identify patients who are at a higher risk for locoregional recurrence, so that aggressive treatment can be given to them. Large volume tumours have a necrotic core which does not respond to radiotherapy. Surgical resection of such tumours and adjuvant radiotherapy is also challenging due to close proximity to important structures and wide field Radiotherapy.

A few studies in literature have shown that Tumour volume is an important factor affecting prognosis as it is the actual tumour load and therefore influences selection of treatment and eventual prognosis. Depth of the tumour and site of the tumour are other important factors. There is paucity of literature correlating tumour thickness, tumour volume and locoregional control (recurrence) in lower gingivobuccal cancers in southern India. Therefore, this study was undertaken to document the oncological outcome (recurrence) following treatment and the impact of tumour volume on it.

REVIEW OF LITERATURE

HISTORY OF CANCER

The oldest description of cancer dates back to 3000-1500 BC. Carcinoma in Greek means a crab. Its Latinized form is “cancer”. Cancer is a term used to characterize abnormal growth of cells, which invade normal tissue and spread to organs.

Roudolf Virchow, the “founder of cellular pathology” provided the pathologic basis for the study of cancer, which gave us a better understanding of the disease process. This in turn laid the basis for the development of cancer surgery. The excised specimen should be examined & a precise diagnosis can be arrived at. More importantly, the pathologists 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 “mobile”, then it could be treated by surgery.[4] 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 he recommended that “the tumour and its lymphatic drainage should be 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 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 1906 A.D. His classic report provides the basis for the technique of radical neck dissection as it is practiced today.

The first “commando” operation, 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 where in the primary tumour in oral cavity, oropharynx is removed in continuity with a segment of mandible along with a neck dissection.[5]

Stephan Ariyan in 1979 A.D described the pectoralis major myo-cutaneous 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 and micro vascular free tissue transfer for reconstruction, development in anaesthesia and transfusion techniques, the prognosis of cancer surgery improved significantly.

ORAL CAVITY - ANATOMY

The various anatomical sites within the oral cavity as described by the American Joint Committee for Cancer staging[6] 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.

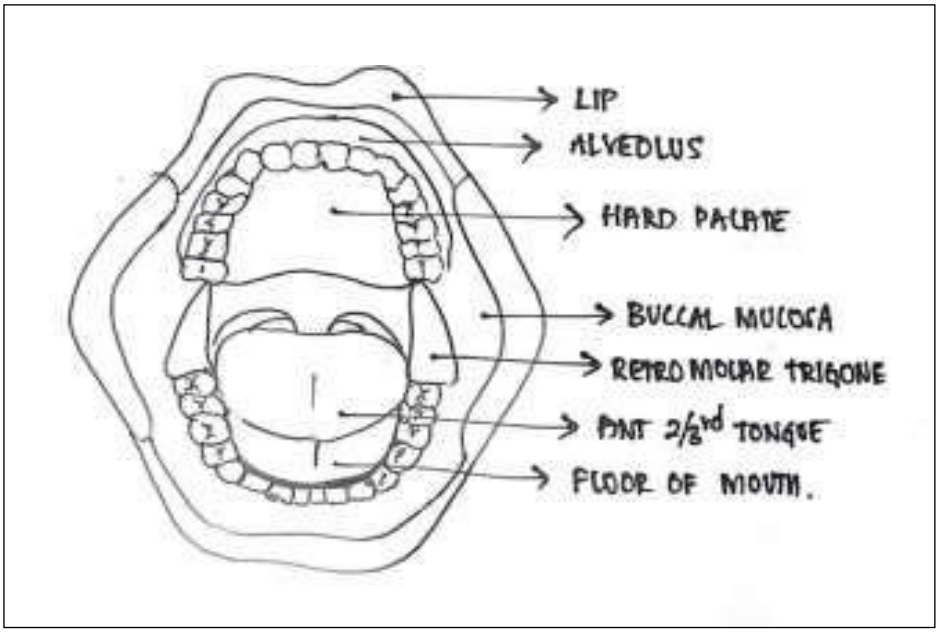


Fig 1: - Oral cavity - subsites

Lip: The lip begins at the vermilion border of the skin. The vermilion surface is that portion of the lip that comes into contact with the opposing lip. It is divided into an upper and lower lip, which join at the commissures of the mouth.

Buccal mucosa: It is the mucous membrane lining of the inner surface of the cheek and lips from the line of contact of the lips to the line of attachment of mucosa to the alveolar ridge (upper and lower) and to the pterygomandibular raphe.

Lower alveolar ridge: Mucosa lining the alveolar process of the mandible from line of insertion in buccal sulcus to floor of mouth mucosa. Posteriorly up to the ascending ramus of the mandible.

Upper alveolar ridge: Mucosa lining the alveolar process of the maxilla, extending from the line of attachment in the upper gingivo-buccal sulcus to the hard palate. Posterior margin extending up to superior end of pterygopalatine arch.

Retromolar gingiva (Retromolar trigone): This is a triangular area over the ascending ramus of the mandible lined by mucosa. Inferior border is formed by lower last molar tooth and apex is at maxillary tuberosity.

Floor of the mouth: This is a semilunar space over the base of tongue muscles i.e. mylohyoid and hyoglossus muscles, extending from the inner surface of the mandibular alveolar ridge to the ventral surface of the tongue. Lower part of anterior pillar of the tonsil forms the posterior boundary. It is divided into two sides by the frenulum of the tongue and contains opening of the submandibular and sublingual salivary gland ducts.

Hard palate: Area between the two-upper alveolus, lined by mucous membrane, formed by palatine process of maxilla. 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 posteriorly. Inferiorly it extends up to the junction of the floor of the mouth at the under-surface of the tongue. It is composed of four areas: the lateral borders, the tip, the ventral surface and the dorsum.

ORAL CAVITY – BLOOD SUPPLY

Branches of external carotid artery provide blood supply to oral cavity. Lingual arteries provide blood supply to the tongue. The lips, buccal mucosa and alveolar ridges receive its blood supply from facial arteries, internal maxillary and inferior alveolar arteries. Palate and upper alveolus are supplied by greater palatine arteries.[7]

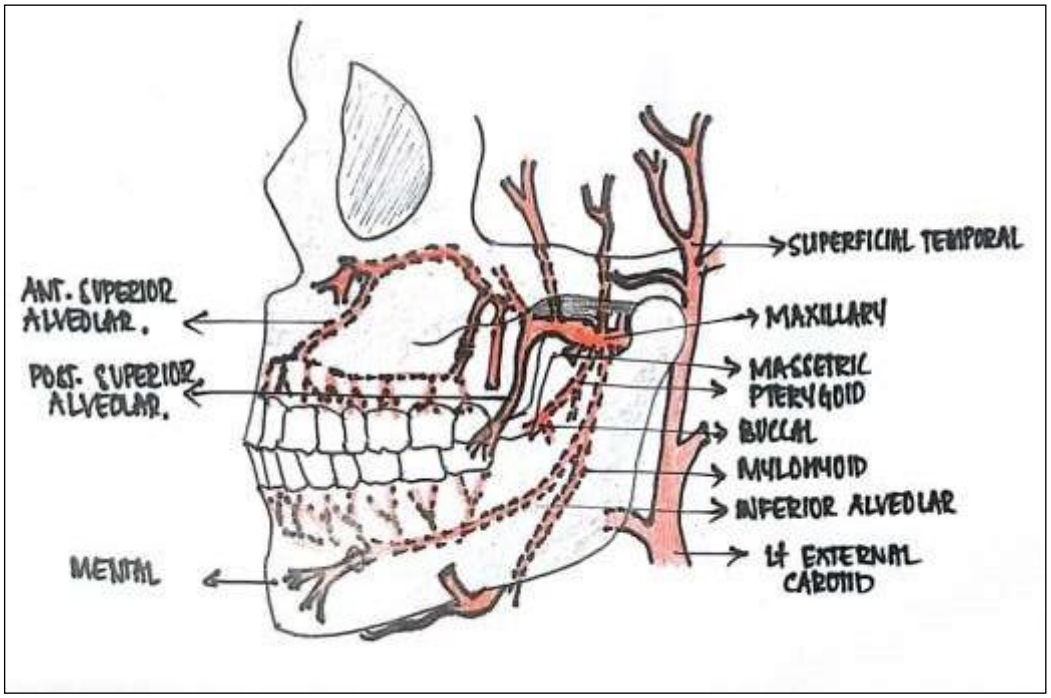


Fig 2: Oral cavity – Blood supply

ORAL CAVITY – NERVE SUPPLY

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. 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.[7]

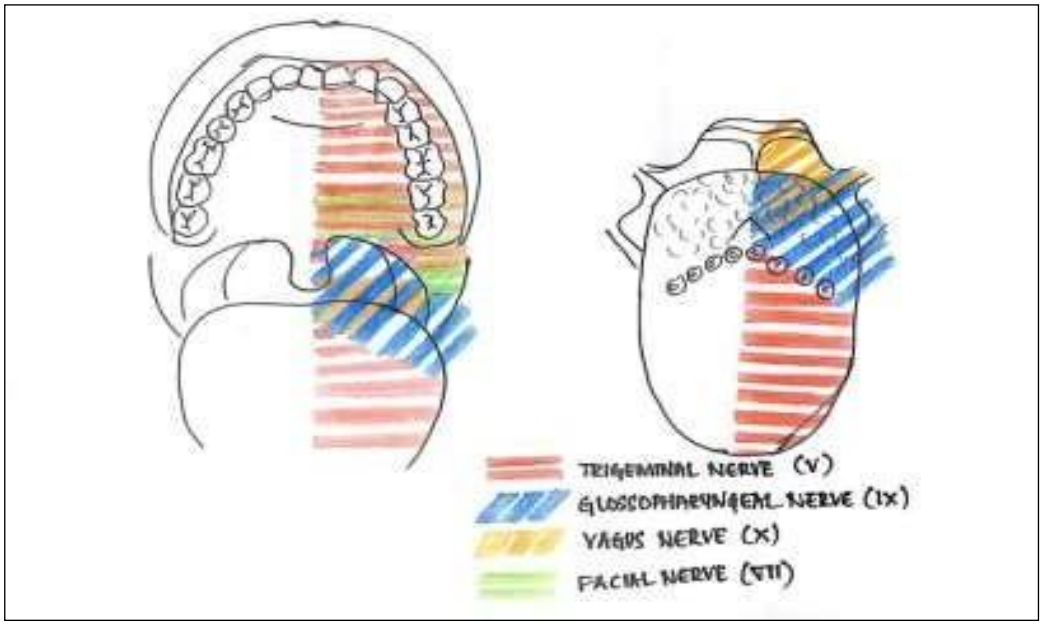


Fig 3: Nerve supply of Oral cavity

HISTORY OF LYMPHATIC SYSTEM

Gaspero Aselli, 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.[8]

Sappey, further described the anatomical understanding of the lymphatic system and his diagrams of lymphatic flow are used even 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 tumour 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. 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 develops as outgrowth of endothelium of veins and lymph vessels sprout in a radiating manner and primary connections with veins are lost.[9] 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 plexus of lymph vessels. Around each nodule vessels are transformed to lymph sinus.

LYMPH NODE GROUPS[9]

Level I: Contains the submental (Ia) and submandibular (Ib) 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. In anterior triangle of neck (from a vertical line dropped from angle of mandible to posterior border of sternocleidomastoid). It is further divided into IIa(anterior) and IIb(posterior) by spinal accessory

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, midline to posterior border of sternocleidomastoid.

Level IV: Contains the lower jugular lymph nodes. It extends from the level of the cricoid cartilage superiorly up to the clavicle inferiorly in anterior triangle of neck (IVa and IVb).

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. It is divided into Va and Vb by inferior belly of omohyoid.

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.[9]

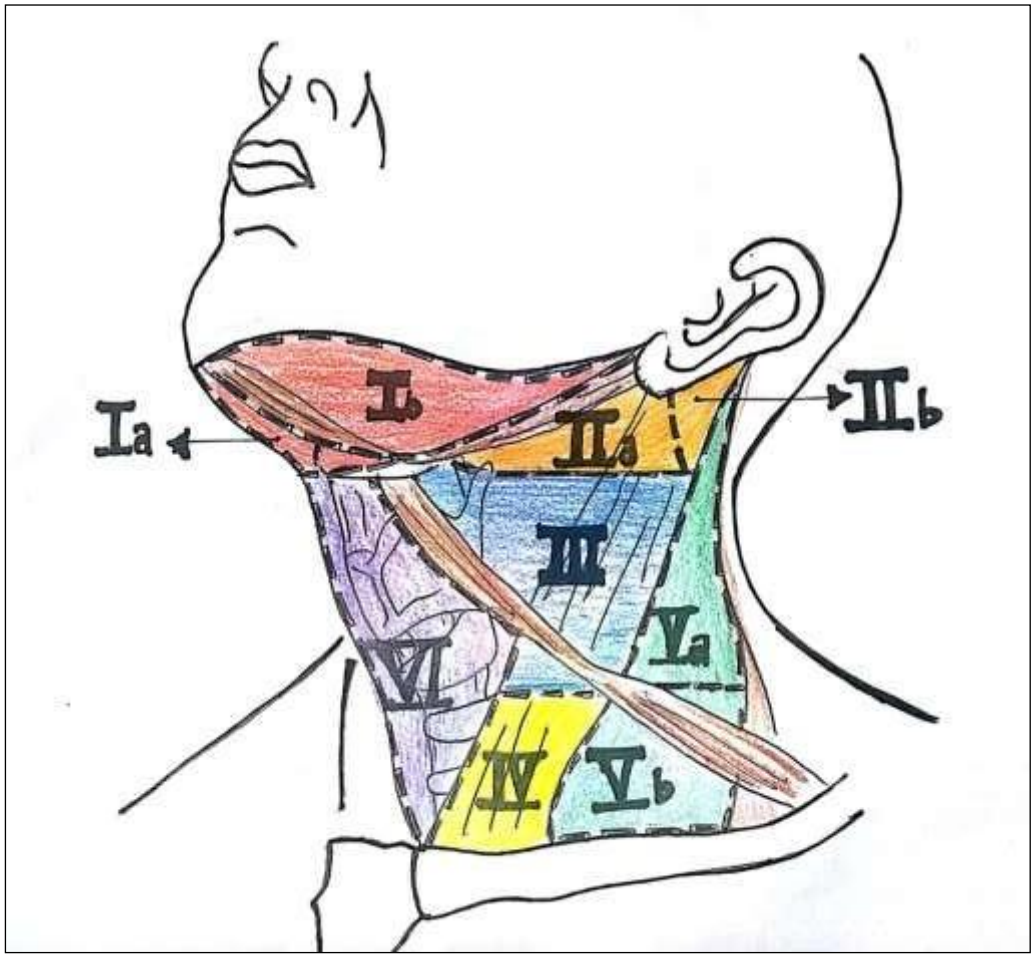


Fig 4: Levels of Lymph nodes in Neck

ORAL CAVITY CANCER

EPIDEMIOLOGY:

According to history, man has always 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.[11]

India, Sri Lanka, Pakistan, Bangladesh, Hungary & France have the highest rates with the India accounting for 30% of newly detected cases.[10] The estimated number of new cancers in India is about seven lakhs, and about 3.5 lakhs people die of cancer every year.[11]

According to the cancer registry of Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, on an average, about 5000 new cancers are registered per year.[12] 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.[13]

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.[9]

Carcinoma of buccal mucosa accounts for 40% of oral cancers in South East Asia.[7] 85% cases occur >50 years of age, except in developing countries where onset can be earlier due to tobacco and 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.[7]

Retromolar trigone incidence in oral cancers is 6 - 7% and is more common in males. Incidence of carcinoma in upper alveolus is 3.5 – 6.5% & hard palate is 1 – 3%. Oral cancers are more common in

males except in hard palate carcinomas where pre-ponderance in females is more due to reverse smoking in certain area. Lower alveolar cancers account for 7.5 – 17.5 % of oral cancers.[7]

However, in Kolar region carcinoma of buccal mucosa is the most common malignancy.[14] It is more prevalent in women due to addiction to tobacco quid chewing. In India, patients present in advanced stage and both buccal mucosa and lower alveolus will be involved making it difficult to identify the epi-centre or starting point of tumour. Such tumours involving the buccal mucosa and lower alveolar complex have been nick named **"Indian oral cancer"** and are high volume disease.

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). 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. Brings about hyperacetylation and hypomethylation of histones which silences tumour suppressor genes.[15]

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. *This is most common risk factor for oral cancer in our region.*

Fig 5: Betel leaves coated with slaked lime and areca nut

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. Brings about hypermethylation of histones.[7]

10] Industrial chemicals

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

12] Immune status: - Immune deficiency 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. Over expression or under expression 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. Other relevant genetic markers may include inducibility of cytochrome p450 enzyme system.[16]

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 and cannot be scrapped out.

Rates of malignant transformation ranges from less than 1% to 17.5%. [17]

Types of Oral Leukoplakia[17]

According to Sugar L and Banoczy J:

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

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

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

According to Lindberg (clinical types):

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

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

According to Burkhardt (microscopic types):

Plain form, corresponding clinically to leukoplakia simplex.

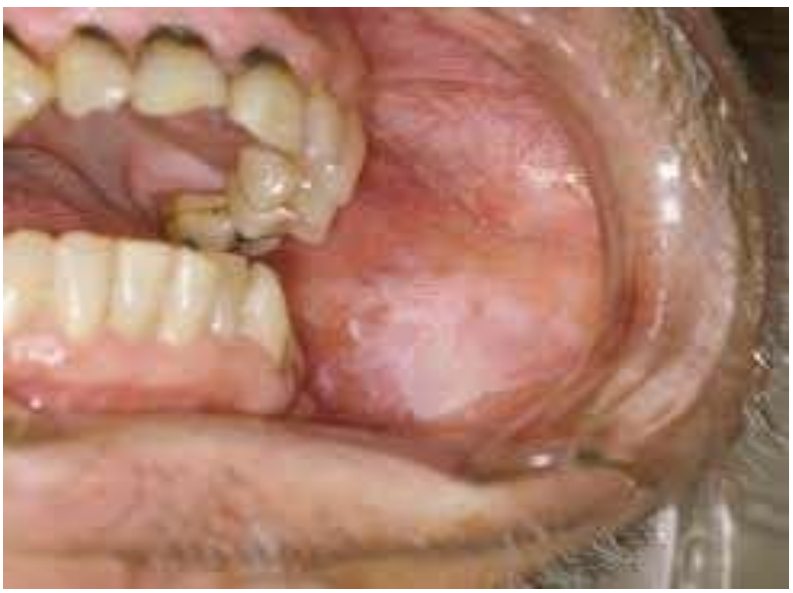
Papillary endophytic, corresponding clinically to erosive leukoplakia.

Papillomatous exophytic, corresponding clinically to verrucous 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.[17]

Fig 7: Showing Leukoplakia over left buccal mucosa



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

Melanoplakia

Oral Submucous fibrosis

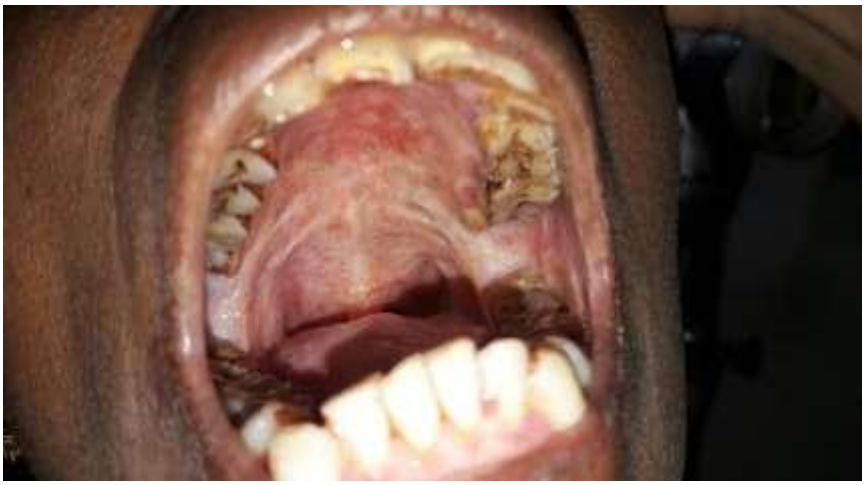


Fig 9: Showing Oral Submucous fibrosis

Sideropenic dysphagia

Oral lichen planus: Rate of malignant transformation is about 4%. [18]

Discoid lupus erythematosus

Hyperkeratosis

Dyskeratosis congenital

Syphilis

TUMOUR BIOLOGY[19]

The development of a tumour involves three phases:

Initiation

Promotion

Progression

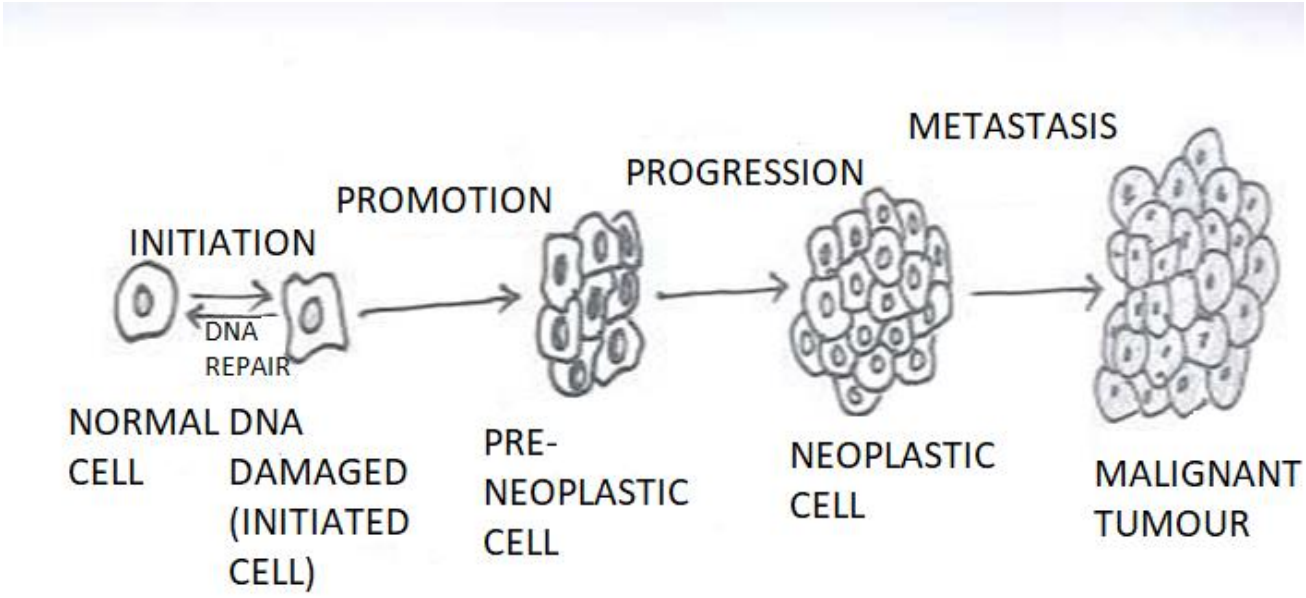


Fig 10: Showing Tumour Biology

TUMOUR ESCAPE MECHANISMS[19]

Tumour related:

Tumour is not immunosensitive

Tumour is not immunogenic

Host related:

Tumour grows too fast for the immune system

Inherited or acquired immunodeficiency

Treatment (radiation, chemotherapeutic drugs) or chemical or physical

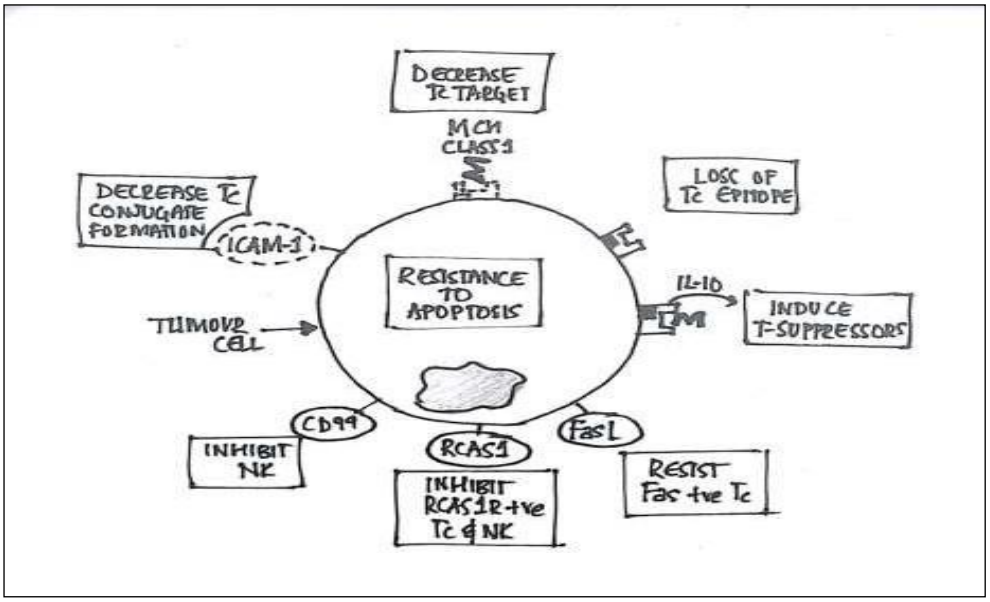
Carcinogens related immunosuppression

Deficiency in antigen presentation by antigen-presenting cells

Lack of access of effector cells to the tumour

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

Fig 11: Showing tumour escape mechanism



CARCINOGENESIS[19]

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. Carcinogenesis 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 over expression 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.

TUMOUR VOLUME

The current TNM staging in oral cancer considers only the two-dimensional size (greatest diameter) of the primary tumour. However, tumour volume shows the exact primary tumour load and may better reflect the prognosis.[3]

Studies in literature have shown that tumour volume is an important prognostic factor in oral cancer. Tumor volume estimation can be done easily by imaging, clinical examination and histopathology. This information plays a major role in selecting treatment and adjuvant treatment and follow up.[3]

In a study done in Brazil in 2013 Tumour Volume was correlated with survival. In this study a tumour volume of 33.6cm^3 was the cut off for locoregional recurrence and poor survival. Among 70 patients with tumour volume less than or equal to 33.6 cm^3, there were 24 recurrences, whereas 30 recurrences were found among 53 patients with greater volume. It was also noted that tumour volume was a predictor for nodal metastasis.[20]

In a similar study in Pakistan in 2012, gross variation in tumour volume was found in patients with same T-stage (T3 and T4) in head and neck cancers. This study also noted that volumetric measurements can refine the TNM staging system. The median tumour volume for patients with recurrent disease was 52cm^3 compared to 22cm^3 for those who did not have a recurrence. It showed that large tumour volume was associated with a significantly higher chance of recurrence. Laryngeal cancers with volumes greater than 46cm^3 and oral cancers with volumes greater than 23.1cm^3 were associated with poor prognosis.[21]

European studies have correlated tumour volume of 18cm^3 or more with poor survival in tongue cancer.[22]

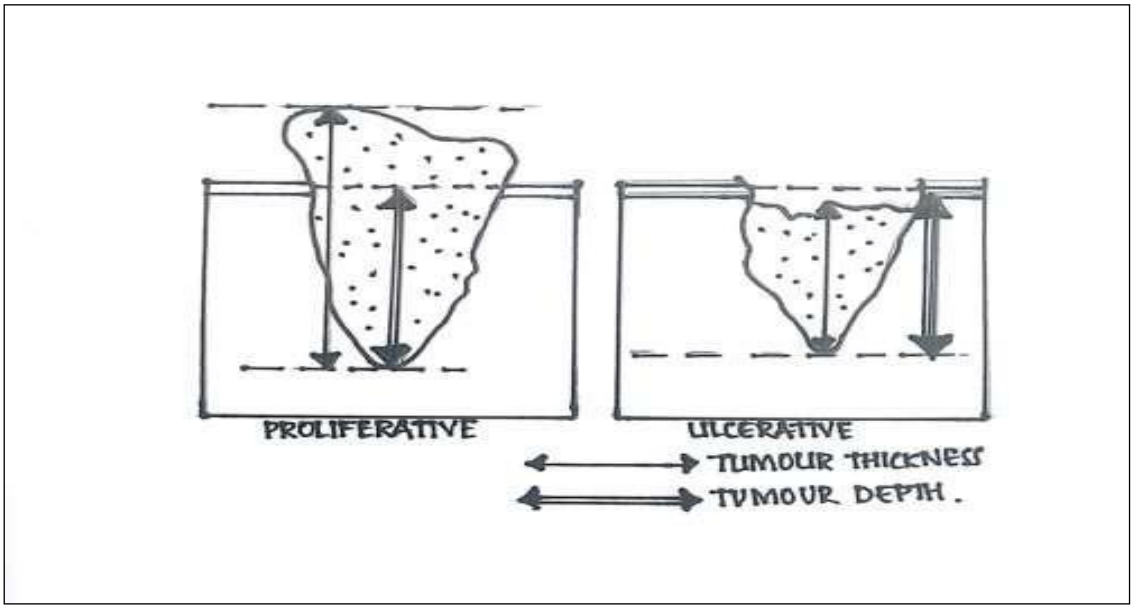
In literature few studies have estimated tumour volume by radiology in cases of carcinoma larynx and pharynx and have found a tumour volume to an important prognostic factor whenever radiotherapy was administered.[23]

Similar studies in literature where squamous carcinoma of larynx and hypopharynx was treated by concurrent chemoradiation, have reported poor survival and higher recurrence rates whenever the tumour volume exceeded $35cm^3$.[24]

TUMOUR THICKNESS AND DEPTH OF INVASION

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 tumour thickness (TT) and both tumour-free survival and metastasis in patients with cutaneous melanoma. Following Breslow's hypothesis, Other authors demonstrated the relationship between lymph-node involvement and tumour thickness to oral cavity malignancy.[25] 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.[25] 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. The space left by the ulcerated tumour should be given importance, because it represents tissue destroyed by the downwards growth of the tumour. 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 Basement membrane of mucosa.[26]

Fig 12: Showing tumour thickness and tumour depth



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 for cervical lymph node metastasis. Infiltration depth was defined as the maximum depth of tumour infiltration (millimetres) below the Basement Membrane of mucosa. In case of ulcerated or exophytic tumours, the reconstructed mucosal surface was used.[27]

In a meta-analysis 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 over-all prognosis.[28] 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. Also, studies have shown that tumour located more towards the midline i.e. lower alveolus, floor of mouth and tongue, showed a higher tendency to throw cervical metastasis.[29]

Therefore, Literature review shows that, cervical lymph node metastasis is the single most important prognostic 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. Because adjuvant therapy may induce severe toxic effects, it is important to find a reliable method to help identify such high-risk patients immediately post-surgery.

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.

But identification of metastatic positive lymph nodes is based on both the quality of neck dissection (i.e. 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.

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 tumours (primary site T-categorization T1 or T2) has been reported to be between 27% and 40%. Step serial sectioning of lymph-node will help to identify micro-metastasis.[30,31]

Level I is the most common site for nodal metastasis from oral cancers (100%), followed by level II (32%), level III (16%), and level IV (8%).[9] 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.[32] 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.[33] Survival was better related to a more aggressive treatment of the neck even in early tumour stages and to adjuvant radiotherapy in advanced tumour stages.

The presence of extra capsular spread reduces the chances of cure by 50%. As mentioned earlier the site, size, differentiation of tumour, perineural invasion, perivascular invasion, inflammatory response and DNA content predicts aggressiveness of cervical lymph node metastasis.[34]

In recent AJCC staging, extra capsular spread from lymph nodes makes the staging N3b. 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 to that of prognosis. However, there is paucity in literature regarding the correlation between tumour volume and recurrence and between tumour volume and lymph node metastasis in oral cancer.

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.

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.[9] The enzymes degrade the basement membrane proteins such as collagen IV, laminin and proteoglycans which allow the spread of tumour cells.[35]

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.[35] 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 lymphatic-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 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.[36] 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.[37] 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, particularly level Ib (sub-mandibular) for buccal mucosa and lower alveolar complex.

The incidence of lymph node metastasis that can be detected clinically is about 60%. The overall incidence of occult metastasis in patients with clinically negative neck node is around 30%. The relative risk of nodal metastasis depends on site, size, thickness, histological features and the immunological and biological factors of the primary tumour.[35] Poorer the differentiation the more likely the tumour metastasises 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.[38]

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.

Lymph node levels that are at greatest risk of harbouring metastases from different primary

DISTANT METASTASIS:

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

TNM CLASSIFICATION[6]

Primary Tumour (T)- AJCC 8th EDITION

TX - Primary tumour cannot be assessed

Tis - Carcinoma in situ

TI - Tumour<2cm , < 5 mm depth of invasion (DOI) DOI is depth of invasion.

T2 - Tumour < 2 cm, DOI > 5 mm and <10 mm or tumour > 2 cm but < 4 cm, and < 10 mm DOI

T3 - Tumour>4 cm or any tumour> 10 mm DOI

T4 - Moderately advanced or very advanced local disease

T4a - Moderately advanced local disease (lip) Tumour invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose) (oral cavity) Tumour invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face)

Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T4.

T4b - Very advanced local disease Tumour invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

Primary Tumour (T) – AJCC 7th EDITION

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)

AJCC 8TH EDITION

NX - Regional lymph nodes cannot be assessed

N0 - No regional lymph node metastasis

NI - Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension ENE(-)

N2 - metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(-)

N2a - metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(-)

N2b - metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension, and ENE(-)

N2c - metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(-)

N3 - metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or metastasis in any node(s) and clinically overt ENE(+)

N3a - metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

N3b - metastasis in any node(s) and clinically overt ENE(+)

AJCC 7TH EDITION

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

M0 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

R0 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

AJCC staging of oral cavity squamous cell carcinoma

THERAPEUTIC MODALITIES FOR ORAL CANCER [9]

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 treatment of non- metastatic tumours by surgical removal of the primary tumour followed by adjuvant radiotherapy or radiotherapy and chemotherapy.

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

RECONSTRUCTION[39]

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:

Split thickness skin grafts Full thickness skin grafts

Buccal, Palatal, Periosteal Mucous membrane flaps

Tongue flaps

Posteriorly based lateral tongue flap

Posteriorly based bilateral tongue flap

Anteriorly based ventral tongue flap

Masseter flap

Nasolabial flap

Medial based deltopectoral flaps

Forehead flap

Sternocleidomastoid myo-cutaneous flap

Trapezius

Platysma myo-cutaneous flap

Pectoralis major myo-cutaneous flap

Latissimus dorsi myo-cutaneous flap

Costochondral grafts

Osteo-myocutaneous flap- fifth rib with pectoralis major myo-cutaneous flap

Spine of scapula with trapezius

Free osteo-cutaneous groin flap

Free osteo-cutaneous fibula flap

Scapular Osseo-cutaneous flap

Radial forearm flap

Radial forearm free osteo-cutaneous flap

Free fibula and osseo-integrated implants

Larger the tumour volume – larger will be the defect and it is a challenge for a surgeon to reconstruction. 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 for maintenance or restoration of the mandibular contour.

QUALITY OF LIFE:

The surgical resection of tumour involving the oral cavity has been associated with significant alteration of normal anatomy, functional deficits and suboptimal reconstruction. Disease free survival, Overall survival and Tumour response rates have been outcome indicators used to judge efficacy of treatment. Although these conventional outcomes have been helpful to clinicians, they affect some of the most basic functions of life. In spite of the most aggressive treatment regimens, there has been little change in overall survival rates for patients with head and neck cancer. Greater awareness of the functional impact of surgical resection on patients' function has led to better reconstruction and rehabilitation techniques and organ preservation whenever possible

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

Different dimensions of quality of life

Functional status

Physical complaints

Psychological distress

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:

Karnofsky Performance Scale

ECOG 11 scale

The Sickness Impact Profile

The University of Washington Quality of Life scale

The Head & Neck Cancer Specific Quality of Life Instrument[40]

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.

OBJECTIVES OF STUDY

(1) To determine tumour volume by pre-operative clinical measurement and imaging of the tumour and by histopathological examination of the resected specimen in patients with squamous cell carcinoma of buccal mucosa and lower gingivobuccal sulcus.

(2) To document the number and site of metastatic lymph nodes in the above patients by histopathological examination.

(3) To follow up the above patients for a minimum period of 6 months following treatment and correlate tumour volume with the locoregional outcome.

MATERIALS AND METHODS

SOURCE OF DATA

This study was conducted in Department of Otorhinolaryngology and Head and Neck Surgery of R L JALAPPA HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR from December 2017 till May 2019. 75 patients were included in study diagnosed with squamous cell carcinoma of buccal mucosa and lower gingivobuccal sulcus clinically staged T2 to T4a and pathologically staged T2 and T3 in were included in this study.

SAMPLE SIZE

Sample size of 75 was estimated based on the recurrence rate observed in a study done in Brazil.

$n=Z_{\alpha}^{2}PQ/ (d)^{2}$ where Z_{α}= standard normal variate at 90%=1.64,

P= prevalence of recurrence,

Q=100-P, Absolute error 10%,

Confidence interval = 90%,

since follow up study up expecting drop-out rate of 10%

TYPE OF STUDY

This is an observational study.

INCLUSION CRITERIA

(1) Oral cavity cancers involving buccal mucosa and lower gingivobuccal sulcus clinically staged T2 to T4a and planned for composite resection and adjuvant treatment.

EXCLUSION CRITERIA

(1) Patients receiving Neoadjuvant chemotherapy or radiotherapy.

(2) Patients with recurrence.

(3) Patients with severe trismus.

(4) Patients who have not completed the treatment.

(5) Patients with pathological skin and bone involvement (pT4a)

METHODS OF COLLECTION OF DATA

75 Patients who underwent surgery for Oral cavity squamous cell carcinoma in Department of Otorhinolaryngology and Head and Neck Surgery of R L JALAPPA HOSPITAL AND RESEARCH CENTRE, TAMAKA, KOLAR from December 2017 to May 2019 were included in this study.

An informed written consent was obtained from all the patients, after proper counselling regarding the procedure being performed and the research being done. Detailed clinical history was elicited with emphasis on habit profile. All the patients were clinically examined with emphasis on site, extent and spread of tumour to the surrounding area.

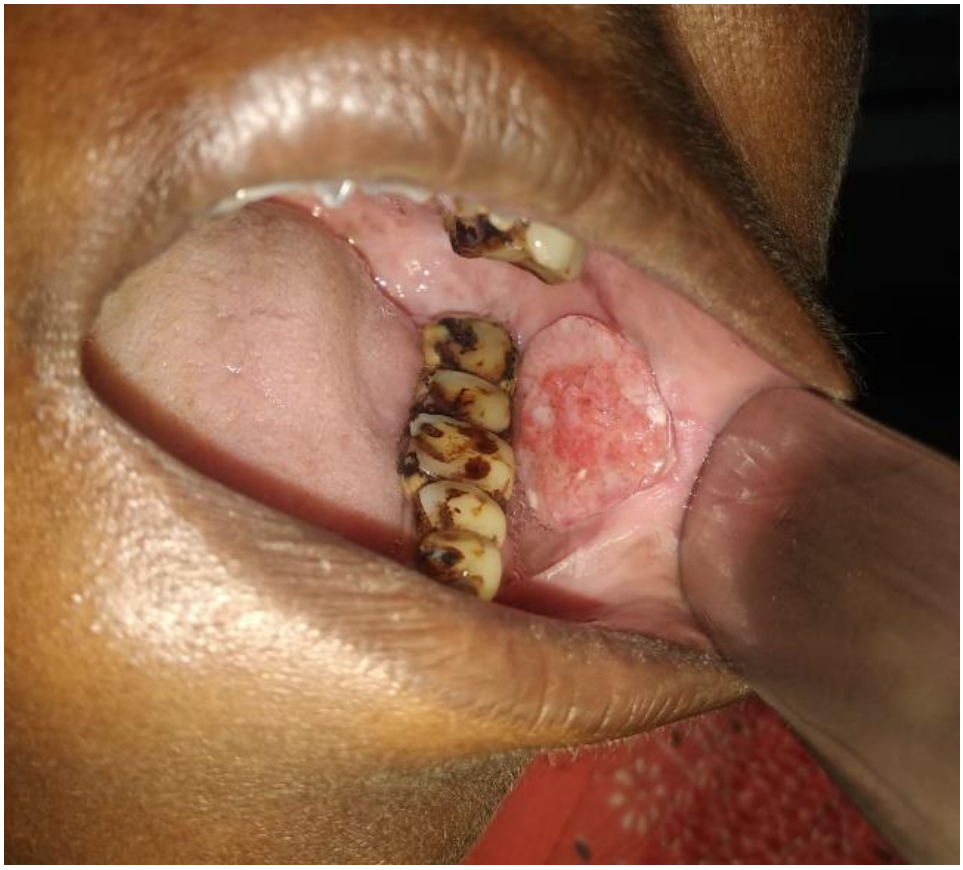


Fig 13: - lesion involving the left Buccal Mucosa (T2)

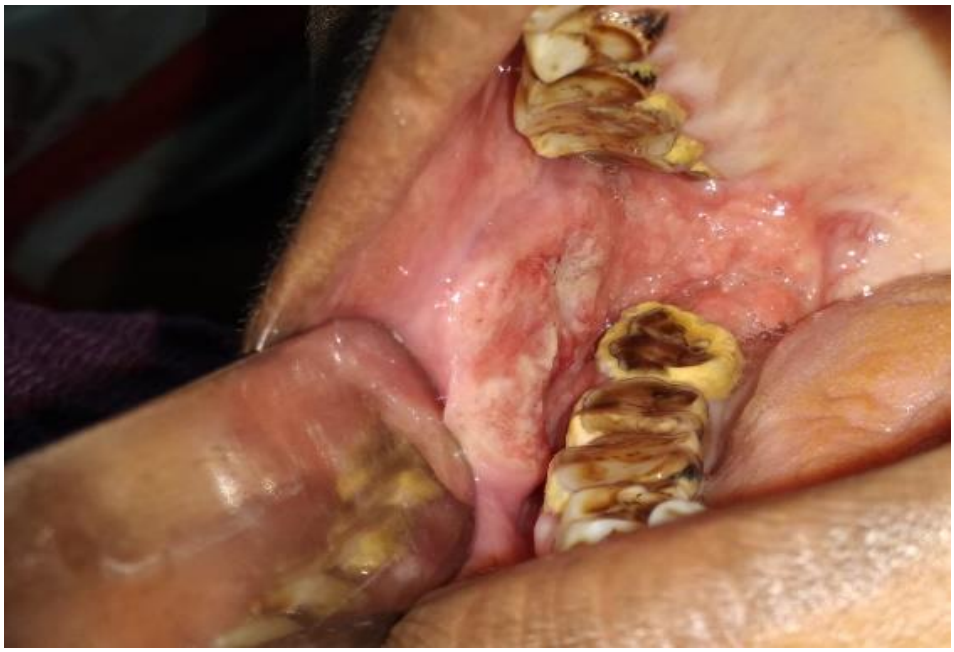


Fig 14: - Lesion involving the right buccal mucosa posteriorly extending to RMT (T3).

Biopsy of the tumour was done and the histopathological findings were noted. CECT scan was done, maximum dimensions in antero-posterior direction, supero-inferior direction and transverse diameter was documented and primary tumour volume was calculated. All these details were documented in a proforma. Clinical staging was done incorporating the imaging findings and documented.

Fig 15: - Coronal section of CECT with puffed cheek technique – showing enhancing lesion in left Buccal mucosa

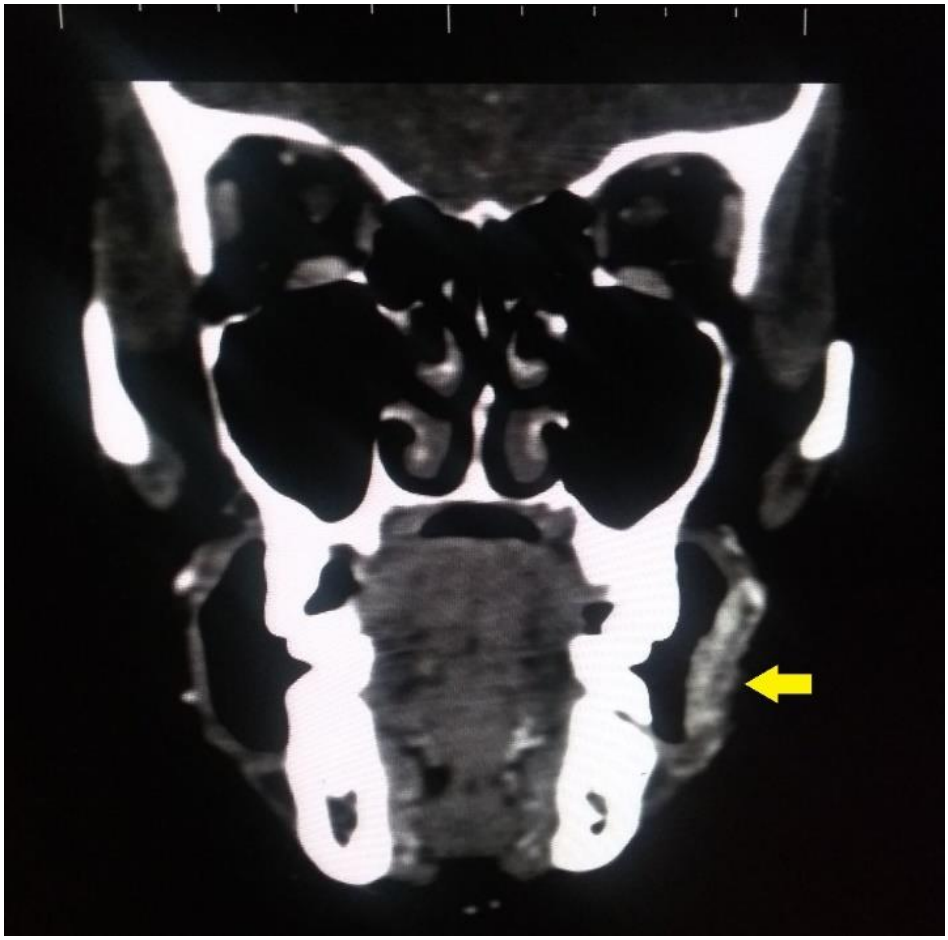
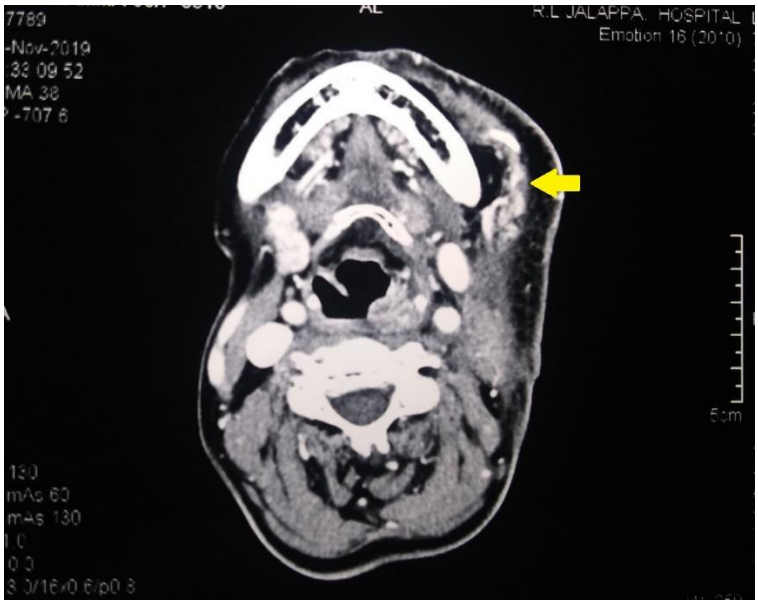


Fig 16: -Axial section of CECT – showing enhancing lesion in left buccal mucosa posteriorly going to RMT.



Patients underwent wide excision of the primary tumour with adequate margins, along with marginal or hemi-mandibulectomy along with neck dissection, according to the clinical staging. Marginal mandibulectomy (5patients) was done when there was when lesion was found abutting the mandible on CT-scan and height of the mandible was adequate. Hemi-mandibulectomy (52 patients) was done when lesion found to be suspicious of mandible erosion on CT-scan, when mandibular body height was inadequate (edentulous) and the primary lesion was adjacent to last two molar tooth where marginal mandibulectomy cannot be done. In our study we have used AJCC 7th Edition.

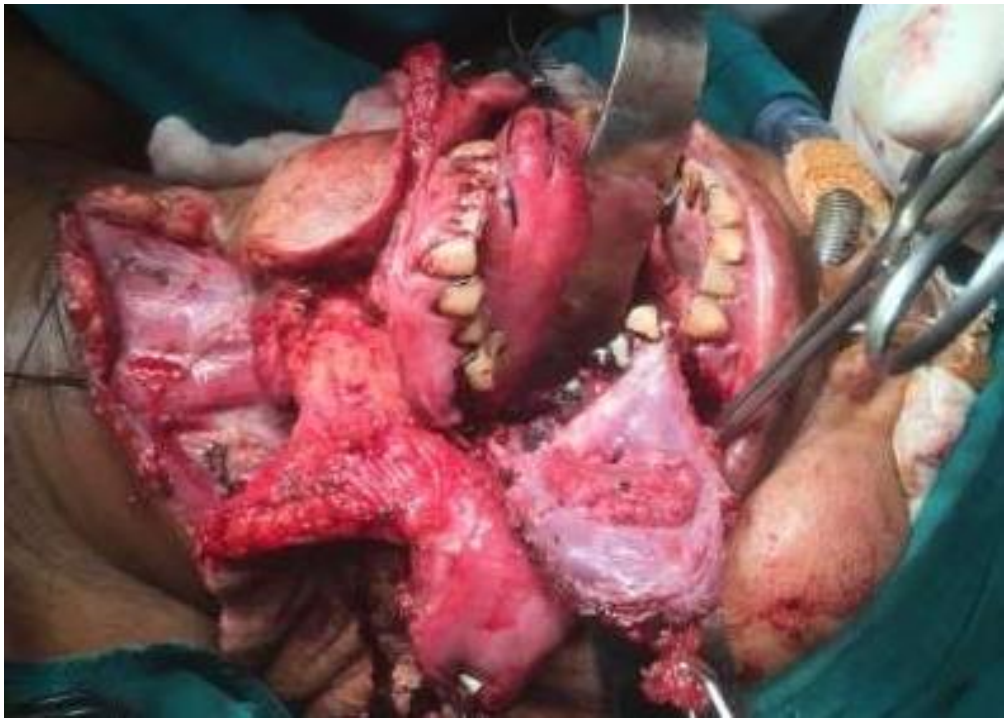


Fig 17: - showing wide excision of primary tumour

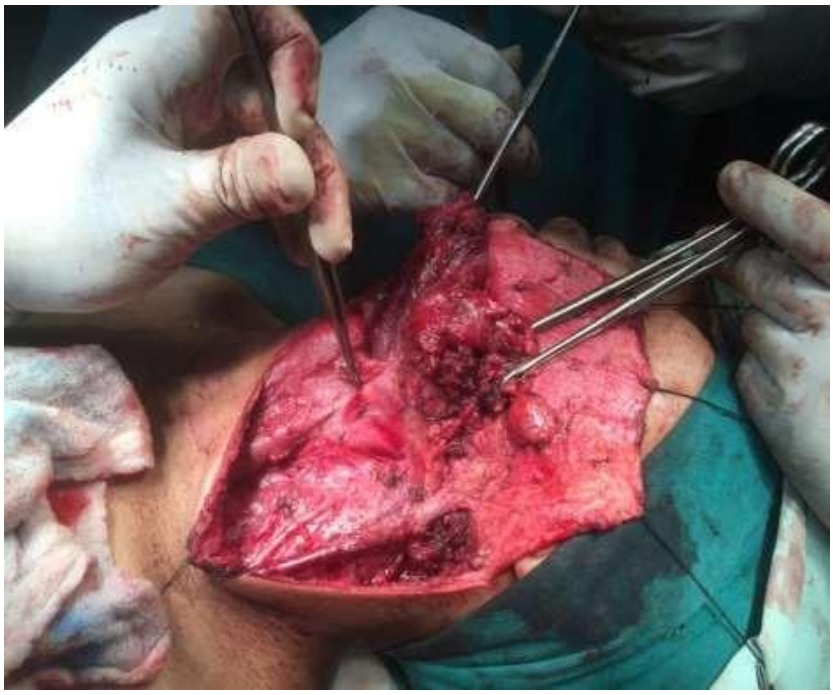


Fig 18: - Neck dissection

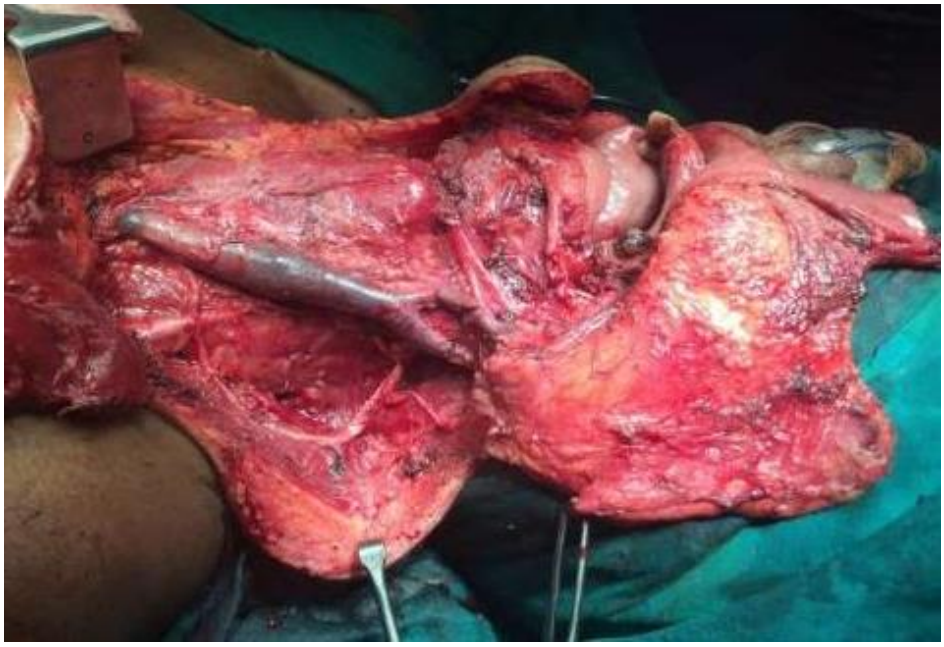


Fig 19: showing post neck dissection and wide excision of primary with hemi-mandibulectomy

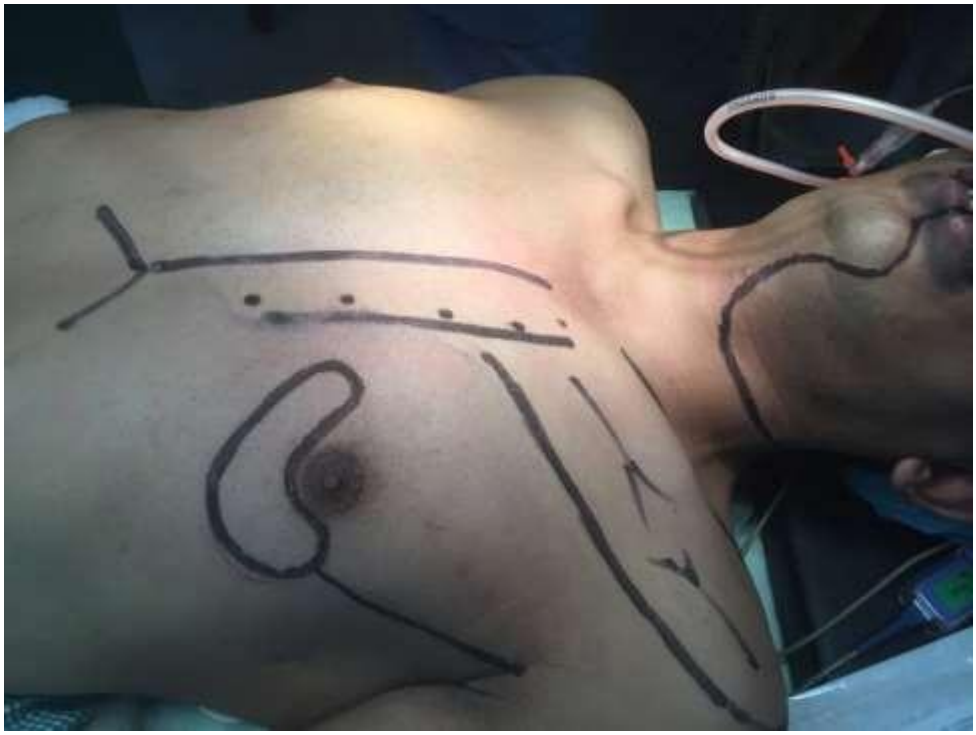


Fig 20: showing preoperative marking for neck dissection and PMMC flap

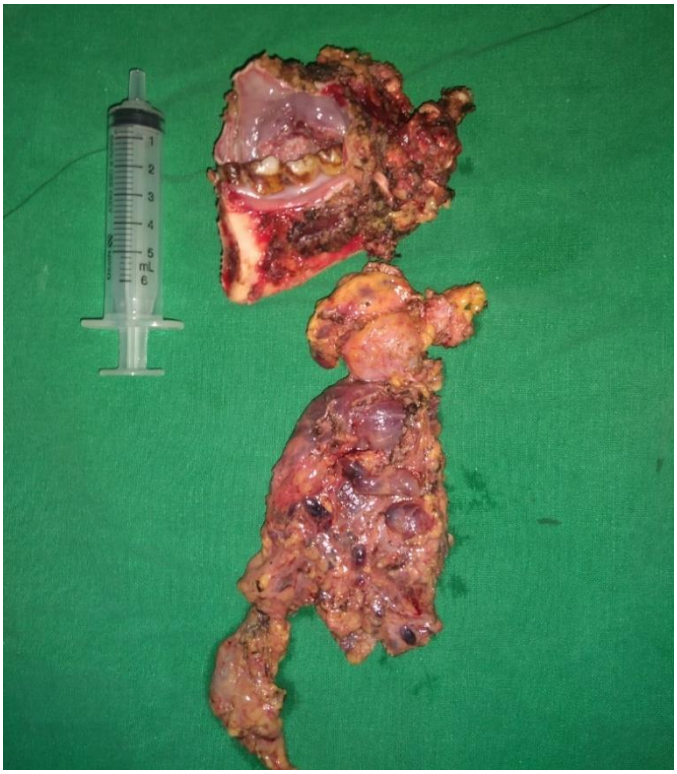


Fig21: - Showing specimen Composite Resection with neck dissection.

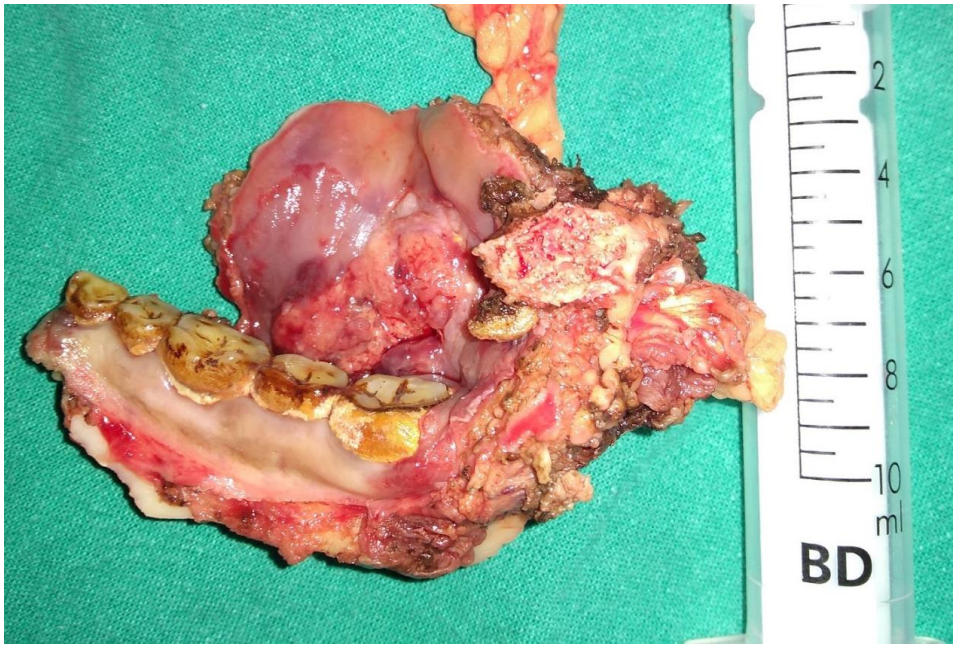


Fig22: - Showing wide excision with Marginal Mandibulectomy.

Following surgery, immediately following excision of the specimen before formalin fixation maximum length, maximum breadth and tumour thickness of the tumour was measured using callipers and clinical tumour volume was calculated. Primary tumour and neck dissection specimen were sent for histopathological examination. The tumour volume was determined by measuring dimensions of gross specimen and histological dimensions were documented. Tumour volume was determined as a product of greatest dimensions. Pathological staging was done and tumour volume based on histopathological examination was documented. Tumour volumes measured clinically, radiologically and by histopathological examination were compared and locoregional outcome (recurrence) was assessed after a follow up period of 1month, 3 months and 6 months.

Fig 23: -A representative diagram of tumour length, breadth and thickness

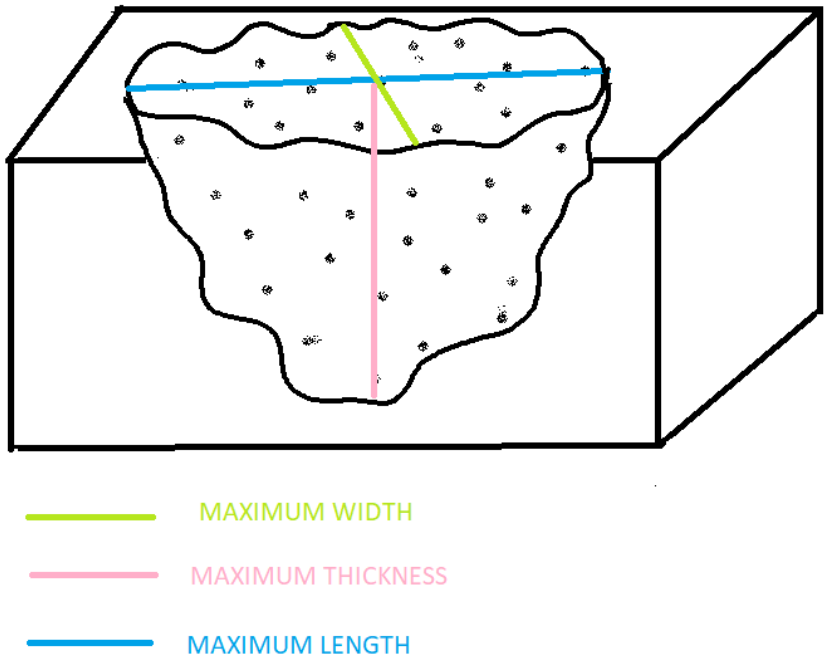


Fig 24: - showing Tumour length measurement using callipers

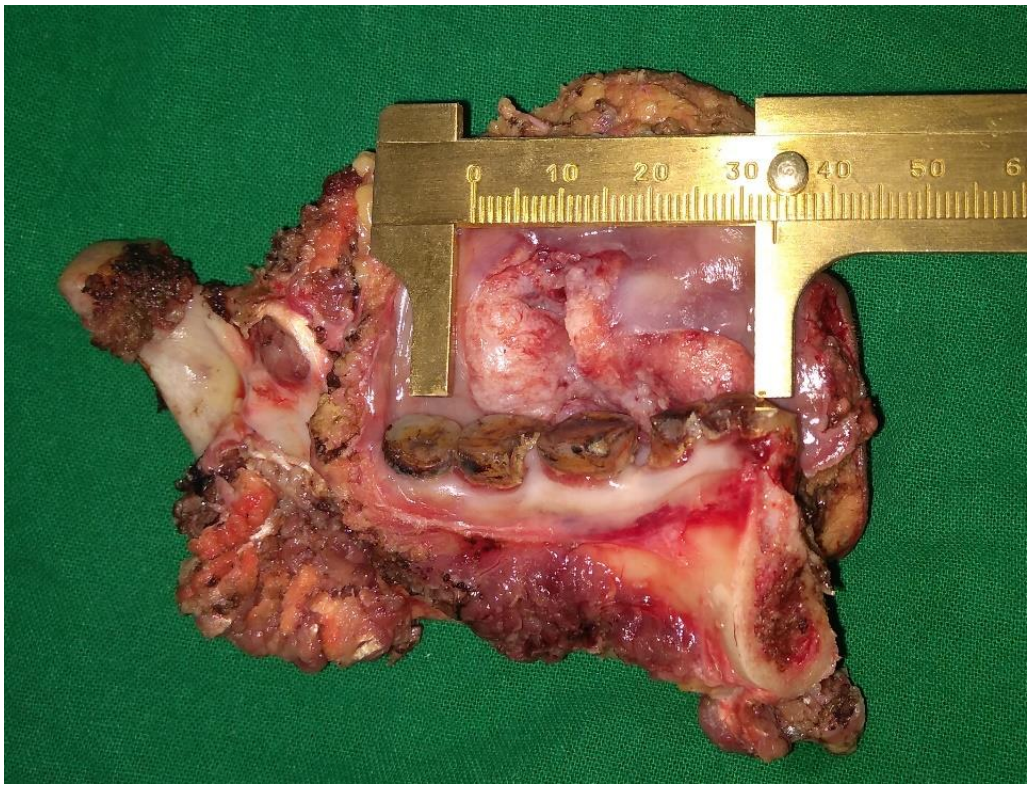


Fig 25: - showing tumour breadth Measurement using callipers.

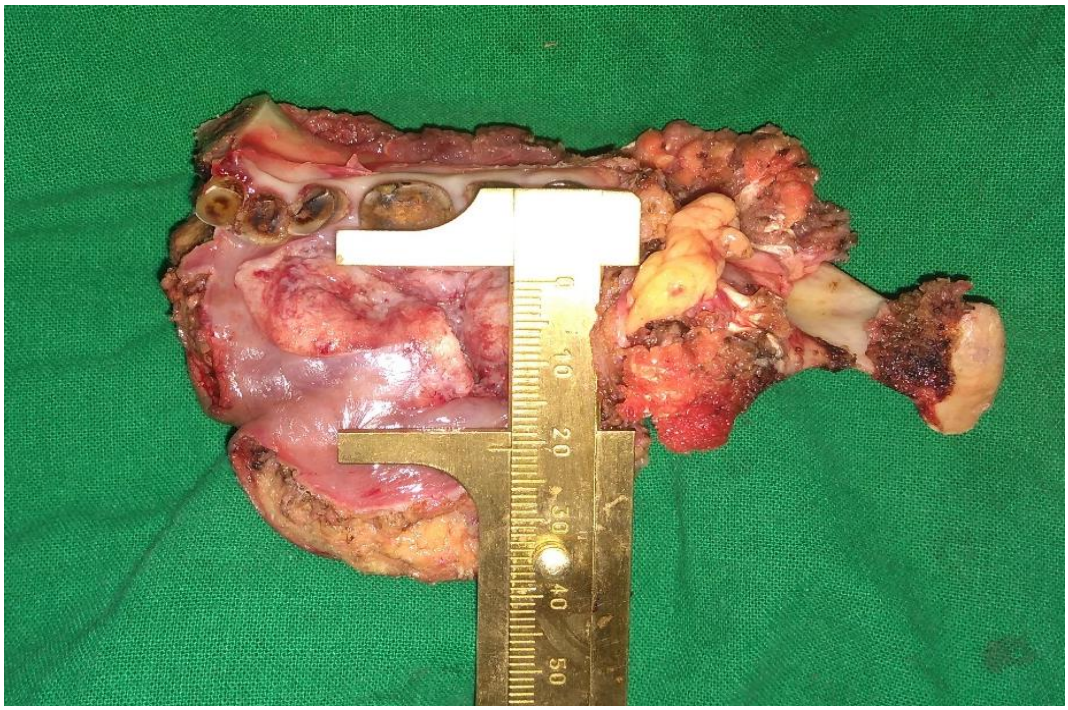


Fig 26: - showing tumour thickness measurement using callipers

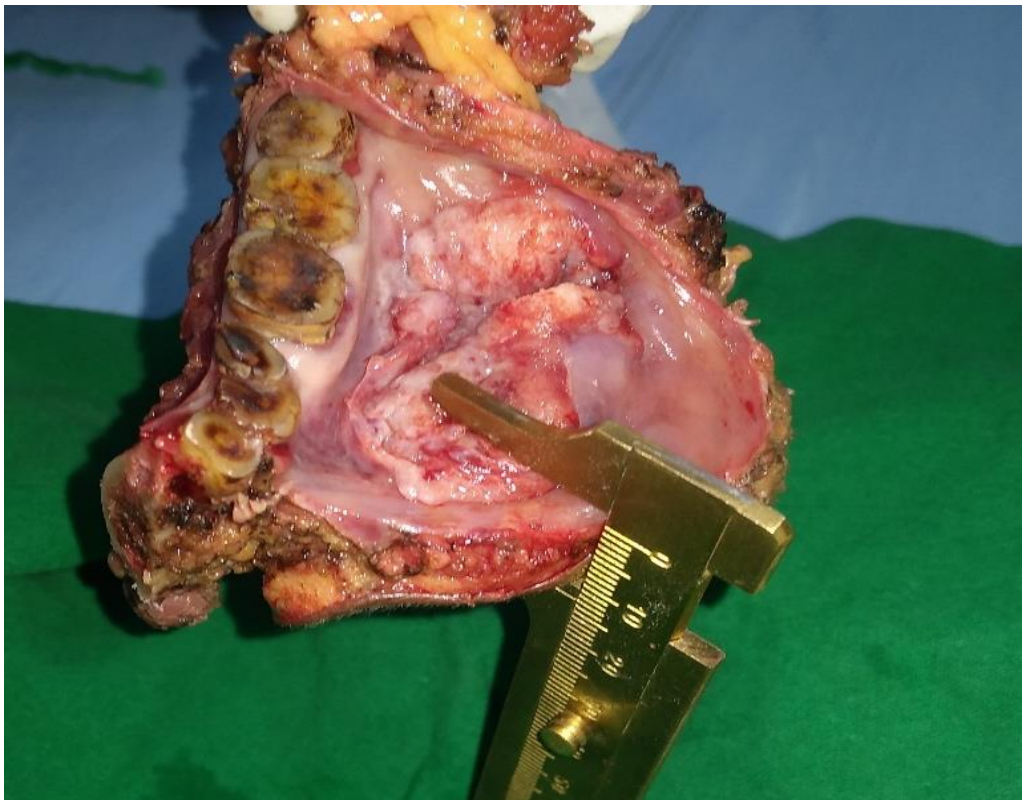


Fig 27 : - Post operative intra-oral PMMC flap.

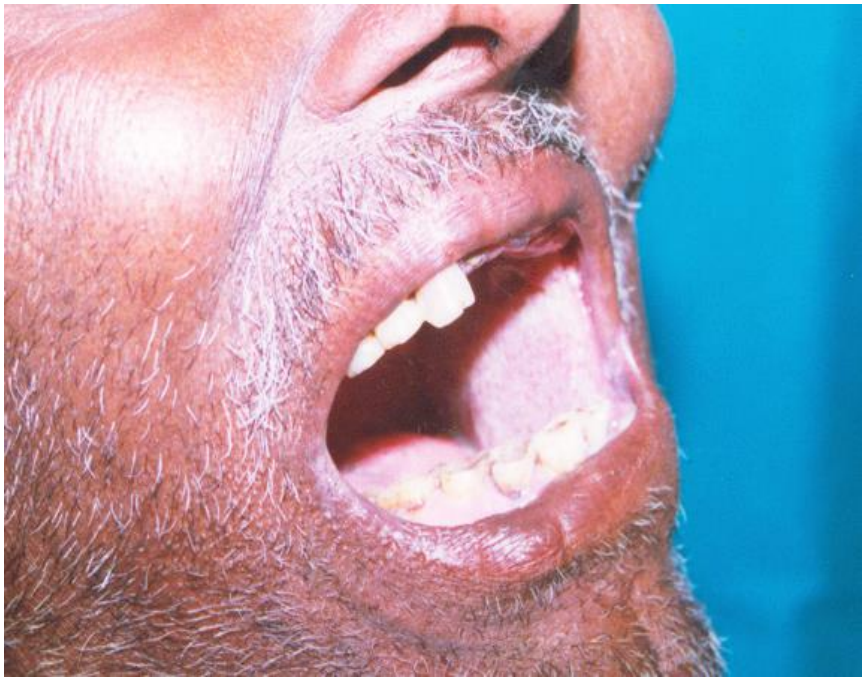


Fig 28 : - post operative Intra-oral supraclavicular flap.

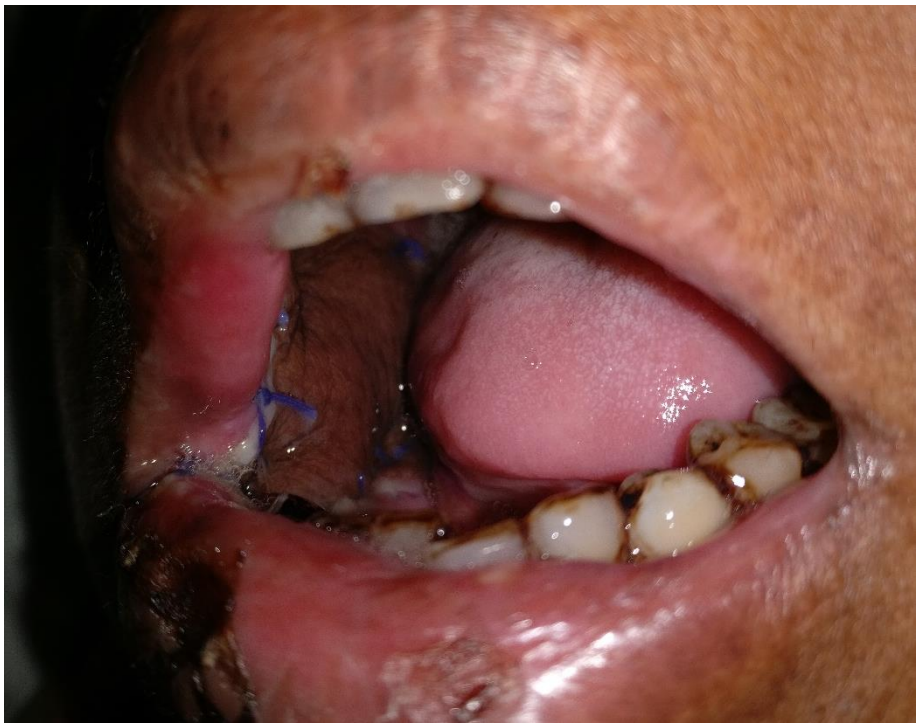
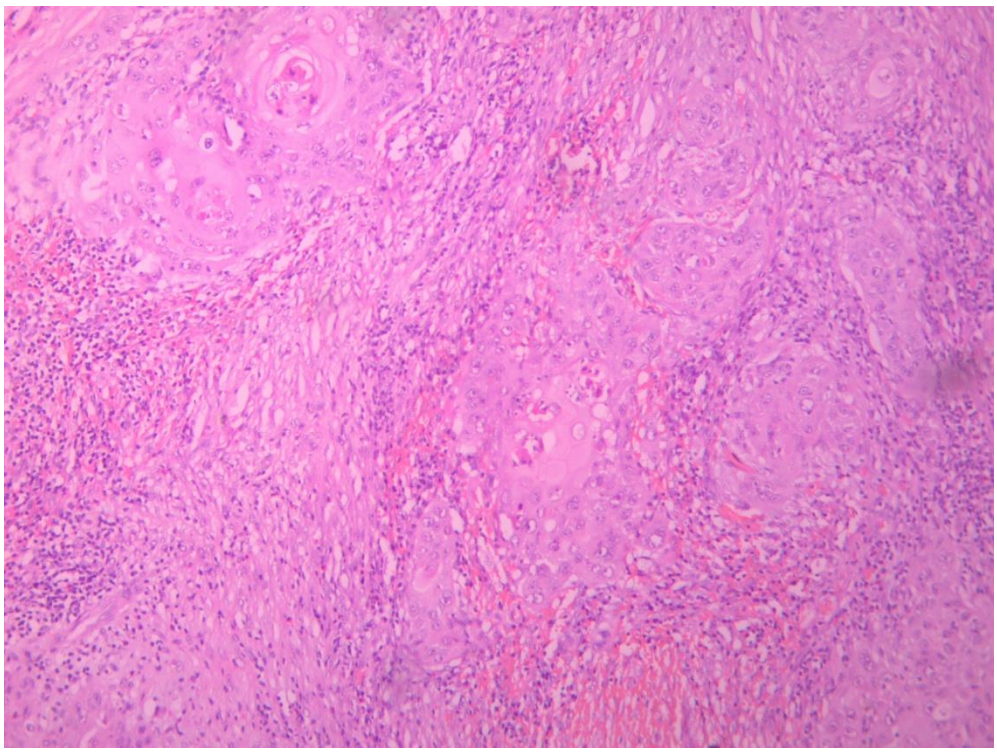


Fig 29 : - Histological picture of Squamous cell carcinoma.



STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables. **ANOVA** was used as test of significance to identify the mean difference between more than two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

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

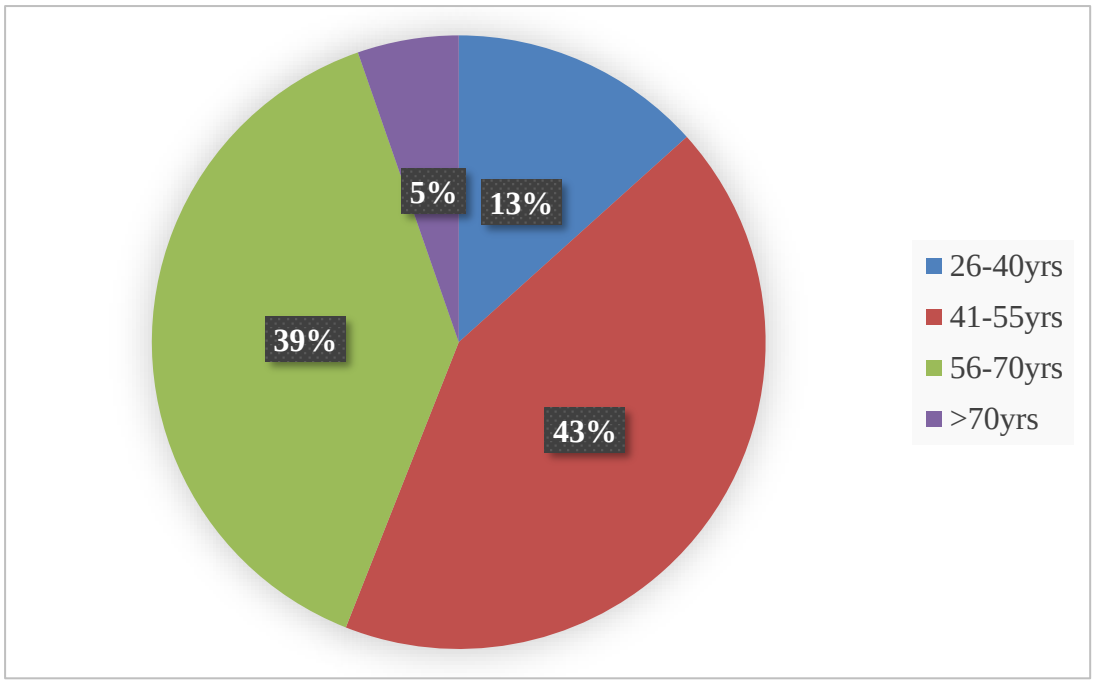
Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyse data

RESULTS

Table 1:- Distribution of subjects according to age group

Age group	Frequency	Percent
26-40yrs	10	13.3
41-55yrs	32	42.7
56-70yrs	29	38.7
>70yrs	4	5.3
Total	75	100.0

Graph 1:- Graph showing Distribution of subjects according to age group

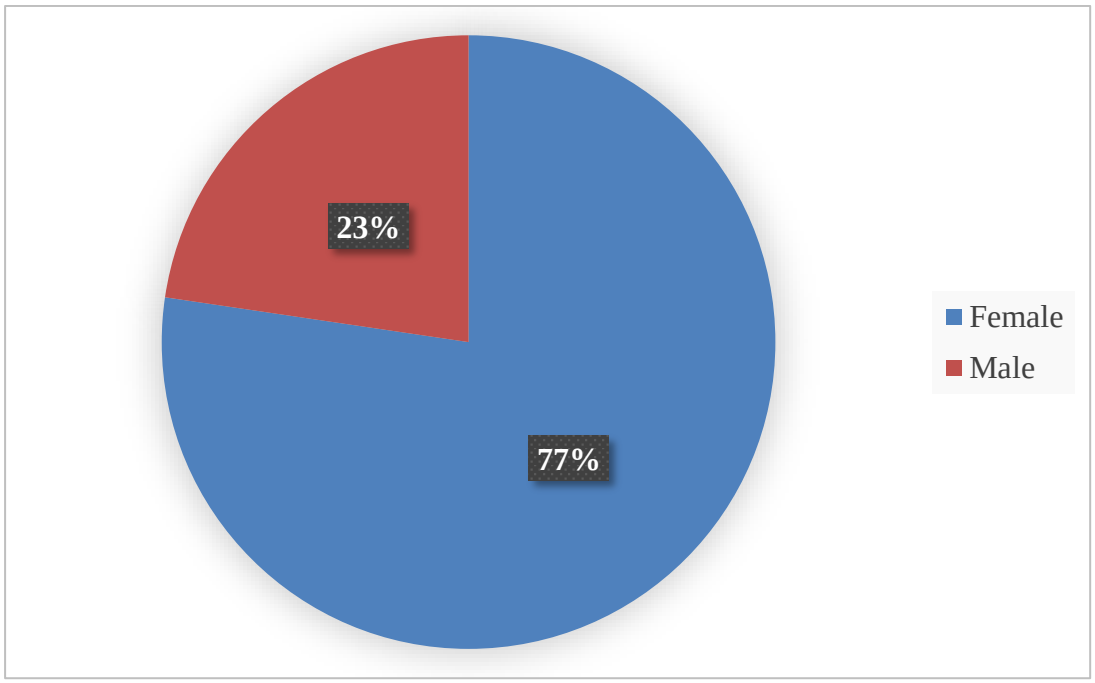


In our study majority of the patients were in the age group of 41 to 55 years (43%), 39 % were in the age group of 56 to 70 years, 13% were in the age group of 26 to 40 years and 5% of patients were above the age of 70years.

Table 2:- Distribution of subjects according to gender

Sex	Frequency	Percent
Female	58	77.3
Male	17	22.7
Total	75	100.0

Graph 2:- Showing Distribution of subjects according to gender

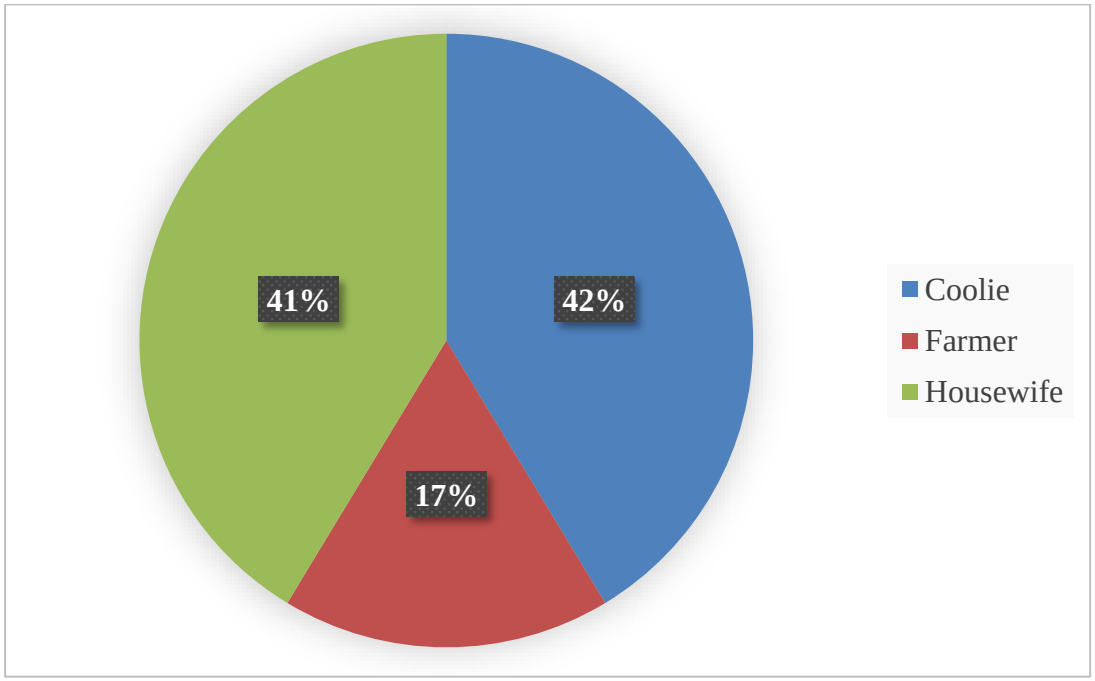


In our study, majority of the patients were females (77%) and 23% were males. Male: female ratio is 1:3.3

Table 3:- Distribution of subjects according to occupation

	Frequency	Percent
Coolie	31	41.3
Farmer	13	17.3
Housewife	31	41.3
Total	75	100.0

Graph 3:- Showing Distribution of subjects according to occupation

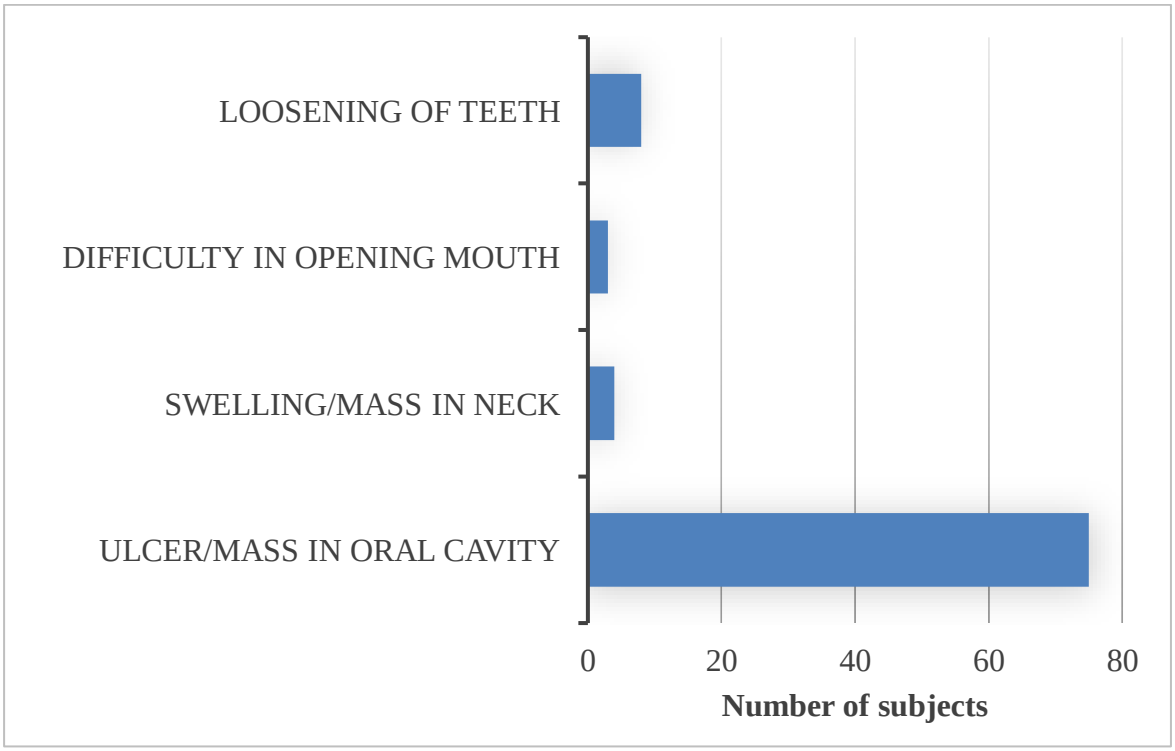


In our study, 42 % of subjects were housewives, 41% were coolie and 17% were farmers by occupation.

Table 4:- Frequency distribution of Chief complaints

	Frequency	Percent
Ulcer/mass in oral cavity	75	100.0
Swelling/mass in neck	4	5.3
Difficulty in opening mouth	3	4.0
Loosening of teeth	8	10.7

Graph 4:- Showing frequency distribution of Chief complaints

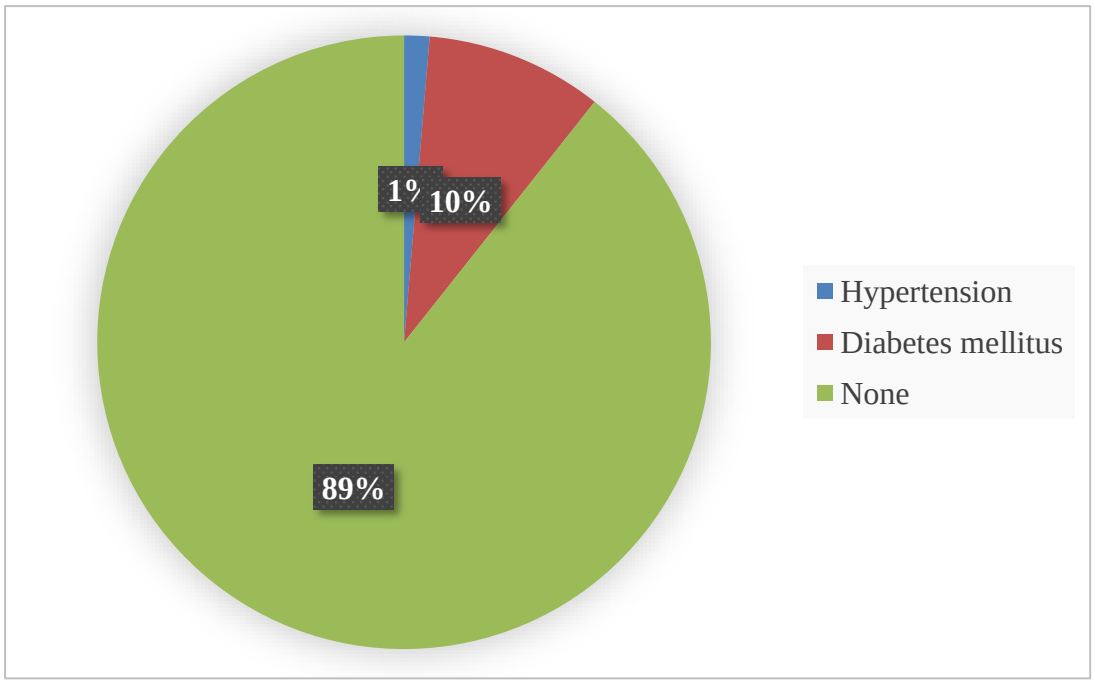


In our study, all subjects presented with ulcer in oral cavity, 10% of subjects had associated loosening of tooth, 5.3% of subjects had swelling over neck and only 4% of subjects had trismus.

Table 5:- Distribution of subjects according to associated co-morbidities

	Frequency	Percent
Hypertension	1	1.3
Diabetes mellitus	7	9.3
None	67	89.4
Total	75	100.0

Graph 5:- showing Distribution of subjects according to co-morbidities

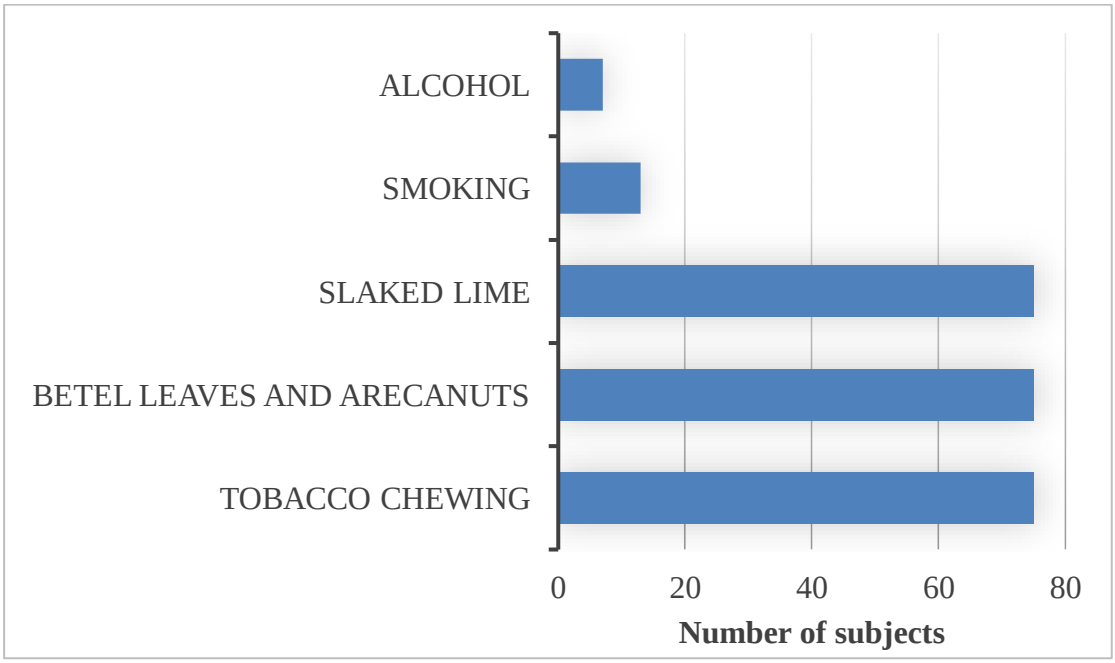


In our study, 89% of patients had no associated co-morbidities, 10% of subjects had associated diabetes and only 1% of subjects had hypertension.

Table 6:- Frequency distribution of Addictive habits practiced by the Subjects

	Frequency	Percent
Tobacco chewing	75	100.0
Betel leaves and areca nuts	75	100.0
Slaked lime	75	100.0
Smoking	13	17.3
Alcohol	7	9.3

Graph 6:- Showing frequency distribution of Addictive habits practiced by the Subjects

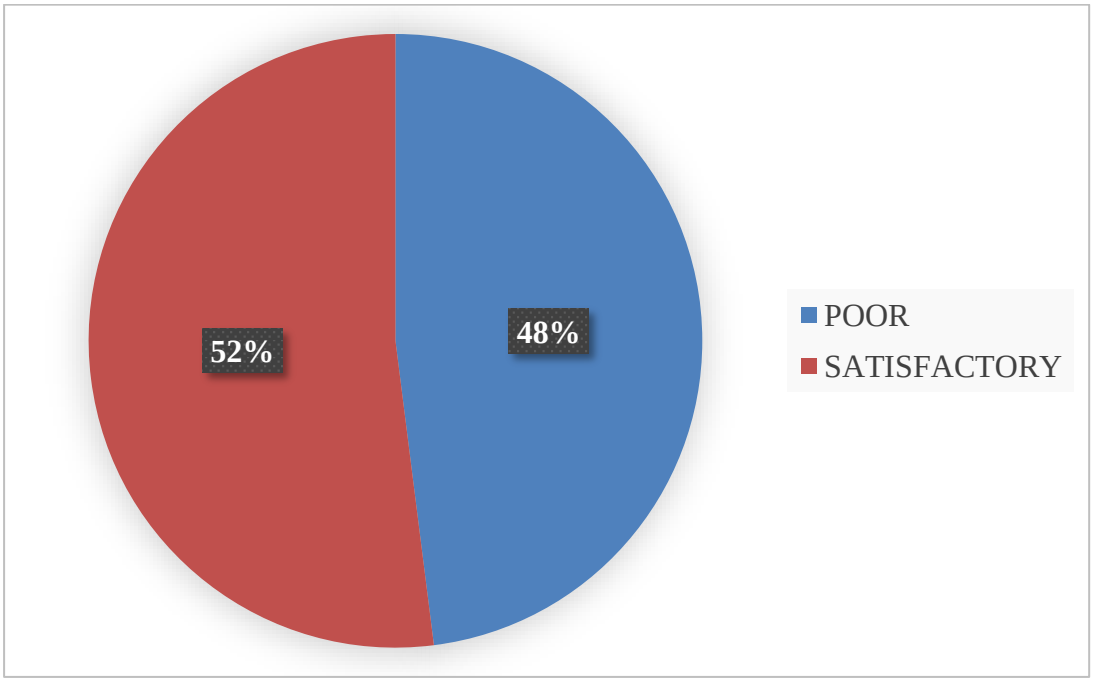


In our study, all subjects had a habit of chewing betel leaves, areca nut, tobacco and slaked lime for varying durations. 17.3% of subjects also had the habit of smoking and 7% of subjects had habit of consumption of alcohol.

Table 7:- Distribution of subjects according to oro-dental hygiene

	Frequency	Percent
POOR	36	48.0
SATISFACTORY	39	52.0
Total	75	100.0

Graph 7:- Showing Distribution of subjects according to oro-dental hygiene

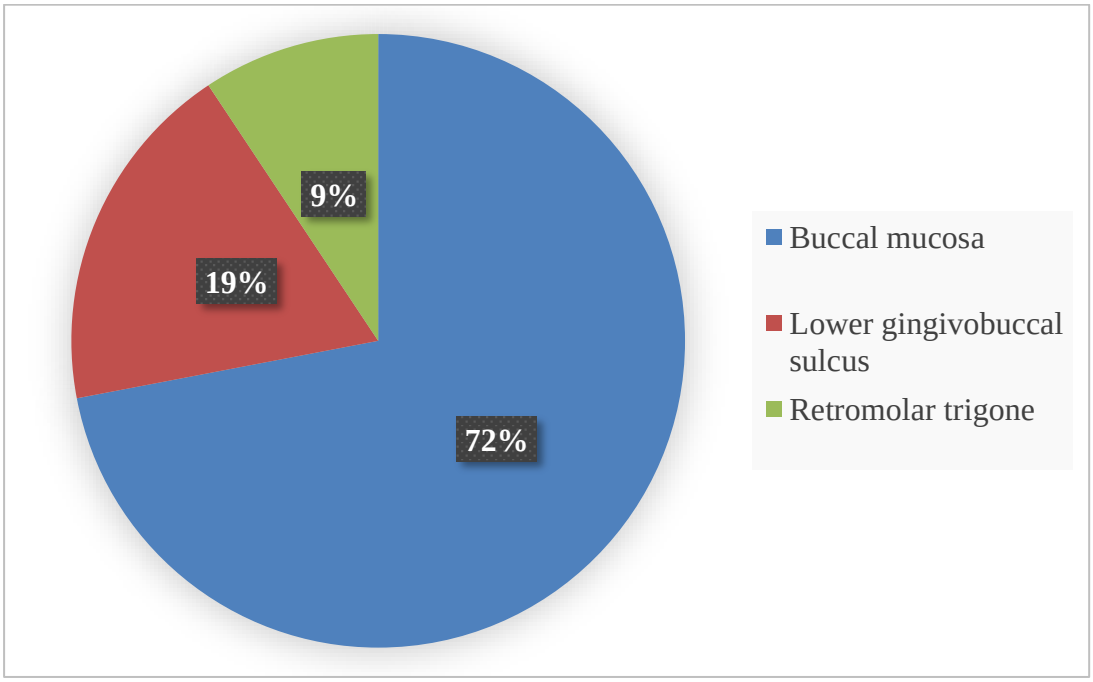


In our study, 48% of subjects had poor oro-dental hygiene and in 52% oro-dental hygiene was satisfactory.

Table 8:- Distribution of subjects according to Site of lesion

Site	Frequency	Percent
Buccal mucosa	54	72.0
Lower gingivobuccal sulcus	14	18.7
Retromolar trigone	7	9.3
Total	75	100.0

Graph 8:- Distribution of subjects according to Site of lesion

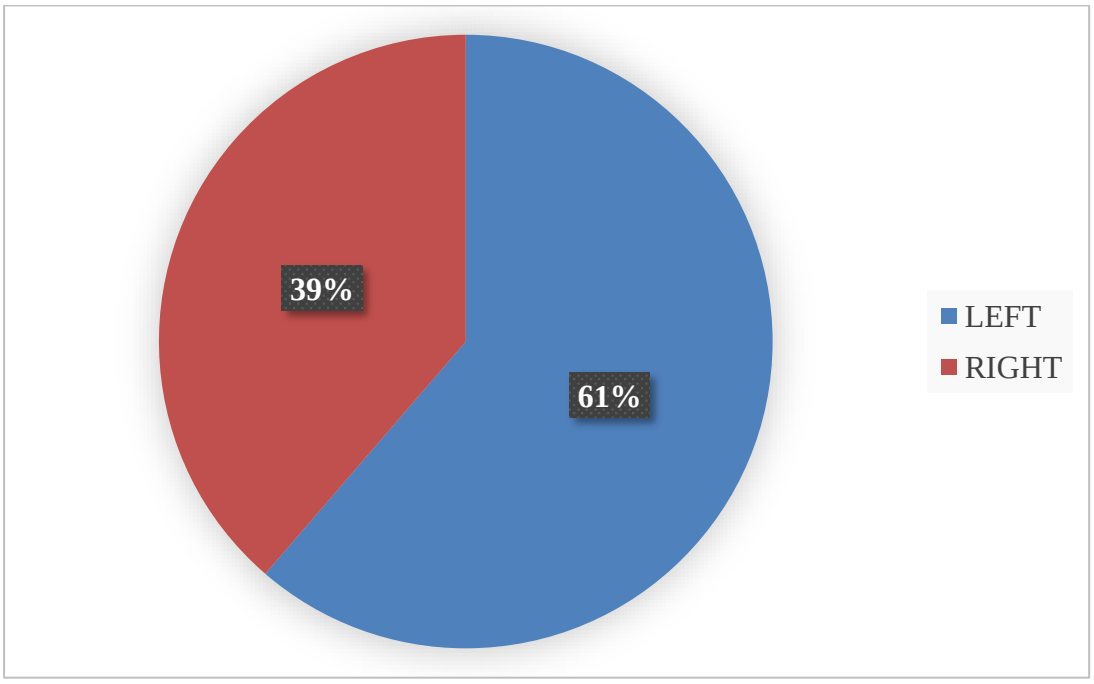


In our study, in 72% of subjects the primary site of lesion was buccal mucosa, in 19% of subjects it was lower Gingivo-buccal sulcus and 9% of subjects it was Retromolar trigone.

Table 9:- Distribution of subjects according to Side of the lesion

	Frequency	Percent
LEFT	46	61.3
RIGHT	29	38.7
Total	75	100.0

Graph 9:- showing Distribution of subjects according to side of the lesion

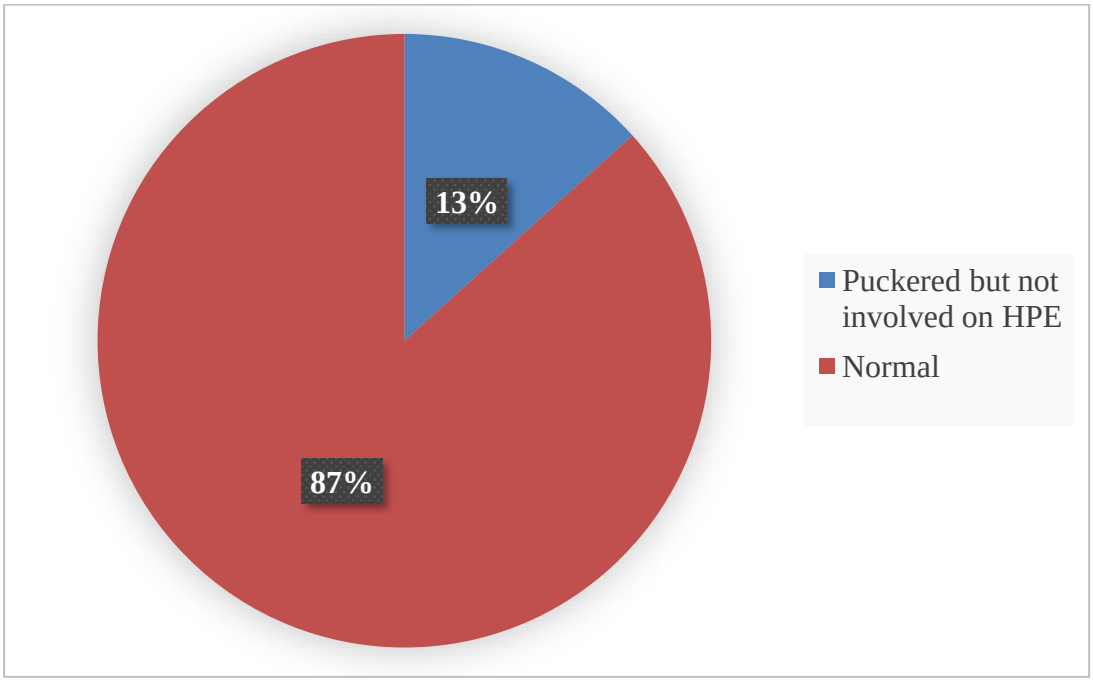


In our study, the lesion was on left side in 61% of patients and in 39% was on right side.

Table 10:- Distribution of subjects according to Skin overlying the lesion

	Frequency	Percent
Puckered but not involved on HPE	10	13.3
Normal	65	86.7
Total	75	100.0

Graph 10:- showing Distribution of subjects according to Skin overlying the lesion

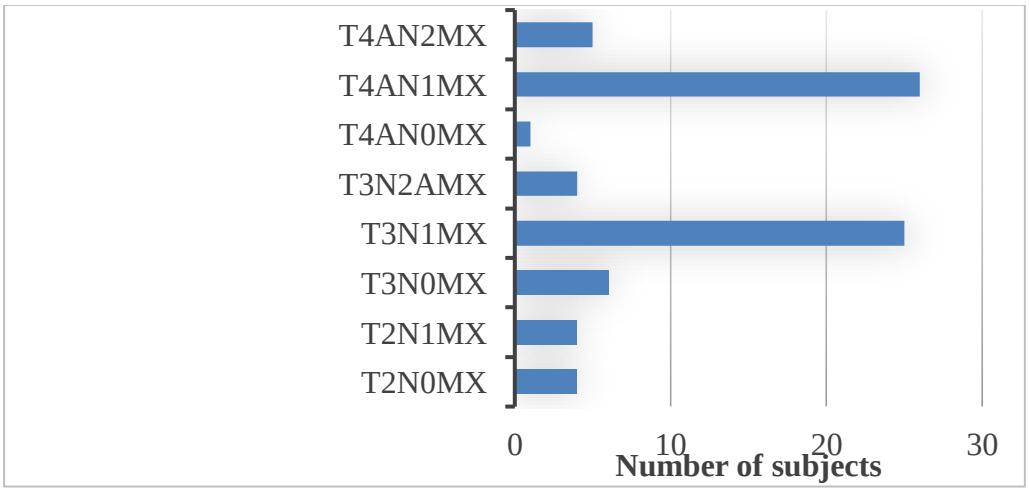


In our study, on clinical examination in 13% of subjects skin appeared thered but was not involved on histopathological examination.

Table 11:- Distribution of subjects according to Clinical staging

Stage	Frequency	Percent
T2N0Mx	4	5.3
T2N1Mx	4	5.3
T3N0Mx	6	8.0
T3N1Mx	25	33.3
T3N2aMx	4	5.3
T4aN0Mx	1	1.3
T4aN1Mx	26	34.7
T4aN2Mx	5	6.7
Total	75	100.0

Graph 11:- Showing Distribution of subjects according to Clinical staging

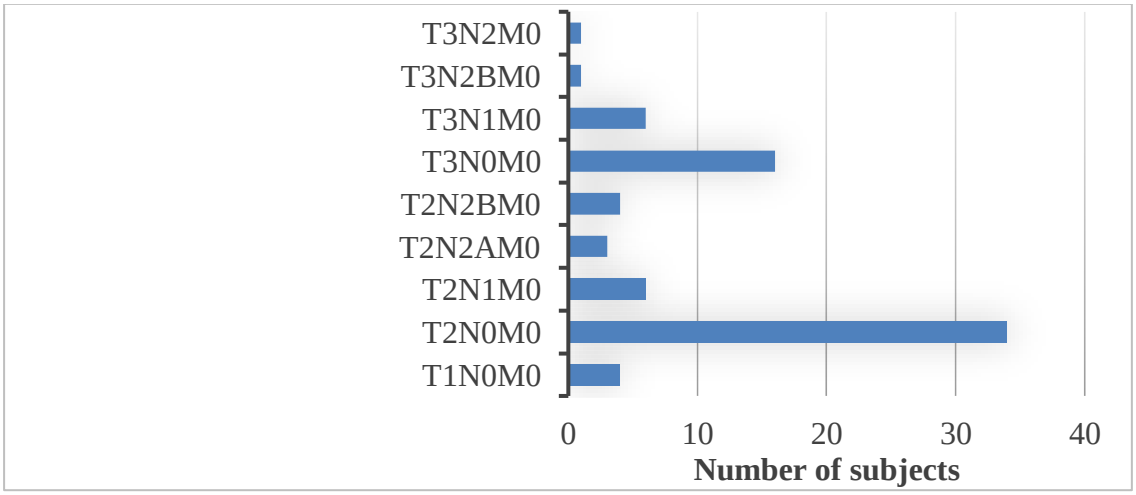


In our study, 26 of the patients were clinically staged T4aN1Mx (34.7%), 25 patient were T3N1Mx(33.3%), 6 patients were T3N0Mx(8%), 5 patients were T4aN2Mx(6.7%), 4 patients were T3N2aMx(5.3%), 4 patients were T2N1Mx(5.3%),4 patients were T2N0Mx(5.3%) and only 1 patient was staged T4aN0Mx(1.3%).

Table 12:- Distribution of subjects according to Pathological staging

	Frequency	Percent
T1N0M0	4	5.3
T2N0M0	34	45.3
T2N1M0	6	8.0
T2N2aM0	3	4
T2N2bM0	4	5.3
T3N0M0	16	21.3
T3N1M0	6	8.0
T3N2bM0	1	1.3
T3N2M0	1	1.3

Graph 12:- Showing Distribution of subjects according to Pathological staging

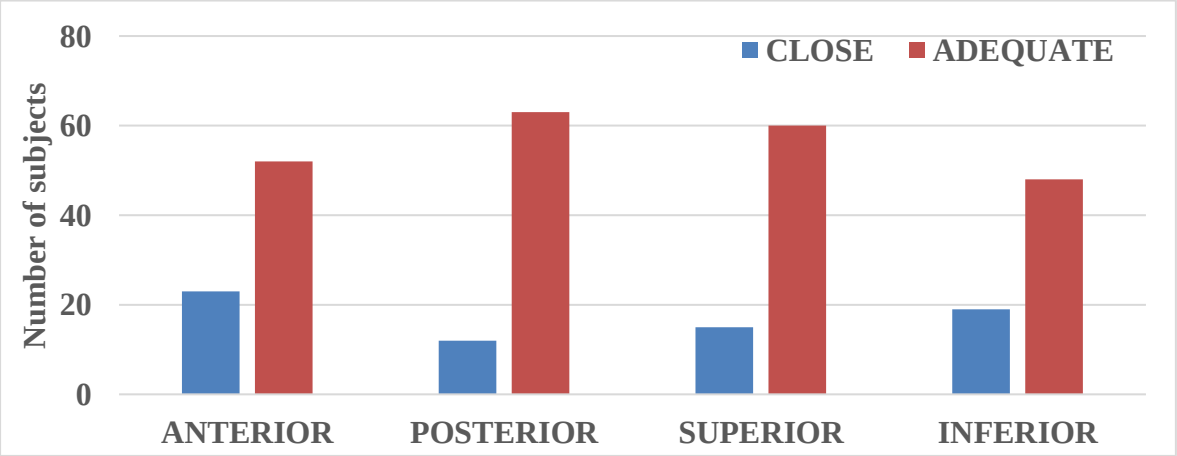


In our study, following histopathological evaluation of the excised specimen most patients were staged T2N0M0(45.3%) followed by T3N0M0 (21%), 6 patients were T2N1M0 and T3N1M0(8%), 4 patients were T1N0M0 and T2N2bM0(5.3%), 3 patients were T2N2aM0(4%), 1 each were staged T3N3aM0 and T3N2bM0 (1.3%).

Table 13:- Distribution of subjects according to Resected margin of the tumour

		Count	N %
ANTERIOR	Close	23	30.7%
	Adequate	52	69.3%
POSTERIOR	Close	12	16.0%
	Adequate	63	84.0%
SUPERIOR	Close	15	20.0%
	Adequate	60	80.0%
INFERIOR	Close	19	28.4%
	Adequate	48	71.6%

Graph 13:- Showing Distribution of subjects according to Resected margin of the tumour

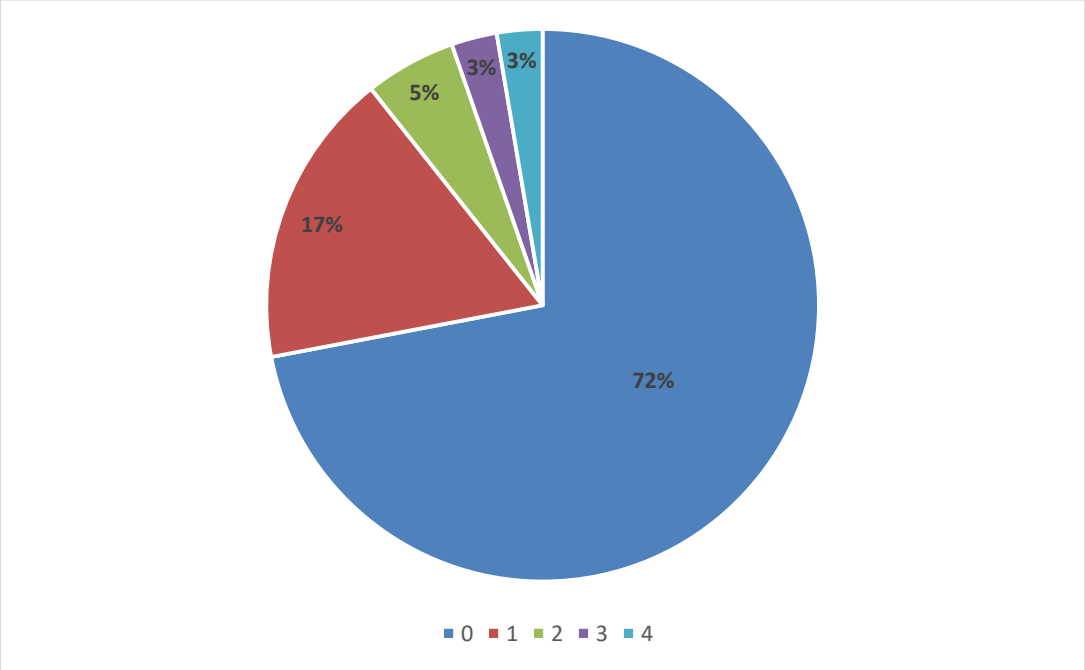


In our study, histopathological examination of the excised specimen following formalin fixation. Close margin following formalin fixation was less than 5mm. 23 patients had close anterior margin, 12 patients had close posterior margin, 15 patients had close superior margin and 19 patients had close inferior margins.

Table 14:- Distribution of subjects according to Number of lymph nodes positive

	Frequency	Percent
0	54	72.0
1	13	17.3
2	4	5.3
3	2	2.7
4	2	2.7
Total	75	100.0

Graph 14:- showing Distribution of subjects according to Number of lymph nodes positive

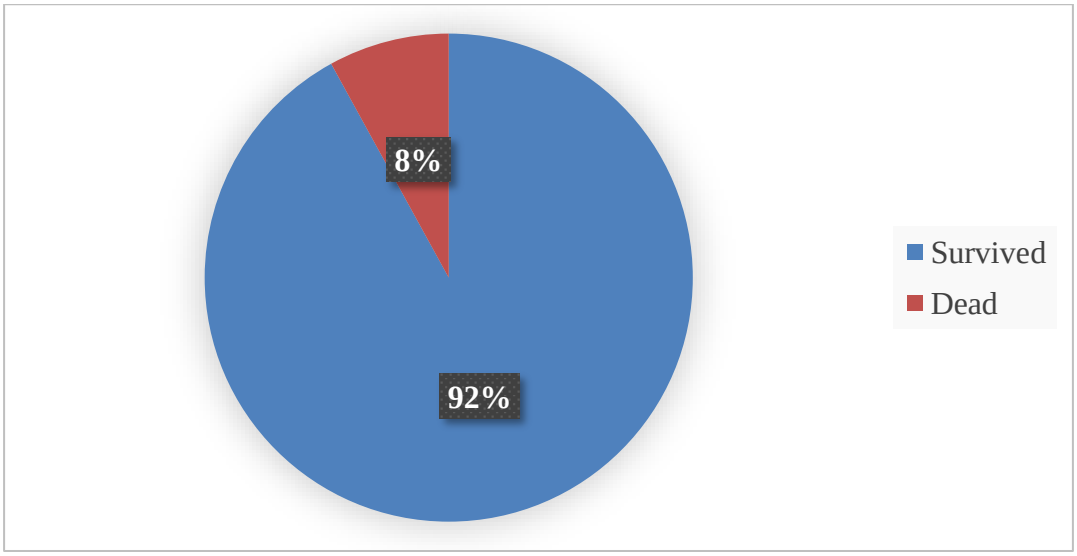


In our study, on histopathological examination of the neck dissection specimens, in 72% of subjects had no positive lymph nodes, 17% of subjects had 1 positive lymph node, 5% of subjects had 2 positive lymph nodes, 3% of subjects had 3 and 4 lymph nodes were positive.

Table 15:- Showing percentage of Recurrences.

	Frequency	Percent
Survived	69	92.0
Recurrence	6	8.0
Total	75	100.0

Graph 15:- showing Percentage of Recurrences.



In our study, 69 patients (92%) of 75 patients were disease free at last follow up with a minimum follow up of 6 months and mean follow up of 12 months, 6 patients (8%) had local and regional recurrence and died due to disease.

93.3% had received Radiotherapy and 26.7% had received Chemotherapy with Radiotherapy.

Table 16:- Comparison of Mean Tumour Volume in subjects who survived with Subjects who had Recurrence

	Survived		Recurrence		P value
	Mean (in cm^3)	SD (in cm^3)	Mean (in cm^3)	SD (in cm^3)	
CT volume	13.5058	13.2425	15.3187	16.7806	0.757
Clinical volume	15.2402	12.3183	18.1125	16.6044	0.536
Histopathological volume	8.5880	7.5624	9.8493	6.4869	0.694

In our study, though there is no statistically significant difference between the tumour volume in subjects who have survived and subjects who are dead, the mean tumour volume is on the higher side in subjects who are dead as compared to the subjects who have survived.

Table 17:- Comparison T-stage with Positive Lymph node

Stage	No. of patients	No. of patients with positive lymph nodes	Percentage of patients with positive lymph nodes
T2	51	13	25%
T3	24	8	33.3%

In our study, 51 patients of 75 were pathologically staged T2 (68%), 24 patients were staged T3 (32%), 13 out of 51 patients - T2 stage had positive lymph nodes (25%), 8 out of 24 patients – T3 stage had positive lymph node (33.3%).

Table 18: - Comparison of Tumour Volume with pathologically Positive Lymph nodes.

	Lymph node status				P value
	Negative		Positive		
	Mean (in cm^3)	SD (in cm^3)	Mean (in cm^3)	SD (in cm^3)	
CT volume	13.0681	12.7041	15.1493	10.4445	0.556
Clinical volume	14.0628	11.1008	19.0886	9.3564	0.071
Histopathological volume	7.6912	7.7720	11.2545	5.9777	0.062

In our study, the mean tumour volume on CT-scan when lymph nodes were positive was 15.15cm^3 and when lymph nodes were negative was 13.06cm^3, the mean tumour volume when measured clinically when lymph node were positive was 19.08cm^3 and when lymph nodes were negative was 14.06cm^3, the mean histopathological tumour volume in patients with positive lymph nodes was 11.25cm^3 and when lymph nodes were negative 7.69cm^3 . The mean Tumour volume was more in patients who had positive lymph nodes.

Table 19: - Comparison of Tumour volume with T-staging

	T2 (in cm^3)	T3 (in cm^3)
CT Volume	10.5	22.6
Clinical Volume	12.7	24.2
Histopathology volume	7.1	14.4

The average tumour volume of T2 tumours clinically was 12.7cm^3, radiologically was 10.5cm^3 and on histopathology it was 7.1cm^3. the average tumour volume of T3 tumours on radiology was 22.6cm^3, clinically 24.2cm^3, histopathology it was 14.4cm^3.

Table 20 : - Comparison of Mean Tumour Volume according to Pathological staging

	CT volume (in cm^3)		Clinical volume (in cm^3)		Histopathological volume (in cm^3)	
	Mean	SD	Mean	SD	Mean	SD
PT1N0Mx	4.0478	4.9451	5.4250	5.8128	.2975	.2072
pT2N0Mx	9.0701	6.1879	10.1229	5.2139	5.5005	4.8919
pT2N1Mx	10.6120	3.9791	16.5350	4.3106	9.1063	3.6518
pT2N2aMx	7.2890	1.0055	10.1500	.4950	3.8000	.8485
pT2N2bMx	15.4465	11.0208	14.1812	12.1017	8.8550	7.4870
pT3N0Mx	23.8190	22.2172	24.5944	13.9804	14.1947	9.4975
pT3N1Mx	22.9460	12.3199	25.6043	10.9070	16.3310	5.3905
pT3N2bMx	28.8960	.	25.0000	.	14.4000	.
pT3N2Mx	15.0600	.	21.0000	.	12.8000	.
P value	<0.01		<0.01		<0.01	

There was a statistically significant difference between staging with respect to tumour volume

Table 21: - Comparison of Mean Tumour Volume according to Clinical Staging

	CT volume (in cm^3)		Clinical volume (in cm^3)		Histopathological volume (in cm^3)	
	Mean	SD	Mean	SD	Mean	SD
T2N0Mx	4.9553	3.7926	4.9310	2.3657	1.3445	1.1617
T2N1Mx	3.8190	2.3672	5.2800	2.6468	2.1498	1.8367
T3N0Mx	8.6137	3.8331	9.9083	1.9454	3.7870	1.5181
T3N1Mx	9.4107	6.2967	12.0276	7.0201	6.4043	4.5778
T3N2aMx	9.9327	3.0077	8.8917	1.2238	4.0667	1.1372
T3N2Mx	8.4000	.	4.7250	.	2.0000	.
T4aN0Mx	10.2600	.	14.0000	.	11.4000	.
T4aN1Mx	23.4452	18.4904	24.4478	12.0073	14.9335	8.2890
T4aN2Mx	8.7468	4.1907	15.6450	5.7521	8.1982	4.0752
P value	<0.01		<0.01		<0.01	

There was a statistically significant difference between staging with respect to tumour volume .

Table 22: - Comparison of Mean Tumour Thickness with Tumour (T)- stage.

	CT-TRANSVERSE DIAMETER (in cm)		TUMOUR THICKNESS (in cm)		HP-THICKNESS (in cm)	
	Mean	SD	Mean	SD	Mean	SD
T1	.8000	.2449	.7000	.2449	.2500	.1732
T2	1.3170	.3181	1.0277	.3424	.9043	.4196
T3	1.4708	.3495	1.5750	.5758	1.3125	.5811
P Value	<0.01		<0.01		<0.01	

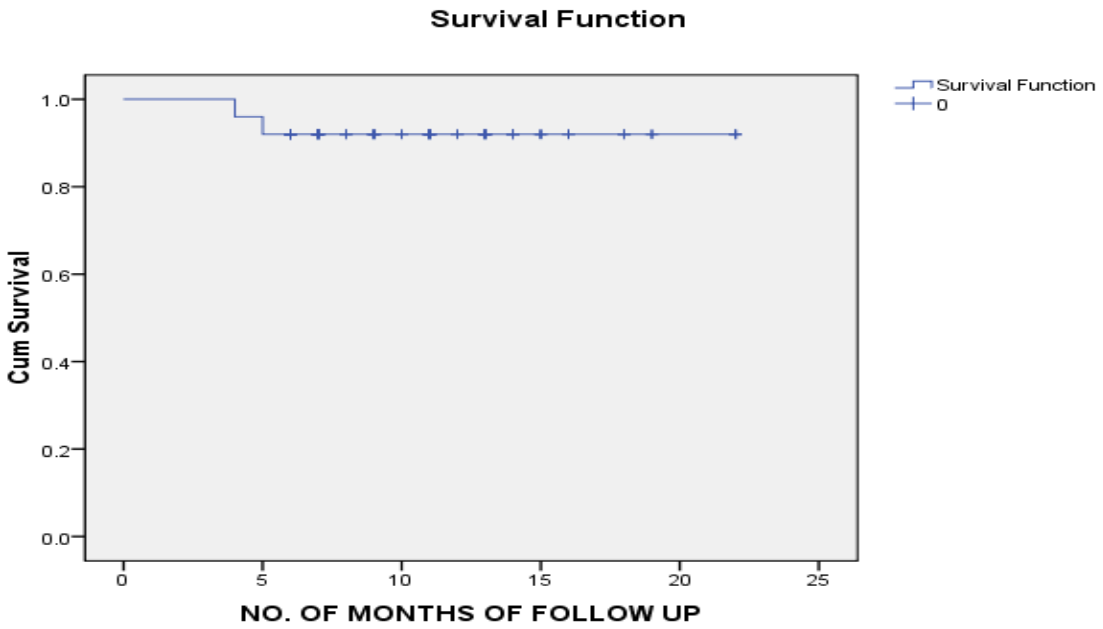
In our study, the mean tumour thickness on CT - in T1 is 0.8cm, T2 is 1.3cm, T3 is 1.4cm, on clinical examination – in T1 is 0.7cm, T2 is 1.02cm, T3 is 1.5cm, on Histopathology – in T1 is 0.25cm, T2 is 0.9cm, T3 is 1.3cm.

Table 23: - Survival Table

Means for Survival Time			
		95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound
20.600	.548	19.525	21.675

Mean survival time 20.6 months with 95% confidence interval (19.525- 21.675)

Graph 24 : - Survival Graph



Survival increases after 5 months. All the events of death occurred within 6 months of follow up

DICUSSION

Head and Neck cancer in India has a specific demographic profile, risk factors, food habits, addictions and family history. Head and neck cancers are an emerging major public health problem, due to changing life style and addictions. Head and cancers in India account for 30% of all cancers in males and 16% of all cancers in females.[1] In our region, oral cavity cancers account for 30% of all cancers and being most common in both males and females.[14] In our study, it was observed that buccal mucosa and lower gingiva-buccal cancers were more common in females, Male to Female ratio was 1:3.3.

In our study, majority (87%) of the patients were in the above the age of 40 years and most of them belonged to lower socio-economic status. 80% of the patients in our region present with locally advanced disease due to lack of awareness and poverty.[14] Locally advanced squamous cell carcinoma of oral cavity are usually high-volume tumours and carry a bad prognosis.

TNM -Classification is the best available staging system for oral cavity squamous cell carcinoma. It is widely accepted as an important nomenclature. Until 2017, two-dimensional size of the tumour was considered in staging the primary tumour. However, this did not represent the actual tumour load. The latest TNM staging 8th edition from 2018, includes depth of invasion which is the third dimension and actually shows the aggressiveness or invasive nature of the tumour.

Tumour volume shows the actual tumour load or the tumour clonogens. therefore, it may be more reliable as a prognostic indicator. Therefore, we conducted this study at RL Jalappa Hospital and research in Kolar to document the tumour volume in oral cancers clinically staged T2 and above and treated with curative intent. However, tumours found to T4 on histopathology (skin and bone involvement) were excluded as skin or bone involvement can make a tumour aggressive irrespective of its size or volume. We aimed to correlate the

tumour volume with oncological outcomes like involvement of regional lymph nodes and disease-free survival. In our study though there was no statistically significant difference between mean tumour volume calculated clinically and radiologically. Tumour volume when calculated on histopathology was very less as compared to tumour volume calculated by clinical method and on radiology. This can be explained by the fact that shrinkage of the tissues occurs following formalin fixation which can be about 30%.[41]

In our study, majority of the patients had pathological T2 (68%) tumours, the rest had T3 tumours (32%). We observed that cervical lymph node metastasis was found in 13 out of 51 patients with T2 disease (25%) and 8 out of 24 patients in T3 disease (33.3%). The average tumour volume of T2 tumours clinically was 12.4cm^3, radiologically was 10.5cm^3 and on histopathology it was 7.1cm^3. the average tumour volume of T3 tumours on radiology was 22.6cm^3, clinically 24.2cm^3, histopathology it was 14.4cm^3. In our study, patients who had recurrences the average tumour volume was found to be more than 15cm3 on clinical examination and was more than 12.3cm^3 on radiology and was more than 8cm3 on histopathology. Among 6 recurrences in our study patients with low tumour volume i.e. 2 patients had close margins of resection (less than 5mm after formalin fixation), however they had depth of invasion more than 6mm. The tumour volume was higher in patients who had died of disease as compared to patients who are alive and disease free. In few European studies, the mean primary tumour volume varied from 1.3cm^3 to 24.2cm^3, volume of 18.3cm^3 is taken as a cut off for large volume tumours, 5-year disease free survival was less than 40%.[22] In a study done in Brazil, tumour volume of more than 33.5cm^3 was observed as an indicator of bad prognosis.[42] In a study done in southern India tumour volume of more than 6cm^3 for squamous cell carcinoma of oral tongue was associated with bad prognosis and higher chances of lymph node metastasis and extracapsular invasion.[43] Both in our study and in literature Tumour volume has a positive correlation with the lymph node metastasis.

Depth of invasion of more than 5mm was a bad prognostic factor in our study. All 6 patients who recurred in our study had depth of invasion more than 6mm. According to the recent AJCC staging system, Depth of more than 5mm is considered locally aggressive disease and depth of more than 10mm is considered advanced disease. Therefore, all these cases who recurred would have been up staged according to 2018 AJCC classification (8^{th} edition). In our study the mean thickness of the tumour was more as the T stage increased. The mean tumour thickness in T1 tumours radiologically (8mm), clinically (7mm), histopathology (3mm), in T2 tumours it was radiologically (11mm), clinical (10mm), histopathology(9mm), in T3 tumours it was radiological(14mm), clinical(15mm), histopathology(13mm). Various other studies in southern India have shown that depth of invasion of greater than 4mm in case of malignancy of tongue have correlated with bad prognosis. A study done in university of Texas, reported depth of invasion of 7mm was taken as a cut off for oral tongue squamous cell carcinoma, when DOI was greater than 7mm it was associated with higher chances of recurrence and occult lymph node metastasis.[44] Depth of invasion (DOI) in oral cavity cancer is important in determining prognosis. DOI of 7.25 mm was most predictive for occult nodal disease and 8 mm for OS and DSS. DOI was an independent predictor of OS and DSS. [45] The rate of nodal metastasis for tongue cancer of a thickness 2.1-4mm was only 11.2%. This increased to 38.5% in patients with tongue cancers that were 4.1–6 mm thick.[45] These authors advocated neck dissection for tumours >4 mm thick for tongue tumours. Various authors have advocated neck dissection as the probability of occult cervical metastasis is greater than 20%. With increasing depth of invasion particularly > 10mm, there is significantly increased risk of occult nodal metastasis (53%) and decrease in 5year survival to 45%.[46] DOI < 5mm have also shown occult metastasis to be present in 23% individuals mandating elective neck dissection even in early stage superficial tongue tumours.[47]

In our study, tumour volume correlated with lymph node metastasis and survival outcome. Thickness of the tumour also had a positive correlation with lymph node metastasis, as tumour thickness is indirectly contributing to tumour volume. Depth of invasion more than 5mm was a poor prognostic factor. Close margins of resection(<5mm) was found to be another bad prognostic factor.

SUMMARY

Head and neck cancer are the sixth most prevalent cancer across the globe but is the most common group of malignancies in India. Oral cavity cancer accounts for almost 50% of the head and neck cancers in India. 60% to 80% of these patients present with advanced disease as compared to 40% in developed countries.

Treatment protocol and prognosis vary widely and are based on the TNM staging of the disease at the time of diagnosis. Till 2017 Tumour (T) -classified by a subjective and two-dimensional measurement. From 2018 Depth of invasion has been incorporated in T-classification. T-classification fails to define the true three-dimensional volume which is more reliable representing the actual tumour load. The five years overall survival in these patients with locally advanced lesions is only about 50%.

We conducted this study at R L Jalappa Hospital and research in Kolar to document the tumour volume in oral cancers clinically staged T2 and above and treated with curative intent. However, tumours found to T4 on histopathology (skin and bone involvement) were excluded as skin or bone involvement can make a tumour aggressive irrespective of its size or volume.

We aimed to correlate the tumour volume with oncological outcomes like involvement of regional lymph nodes and disease-free survival. In our study though there was no statistically significant difference between mean tumour volume calculated clinically and radiologically. Tumour volume when calculated on histopathology was less as compared to tumour volume calculated by clinical method and on radiology. Tumour volume was calculated as a product of greatest dimensions in length, breadth and thickness of tumour.

In our study, majority of the patients had pathological T2 (68%) tumours, the rest had T3 tumours (32%). We observed that cervical lymph node metastasis was found in 13 out of 51 patients with T2 disease (25%) and 8 out of 24 patients in T3 disease (33.3%) The average

tumour volume of T2 tumours clinically was 12.4cm^3, radiologically was 10.5cm^3 and on histopathology it was 7.1cm^3. the average tumour volume of T3 tumours on radiology was 22.6cm^3, clinically 24.2cm^3, histopathology it was 14.4cm^3. In our study, patients who had recurrences the average tumour volume was found to be more than 15cm3 on clinical examination and was more than 12.3cm^3 on radiology and was more than 8cm3 on histopathology. Among 6 recurrences in our study patients with low tumour volume i.e. 2 patients had close margins of resection (less than 5mm after formalin fixation), however they had depth of invasion more than 6mm. The tumour volume was higher in patients who had died of disease as compared to patients who are alive and disease free.

Depth of invasion of more than 5mm was a bad prognostic factor in our study. All 6 patients who recurred in our study had depth of invasion more than 6mm. According to the recent AJCC staging system, Depth of more than 5mm is considered locally aggressive disease and depth of more than 10mm is considered advanced disease. Depth of invasion is more representative than tumour thickness as a prognostic factor because it indicates tumour aggressiveness and penetration into surrounding tissue.

In our study, tumour volume correlated with lymph node metastasis and survival outcome. Thickness of the tumour also had a positive correlation with lymph node metastasis, as tumour thickness is indirectly contributing to tumour volume. Depth of invasion more than 5mm was a poor prognostic factor. Close margins of resection(<5mm) was found to be another bad prognostic factor. Our findings showing positive correlation of tumour volume with staging, lymph node metastasis and recurrence was similar to other studies particularly in Brazil and other parts of India where larger tumour volume correlated with disease aggressiveness and lymph node metastasis.

CONCLUSION

1 - There is high prevalence of oral cancer in Kolar region.

2 -Tumour volume is a reliable indicator of tumour load and therefore has a significant impact on prognosis in oral cancers, when adverse factors like skin and bone involvement are excluded.

3 -Depth of invasion by the tumour is an important factor in staging and prognosis and has been incorporated in 8th Edition – AJCC classification (2018)

4 - Tumours with larger volume have a higher chance of recurrence.

5 -Tumours with larger volume have higher frequency of lymph node metastasis.

6 - Tumour thickness has also correlated with lymph node metastasis, as tumour thickness also contributes to tumour volume.

7 - Depth of invasion of more than 5mm is a poor prognostic factor.

8 - Close margin of resection (<5mm after formalin fixation) is a bad prognostic factor.

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ANNEXURES

PROFORMA

PERSONAL DETAIL

Name: Age: Sex:

Address :Date: Occupation:

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

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		
Difficulty in speech		
Loosening of teeth		
Earache		

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 –

- Tobaccochewing :

Type – Betel nut ☐

Pan masala ☐

Gutka ☐

Duration - Frequency –

Side – Right/ Left

BothLeaves overnight – Y/N

Tobacco – Y/N Lime – Y/N

Stopped since –

(if stopped)

- Smoking :

Type – Filtered Cigarette ☐

Unfiltered Cigarette ☐

Beedi ☐

Hookha ☐

Pipe ☐

Duration - Packs/Day -

- Alcohol :

Duration - Type -

Amount/day -

Stopped since (if stopped):

GENERAL PHYSICAL EXAMINATION

Built: Poor ☐ Nutritional status: Poor ☐

Medium ☐ Satisfactory ☐

Well-built ☐

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/ TrismusGrade of Trismus (if any):

  Oro-dentalHygiene:Poor/ Satisfactory Nicotine stains:Y/ N

  Site: Buccal mucosa ☐
  RetromolarTrigone ☐
  lower alveolus ☐
  upper alveolus ☐
  Hard palate ☐
  tounge ☐
  floor of mouth

  Side: Right ☐ Upper ☐
  Left ☐ Lower ☐

Type of Lesion:

Verrucous ☐
Ulceroproliferative ☐
Ulcerative ☐
Infiltrative ☐

Dimension: site

size

Thickness

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:

Contrast Enhanced CT SCAN

DIMENSIONS

VOLUME

BIOPSY REPORT:

TREATMENT:

Surgery done:

Date of surgery

Primary tumour:(Gross)

Site:
Tumor size: Length Breadth Thickness

Volume

Histopathological report:

Dimension- Length

Breadth

Thickness

Histological type: squamous cell carcinoma

- CONVENTIONAL
- VERUCCOUS
- PAPILLARY
- ACANTHOLYTIC

Histopathological grade:

Well differentiated ☐

Moderately differentiated ☐

Poorly differentiated ☐

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

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

Extra-capsular spread: Present ☐ Not identified ☐

pTNM staging:

Adjuvant treatment –

chemoradiation –Drug and dose

Fractions of radiation

Chemotherapy – drug and dose

Follow up- following completion of treatment

1st month –

Recurrence –Y/N

3rd month –

Recurrence –Y/N

6th month –

Recurrence –Y/N

PATIENT INFORMATION SHEET

Study title: **Evaluation of Tumour volume as a prognostic factor in locoregional outcome of Lower gingivobuccal cancers.**

Study location: R L Jalappa Hospital and Research Centre attached to Sri DevarajUrs Medical College, Tamaka, Kolar.

Details-

Patients diagnosed having buccal mucosa and lower ginivo-buccal cancer and admitted to R.L.Jalappa Hospital will be included in this study. Patients planned for surgery followed by Adjuvant treatment. Patients in this study will have to undergo routine preoperative investigations, CECT for evaluation of primary tumour.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

Dr.Brindha.H.S (Post graduate)

Department of Otorhinolaryngology

SDUMC Kolar

INFORMED CONSENT FORM

I Mr/Mrs. have been explained in my own understandable language, that I will be included in a study which is tumour volume as independent prognostic factor in locoregional outcome of oral cavity cancer, being conducted in RL JALAPPA HOSPITAL.

I have been explained that my clinical findings, investigations, intraoperative findings, post-operative course, will be assessed and documented for study purpose.

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

I have been explained about the follow up details and possible benefits and adversities due to interventions, in my own understandable language.

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

I have principal investigator mobile no for enquiries.

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

Signature of the patient:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place:

KEY TO MASTER CHART

1. OC – oral cavity
2. Du in Ms – Duration in months
3. AP DIA in cm – Anteroposterior Diameter in cm
4. SI DIA in cm – Superoinferior Diameter in cm
5. CT – Computed Tomography
6. HP – Histopathology
7. TV – Tumour Volume
8. LN – Lymph Node