A COMPARATIVE STUDY OF ONCOLOGICAL OUTCOME BETWEEN SURGERY ALONE AND NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED ORAL CANCERS

By

DR. ARJUN GUPTA

DISSERTATION SUBMITTED TO
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY
IN
OTORHINOLARYNGOLOGY

Under the guidance of

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MAY-2021

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LIST OF ABBREVIATIONS

NACT	Neoadjuvant chemotherapy
SCC	Squamous Cell Carcinoma
AJCC	American Joint Committee of Cancer
CECT	Contrast Enhanced Computed Tomography
RT	Radiotherapy
CT	Chemotherapy
ENE	Extra Nodal Extension
KPS	Karnofsky Performance Status
EORTC	European Organization for Research and Treatment of Cancer
RTOG	Radiation Therapy Oncology Group
NCI	National Cancer Institute
NAD	No Abnormality Detected

ABSTRACT

BACKGROUND:

Prevalence of Oral cancers has been increasing across the globe. In India 30% of malignancies are Head and Neck cancers and almost 50% among them are oral squamous cell carcinomas. Oral cancers and their surgery adversely affect quality of life and important functions like speech, mastication, swallowing and aesthetics and are aggressive with a tendency towards rapid infiltration into adjoining tissues and lymph node metastasis. 80 % of our patients present in a locally advanced stage making them inoperable or difficult to resect with resultant post operative morbidity. Neoadjuvant Chemotherapy in such cancers is still controversial. It has been tried in order to control progression of cancer till definitive treatment (surgery + adjuvant treatment) is administered, or to down stage the tumor prior to surgery. In this study we intend to compare the oncological outcome in age and stage matched patients undergoing surgery alone followed by adjuvant treatment and those subjected to Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy followed by surgery and adjuvant treatment in locally advanced oral squamous cell carcinoma staged T4a & T4b.

OBJECTIVES:

1. To document the oncological outcome of 2 cycles of Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy given at 3 weekly intervals followed by surgery and adjuvant treatment in locally advanced (T4) oral cancers.

2. To document the oncological outcome of surgery alone (upfront surgery) followed by adjuvant treatment in locally advanced (T4) oral cancers.
3. To compare the oncological outcome with regard to loco-regional control and surgical complications in the above mentioned 2 groups.

METHODS:

The comparative observational study included 60 patients with locally advanced oral cancer staged T4 according to AJCC classification (8^{th} edition) at R.L. Jalappa Hospital And Research Centre, Kolar from December 2018 to November 2020.

Patients were randomized and divided into 2 groups. Group A having patients receiving Neoadjuvant Chemotherapy with 2 cycles of Paclitaxel and Carboplatin followed by surgery and adjuvant treatment. Group B having patients undergoing surgery followed by adjuvant treatment.

The surgery included Composite Resection + Neck dissection in all cases. Adjuvant treatment included Radiotherapy or Chemotherapy + Radiotherapy. The complications after treatment and locoregional control was compared between the 2 groups after a minimum follow up of 1 year.

RESULTS

This comparative study included 30 patients in each group. Majority of the patients were females in the age group of 50-60 years. Patients staged T4a were 37(61.6%) and 23(38.3%) patients were staged T4b. 83.3% patients had N1 & 16.7% had N2b nodal status. The most common location of the primary tumor was buccal mucosa seen in 73.3% patients followed by lower alveolus 16.7%.

Infratemporal involvement was seen in about 40% of patients in both groups. In the neoadjuvant chemotherapy group, 30% had partial response, 37% had stable disease and 33% had progressive disease following 2 cycles of Neoadjuvant Chemotherapy.

The superior margin was found to be the closest margin in both groups being 5mm with a range from 1-9mm.The mean depth of invasion in both groups was 6-7mm. Perineural invasion and lymphovascular spread was seen in less than 10% patients in each group. Extranodal spread was observed in 23.3% patients in Neoadjuvant Chemotherapy group and 36.7% patients in surgery alone group. The surgical complications encountered were similar in both groups about 10% patients with partial flap necrosis and 26% patients with orocutaneous fistula. After a mean follow up of 18 months and minimum follow up of 1 year, 6.6% had local recurrence, 16% had locoregional recurrence and 13% had regional recurrence in Neoadjuvant chemotherapy group. In the surgery alone group, 16.6% patients had local recurrence, 23% had locoregional recurrence and 13% had regional recurrence. Though, the locoregional control rates were similar both groups, the subset with progressive disease in Neoadjuvant chemotherapy group recurred early and had poor prognosis. The patients with stable disease and partial response with neoadjuvant chemotherapy had lesser frequency of recurrence. The resection of the primary tumor was easier with wider margins among patients who had partial response to neoadjuvant chemotherapy (70%).

At last follow up 50% patients in the Neoadjuvant Chemotherapy group were alive without disease 36.67% were alive with disease whereas in the surgery alone group 43.33% were alive without disease 50% patients were alive with disease. Average time taken for recurrence was about 9 months.

CONCLUSION:

Among patients with oral squamous cell carcinoma staged T4, the resectable tumors had better outcome with surgery alone compared to Neoadjuvant chemotherapy followed by surgery.

Adjuvant treatment is mandatory in both groups. The frequency of surgical complications is not affected by Neoadjuvant chemotherapy. Similar observations have been made in other studies in literature. Partial responders following Neoadjuvant chemotherapy have wider margins of resection and better loco-regional control compared to surgery alone group. Paclitaxel based Neoadjuvant chemotherapy is advisable in very advanced oral squamous cell carcinoma.

KEYWORDS:

Oral squamous cell carcinoma, neoadjuvant chemotherapy, composite resection, neck dissection, compartment clearance of infratemporal fossa, loco-regional control, recurrence

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

OBJECTIVES

REVIEW OF LITERATURE

MATERIALS AND METHODS

RESULTS

DISCUSSION

CONCLUSION

SUMMARY

BIBLIOGRAPHY

ANNEXURES

INTRODUCTION

Prevalence of Oral cancers has been increasing across the globe. Oral cancers are the 6th most common malignancy in the world. [1] Majority of these cancers are from South East Asia. In India 30% of malignancies are Head and Neck cancers and almost 50% among them are oral squamous cell carcinomas. [2] The main cause of this high prevalence in India is addiction to chewable tobacco, areca nut and betel leaves. [3]

Oral cancers affect quality of life and important areas for functions like talking, mastication, swallowing and aesthetics and are aggressive with a tendency towards rapid infiltration into adjoining tissues and lymph node metastasis.

80 % of our patients present in a locally advanced stage making them inoperable or difficult to resect with post operative morbidity involving loss of structure and function. [4] This can affect adequacy of upper airway, speech, mastication and swallowing as well as aesthetic appearance.

Surgery is the main stay of treatment and is extensive involving Composite resection of the tumor (with skin and mandible in some cases), Neck dissection, Compartment clearance of Infratemporal fossa (in T4b tumours) and complex reconstruction.

Adjuvant treatment includes Radiotherapy or Chemotherapy with Radiotherapy with added sequelae and morbidity. However, recurrences are quite common in such locally advanced tumours even after aggressive multimodality treatment.

The complications of surgery include flap necrosis, wound break down, orocutaneous fistula, sepsis, hemorrhage and vessel blow outs, chylous fistula, nerve injuries etc. The complications of Chemotherapy include bone marrow suppression, febrile neutropenia, ototoxicity, nephrotoxicity, neurotoxicity etc. The complications of Radiotherapy are mucositis, osteoradionecrosis, desquamation, wound break down etc.

Only recently the overall and disease free survival has marginally increased in this dreaded disease.

Neoadjuvant Chemotherapy in such cancers may be necessary in order to control its progression till definitive treatment (surgery) is done or to down stage the tumor prior to surgery.

In literature there is a controversy with regard to use of Neoadjuvant Chemotherapy in locally advanced oral cancers as some authors feel it benefits the outcome and others disagree. [5,6]

Cisplatin has been the first line chemotherapeutic drug in Head and Neck squamous carcinomas. Recently Taxanes have been found to be equally or more useful as chemotherapeutic agent in these cancers. [7]

In this study we intend to compare the oncological outcome in age and stage matched patients undergoing surgery alone followed by adjuvant treatment and those subjected to Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy followed by surgery and adjuvant treatment in locally advanced oral squamous cell carcinoma staged T4a or T4b.

RESEARCH HYPOTHESIS:

Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy prior to definitive treatment in stage IV oral squamous cell carcinoma maybe helpful in down staging the disease and improves loco-regional control

RESEARCH QUESTION:

Can Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy prior to definitive treatment in stage IV oral squamous cell carcinoma downstage the disease and help in resection and improve locoregionalcontrol?

OBJECTIVES OF THE STUDY

1. To document the oncological outcome of 2 cycles of Paclitaxel and Carboplatin based Neoadjuvant Chemotherapy given at 3 weekly intervals followed by surgery and adjuvant treatment in locally advanced (T4) oral cancers.

2. To document the oncological outcome of surgery alone (upfront surgery) followed by adjuvant treatment in locally advanced (T4) oral cancers.

3. To compare the oncological outcome with regard to loco-regional control and surgical complications in the above mentioned 2 groups.

REVIEW OF LITERATURE

Head and neck cancer is the 5th most commonest malignancy worldwide. An upward trend is seen in morbidity and mortality rates of squamous cell carcinoma (SCC) of oral cavity in industrialized areas. Oral cancer is the 6th most common cancer worldwide with high prevalence in South Asia. Oral cancers are most prevalent in Kolar and constitute 29.66% of total cancer incidence in kolar.[1]

Carcinoma means a Greek word meaning a crab. Its latinised form is "cancer". Another term for cancer is malignancy from its Latin roots malignus and genus meaning endangering harm. Cancer is a term used to characterize abnormal growths of cells which may result in the invasion of normal tissue or the spread to organs.

In the historical review, buccal mucosa and alveolar malignancies have been dated back to time before Christ: references have been made to such tumors by Edwin Smith Papyrus(2300 B.C.)and by Ekers Papyrus (1500 B.C.)

Sir Henry T Batlin, a surgeon from St. Bartholomew's Hospital, London in 1885 A.D, performed wide excision of head and neck cancers with mandible and lymphatics of the upper neck. He along with Kocher, emphasized the advantage of excising metastatic lymph nodes.

EMBRYOLOGY

The stomatodeum bounded by brain above and pericardial sac below becomes apparent at 4th week of intrauterine life. The breakdown of bucco-pharyngeal membrane causes mouth to become continuous with the developing pharynx.

Mesodermal condensation in lateral wall and floor of the pharynx gives rise to branchial arches which differentiate to produce cartilaginous bar, branchial musculature and branchial arch artery with each arch receiving an afferent and efferent nerve supply, post and pre-trematic nerve supply. [10]

The mandibular process arising from the lateral aspects of developing head fuse by the 6th week in midline and the maxillary process arising as buds from mandibular processes, grow forwards and meet with lower end of nasal septum and its contralateral side in the midline. Fusion of maxillary processes separates primitive nasal cavity from primitive oral cavity.[8]

ORAL CAVITY - ANATOMY

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

- Lip

-Tongue (Anterior 2/3rd)

-Floor of mouth

-Gingiva - Upper alveolus

- Lower alveolus

-Buccal mucosa

-Retromolar trigone

-Hard palate

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

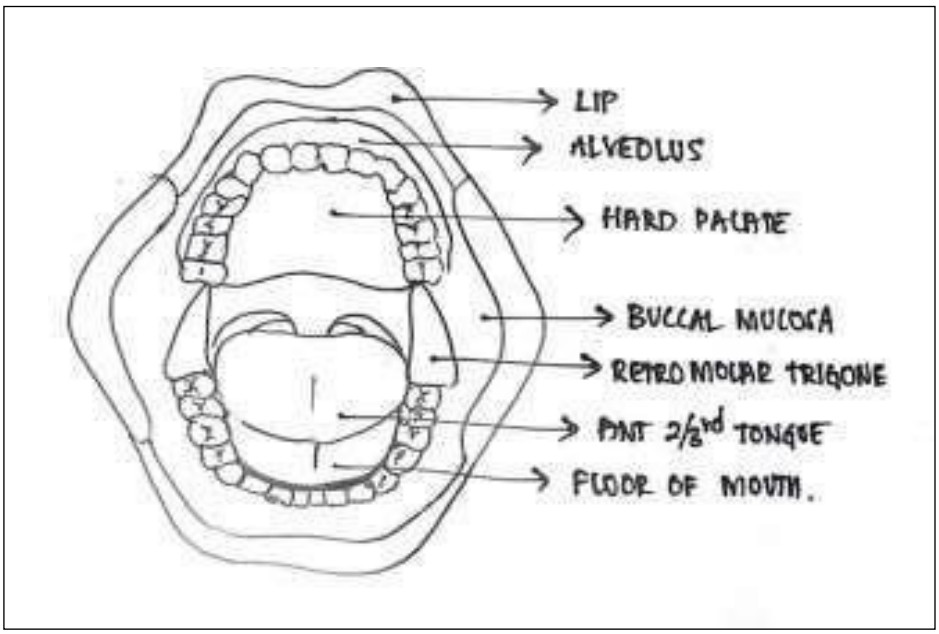


Fig 1: - Oral cavity - subsites

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

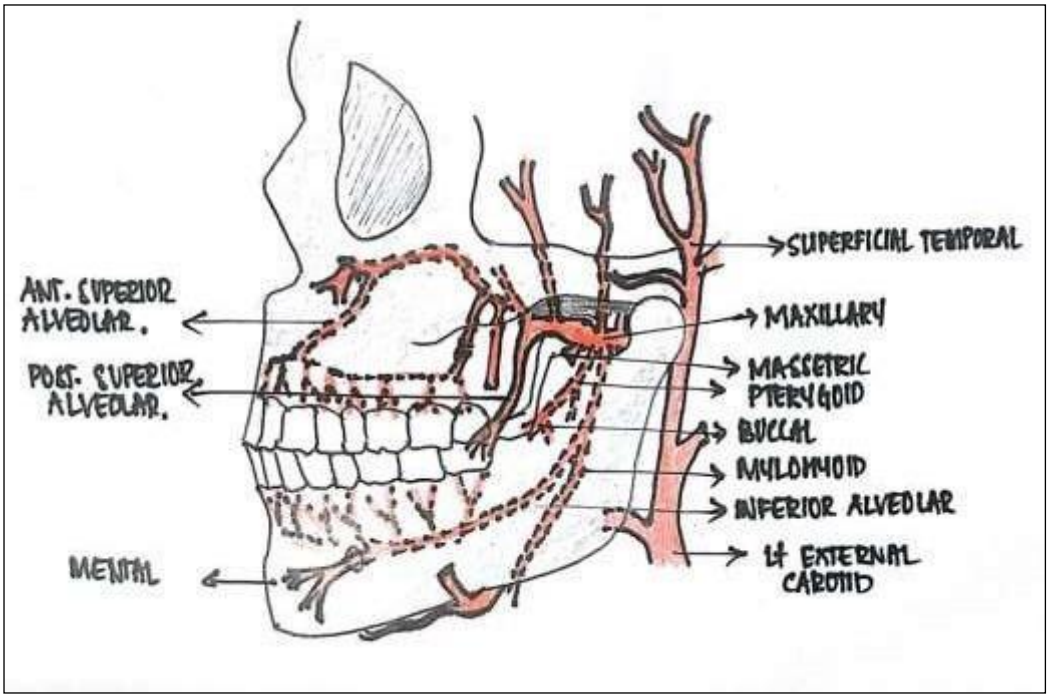


Fig 2: Oral cavity – Blood supply

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.[10]

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.[12]

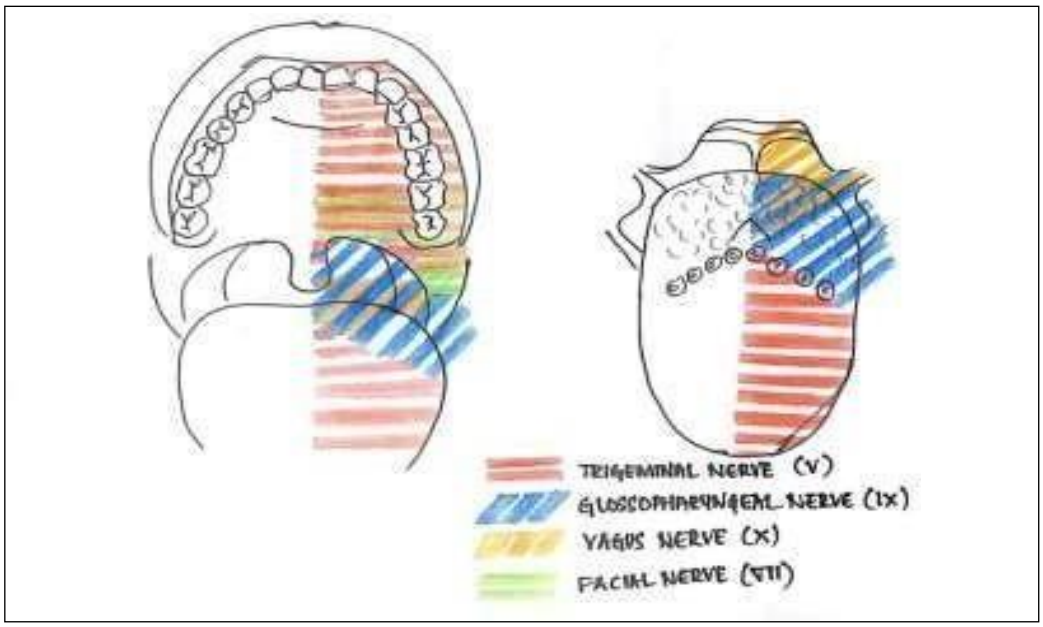


Fig 3: Nerve supply of Oral cavity

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.[11]

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[12]

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.[12]

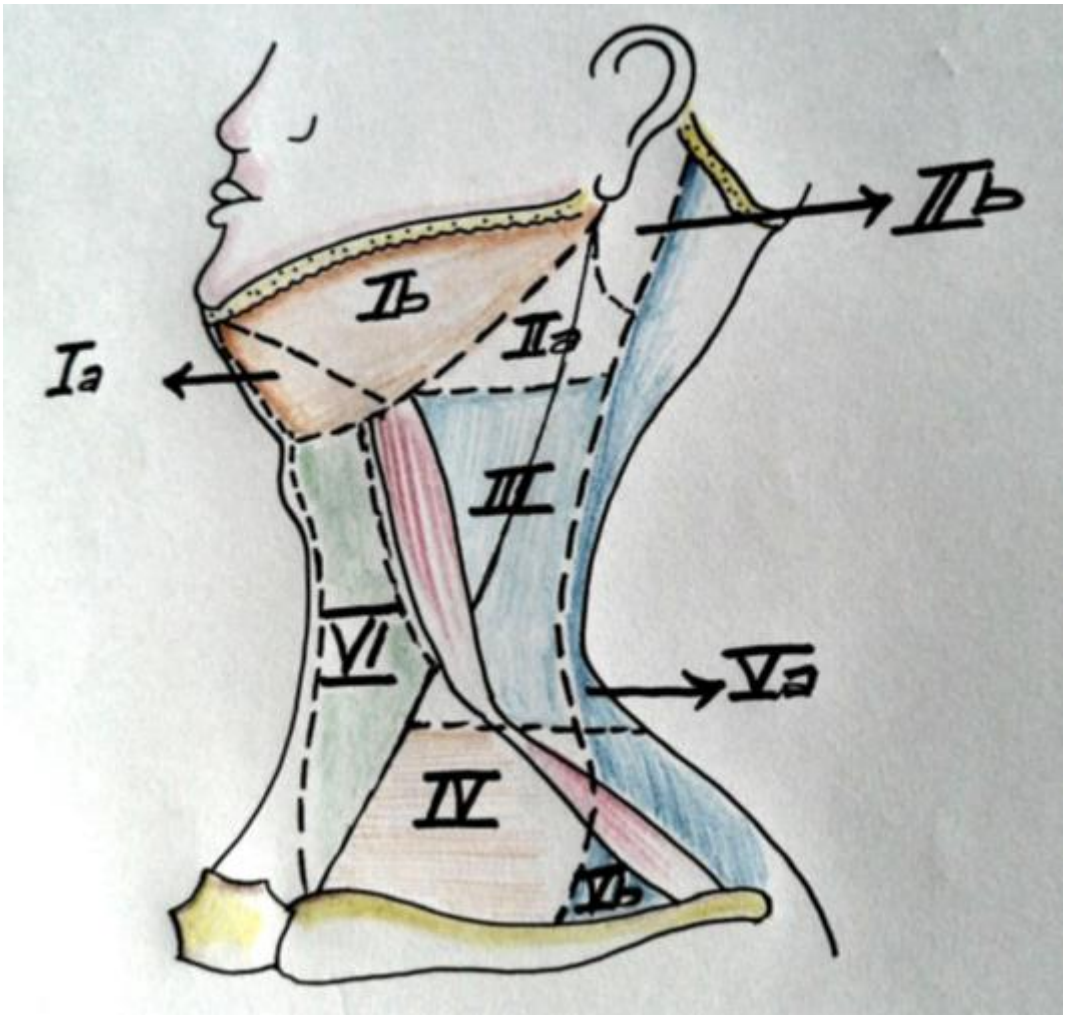


Fig 4: Levels of Lymph nodes in Neck

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.[13]

India, Sri Lanka, Pakistan, Bangladesh, Hungary & France have the highest rates with the India accounting for 30% of newly detected cases.[14]

The estimated number of new cancers in India is about seven lakhs, and about 3.5 lakhs people die of cancer every year.[13]

According to the cancer registry of Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, on an average, about 5000 new cancers are registered per year.[15] 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.[16]

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.[12]

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.[10]

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.[10]

However, in Kolar region carcinoma of buccal mucosa is the most common malignancy.[17] 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.

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-flavored 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.[18]

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

Sepsis: - Septic and decayed teeth.

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

Spices

Syphilis

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

Snuff dipping and other tobacco products

Fig 6: showing various forms of tobacco consumption

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.[10]

Industrial chemicals

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

Immune status: - Immune deficiency due to low cell mediated immunity.

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 anemia and Ataxia telangiectasia have all been associated with oral cavity cancers. Other relevant genetic markers may include inducibility of cytochrome p450 enzyme system.[19]

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

Sunlight exposure

Cirrhosis of liver

Diet

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.

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%. [20]

Types of Oral Leukoplakia[20]

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.[20]

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.

Melanoplakia

Oral Submucous fibrosis

Sideropenic dysphagia

Oral lichen planus: Rate of malignant transformation is about 4%. [21]

Discoid lupus erythematosus Hyperkeratosis Dyskeratosis congenital Syphilis

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.[12] The enzymes degrade the basement membrane proteins such as collagen IV, laminin and proteoglycans which allow the spread of tumour cells.[22]

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 sub capsular 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 intra nodal 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.[23] 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.[24] 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.[22] Poorer the differentiation the more likely the tumour metastasize early. The tumour with infiltrative margin is more likely to metastasize than those with pushing margin.

The following table describes the lymph node levels and the nodes that are at greatest risk of harboring metastases from different primary sites.[25]

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 harboring 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[9]

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(+)

REGIONAL LYMPH NODE : 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

Table 1: 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

GENERAL PRINCIPLES FOR SELECTION OF TREATMENT:

2 forms of curative treatment of head & neck squamous cell carcinoma:

Surgery

Radiation

However advanced tumours require multimodality treatment i.e

1- Neoadjuvant chemotherapy (NACT) → surgery → radiotherapy (RT)

chemotherapy (CT) +RT

2- Surgery → RT/CT +RT

T4 SCC's are further divided into:

T4a (resectable) & T4b (unresectable) by AJCC 2002 AJCC 7 edition has reclassified T4a as moderately advanced local disease and T4b as very advanced local disease.

Studies have shown that not all T4b tumours is unresectable and that some of these patients can be offered surgery as the primary treatment rather than just palliation. Those tumours involving skull base or with encasement of carotid artery are excluded. Better reconstruction options in recent times have allowed to reduce the morbidity associated with such radical surgeries.

Advantages of surgery compared to radiation therapy offering similar cure rates:

1- Limited amount of time exposed to treatment

2- Treatment time is shorter & risk of radiation sequelae are avoided

4- Irradiation is reserved for subsequent head & neck primary tumour which may not be suitable for surgery

MALIGNANT CONDITIONS OF ORAL CAVITY[26]

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

Variants of squamous cell carcinoma:

- Verrucous carcinoma: It is a low-grade highly well differentiated carcinoma with keratinising exophytic or warty appearance. The cellular response is usually prominent.
- Sarcomatoid carcinomas/Pseudo sarcoma/Pseudosarcomatous squamous carcinoma / pleomorphic carcinoma/metaplastic carcinoma/epidermoid carcinoma- spindle cell variant
- Adenosquamous cell carcinoma
- Adenoid squamous cell carcinoma
- Basaloid squamous carcinoma
- Basal cell carcinoma
- Lymphoepithelioma
- Malignant oral salivary gland tumors
- Adenoid cystic carcinoma
- Adenocarcinoma
- Mucoepidermoid carcinoma
- Melanoma of oral cavity

TUMOUR BIOLOGY[27]

The development of a tumour involves three phases:

a) Initiation

b) Promotion

c) Progression

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

TUMOUR ESCAPE MECHANISMS[27]

A) Tumour related:

a) Tumour is not immune-sensitive

1) No expression of tumour-specific antigens
2) No or low expression of major histocompatibility complex molecules correlated with tumour aggressiveness and metastatic potential
3) No antigen processing or presentation (masked/modulated)
4) Resistance to immune cell-mediated killing, such as induction of apoptosis through the apoptosis-inducing molecule F

b) Tumour is not immunogenic

1) Lack of co-stimulatory molecules, therefore do not induce an immune response
2) Secretion of immunosuppressive factors that inhibit T-cell functions or defects in T cells
3) Shedding of tumour antigens that down regulate T-cell molecules
4) Induction of T-cell tolerance
5) Induction of T-cell apoptosis (programmed cell death)

B) Host related:

1) Tumour grows too fast for the immune system
2) Inherited or acquired immunodeficiency
3) Treatment (radiation, chemotherapeutic drugs) or chemical or physical carcinogens related immuno-suppression
4) Deficiency in antigen presentation by antigen-presenting cells

5) Lack of access of effector cells to the tumour
6) Expression of immune-dominant antigens on parental tumour that prevents stimulation with other tumour antigens
7) Age-long latent period of carcinogens -Failure of an anti-tumour immune response related to age

CARCINOGENESIS [27]

Tumour development represents the loss of the normal signaling 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. Over-expression 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, 11g,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.

THERAPEUTIC MODALITIES FOR ORAL CANCER[12]

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 factors) and those related to the treatment delivery team (physician factors).

PHYSICIAN FACTORS:

Surgery

Radiotherapy

Chemotherapy

Combined modality treatment

Dental

Rehabilitation services

Prosthetics

Support services

Photodynamic therapy

Immunotherapy

Gene therapy

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

TUMOUR FACTORS:

- Site
- Size (T stage)
- Location (anterior versus posterior)

- Proximity to bone (mandible)
- Lymph node metastasis
- Previous treatment
- Histology (type, grade, depth of invasion)

PATIENT FACTORS:

- Age
- General medical condition
- Tolerance
- Occupation
- Acceptance and compliance with regards to treatment
- Lifestyle (smoking, drinking, tobacco chewing)
- Socio-economic consideration
- Nutrition

CLASSIFICATION OF NECK DISSECTION

1991 classification

1. Radical neck dissection

2. Modified radical neck dissection

3. Selective neck dissection.

a) Supraomohyoid

b) Lateral

c) Posterolateral

d) Anterior

4. Extended neck dissection.

2001 CLASSIFICATION BY THE COMMITTEE FOR HEAD AND NECK SURGERY AND ONCOLOGY OF THE AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY (AAO-HNS)

1. Radical neck dissection

2. Modified radical neck dissection

3. Selective neck dissection:

4. Extended Neck dissection

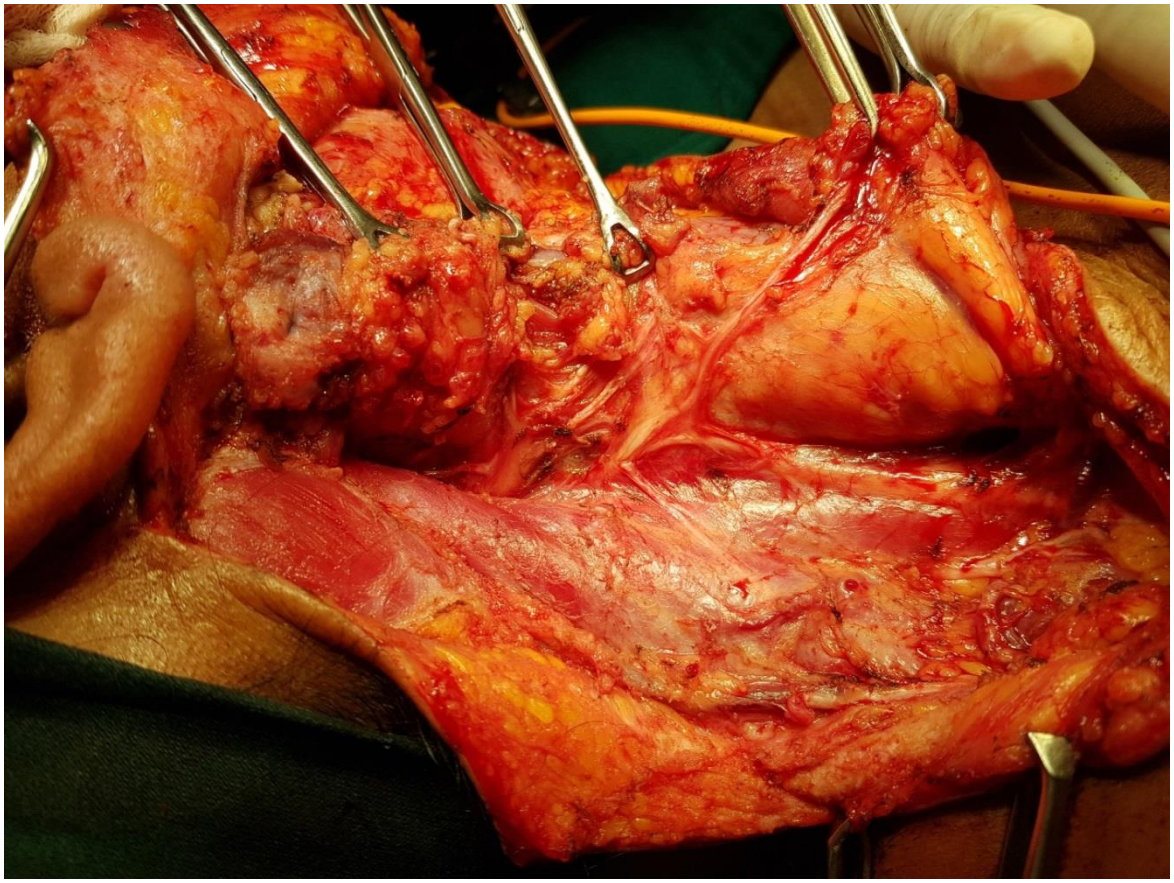


Fig 7: Modified Radical Neck dissection

RECONSTRUCTION[28]

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

1. Split thickness skin grafts

   Full thickness skin grafts

2. Mucous membrane flaps

3. Tongue flaps

a) Posteriorly based lateral tongue flap

b) Posteriorly based bilateral tongue flap

c) Anteriorly based ventral tongue flap

4. Masseter flap

5. Nasolabial flap

6. Medial based delto-pectoral flap

7. Forehead flap

8. Sternocleidomastoid myocutaneous flap

9. Trapezius

10. Platysma myocutaneous flap

11. Pectoralis major myocutaneous flap

12. Latissimus myocutaneous flap

13.Costochondral grafts

14.Osteo-myocutaneous flap-fifth rib with pectoralis major myocutaneous flap-Spine of scapula with trapezius

15. Free osteo-cutaneous groin Map

16. Free osteo-cutaneous fibula flap

17. Scapular Osseo-cutancous flap

18. Radial forearm flap (microvascular free flap)

19. Radial forearm free osteocutaneous flap

20. Free fibula and osseo-integrated implants

21. Anterolateral thigh free flap

Whenever possible, immediate single stage reconstruction is preferred over laved reconstruction, when the former can be achieved with acceptable success rates and low morbidity. Immediate restoration of the mandible prevents the development 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 most difficult to duplicate and is necessary for wearing dentures. Preservation of chewing, provision of a base for dental appliances and preservation of a normal appearing lower third of the face are achieved by preservation of the buccal sulcus and the oral floor, which are all essential reasons for maintenance or restoration of the mandibular contour.

QUALITY OF LIFE

The surgical resection of tumor involving the oral cavity has been associated with significant destruction of normal anatomy, functional deficits and suboptimal reconstruction. Historically, disease-free survival, overall survival and tumour response rates were the traditional outcome measures used to judge efficacy of

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

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

Different dimensions of quality of life

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

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

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

1) Karnofsky Performance Scale[30]
2) The Sickness Impact Profile
3) The University Of Washington Quality Of Life Scale
4) The Head & Neck Cancer Specific Quality Of Life Instrument[30]

1) Karnofsky Performance Scale:

The AJCC strongly recommends recording of KPS (The Kamofsky 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.

ROLE OF NEOADJUVANT CHEMOTHERAPY

Once cancer is diagnosed the patient may require medical treatment and specialized care for months and often years. The principal modes of therapy namely surgery, radiotherapy and chemotherapy may be given alone or in combination. When cancer treatment is not curative, maintaining the highest possible quality of life is paramount for many patients, supportive and palliative care are essential and this often involves a range of professional services that extend beyond the discipline of oncology". [31]

Treatment of patients with cancer of all ages requires a specific ethical and psychological approach. Most patients move through a state of denial and later acceptance as the diagnosis and treatment of the disease progresses "Cancer" is often considered as a mutilating self-destructive process. Surgeons involved in the Cure of cancer must help patients to regain their autonomy in decision-making and self determination.

Surgery remains the primary option for the care for many cancers. However on occasions, curative resection is impossible or the prognosis following resection remains unsatisfactory. To combat such poor out come, adjuvant therapies combining chemotherapy and radiotherapy have been developed and when added to surgery may be regarded as an integral part of modern surgical oncology. Neoadjuvant use of chemotherapy has been developed to help down stage tumors. Some unresectable tumors may become resectable following such treatment". Neo adjuvant chemotherapy could induce "down staging" of the tumour and thus improve operability.

Response rates in patients with chemotherapy - naive disease are in excess of 50% and this has encouraged investigators to use chemotherapy as neoadjuvant treatment, as a post-surgical adjuvant, concurrently with radiation, via regional infusion and in the treatment of recurrent and metastatic disease.

The value of chemotherapy in improving the quality of life of patients by palliating symptoms and pain even in the absence of survival advantage is becoming evident. Neoadjuvant chemotherapy was first described by Prei, in 1982 for the treatment of head and neck cancer. A study by Lawton et al and Onnis et al showed that the percentage of patients whose tumours were optimally debulked was higher in the group who received neoadjuvant chemotherapy as compared with those whose tumours were primarily debulked.

Some proponents of neoadjuvant chemotherapy propose it as the primary approach in all cases of advanced stage disease, citing less intra operative blood loss, decreased Intensive care unit stays, decrease period of post operative hospitalization as well as Increased patient comfort. Shrinking the tumour not only makes the surgical procedure more feasible but also prevents metastasis. In addition, there are patients - including those with recent pulmonary emboli, severe recent myocardial infarction, uncontrolled respiratory or thyroid disease and malnutrition - who are not good surgical candidates. Such patients are prime candidates for neoadjuvant chemotherapy following a maximal surgical effort.[31]

Administration of neoadjuvant chemotherapy followed by radical surgery is one approach that has emerged to increase tumour shrinkage, thus allowing more optimal debulking

There remains a need for new treatment techniques to increase survival and cure rates in patients with locally advanced disease and to improve the palliation of those who present with incurable diseases.[32]

ORGAN PRESERVATION STUDIES[33]

1. **EORTC (European Organization for Research and Treatment of Cancer)**

Study

Experimental group

3 cycles of chemotherapy (cisplatin and 5fluorouracil) were used and partial response or complete response was assessed. Patients with complete response were taken for radiotherapy

Control group

Partial laryngopharyngectomy and postoperative radiotherapy was given.

Results

- Three years disease free survival rate better in chemo arm but equal 5 years disease free survival rate.
- No difference in locoregional control
- Decreased metastasis with chemotherapy arm.
- Improvement in overall survival rate in chemotherapy arm
- Rate of functional larynx at 3 years is 42% and 5years is 35%

2. **VÀ study. (Department of Veteran Affairs laryngeal cancer study)**

Study

Experimental arm

Two cycles of chemotherapy (cisplatin and 5 fluorouracil) were given. Partial or complete response was assessed. Those who had above response were given third cycle of chemotherapy and followed by radiotherapy. The non responders underwent total laryngectomy and post operative radiotherapy

Control arm

The patients were directly taken for total laryngectomy and post operative radiotherapy

Results

- Over all tumour response to chemotherapy was 85%.
- Two year and 10-year survival rate showed significant difference in survival.
- Only 36% in organ preservation group required total laryngectomy.
- More local recurrences but less metastasis.
- Overall laryngeal preservation rate was 64%.
- Better quality of life

3. **RTOG study (Radiation Therapy Oncology Group)**

Aim

To determine role of induction chemotherapy as compared to concurrent chemotherapy as compared to radiation alone in laryngeal preservation in patients with stage III and stage IV cancers.

Results

- Three year and 5 year survival no difference.
- Loco-regional control better in concurrent chemo-radiation.
- Less metastasis in concurrent group
- Laryngeal preservation was 84% in concurrent group. 72% in induction chemotherapy and radiotherapy and 67% in radiotherapy alone.

CELL KINETIC CONCEPTS

Both normal and tumour cells have a certain growth capacity and are influenced and regulated by various internal and external forces. The differential growth and regulatory influences occurring in both normal and tumour tissues form the basis of effective cancer treatment.

Patterns of Normal Growth

All normal tissues are capable of cellular division and growth. Normal tissues grow in three general patterns, which are classified as Static, Renewing, and Expanding.

The static cells consist of relatively well-differentiated cells that after initial proliferative activities in the embryonic and neonatal period, rarely undergo cell division (e.g., striated muscle and neurons).

The expanding cells are characterized by the capacity to proliferate under special stimuli (e.g., tissue injury). Under those circumstances, normal quiescent tissue (e.g liver or kidney) undergoes a surge of proliferation with re-growth.

The renewing cells are in a constantly proliferative state. There is constant cell division, a high degree of cell turnover, and constant cell loss (e.g., bone marrow, epidermis, and gastrointestinal mucosa).

Cancer Cell Growth:

Cell growth represents a disruption in normal cellular brake mechanisms resulting in continued proliferation and eventual death of the host. Although cell proliferation occurs continuously in human tumours, there is evidence that it does not take place more rapidly in cancers than in normal tissue. It is not the speed of cell proliferation but the failure of the regulated balance between cell loss and the cell proliferation that differentiates tumour tissues from normal tissues.

Gompertzian Growth:

The characteristics of cancer growth have been assessed by multiple studies in animals and limited studies in humans. When tumours are extremely small, growth follows an exponential pattern but later seems to slow down. Such a growth pattern is known as Gompertzian growth. More simply. Gompertzian growth means, as the tumour mass increases, the time required to double the tumour volume also increases

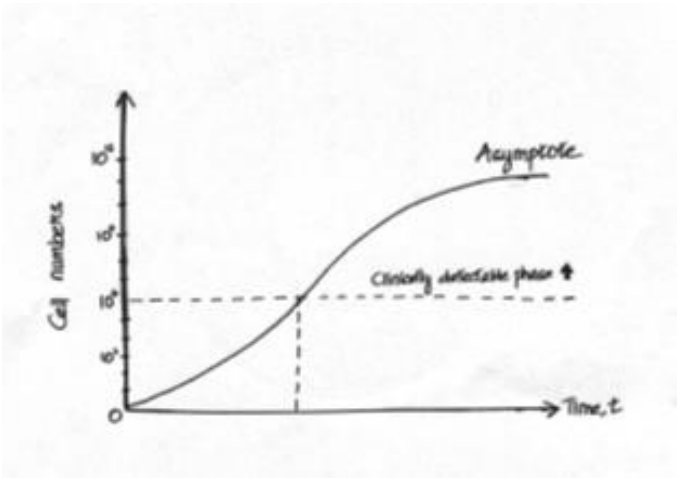


Fig 8: Gompertzian Growth

Doubling Time:

The doubling time of a human tumour is the time that it takes for the mass to double in size. There is considerable variation in doubling time of human tumor. For example, embryonal tumours, lymphoma, and some malignant mesenchymal tumours have relatively fast doubling times (20-40 days), whereas adeno-carcinomas and squamous cell carcinomas have relatively slow doubling times (50–150 days). Metastases generally have faster doubling times than primary lesions. If it is assumed that exponential growth occurs early in a tumour's history and that the tumour starts from a single malignant cell, then a Imm mass will have undergone approximately 20 tumour doubling, at 5 mm mass (a size that might be first visualized on x-ray film) will have undergone 27 doublings, and a Imm mass will have undergone 30 doublings. If such a lesion were discovered clinically, the physician would assume that the tumour had been detected early.

The reality is that it would have already undergone 30 doublings or would have been present approximately 60% of its life span. Growth patterns and doubling time relate to the growth of the tumour mass as a whole. The generation time is the duration of the cycle from M phase to M phase. Variation occurs in all phases of the cell cycle, but the variation is greatest during the Gl period. The events controlling this variation are well understood. These cell cycle events have important implications for cancer therapy. Different sensitivities to chemotherapy and radiotherapy are associated with different proliferative states. Dividing cancer cells that are actively traversing the cell cycle are very sensitive to chemotherapeutic agents. Cells in a resting state (Go) are relatively insensitive to chemotherapeutic agents, although they occupy space and contribute to the bulk of the tumour.

In cell kinetic studies of human tumours the duration of the S Phase (DNA synthesis phase) is relatively similar for most human tumours, ranging from a low of 10 hours to a high of approximately 31 hours. The length of the cell cycle in human tumours varies from slightly more than half-a-day to perhaps 5 days. With cell cycle times in the range of 24 hours and doubling times in the range of 10-1000 days, it is clear that only a small proportion of tumour cells are in active cell division at any given time.

Two major factors that affect the rate at which tumours grow are the growth fraction and cell death. The growth fraction is the number of cells in the tumour mass that are actively undergoing cell division. Tumour growth may be altered by the following factors:

Cytotoxic chemotherapy, which alters both the generation time and the growth fraction of tumours.

Hormones, which appear to alter the growth fraction without changing the generation time.

X-ray therapy, which alters both the generation time and the growth fraction. Alterations in oxygen tension and vascular supply, which alter the growth fraction without altering generation time.

The cell cycle:

Cell replication proceeds through a number of phases that are increasingly well-defined biochemically. Many cytotoxic agents act on more than one site of the cell cycle, including those classified as "phase-specific." Certain oncogenes are activated at specific phases in the cell cycle.

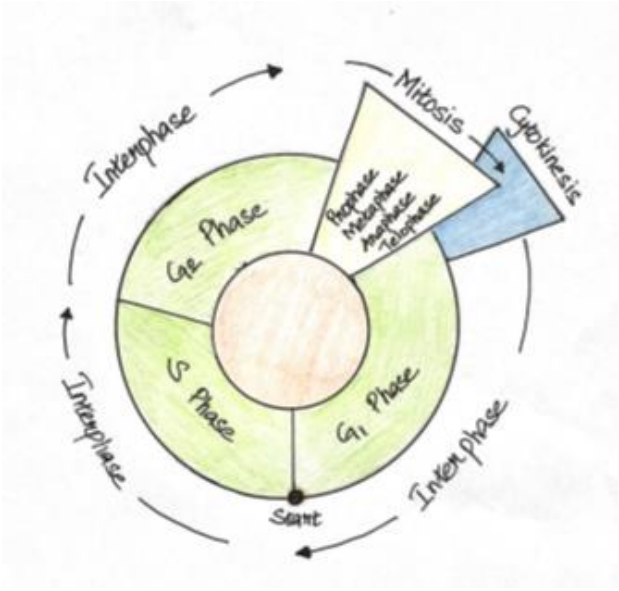


Fig 9: Cell Cycle

GO RESTING

A. In the Go phase (gap 0 or resting phase) cells are generally programmed to perform specialized functions. Cells in the Go phase are, for the most part, refractory to chemotherapy.

B. In the Gl phase (gap 1 or interphase) proteins and RNA are synthesized for many of the enzymes necessary for DNA synthesis are manufactured, or phase specific drug: L-asparaginase.

C. In the S phase (DNA synthesis) the cellular content of DNA doubles. S- phase specific drugs: Procarbazine and antimetabolites.

D. In the GI phase (gap 2) DNA synthesis ceases, protein and RNA synthesis continues, and the microtubular precursors of the mitotic spindle are produced Phase specific drugs: Bleomycin and plant alkaloids.

E. In the M phase (mitosis) the rates of protein and RNA synthesis diminish abruptly while the genetic material is segregated into daughter cells. After completion of mitosis, the new cells enter either the Go or Gt phase. M-phase specific drugs: plant alkaloids.

Mechanisms of drug activity

Cytotoxic agents can be roughly categorized by their activities relative to the cell generation cycle.

Phase nonspecific

a. Cycle-nonspecific drugs kill nondividing cells (e.g., Steroid hormones, Antitumor antibiotics except Bleomycin).

b. Cycle-specific-phase-nonspecific drugs are effective only if the cells proceed through the generation cycle, but they can inflict injury at any point in the cycle (e.g..Alkylating agents).

c. Pharmacokinetics- Cycle-nonspecific and cycle-specific-phase-nonspecific drugs generally have a linear dose-response curve. The greater the amount administered, the greater the fraction of cells killed.

Catabolic enzymes.

Exposure to a drug can induce the production of catabolic enzymes that result in drug resistance. The drug is catabolized more rapidly inside the cell by gene amplification of DNA for the specific catabolic enzymes. Examples include increased dihydrofolate

reductase, which metabolizes methotrexate: deaminase, which deactivates cytarabine; and glutathione., which inactivates alkylating agents.

Glutathione (GSH)

Is essential for the synthesis of DNA precursors. Increased levels of GSH enzymes have been found in various cancers and not in their surrounding normal tissue. GSH and its enzymes scavenge free radicals and appear to play some role in inactivation of alkylating agents through direct binding, increased metabolism, detoxification, or repairing DNA damage. Alkylating agents share cross resistance related to DNA repair in some settings.

DNA topoisomerases

DNA is attached at regular intervals to the nuclear matrix at sites called "domains," which are wound together with their paired DNA molecules. Topoisomerases participate in the separation and resealing of DNA molecules during cell division.

Differential Sensitivity

For any neoplastic agent to be effective, it must have greater toxicity for the Malignant cells than for the patient's normal cells. In that sense, all useful chemotherapeutic agents have greater activity against rumors than against normal tissues.

The window between antitumor effect and normal tissue toxicity may be narrow because most chemotherapeutic agents work by disrupting DNA or RNA synthesis, affecting crucial cellular enzymes, or by altering protein Synthesis

Normal cells also use these vital cellular processes in ways similar to those of malignant cells, particularly fetal or regenerating tissue or normal cell populations in which constant cell proliferation is required (e.g., bone marrow, gastrointestinal epithelium, and hair follicles). As a result, the differential effect of antineoplastic drugs on tumor as compared with normal tissues is quantitative rather than qualitative, and every chemotherapeutic agent produces some degree of injury to normal tissue. The normal tissue toxicity produced by most chemotherapeutic agent's correlates with the intrinsic cellular proliferation of the target tissue. This explains why toxicities, such as blood count suppression, mucosal injury, and alopecia are often seen with most chemotherapeutic regimens.

Therapeutic Index:

The net effect of a chemotherapeutic agent on the patient is often referred to as the drug's therapeutic index (i.e., a ratio of the doses at which therapeutic effect and toxicity occur).

Log kill hypothesis

Chemotherapeutic agents appear to work by first-order kinetics (.e.. they kill a constant fraction of cells rather than a constant number). This concept has important conceptual implications in cancer treatment. For instance, a single exposure of tumor cells to an anti neoplastic drug might be capable of producing 2-5 logs of cell kill. wih typical body tumor burdens of 10' cells (1 kg), a single dose of chemotherapy is unlikely to be curative.

This explains the need for intermittent courses of chemotherapy to achieve the magnitude of cell kill necessary to produce tumor regression and cure. It also provides a rationale for multiple drug or combination chemotherapy. This is the basis for using adjuvant chemotherapy in carly stages of disease when subclinical numbers of cancer cells are suspected.

PHARMACOLOGY AND SELECTION OF CYTOTOXIC DRUGS[34]

DRUG SELECTIVITY

Depends upon either

Differential drug distribution

The presence of specific target reactions in sensitive tissues and the absence of these target reactions in insensitive tissues

Kinetic differences between tumour and normal tissues - kinetic referring to the rates of reactions and in particular, the rate of the cell cycle and the proportion of cells in cycle in different tissues.

Pharmaco-Kinetics

Is the study and characterization of the time course of drug absorption, distribution, metabolism and excretion as well as the relationship of these processes to the therapeutic and toxic effects of drug treatment. A complete pharmacokinetic description of a drug includes its time concentration profile in every tissue of the body from the time of administration to its exertion.

In general if the drugs are administered at standard dose with dose reductions in patients with abnormal organ function these side effects are not hazardous. Subjectively, the most troublesome side effects are nausea, vomiting and mucositis. Improvements in use of antiemetic drugs, including high dose metoclopramide, Dexamethasone and lorazepam have reduced the severity of nausea and vomiting associated with cisplatin treatment. New serotonin antagonist antiemetic are proving to be a significant advance in controlling the nausea and vomiting caused by cytotoxic drugs.

Alopecia may accompany cytotoxic chemotherapy. Scalp tourniquet for half an hour or so over the period of intravenous cytotoxic treatment and chilling of the scalp by ice packs reduce the frequency of hair loss.

Cisplatin[35]

Other names. cis-Diamminedichloroplatinum (II), DDP, CDDP, Platinol.

Mechanism of action: Binding and cross-linking strands of DNA.

Primary indications.- Usually used in combination with other cytotoxic drugs.

Testis, ovary, endometrial, cervical, bladder, head and neck. gastrointestinal, and lung carcinomas, Soft-tissue and bone sarcomas and Non-Hodgkin's lymphoma.

Usual dosage and schedule

40-120 mg/m intravenously on day I as infusion every 3 weeks.

15-20 mg/m intravenously on days 1-5 as infusion every 3-4 weeks.

Special precautions

Do not administer if serum creatinine level is more than1.5mg/dl. Irreversible renal tubular damage may occur if vigorous diuresis is not maintained, particularly with higher doses (>40 mg/m) and with additional concurrent nephrotoxic drugs, such as the aminoglycosides. At higher doses, diuresis with mannitol with or without furosemide plus vigorous hydration are mandatory.

An acceptable method for hydration in patients without cardiovascular impairment for cisplatin doses up to 80 mg/m is as follows. have patient void, and begin infusion of 5% dextrose in half-normal saline with potassium chloride (KCI) 20 mEq/liter and magnesium sulfate (MgSO4.)gm/ litter (8 mEq/liter), run at 500 ml/hour for 1.5-2.0 liters.

After 1 hour of infusion, give 12.5 gm of mannitol by IV push.

Immediately thereafter start the cisplatin (mixed in normal saline at 1 mg/ml) and infuse over 1 hour through the sidearm of the intravenously, while continuing the hydration.

Give additional mannitol (12.5-50.0 gm by intravenously push) if necessary to maintain urinary output of 250 ml hour over the duration of the hydration. If patient gets more than 1 liter behind on urinary output or signs or symptoms of congestive heart failure develop. 40 mg of furosemide may be given.

For doses more than 80 mg/m a more vigorous hydration is recommended.

Have patient void, and begin infusion of 5% dextrose in half-normal saline with KCI 20 mEq/liter and MgSO4. 1 gm/liter (8 mEq/liter); run at 500 ml/hour for 2.5-3.0liters.

After 1 hour of infusion, give 25 gm of mannitol by intravenously push.

Continue hydration.

After 2 hours of hydration, if urinary output is at least 250 ml/hour, start the cisplatin (mixed in normal saline at 1 mg/ml) and infuse over 1-2 hours (1 mg/m /minute) through the sidearm of the intravenously, while continuing the hydration Give additional mannitol (12.5-50 gm by IV push) if necessary to maintain urinary output of 250 ml/hour over the duration of the hydration. If patient gets more than 1 liter behind on urinary output or signs symptoms of congestive heart failure develop, 40 mg of furosemide may be given.

For patients with known or suspected cardiovascular impairment (ejection fraction <45%), a less vigorous rate of hydration may be used, provided the dose of cisplatin is limited (e.g., < 60 mg/m"). An alternative is to give carboplatin.

Toxicity

Myelosuppression - Mild to moderate, depending on the dose. Relative lack of myelosuppression allows cisplatin to be used in full doses with more myelosuppressive drugs. Anemia is common and may have a hemolytic anemia often is amenable to erythropoietin therapy.

Nausea and vomiting - Severe and often intractable vomiting regularly begins within 1 hour of starting cisplatin and lasts 8-12 hours. Prolonged nausea and vomiting occur occasionally. Nausea and vomiting may be minimized by the use of a combination antiemetic regimen eg. ondansetron or metoclopramide and lorazepam, dexamethasone

Mucocutaneous effects - None

Renal tubular damage - Acute reversible and occasionally irreversible nephrotoxicity may occur, particularly if adequate attention is not given to achieving sufficient hydration and diuresis. Nephrotoxic antibiotics increase risk of acute renal failure.

Ototoxicity - High-tone hearing loss is common, but significant hearing loss in vocal frequencies occurs only occasionally. Tinnitus is uncommon.

Severe electrolyte abnormalities - These abnormalities.e.g., marked hyponatremia, hypomagnesemia, hypocalcemia, and hypokalemia, may be seen up to several days after treatment.

CARBOPLATIN[35]

MECHANISM OF ACTION

Same as cisplatin

DOSAGE

20mg x min/ml can be safely administered in 200ml of dextrose 5% in water over two hours. It is administered as a rapid intravenous infusion

EXCRETION

Kidneys excrete it predominantly and cumulative urinary excretion of platinum is 54% to 82%.

USES

Fasier to administer.

Extensive hydration not required because of lack of nephrotoxicity at standard doses:

Is reconstituted in chloride free solutions.

TOXICITY

MYELOSUPPRESSION

- It is a dose limiting toxicity of carboplatin the drug is most toxic to platelet precursors Neutropenia and anaemia are frequently observed.

NAUSEA AND VOMITING

- It is frequent, less severe, shorter in duration and can be easily controlled with standard anti emetics,

ALOPECIA

NEURO TOXICITY, NEPHROTOXICITY AND OTOTOXICITY ARE LESS COMMON

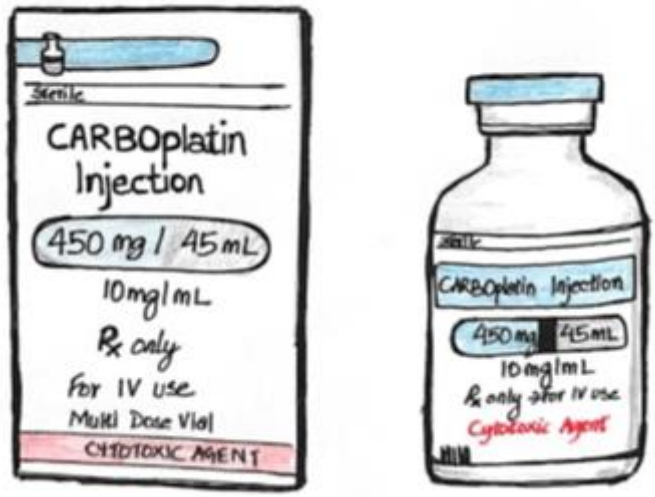


Fig 10: Carboplatin Vial

TAXANES[36]

HOW TAXOL WAS DISCOVERED AND RENAMED PACLITAXEL

The taxanes bind to the interior surface of the microtubule lumen. They disrupt microtubule dynamics by stabilizing the microtubule against depolymerization and infact enhance microtubule polymerization, promoting the nucleation and elongation phases of the polymerization reaction and reducing the critical tubulin subunit concentration required for microtubule assembly

Between 1960 and 1981, the National Cancer Institute (NCI) and the U.S. Department of Agriculture (USDA) collaborated on a plant screening program to identify naturally occurring compounds with anticancer activity. Samples from a single Pacific yew tree, *Taxus brevifolia*, were obtained. Crude extracts from bark was found to be cytotoxic. Mansukh Wani and Monroe Wall, had isolated and identified the active ingredient from the bark of *T. brevifolia* and named it taxol, based on its species of origin and the presence of hydroxyl groups. In 1971, they published the structure of taxol.

MECHANISM OF ACTION

Paclitaxel belongs to the family of cytoskeletal drugs that target tubulin. As a result, paclitaxel treatment leads to abnormality of the mitotic spindle assembly, chromosome segregation, and consequently defects of cell division. By stabilizing the microtubule polymer and preventing microtubules from disassembly, paclitaxel arrests cell cycle in the G_0/G_1 and G_2/M phases and induces cell death in cancer. It has been known that inhibition of mitotic spindle using paclitaxel usually depends on its suppression of microtubule dynamics. However, recent studies demonstrated that only

low-dose paclitaxel can do so, in contrast, high-dose paclitaxel might suppress microtubule detachment from the centrosomes. The binding site for paclitaxel has been identified to be the subunit of beta-tubulin. Paclitaxel has other mechanisms of action than for microtubule targeting.

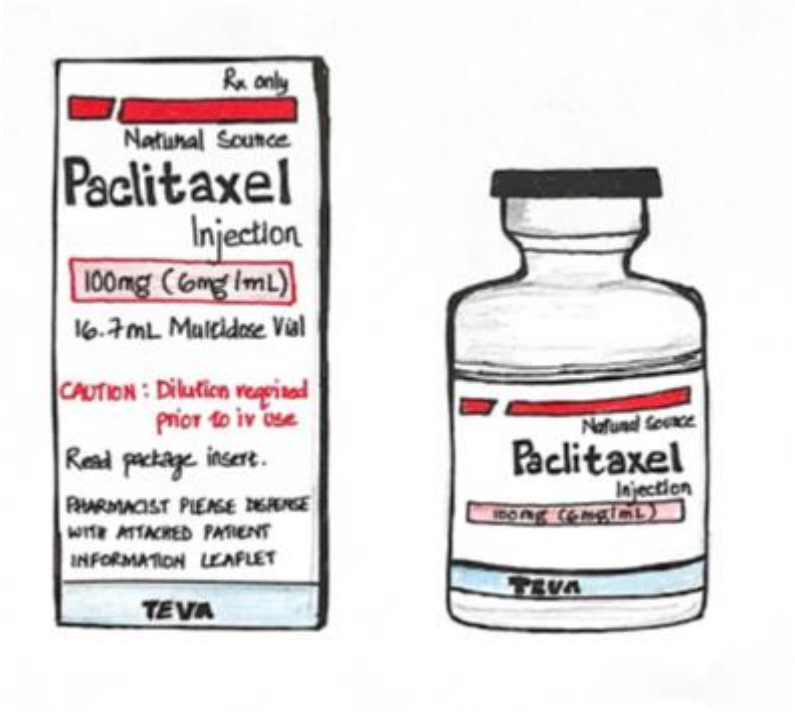


Fig 11: Paclitaxel vial

DOSAGE : 175mg/m^2 can be safely administered in 200ml of dextrose 5% in water over two hours.

EXCRETION: Mainly excreted in the feces with the hydroxylated metabolites as the major excretory products

TOXICITY:

1. Neutropenia
2. Leucopenia
3. Febrile Neutropenia
4. Anaemia
5. Hypoesthesia
6. Stomatitis

Oral cancers extending to Infra temporal fossa were considered inoperable till last decade. However a study done by Liao et al. reported encouraging results following surgery in oral cavity cancers extending to infra temporal fossa below the sigmoid notch of mandible. The 5 years loco-regional control rate was 47%. [37]

Furthermore loco-regional control rate using compartment resections for tumors involving masticator space have shown encouraging results in these advanced cancers. [37,38]

However in a significant number of patients the disease grossly extends into infra temporal fossa or is associated with extensive fungation which makes resectability difficult. [39,40]

A few studies have tried Neoadjuvant chemotherapy in patients to downsize the disease and achieve adequate clearance during resection.It made difficult and borderline inoperable tumors resectable in a few studies.

Neoadjuvant chemotherapy can be given by various drug regimes. These include Cisplatin alone, Cisplatin with 5 Fluorouracil or Paclitaxel with carboplatin, and a 3 drug regimen involving paclitaxel, cisplatin and 5 fluorouracil. A study done in 2014 analyzed 721 patients with Oral Cancers which were technically unresectable and found that 43% of these patients had sufficient reduction in tumor size that made them resectable.

Furthermore using 3 drug regimen achieved resectability in 66.21% and two drug regimen in 40.34% along with a decrease in the loco regional control rate which was 20.6%. For patients undergoing surgery, the Loco regional control was 32% and 15% for the nonsurgical group. [5] Similar results have been observed in other studies where Neoadjuvant Chemotherapy downgraded the tumor and made them resectable. [41,42]

Studies also document that 3 drug regimen of Neoadjuvant chemotherapy for locally advanced oral cancers was more beneficial where patients could tolerate the toxicity. They showed significant improvements in terms of response rates and time to treatment failure. However a clear overall survival advantage was however observed only in unresectable disease. [43]

There still exists a controversy in the use Neoadjuvant chemotherapy in locally advanced oral cancers as studies done in India and abroad showed that there is limited role of Neoadjuvant Chemotherapy use in locally advanced resectable oral cancers. [6]

Neoadjuvant chemotherapy was found to benefit patients with second primary tumors who had received radiation for oral cancers earlier.

There is a consensus in literature that Neoadjuvant chemotherapy is beneficial in locally advanced unresectable oral cancers, but has shown no such advantage in locally advanced resectable oral cancer. [42] The role of Neoadjuvant chemotherapy in minimizing distant metastasis needs to be validated.

Neoadjuvant chemotherapy definitely carries toxicity but the levels of toxicity and complete response from treatment were found to be low using concurrent chemotherapy and radiotherapy using Paclitaxel and carboplatin followed by surgery in advanced oral cancers in a German study with overall survival of 84.9% after 5 years. [7] However this was a small study.

Therefore literature suggests Neoadjuvant chemotherapy to be used in inoperable (locally advanced) tumors and its role in operable locally advanced oral cancers is still controversial. Its usefulness in preventing distant metastasis or extensive cervical lymph node metastasis still requires validation.

MATERIALS AND METHODS

TYPE OF STUDY

- This is a Comparative Observational study.

SOURCE OF DATA:

The study was done in 60 patients with locally advanced oral cancer staged T4 according to AJCC classification (2018) presenting to the Department of Otorhinolaryngology and Head and Neck Surgery in R.L. Jalappa Hospital And Research Centre, Tamaka, Kolar from December 2018 till November 2020.

SAMPLE SIZE

Sample size is calculated based on the complete pathological response number of locally advanced oral cancer patients.

Reference study : Average patients admitted in our hospital with locally advanced oral cancer (staged T4) over the past 3 years and the study on locally advanced oral cancer treated by surgery alone and neoadjuvant chemotherapy followed by surgery done by Zhong et al in 2013.

According to above references within confidence interval of 95% and absolute error of 0.1 by using following formula:-

Formula

$H_o : P_1 = P_2$; $H_a : P_1 \neq P_2$

$$n = \frac{\left\{ Z_{1-\frac{\alpha}{2}} \sqrt{2\,\bar{P}\,(1-\bar{P})} + Z_{1-\beta} \sqrt{P_1\,(1-P_1) + P_2\,(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

Where,

$$\bar{P} = \frac{P_1 + P_2}{2}$$

P_1 : Proportion in the first group

P_2 : Proportion in the second group

α : Significance level

$1-\beta$: Power

Proportion in group I	= .60
Proportion in group II	= .25
Risk difference	= 0.35
Power(%)	= 80
Alpha Error(%)	= 5
Side	= 2
Required sample size for each arm	= 30

Proportion in group II	= .25
Risk difference	= 0.35
Power(%)	= 80
Alpha Error(%)	= 5
Side	= 2
Required sample size for each arm	= 30

METHODOLOGY

Biopsy proven locally advanced oral squamous cell carcinoma patients staged T4 according to AJCC classification 2018 presenting to Department of Otorhinolaryngology & Head and Neck Surgery, R L Jalappa Hospital and Research Centre, Kolar, were recruited after assessing the disease and obtaining informed written consent for the study as well as for multimodality treatment.

INCLUSION CRITERIA

All locally advanced (T4a and T4b) oral squamous cell carcinoma patients aged 35 to 65 years in Department of Otorhinolaryngology & Head and Neck Surgery in R L Jalappa Hospital and Research Centre, Kolar, planned for curative multi modality treatment.

EXCLUSION CRITERIA

1. Recurrent Tumors
2. Extension to Skull Base
3. Extension to Prevertebral Space
4. Encasement of Carotids
5. Past history of Anti malignant chemotherapy

All patients underwent blood investigations comprising of complete blood counts, renal function test and serum electrolytes along with pre treatment Contrast Enhanced Computed Tomography of Oral cavity, infratemporal fossa and neck.

Age and Stage matched patients included in the study were randomized using 6 Block randomization into 2 groups.

Group A : Patients receiving Neoadjuvant Chemotherapy with Paclitaxel 175miligram/m^2 and Carboplatin (according to area under curve) followed by Surgery of Composite Resection (+ Infratemporal compartment clearance in T4b tumors) + Neck Dissection + Reconstruction followed by adjuvant treatment in the form of Radiotherapy or chemotherapy with Radiotherapy.

All patients in this group underwent repeat Contrast Enhanced Computed Tomography of oral cavity, infratemporal fossa and neck after 2 cycles of Neoadjuvant chemotherapy given at 3 weekly intervals.

Group B : Patients undergoing surgery of Composite Resection (+ Infratemporal compartment clearance in T4b tumors)+ Neck Dissection + Reconstruction followed by adjuvant treatment in the form of Radiotherapy or chemotherapy with Radiotherapy.

Surgery for all patients in both groups was performed by the same senior Head & Neck surgeon to minimize bias.

Post treatment Contrast Enhanced Computed Tomography of oral cavity, infratemporal fossa and neck was done 2 months after completion of treatment and findings were documented.

The histopathological examination of the resected specimens was performed and tumor dimensions including depth of tumor, skin and bone erosion, adequacy of resected margins, perineural invasion, lymphovascular invasion, lymph node metastasis and extra nodal spread if any were documented. Special care was taken to document the adequacy of margins in the infratemporal fossa.

A comparison was made between the above 2 groups of patients with regard to surgical complications like partial flap necrosis and orocutaneous fistula. The local, regional (metastatic cervical lymph nodes) and locoregional recurrences were documented and analysed.

The post operative complications or adverse events if any and time taken for recovery were documented. The patients were followed up for minimum of 1 year after completion of Adjuvant treatment.

The compliance to adjuvant treatment, toxicity and break in Adjuvant treatment was documented. Locoregional control was assessed by 2 monthly periodic clinical examination and imaging for local recurrence and regional lymph node or distant metastasis if any were documented.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test 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

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 analyze data

RESULTS

Group A: - Patients receiving Neoadjuvant Chemotherapy with Paclitaxel 175miligram/m^2 + Carboplatin (area under the curve) followed by Surgery - Composite Resection + Neck Dissection + Reconstruction followed by adjuvant treatment in the form of Radiotherapy/Chemotherapy +Radiotherapy.

Group B: - Patients undergoing surgery - Composite Resection + Neck Dissection + Reconstruction followed by adjuvant treatment in the form of Radiotherapy/Chemotherapy +Radiotherapy.

In this study involving 60 patients, 30 patients were in each group. The mean age among the Neoadjuvant chemotherapy followed by surgery group was 53.43 years with a standard deviation of 7.23 and the mean age for the surgery alone group was 56.27 years with a standard deviation of 8.76. Out of the 24 patients (80%) were females in each group and 6 (20%) male patients in each group.

Patients staged T4a were 37(61.6%) and 23(38.3%) patients were staged T4b. Majority of the patients 50 (83.3%) presented with N1 nodal status and 10(16.7%) presented with N2b nodal status. The most common location of the primary tumor was buccal mucosa seen in 44(73.3%) patients followed by lower alveolus 10(16.7%) patients and lower gingivobuccal sulcus seen in 5 (8.4%) patients.

Table 2:- Comparison of mean age among patients between 2 groups

	Mean	Std. Deviation	P Value
Group A	53.43	7.233	0.177
Group B	56.27	8.769	

There was no statistically significant difference found between two groups with respect to age.

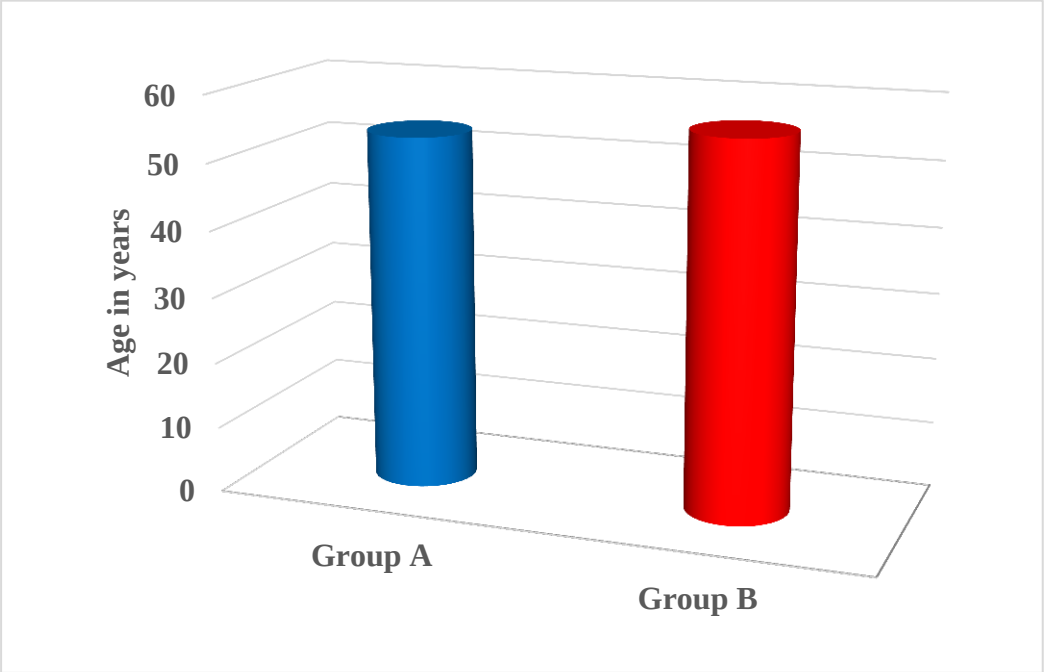


Figure 12:- Graph showing Comparison of mean age among patients between groups

Table 3:- Distribution of patients according to gender between two groups

	Group A	Group B	Total
Female	24	24	48
	80.0%	80.0%	80.0%
Male	6	6	12
	20.0%	20.0%	20.0%
Total	30	30	60
	100.0%	100.0%	100.0%

P Value 1.00, there was no statistically significant difference found between two groups with respect to gender.

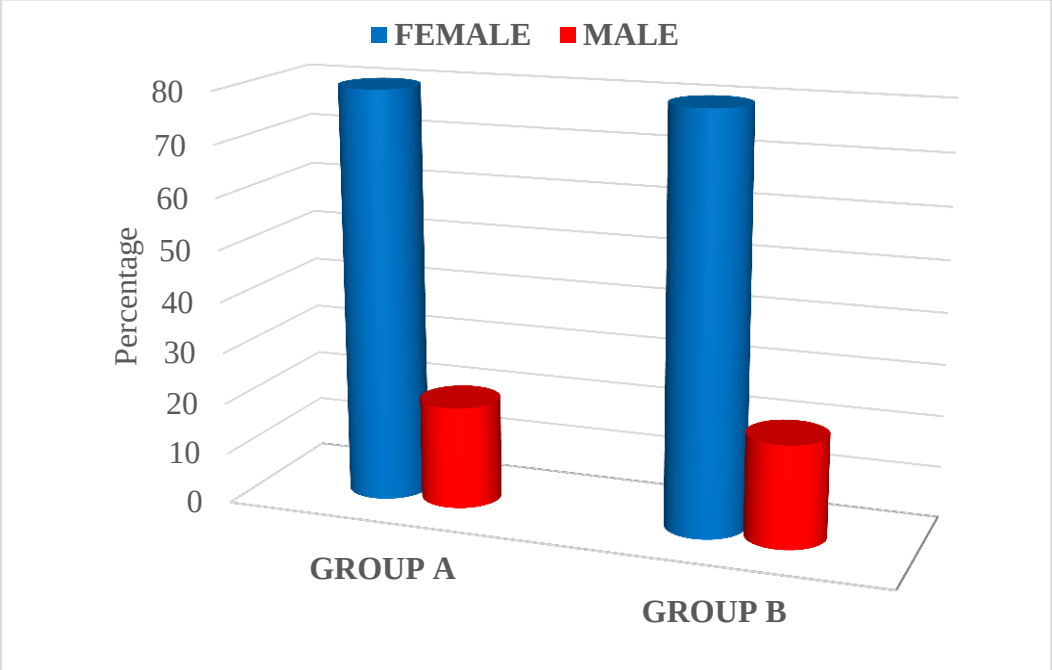


Figure 13:- Graph showing Distribution of patients according to gender between two groups

Table 4:- Distribution of patients according to site between two groups

	Group A	Group B	Total
Left Buccal mucosa	13	10	23
	43.3%	33.3%	38.3%
Left Lower Alveolus	2	4	6
	6.7%	13.3%	10.0%
Left Lower Gingivobuccal sulcus	3	1	4
	10.0%	3.3%	6.7%
Right Buccal mucosa	10	11	21
	33.3%	36.7%	35.0%
Right Lower Alveolus	1	3	4
	3.3%	10.0%	6.7%
Right Lower Gingivobuccal sulcus	0	1	1
	.0%	3.3%	1.7%
Right Retromolar trigone	1	0	1
	3.3%	.0%	1.7%
Total	30	30	60
	100.0%	100.0%	100.0%

P Value 0.530, there was no statistically significant difference found between two groups with respect to site

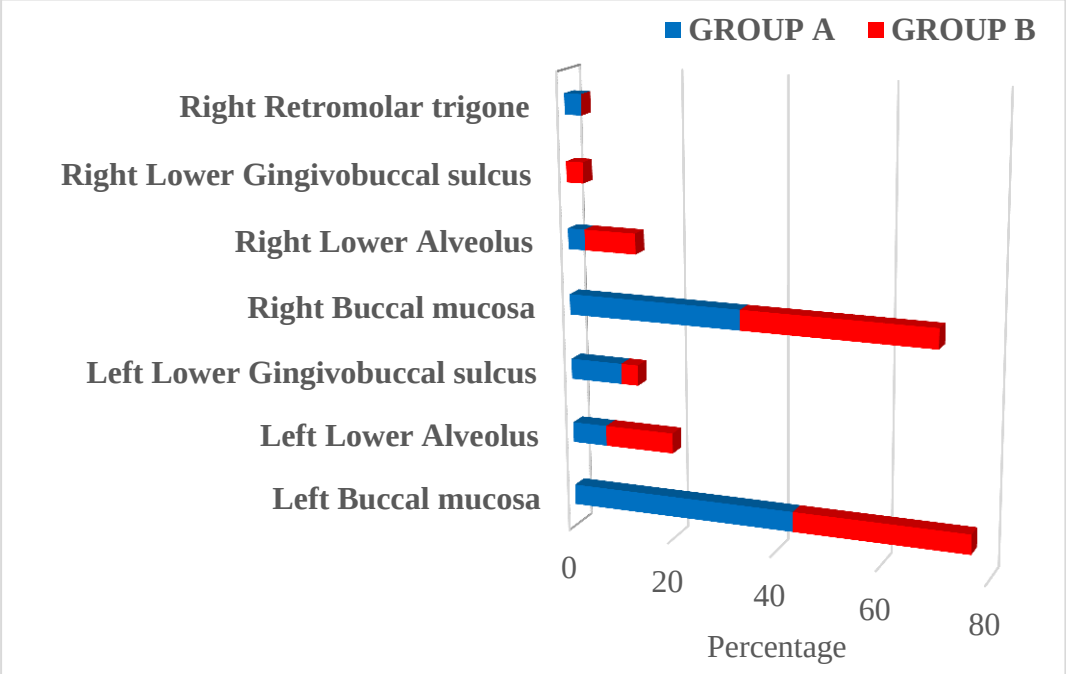


Figure 14:- Graph showing Distribution of patients according to site between two groups

Table 5:- Distribution of patients according to staging between two groups

	Group A	Group B	Total
T4a	16	21	37
	53.3%	70%	61.66%
T4b	14	9	23
	46.7%	30%	38.3%
Total	30	30	60
	100.0%	100.0%	100.0%

P Value 0.012, there was a statistically significant difference found between two groups with respect to staging.

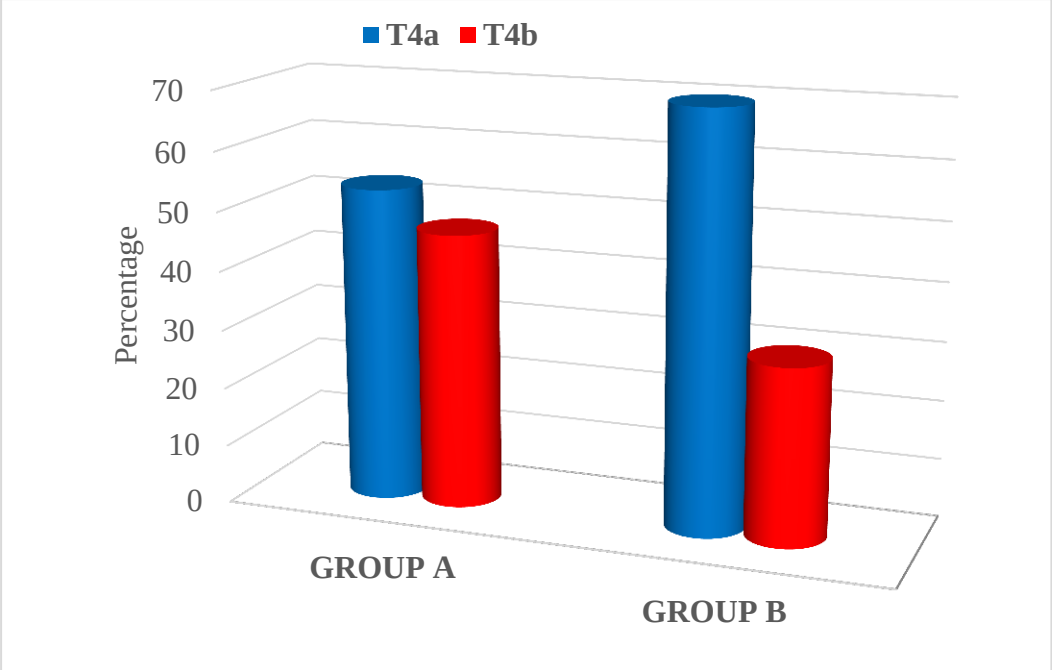


Figure 15:- Graph showing Distribution of patients according to staging between two groups

This difference in staging between 2 groups though unintentional favored more the in surgery alone group as few patients refused Neoadjuvant chemotherapy when given the choice between Neoadjuvant chemotherapy and surgery alone and a few tumors which were clinically staged T4a were actually T4b on per operative findings and histopathology.

The number of patients having infratemporal involvement in the Neoadjuvant Chemotherapy followed by surgery group were 13 (43.3%) and 11 (36.6%) in the surgery alone group.

Table 6:- Distribution of patients according to Infratemporal fossa involvement between two groups

Infratemporal fossa involvement	Group A	Group B	Total
Absent	17	19	36
	56.7%	63.3%	60.0%
Present	13	11	24
	43.3%	36.6%	40.0%
Total	30	30	60
	100.0%	100.0%	100.0%

P Value 0.024, there was a statistically significant difference found between two groups with respect to ITF involvement.

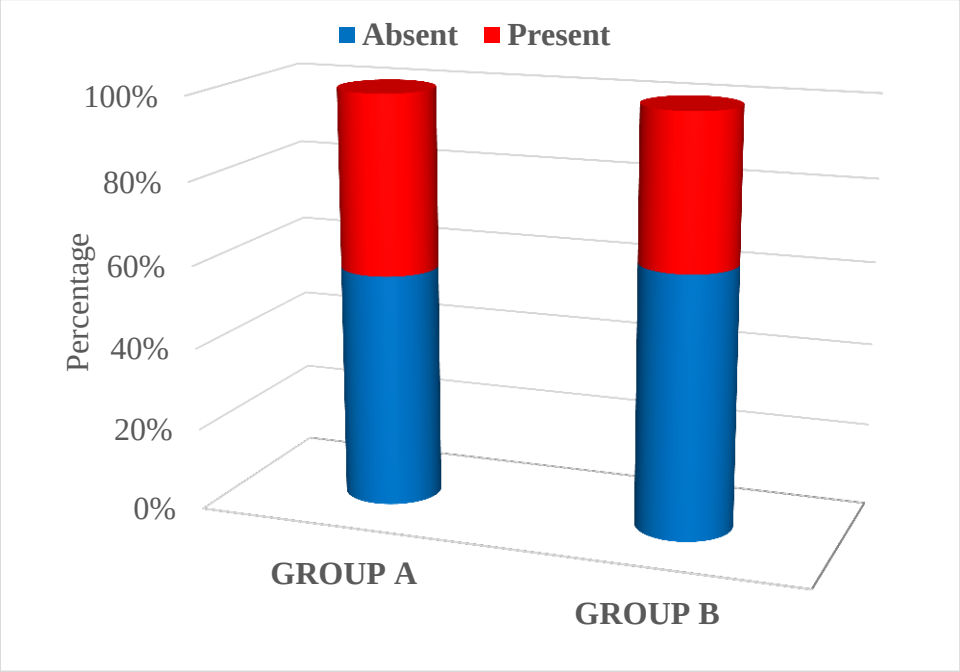


Figure 16:- Graph showing Distribution of patients according to Infratemporal fossa involvement between two groups

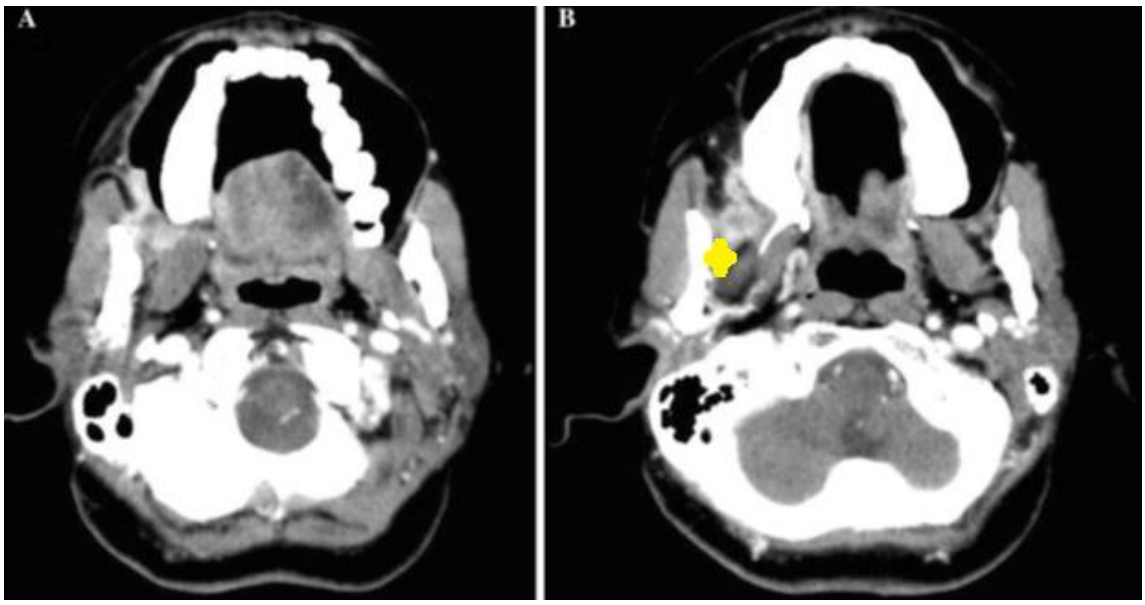


Fig : 17 (A and B) Infratemporal fossa involvement

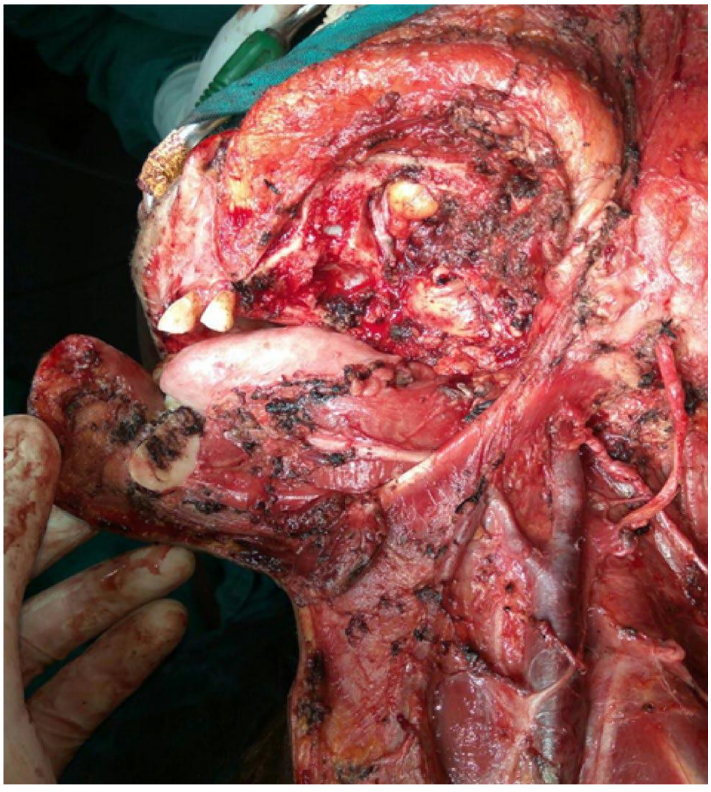


Fig 18: Compartment resection of Infratemporal Fossa + Composite Resection

Table 7:- Distribution of patients according to nodal status between two groups

	Group A	Group B	Total
N1	23	27	50
	76.7%	90.0%	83.3%
N2	7	3	10
	23.3%	10.0%	16.7%
Total	30	30	60
	100.0%	100.0%	100.0%

P Value 0.166, there was no statistically significant difference found between two groups with respect to nodal status.

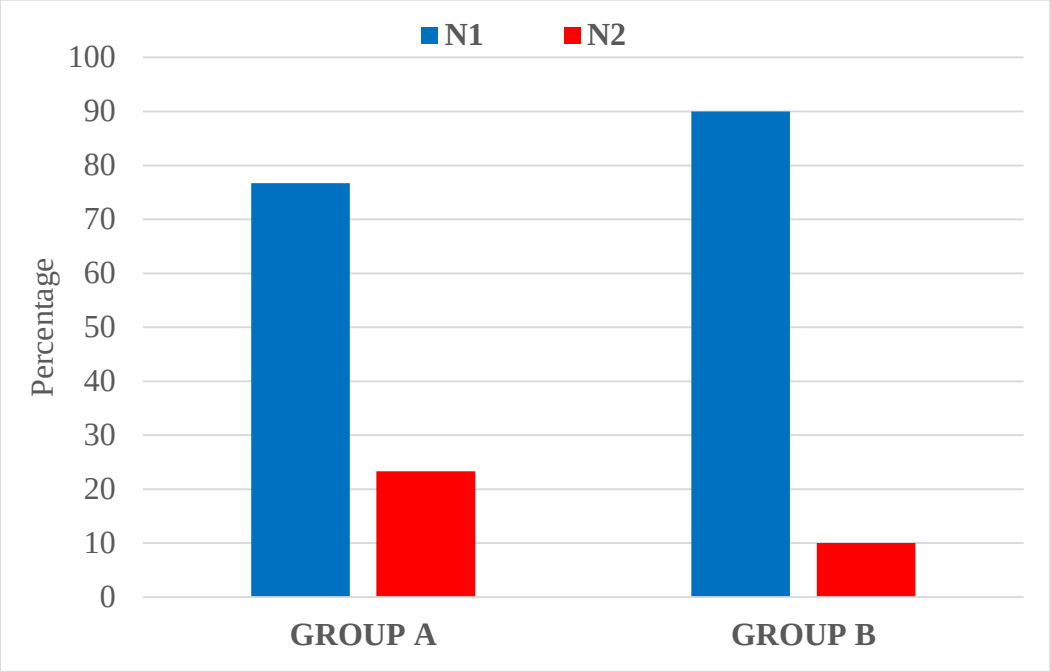
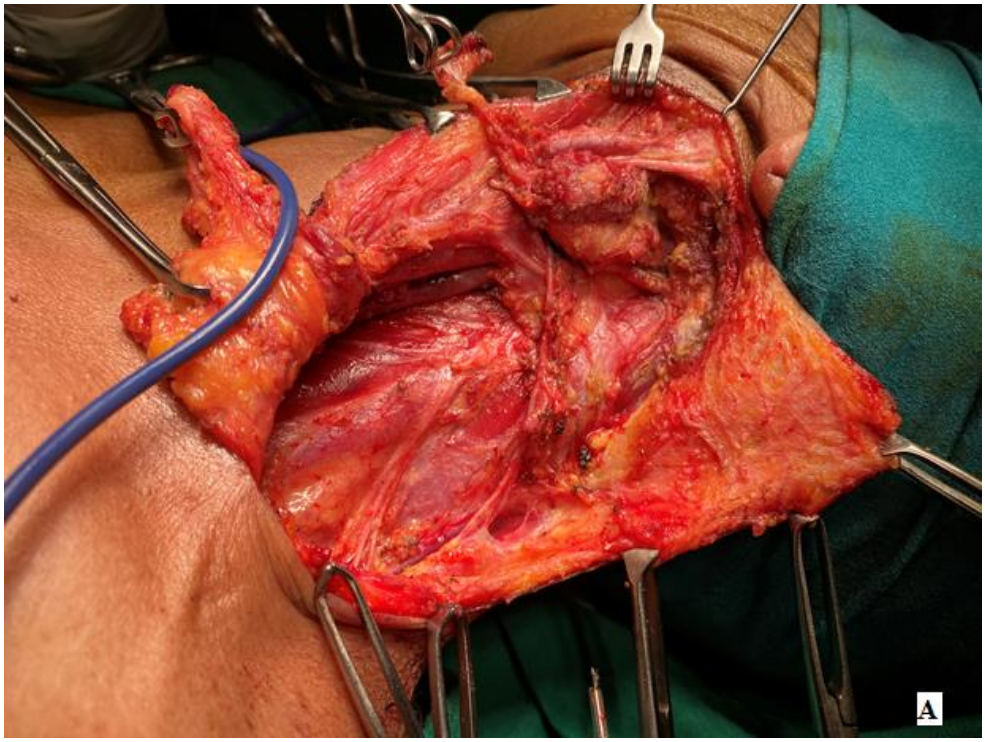


Figure 19:- Graph showing Distribution of patients according to nodal status between two groups



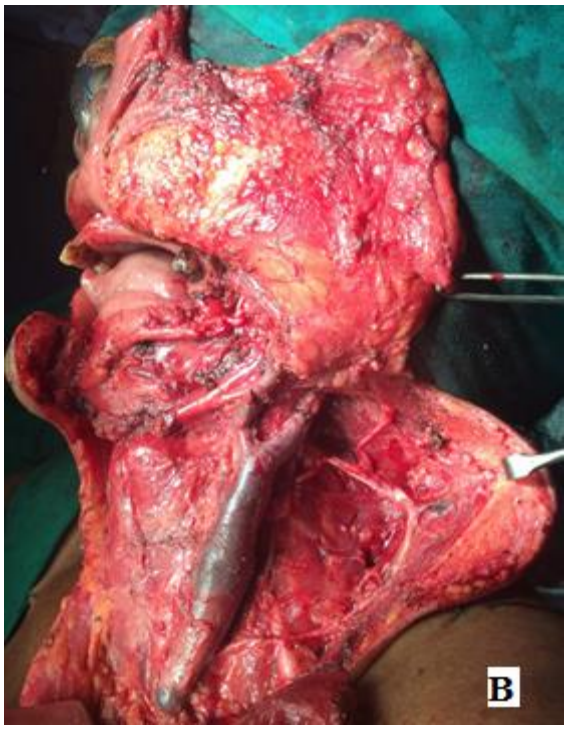


Fig 20 : (a)Neck dissection (b) Composite Resection + Modified Radical Neck Dissection

In the neoadjuvant chemotherapy followed by surgery group, the response of Neoadjuvant chemotherapy following 2 cycles of Paclitaxel and Carboplatin was of 3 types namely, Partial response (More than 30% reduction in tumor volume), stable disease (no significant change) and progressive disease (increase in the size of the tumor). 9 out of 30 patients (30%) had partial response, 10 out of 30 patients (33.3%) had progressive disease and 11 out of 30 patients (36.7%) had stable disease.

The response to Neoadjuvant chemotherapy based on stage specific patients was:- Among patients staged T4a, partial response was seen in 4 (25%) patients, 6 (37.5%) had progressive disease and 6 (37.5%) had stable disease and patients staged T4b, 5 (35.7%) had partial response, 4 (28.6%) had progressive disease and 5 (35.7%) had stable disease.

Table 8:- Distribution of patients according NACT response

	n	%
Partial	9	30
Progressive	10	33.3
Stable	11	36.7
Total	30	100

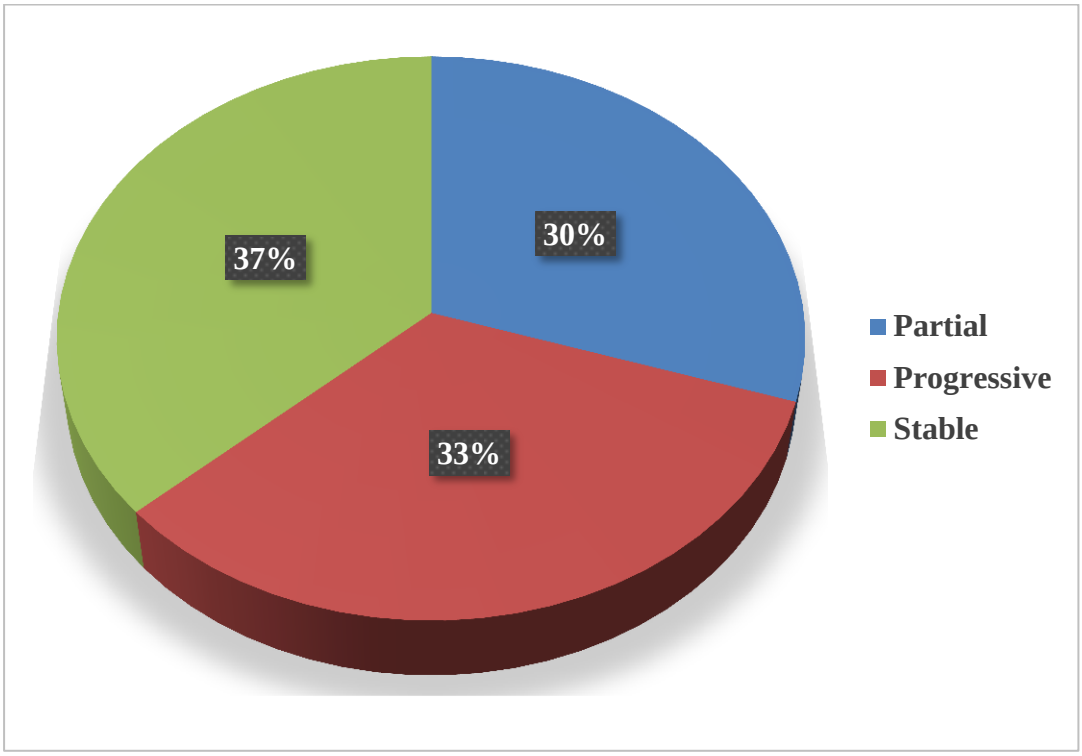


Figure 21:- Graph showing Distribution of patients according NACT response.

Table 9:- Distribution of patients according to response to NACT and staging

	T4a	T4b	P value
Partial	4	5	0.790
	25%	35.7%	
Progressive	6	4	
	37.5%	28.6%	
Stable	6	5	
	37.5%	35.7%	

P value 0.420, there was no statistically significant difference found between response to NACT and staging

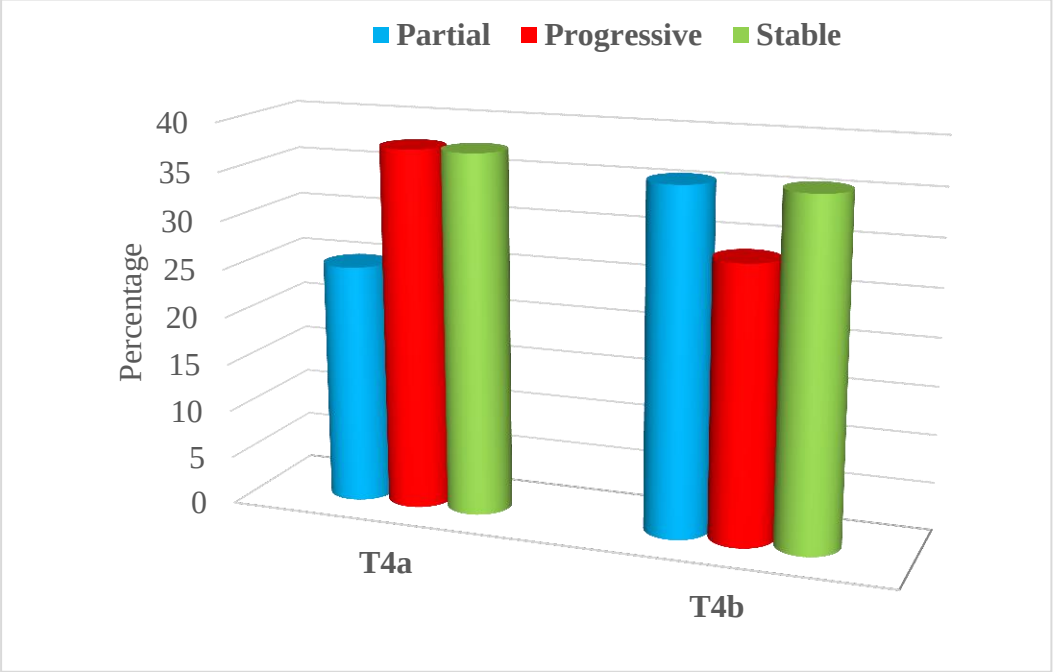


Figure 22:- Graph showing Distribution of patients according to response to NACT and staging.

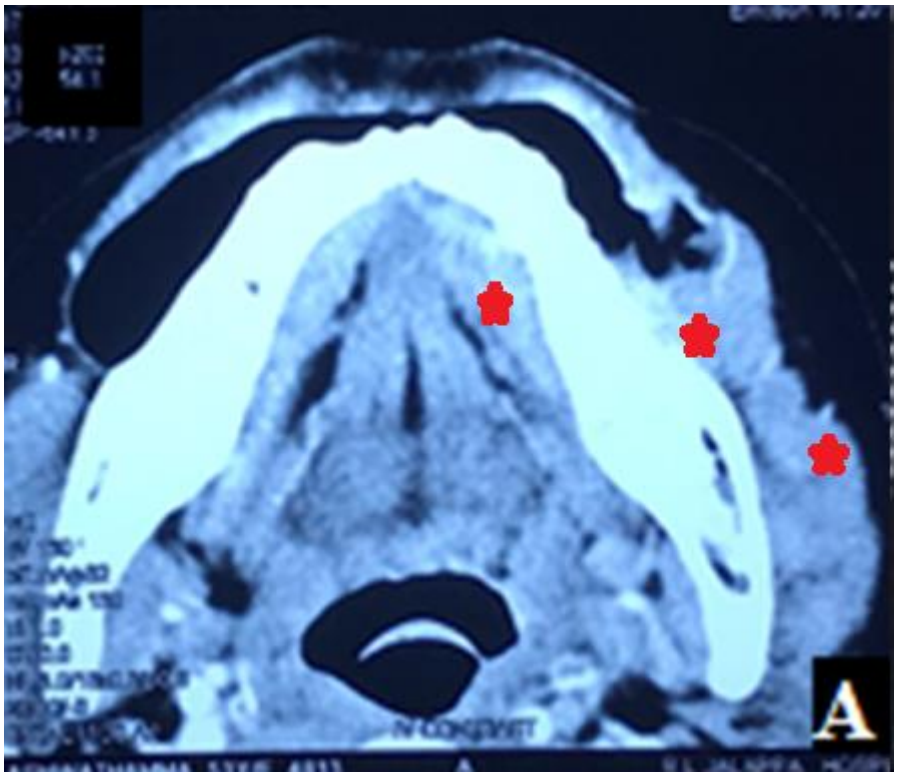


Figure 23: (A) CECT showing response to NACT – Partial response

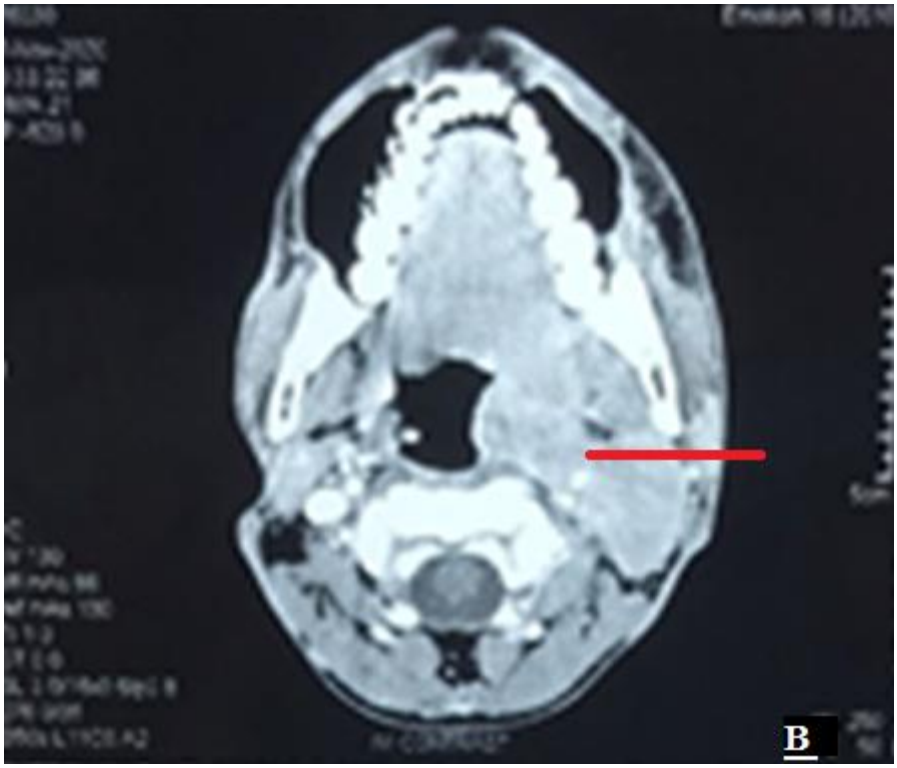


Fig 23 ⊗B) CECT showing response to NACT- Progressive disease

In the Neoadjuvant Chemotherapy followed by surgery group, skin involvement was seen in 17 out of 30 (56.7%) and 22 out of 30 (73.3%) patients had bone involvement. In the surgery alone group 13 patients out of 30 (43.3%) had skin involvement and 26 out of 30 (86.7%) patients had bone involvement. In total out of the 60 patients, 30 patients had skin involvement and 48 patients had bone involvement.

Table 10:- Frequency Distribution of skin involvement and bone involvement between two groups

	Group A	Group B	Total	P value
Skin involvement	17	13	30	0.301
	56.7%	43.3%	50.0%	
Bone involvement	22	26	48	0.196
	73.3%	86.7%	80.0%	

There was no statistically significant difference found between two groups with respect to Skin involvement and Bone involvement.

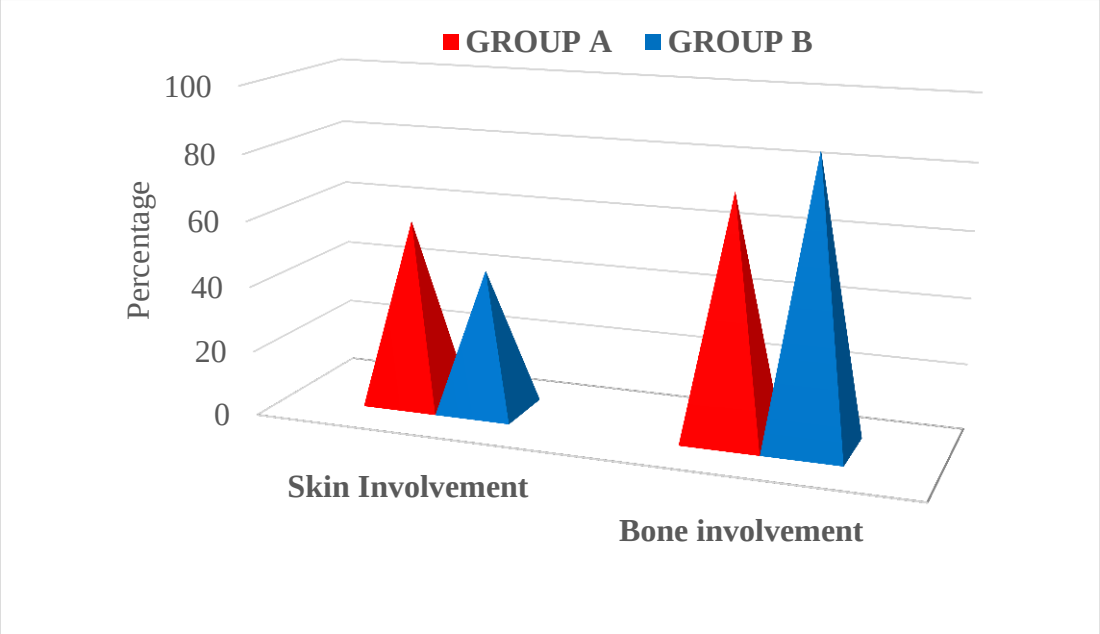
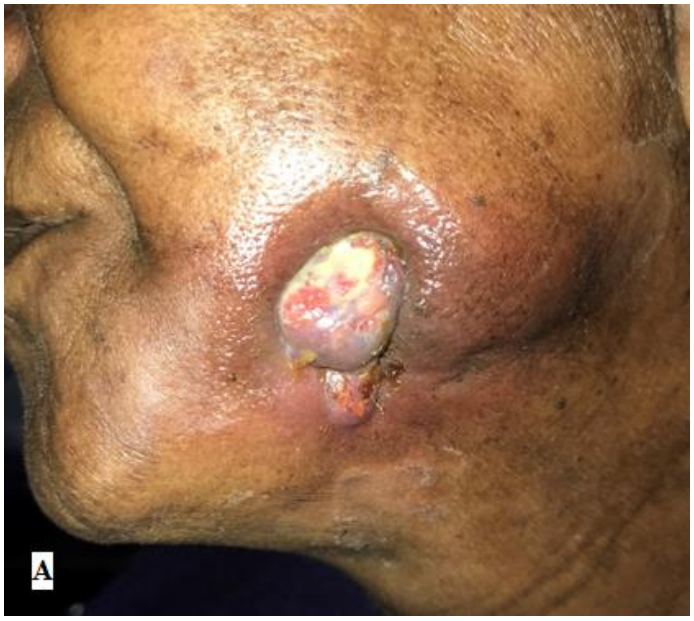


Figure 24:- Graph showing Distribution of skin involvement and bone involvement between two groups



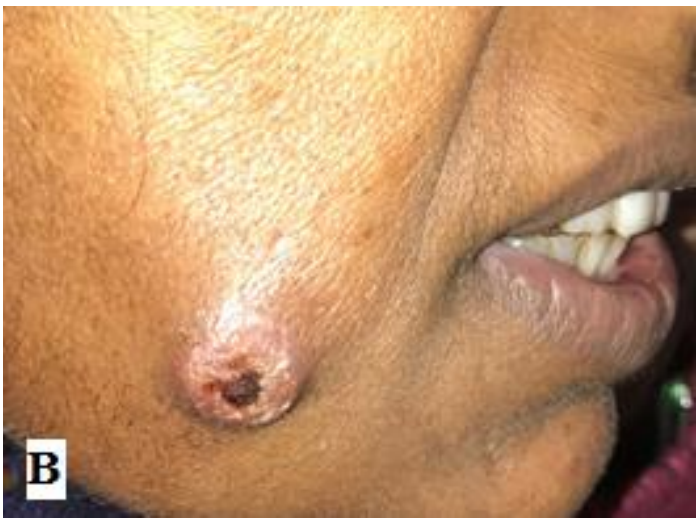


Fig 25 (A & B): Skin Involvement

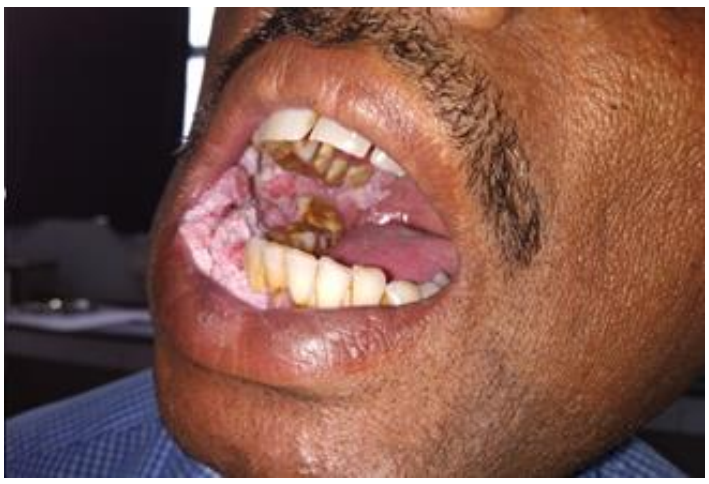


Fig 26: Bone involvement

The closest margin was observed in both the groups and found that the mean closest margin in the Neoadjuvant chemotherapy followed by surgery was 5mm with a range from 1-10mm whereas in the surgery alone group was 4mm with a range from 1-9mm. the most commonest margin which was found close was the superior margin. 2 patients had positive margins 1 from each group.

Table 11: Distribution of patients according to close margins

	Group A		Group B	
	Mean	Range	Mean	Range
Closest margin(mm)	5	(1-10)	4	(1-9)

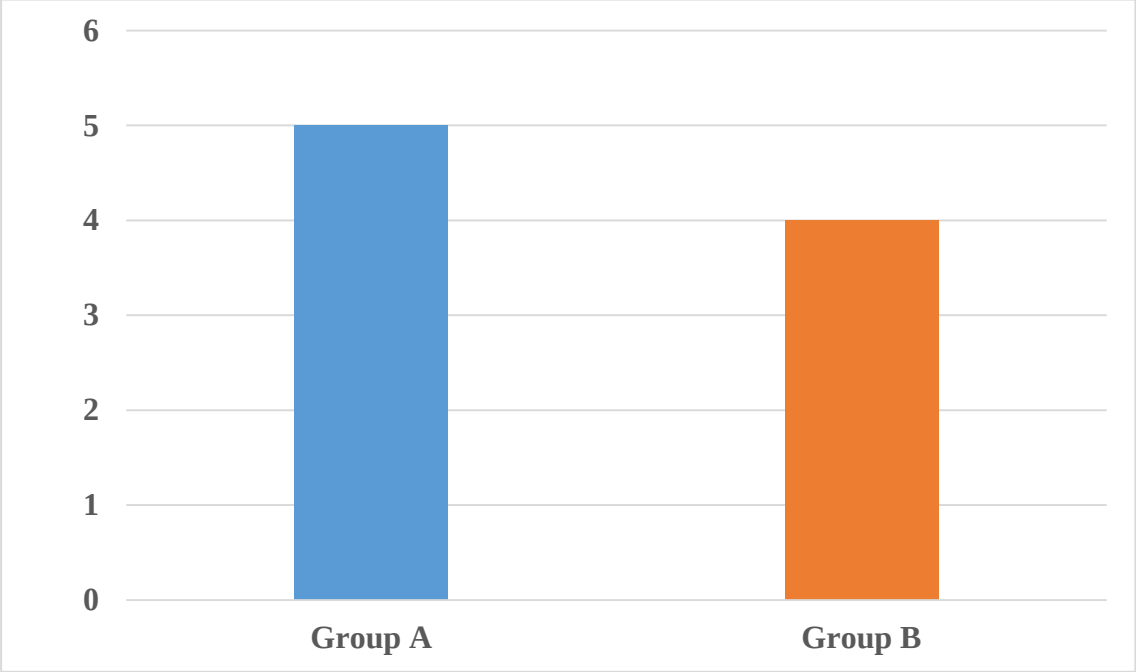


Figure 27: Graph showing Comparison of mean closest margin

The mean depth of invasion in the Neoadjuvant Chemotherapy followed by surgery group was 7mm with a standard deviation of 2.1 whereas in the surgery alone group the mean depth of invasion was 6.17mm with a standard deviation of 2.7.

Perineural invasion was seen in 4 out 60 patients with 2 (6.7%) patients belonging to Neoadjuvant Chemotherapy followed by surgery group and 2 (6.7%) in the surgery alone group. Lymphovascular spread was seen in 5 out 60 patients with 3 (10%) patients belonging to Neoadjuvant Chemotherapy followed by surgery group and 2 (6.7%) belonging to surgery alone group. Extranodal spread was observed in 18 patients with 7 (23.3%) belonging to Neoadjuvant Chemotherapy followed by surgery group and 11 (36.7%) belonging to surgery alone group.

Table 12:- Comparison of mean depth of invasion among patients between groups

	Mean	Std. Deviation	P Value
Group A	7	2.1	0.233
Group B	6.17	2.7	

There was no statistically significant difference found between two groups with respect to depth of invasion.

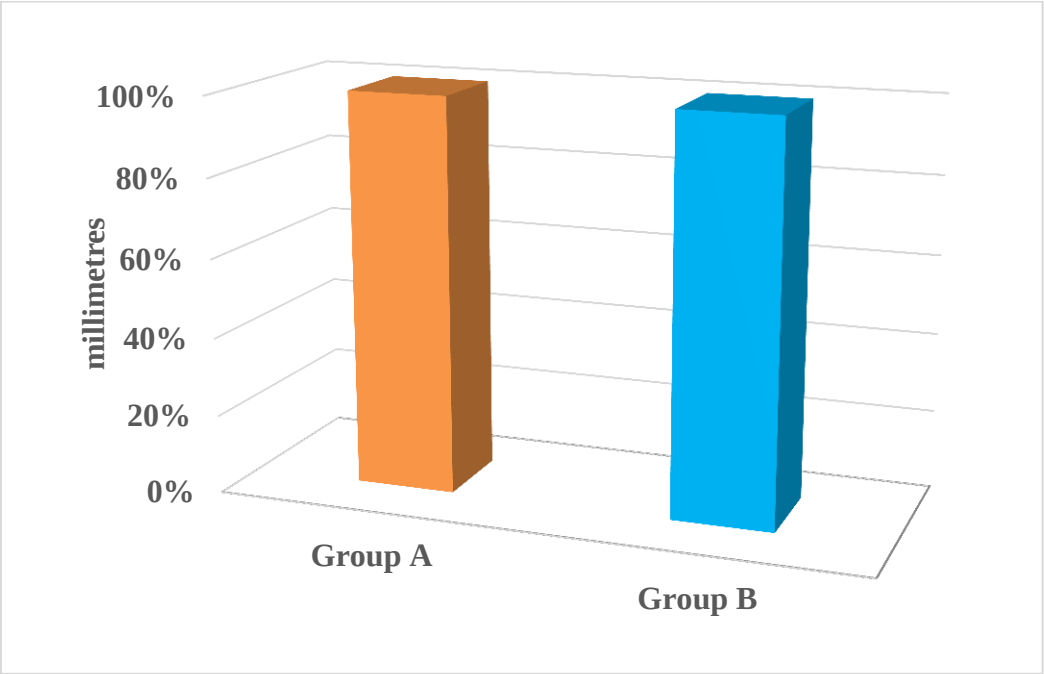


Figure 28:- Graph showing Comparison of mean depth of invasion among patients between groups

Table 13:- Frequency Distribution of Perineural involvement, Lympho vascular spread and Extra nodal spread between two groups

	Group A	Group B	Total	P value
Perineural involvement	2	2	4	1.00
	6.7%	6.7%	6.7%	
Lympho vascular spread	3	2	5	0.640
	10.0%	6.7%	8.3%	
Extra nodal spread	7	11	18	0.259
	23.3%	36.7%	30.0%	

There was no statistically significant difference found between two groups with respect to Perineural involvement, Lympho vascular spread and Extra nodal spread.

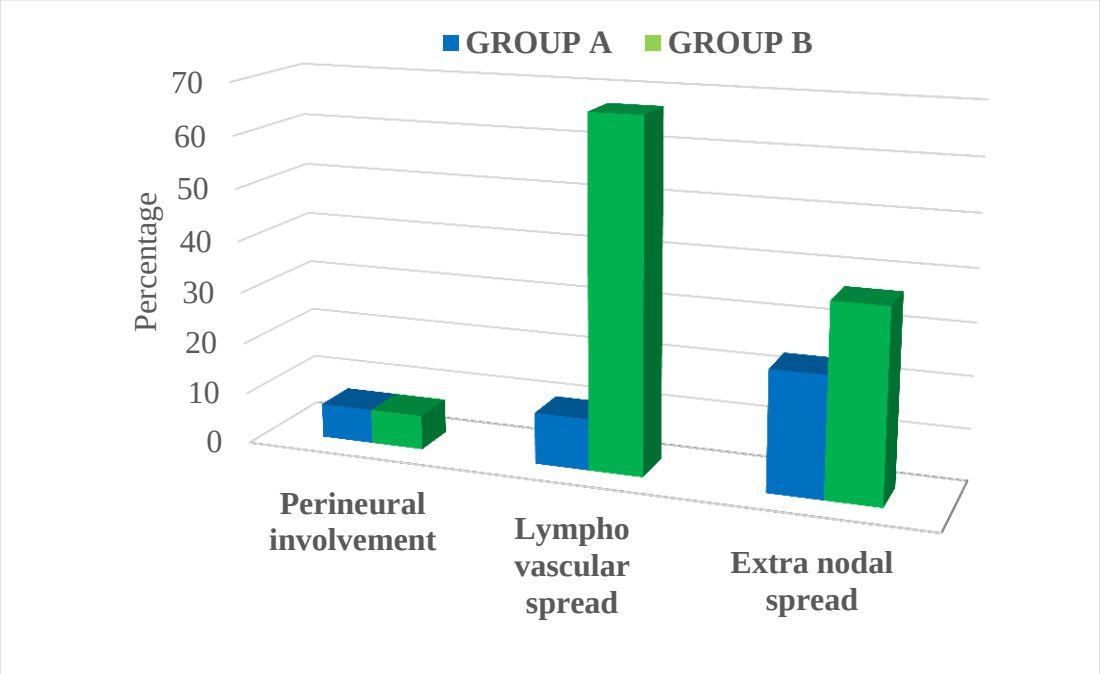


Figure 29:- Graph showing Frequency Distribution of Perineural involvement, Lympho vascular spread and Extra nodal spread between two groups.

The surgical complications encountered were mainly partial flap necrosis and orocutaneous fistula. Out of the 30 patients in the neoadjuvant chemotherapy followed by surgery, only 23 patients underwent surgery and 7 patients having progressive disease following 2 cycles of Neoadjuvant chemotherapy were subjected to palliative chemotherapy with radiotherapy. Overall, Partial flap necrosis was seen in 9.4% of the patients operated and orocutaneous fistula was seen in 26.41% patients operated. 64.15% of the patients operated had no surgical complication. Out of the 23 patients operated in the Neoadjuvant chemotherapy group, partial flap necrosis was seen in 3(13.04%) patients and orocutaneous fistula was observed in 6 (26.08%) patients. In the surgery alone group, 2 (6.7%) patients had partial flap necrosis and 8 (26.7%) patients had orocutaneous fistula.

Table 14:- Distribution of patients according to surgical complications between two groups

	Group A	Group B	Total	P value
None	14	20	34	0.775
	60.86%	66.7%	64.15%	
Partial Flap necrosis	3	2	5	
	13.04%	6.7%	9.4%	
Orocutaneous fistula	6	8	14	
	26.08%	26.7%	26.41%	

There was no statistically significant difference found between two groups with respect to surgical complications.

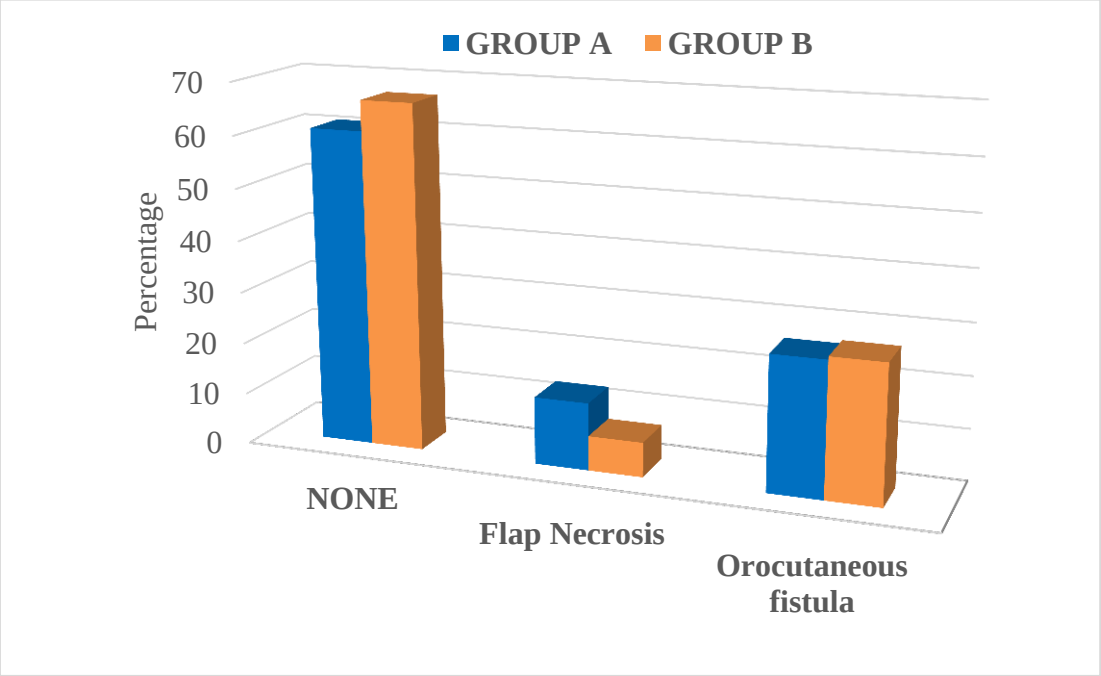


Figure 30:- Graph showing Distribution of patients according to surgical complications between two groups

On the last follow up for all the patients, it was observed that 15 (50%) patients in the Neoadjuvant Chemotherapy followed by surgery group were alive without disease and 11 (36.67%) were alive with disease, 3 patients have died due to disease and 1 patient was lost to follow up. In the surgery alone group 13 patients (43.33%) were alive without disease and 15 (50%) patients are alive with disease, 1 patient died due to hepatic failure and 1 patient was lost to follow up.

Table 15:- Distribution of patients according to status at last follow up between two groups

	Group A	Group B	Total	P value
NAD	15	13	28	0.327
	50%	43.33%	46.67%	
Alive with disease	11	15	26	
	36.67%	50%	43.33%	
Total	26	28	54	
	100%	100%	100%	

There was no statistically significant difference found between two groups with respect to status at last follow up.

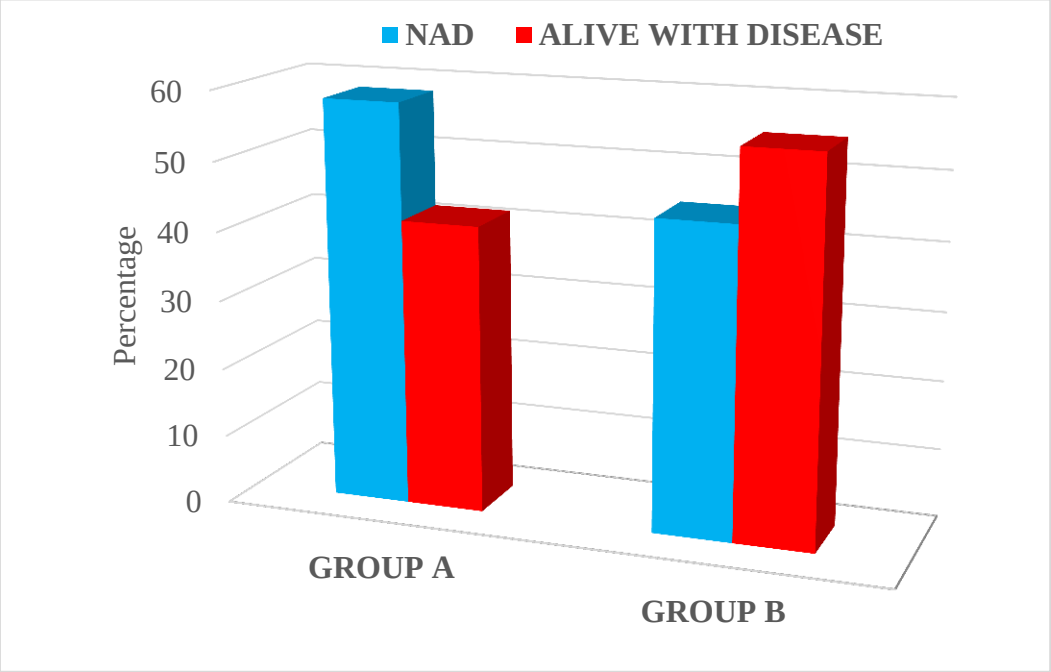


Figure 31:- Graph showing Distribution of patients according to status at last follow up between two groups.

The recurrence noted in all patients were divided into 3 categories namely local disease recurrence where the recurrent disease was situated in or adjacent to the operated area (primary tumor), regional disease recurrence where the disease spreads to the cervical lymph nodes and locoregional disease recurrence where the recurrent disease is present in both the locations. It was observed that in the Neoadjuvant Chemotherapy followed by surgery group, local disease recurrence was seen in 2 (6.67%), regional disease was seen in 4 (13.3%) patients and locoregional disease was seen in 5 (16.7%) patients. In the surgery alone group, the local disease recurrence was seen in 5 (16.67%) patients, 4 (13.3%) patients had regional disease recurrence and 7 (23.3%) patients had locoregional disease recurrence. Overall 10% of the patients had local disease recurrence, 13.3% patients had regional recurrence and 21.7% patients had locoregional recurrence. In the patients receiving Neoadjuvant Chemotherapy, 30% of patients which had partial response had a better oncological outcome when compared to the surgery alone group.

Table 16:- Comparison according to different Recurrence between two groups

Recurrence	Group A	Group B	Total
Local	2	5	7
	6.67%	16.6%	11.6%
Locoregional	5	7	12
	16.7%	23.3%	20%
Regional	4	4	8
	13.3%	13.3%	13.3%

P value 0.420, there was no statistically significant difference found between two groups with respect to recurrence.

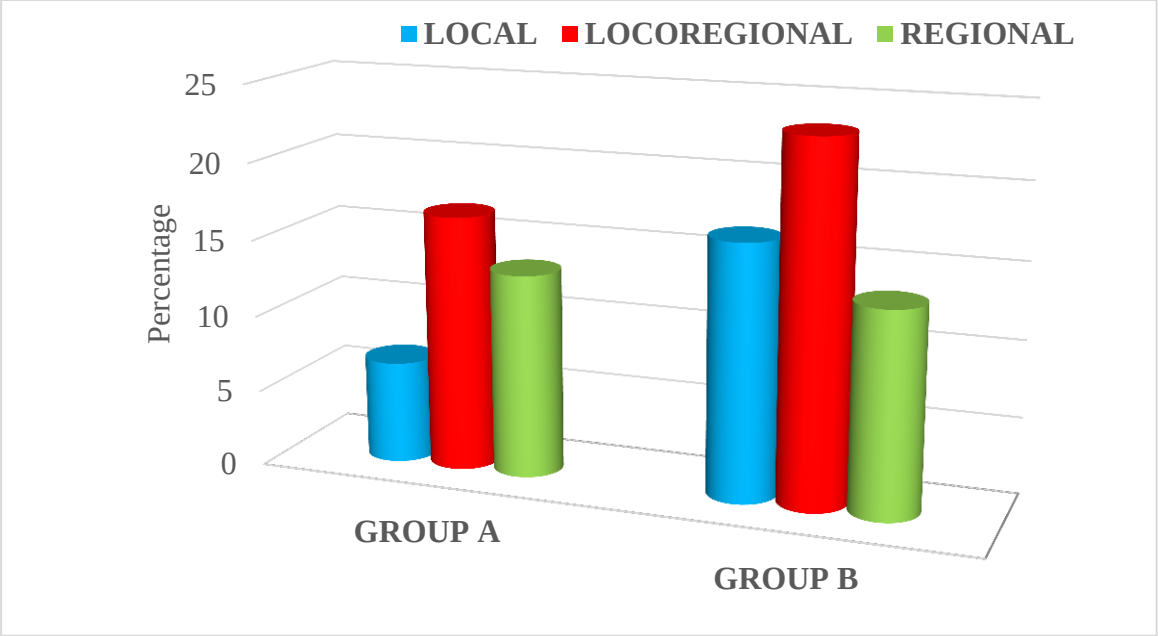


Figure 32:- Graph showing Comparison according to different Recurrence between two groups.

On observing the recurrence of disease based on the staging, patients staged T4aN1 were 36 out of which 11 had recurrence, patients staged T4aN2 were 5 out of which 3 had recurrence. Patients staged T4bN1 were 14 out of which 9 had recurrence and patients staged T4bN2 were 5 out of which 4 had recurrence.

Table 17:- Comparison of recurrence according to staging

		Nodal Status	
		N1	N2
T4a	Number	36	5
	Recurrence	11	3
T4b	Number	14	5
	Recurrence	9	4

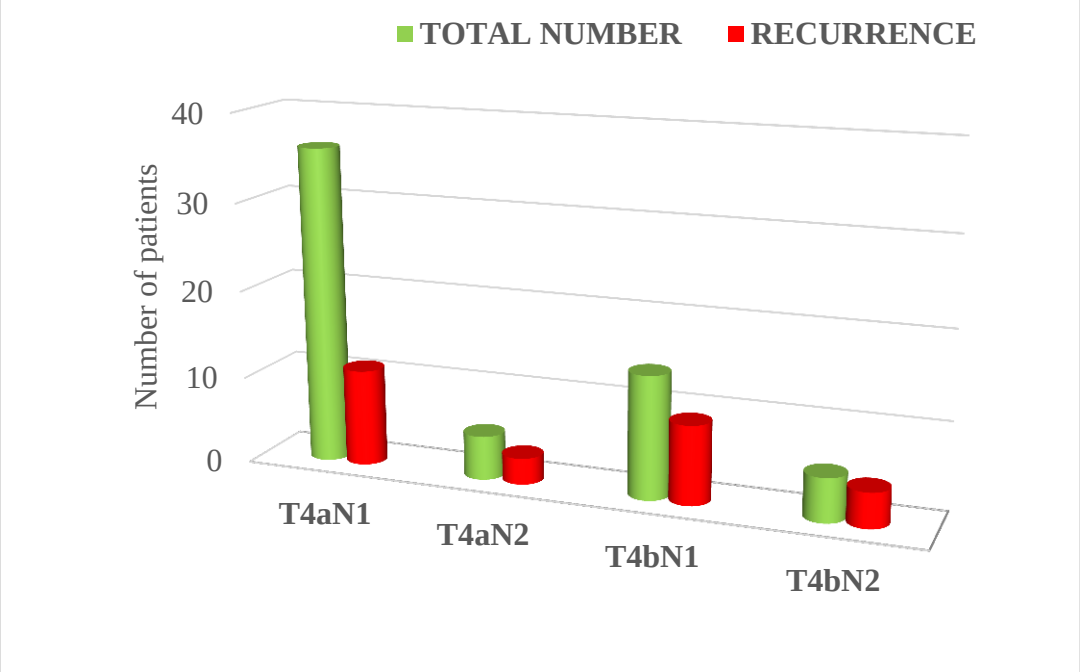


Figure 33:- Graph showing Comparison of recurrence according to staging

Table 18:- Comparison of recurrence according to staging between groups.

	Group A			
	N1		N2	
	Total	Recurrence	Total	Recurrence
T4a	12	3	4	2
T4b	11	6	3	2
	Group B			
	N1		N2	
	Total	Recurrence	Total	Recurrence
T4a	24	8	1	1
T4b	3	3	2	2

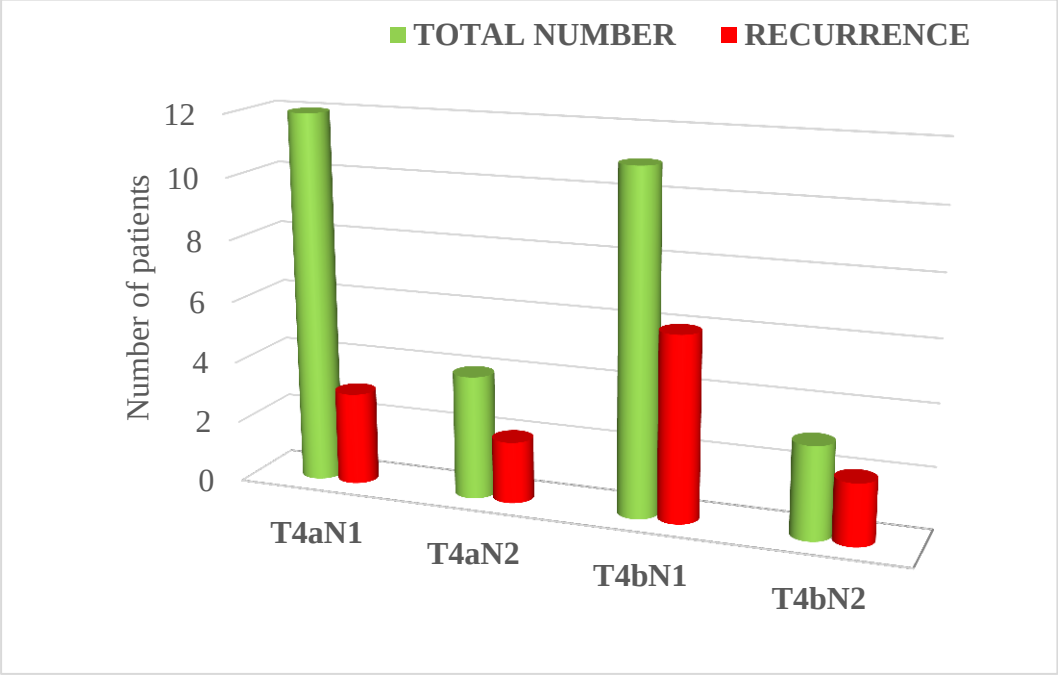


Figure 34:- Graph showing Comparison of recurrence according to staging in Group A

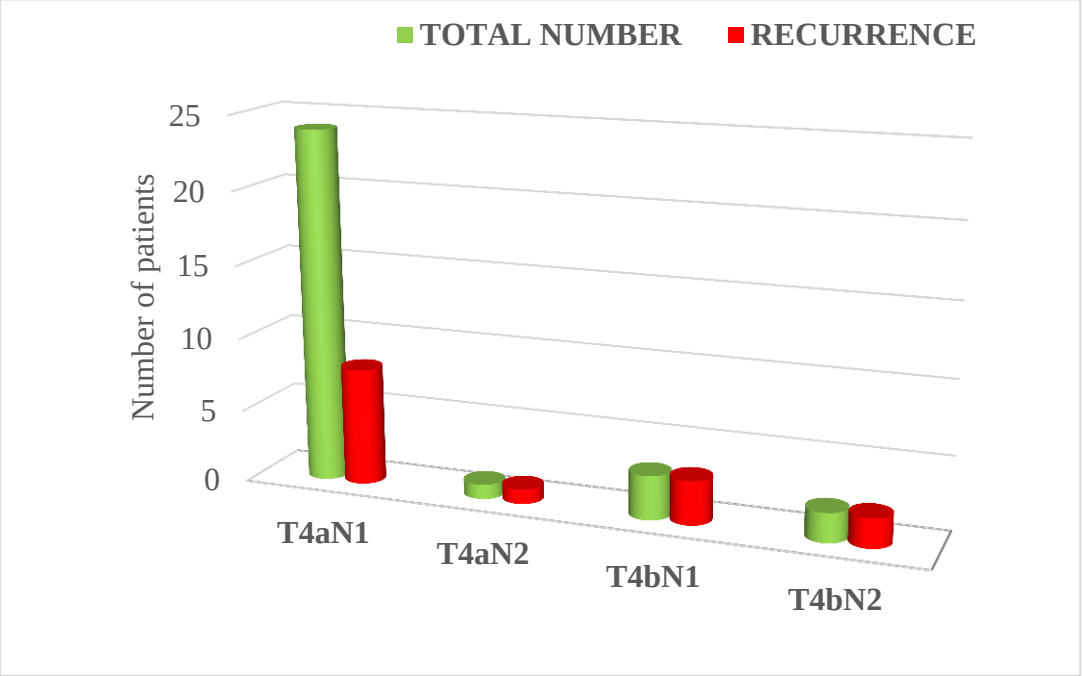


Figure 35:- Graph showing Comparison of recurrence according to staging in Group B

The time taken for recurrence to occur was seen in 3 different time frames namely less than 6 months, 6 months to 1 year and more than 1 year. These time frames were further evaluated with the site of recurrence in each group. It was observed that in the Neoadjuvant chemotherapy followed by surgery group local disease was seen in 1 (33.3%) patients and locoregional disease was seen in 1 (20%) patients in less than 6 months. Local disease recurrence was seen in 1 (33.3%) patients, regional disease recurrence was seen in 3 (100%) patients and locoregional disease recurrence was seen in 4 (80%) patients between 6 months to 12 months. In the time frame from more than 12 months, 1 (33.3%) patient had local disease recurrence. In comparison to the surgery alone group, 4(50%) patients having locoregional disease and 1(20%) patient had regional disease in less than 6 months. In the time frame from 6 months to 12 months, 3 (100%) patients had local disease, 4(50%) patients had locoregional disease recurrence and 1(20%) patient had regional disease recurrence. 3 (60%) patients had regional disease recurrence after 12 months from treatment.

Table 19:- Distribution of recurrence according to their time when they recurred

	Group A		
	<6month	6month-1yrs	>1yrs
Loco regional	1(20%)	4(80%)	0
Local	1(33.3%)	1(33.3%)	1(33.3%)
Regional	0	3(100%)	0
	Group B		
	<6month	6month-1yrs	>1yrs
Loco regional	4(50%)	4(50%)	0
Local	0	3(100%)	0
Regional	1(20%)	1(20%)	3(60%)

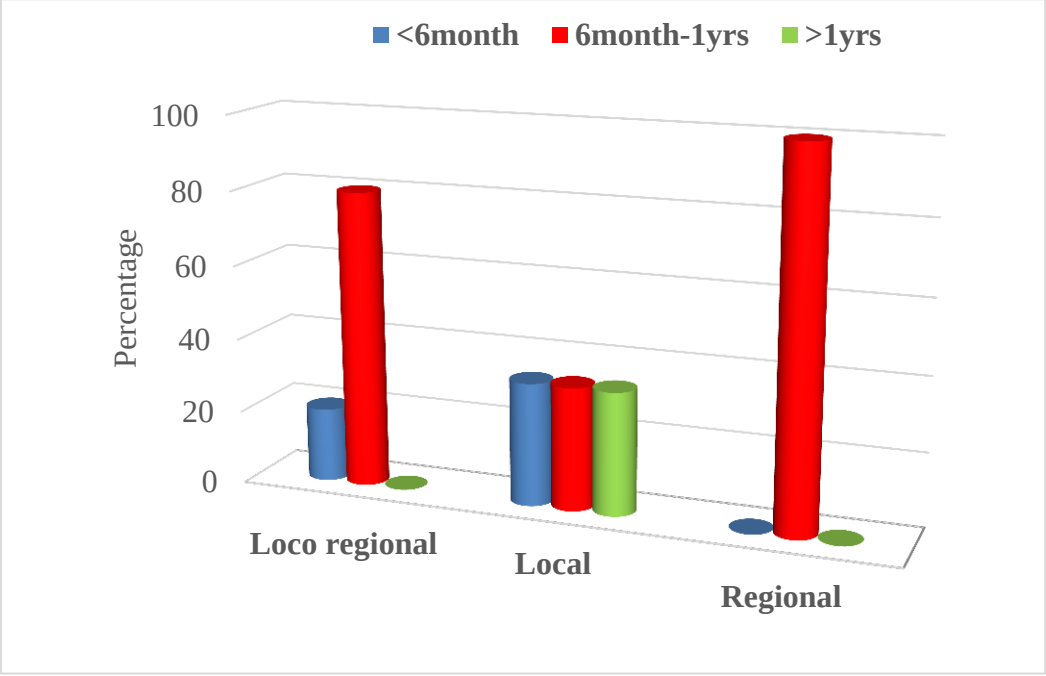


Figure 36:- Distribution of recurrence according to their time in Group A

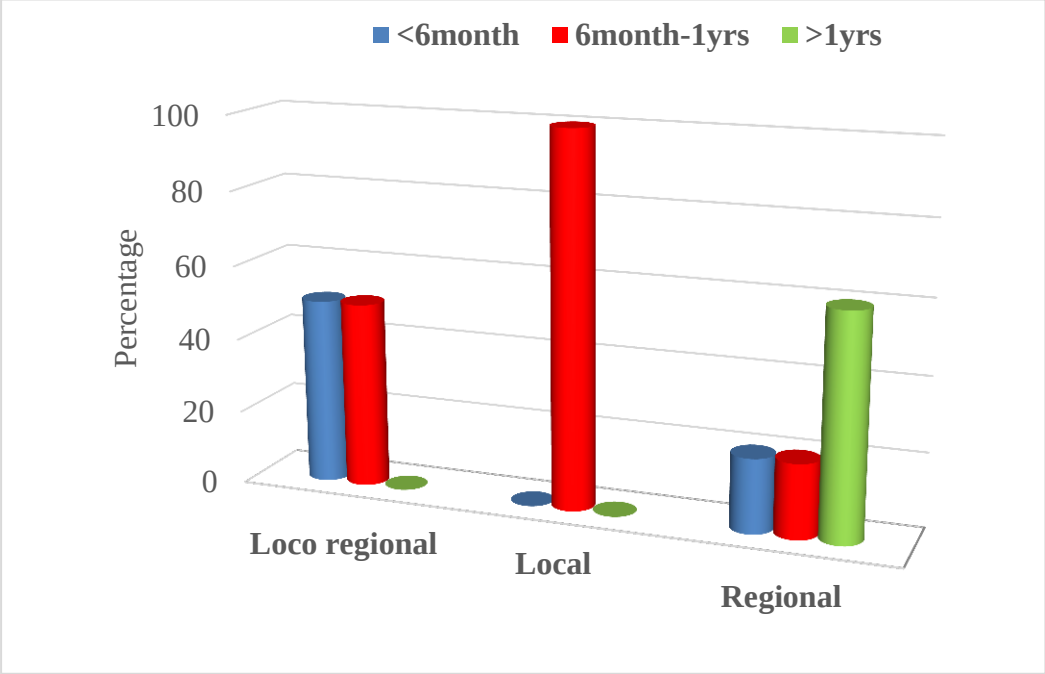


Figure 37:- Distribution of recurrence according to their time in Group B

The adverse histopathological factors attributing towards recurrence are:- positive margins, depth of invasion of more than 1cm, extranodal spread, lymphovascular spread & perineural invasion. While comparing both the groups, it was observed that in the neoadjuvant chemotherapy followed by surgery group, close margins were seen in 3 patients with 1 patient having a positive margin, 4 patients had extranodal spread and 1 patient had a positive margin and depth of invasion of more than 1 cm. on the other hand we observed that in the surgery alone group, 3 patients had close margins with 1 patient having positive margin, 6 patients had extranodal spread, 2 patients had lymphovascular spread, 1 patient had perineural invasion and 1 patient had a combination of perineural invasion, lymphovascular spread & extranodal spread. All these various factors on histopathology have led to disease recurrence.

Table 20:- Comparison of adverse histological factors for recurrence between two group

	Group A	Group B
Close/positive margins	3(30%)	3(18.75%)
positive margin, depth of invasion >1cm	1(10%)	0
Extranodal spread	4(40%)	6(37.5%)
Lympho vascular spread	0	2(12.5%)
Perineural invasion	0	1(6.25%)
perineural invasion, lymphovascular spread, extranodal spread	0	1(6.25%)

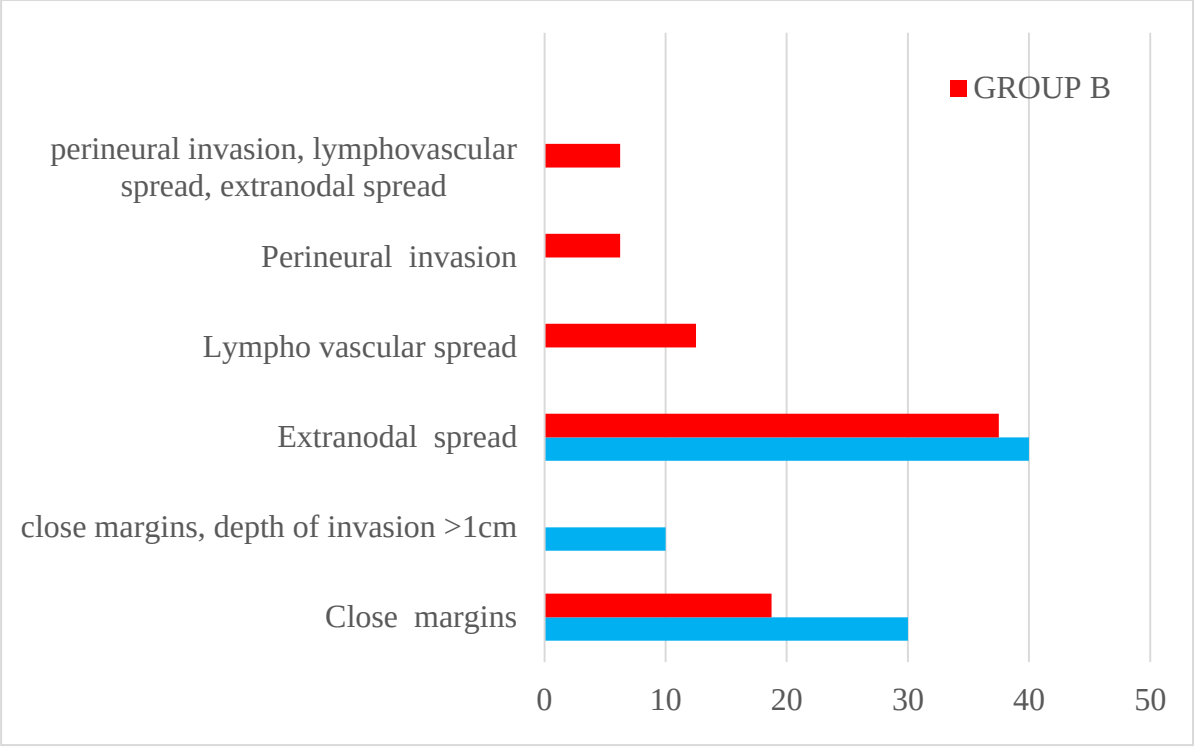


Figure 38:- Graph showing Comparison of reason for recurrence between two groups

When observing the indications for adjuvant chemotherapy with radiotherapy between the 2 groups, it was found that multiple factors led to subjecting these patients for adjuvant chemotherapy with radiotherapy namely close margins, positive margins, depth of invasion of more than 1 cm, extranodal spread, lymphovascular spread & perineural invasion. A combination of these histopathological findings was seen in most of the patients.

Table 21:- Comparison of indication for adjuvant chemotherapy with radiotherapy between two group

	Group A	Group B
Close margins	1(14.3%)	2(16.67%)
close margins, depth of invasion >1cm	1(14.3%)	0
Extranodal spread	3(42.8%)	1(8.33%)
extranodal spread, close margin	2(28.6%)	5(41.67%)
extranodal spread, close margin, lymphovascular spread	0	2(16.66%)
perineural invasion	0	1(8.33%)
perineural invasion, lymphovascular spread, extranodal spread	0	1(8.33%)

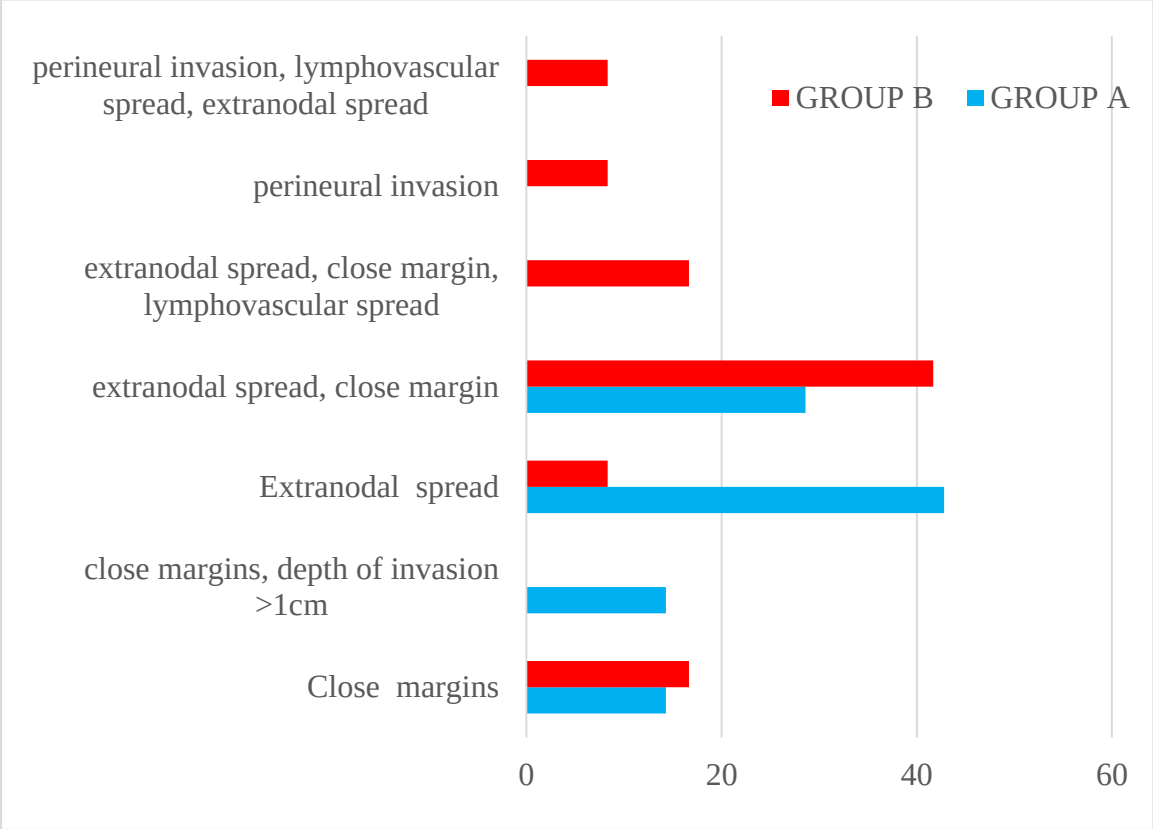


Figure 39:- Graph showing Comparison of reason for chemotherapy between two group

Out of 10 patients who had progressive response from Neoadjuvant chemotherapy, 3 patients underwent surgery and 7 patients received palliative treatment in the form of chemotherapy with radiotherapy. Of the 3 patients who underwent surgery from the patients with progressive response to neoadjuvant chemotherapy, 1 patient had lymphovascular spread and extranodal spread on histopathology and had locoregional disease recurrence after 6 months of treatment, 1 patient had perineural invasion on histopathology and had regional disease recurrence after 6 months of treatment and 1 patient having lymphovascular spread and extranodal spread on histopathology died within 7 months of treatment.

The overall survival that we observed with a minimum follow up of 1 year and a mean follow up of 18 months was found to be better in the neoadjuvant followed by surgery group. We observed that out of the 11 recurrences in the neoadjuvant followed by surgery group, 34.8% patients recurred after 6 months and 8.7% patients recurred before 6 months. Whereas, in the surgery alone group, out of the 16 patients who recurred, 26.6% patients recurred after 6 months, 16.67% patients recurred before 6 months and 10% patients recurred after 12 months. Hence, the survival of patients receiving neoadjuvant chemotherapy is marginally better than surgery alone.

GROUP A

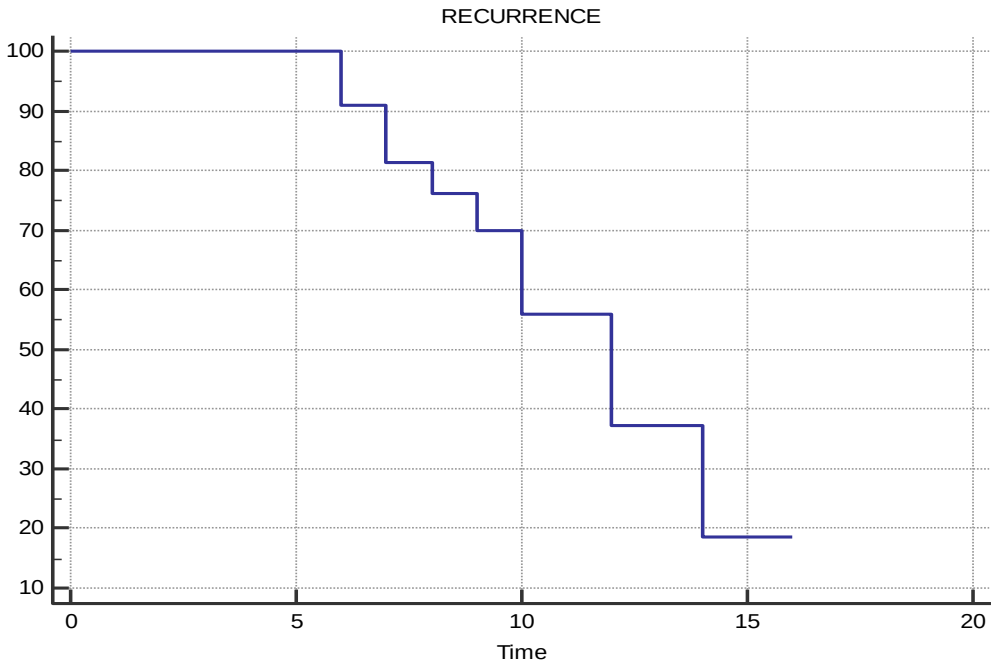


Fig 40: Kaplan Meyer Curve for recurrences in Group A

GROUP B

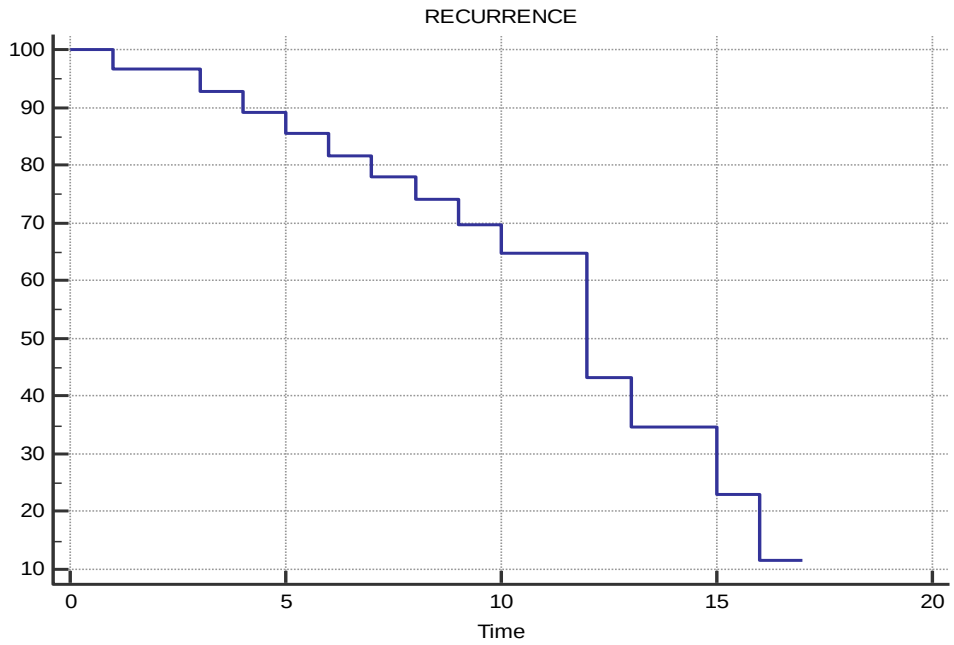


Fig 41: Kaplan Meyer Curve showing recurrences in Group B

Comparison of group A and Group B

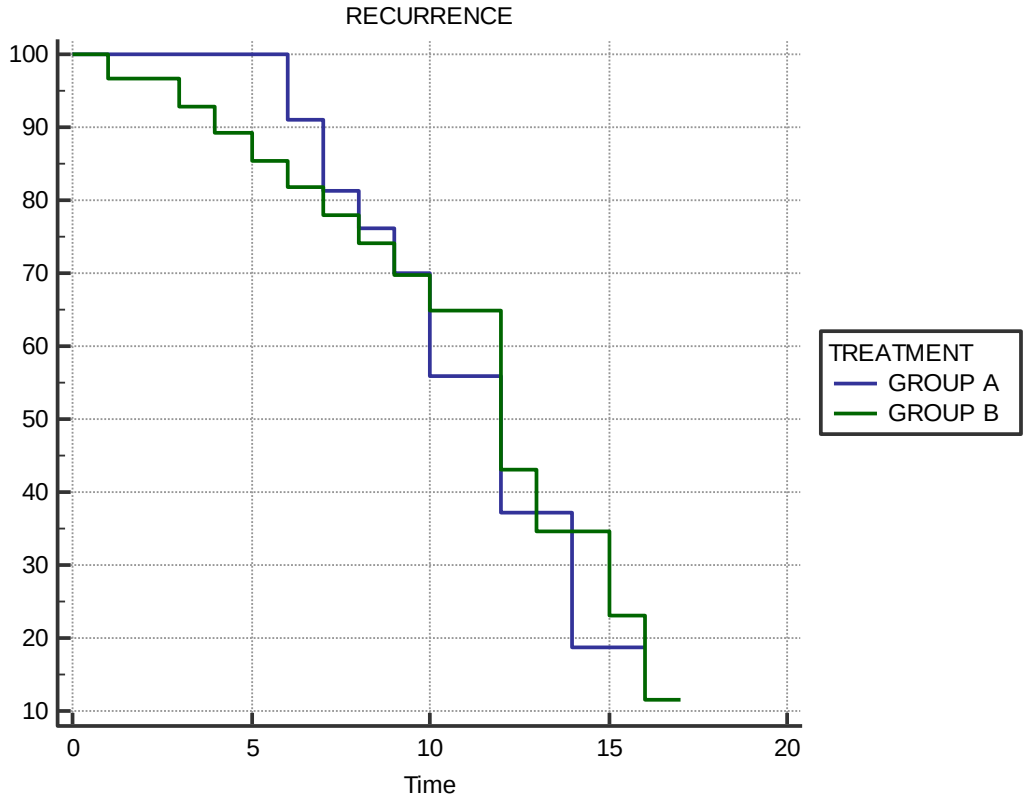


Fig 42 : Kaplan Meyer Curve showing comparison of recurrences in both groups

DISCUSSION

This study comparing the oncological outcome and surgical complications between locally advanced (T4a and T4b) oral squamous cell carcinoma treated by surgery followed by adjuvant treatment and neoadjuvant chemotherapy followed by surgery and adjuvant treatment included stage and age matched patients who were randomized into the above mentioned 2 groups.

There have been few studies in literature which have compared the outcome of surgery followed by adjuvant treatment and neoadjuvant chemotherapy followed by surgery and adjuvant treatment. Most of these studies have been in western countries. However, the above mentioned western studies were on resectable locally advanced disease staged T3 and T4a. In contrast, our study included only T4 disease with 40% of the subjects staged T4b. There have been few studies in India to document the outcome of Neoadjuvant Chemotherapy on loco-regional control and surgical outcome in patients with very advanced oral squamous cell carcinoma.[44,45] To the best of our knowledge there has been no study in India which compares the oncological outcome after surgery alone with adjuvant treatment versus Neoadjuvant chemotherapy followed by surgery and adjuvant treatment in T4 staged oral squamous cell carcinoma.

Our hospital is a tertiary care teaching hospital in a rural and economically backward region having a high prevalence of oral squamous cell carcinoma. Studies done in our institution and other institutions in this region show that Head & Neck cancers account for 30% of cancers in this region, the most common being buccal mucosa

cancers. Majority of the patients in this study were female patients aged between 50-60 years. This can be explained by the fact that the female population in this region is addicted to chewable carcinogens like tobacco quid and have a tendency to retain the quid in the cheek which is often kept overnight.

This also explains the high frequency of buccal mucosa and lower gingiva-buccal cancers in this region. Majority of the patients in this region present with locally advanced disease. The reasons for this late presentation are poverty, ignorance and lack of awareness, neglect of the female population and failure to recognize early disease by health care providers in the periphery.

About 60% of the patients in our study were staged T4a and about 40% were staged T4b. These were selected T4b tumours having extension to infratemporal fossa but were operable according to the various studies over the last decade which show that T4b tumours not reaching above the upper margin of lateral pterygoid on imaging have a reasonably good outcome which is almost similar to T4a following a proper compartment resection of infratemporal fossa. Though, the study subjects were randomized into 2 groups (Group A- Neoadjuvant Chemotherapy followed by surgery and adjuvant treatment and Group B – surgery alone followed by adjuvant treatment), there was an unintentional tendency towards higher number of T4b tumours in Group A. This was because some tumours clinically and radiologically staged T4a and included in Group A turned out to be T4b after histopathological examination due to microscopic disease extending to infratemporal fossa. A small number of patients staged T4a and designated to Group A refused Neoadjuvant Chemotherapy.

The patients designated to Group A in our study (Neoadjuvant Chemotherapy group) received 2 cycles of neoadjuvant chemotherapy which included Paclitaxel and Carboplatin given in 3 weekly cycles. This was in contrast to studies done in China and USA where 3 drug regimens (Docetaxel + Cisplatin + 5 Fluorouracil) were used.[41,45,46] We restricted our patients to 2 drug regimen because the patients in our region are undernourished and toxicity with a 3 drug regimen could have resulted in higher number of drop outs. Unlike a few western studies, our Neoadjuvant chemotherapy was restricted to 2 cycles only as we did not want to risk progressive disease resulting in inoperable tumours.

The main end points in our study were loco-regional control and complications of treatment. This was in contrast to few western studies which attempted to include conservative surgery and oral function preservation as one of the main end points. The adjuvant treatment following surgery in our study included both Radiotherapy as well as chemotherapy with radiotherapy. This differed from Chinese and American studies which had only Radiotherapy as the adjuvant treatment.[41,44] Some patients received adjuvant radiotherapy with chemotherapy in our series because a significant number of patients had infratemporal fossa involvement where close margins of resection are quite common.

In our study, 30% of the patients in the Neoadjuvant chemotherapy group (Group A) had progressive disease. Only 30% of this subset could be taken up for surgery and the others were found to be inoperable. This is probably because we used 2 drug regimen of Neoadjuvant chemotherapy and our patients had stage IV disease. Similar outcome with Neoadjuvant chemotherapy was documented in the Chinese study done

in Shanghai where about 65% of the patients had either good or partial response to NACT. Western studies also document a few deaths and drop outs in the Neoadjuvant chemotherapy group due to toxicity, non-compliance or progressive disease.[47,48]

In our study, there was no difference between the 2 groups during surgery with regard to vascularity and surgical planes. During the post-operative period, there was marginally higher tendency towards reconstructive flap necrosis in Neoadjuvant chemotherapy group and a marginal increase in number of orocutaneous fistulas in surgery alone group. However, the difference in rate of complications between the 2 groups was not statistically significant. In contrast to our findings, studies done in USA show a higher complication rate following surgery in the neoadjuvant chemotherapy group.[48] This could be due to the 3 drug chemotherapy regimens in western countries and tendency towards obesity in western countries which can also affect peripheral blood vessels leading to complications. The Chinese study showed no difference between the 2 groups.[41]

In our study, there was no statistically significant difference between the 2 groups with regard to skin involvement and bone involvement.

With regard to disease clearance (primary tumor), the margins of resection were almost similar in the 2 groups in our study. This could be due to the compartment resection in patients with infratemporal fossa disease and wide margins maintained by the same senior surgeon. Few studies have documented good reduction in size of tumor and a tendency towards organ preservation following Neoadjuvant chemotherapy. Some studies also document complete response in a small number of

patients after chemotherapy. They have used the response rates to chemotherapy as one of the main factors to decide upon organ preservation. However, studies in Italy and a meta-analysis show no advantage in administering neoadjuvant chemotherapy. However, literature mentions that the shrinkage in tumor volume may make the resection easier. In our study, there was no attempt at organ preservation or reduction in margins of resection. Only 1 case in each group had a positive margin (superior margin) in our study. The closest margin of resection in both groups was the superior margin. This is because many patients in our study had disease reaching infratemporal fossa or upper alveolus. Similar findings have been documented by Liao et al as well as Indian authors who have popularized curative resection in selected cases of oral cancer extending to infratemporal fossa. Positive or close margins of resection were found to be a risk factor for recurrence in our study. Similar observations have been made in a meta-analysis as well as various studies in literature.[8,37,38,39]

In our study the mean depth of invasion in group A was 7mm and Group B was 6.2 mm. There was no statistically significant difference between the 2 groups with regard to depth of invasion. However, in both the groups the depth of invasion was more than the lower cut off (5mm) for T3 according to AJCC staging (8^{th} edition).[9] Many patients had full thickness tumour in the cheek.

Therefore, no attempt was made to have a conservative approach after Neoadjuvant chemotherapy. Literature has shown that depth of invasion 4mm or more in tongue and 5mm or more in buccal mucosa is associated with higher chances of lymph node metastasis and local recurrence.[38] The other adverse histopathological risk factors like perineural spread and lymphovascular invasion were also similar in both the groups in

our study. Therefore, the 3rd dimension of the tumour was similar in both the groups in this study and did not impact the comparative outcome.

In our study, there was no statistically significant difference in the metastatic lymph node status between the 2 groups. All patients in both the groups were found to have at least 1 metastatic lymph node. However, there was a marginally higher frequency of N2 nodal status in the neoadjuvant chemotherapy group compared to surgery alone group. The number of nodal recurrences (regional) were identical (13%) in both the groups. A large study done in China also showed no statistically significant difference with regard to nodal recurrences in patients who received neoadjuvant chemotherapy before definitive treatment and those who did not. However, a study done in California showed that neoadjuvant chemotherapy improved the outcome in patients with oral squamous cell carcinoma having advanced nodal disease.[46] This shows that neoadjuvant chemotherapy as well as adjuvant chemo-radiation in advanced nodal disease is helpful. Observations have also been made in literature that the frequency of distant metastasis is less in patients who have received chemotherapy both as neoadjuvant and/or as adjuvant in oral cancer. A large Italian study has also shown similar results. An international collaborative study to document the control rates in oral cancer in the last decade of 1990's and the 1st decade of this millennium has also shown better control rates in this millennium and incorporation of multimodality treatment approach (including chemotherapy and targeted therapy) have been responsible for better outcomes.[47,48]

Various studies in literature mainly published in 2013 and 2014 have shown that neoadjuvant chemotherapy does not improve disease specific or overall survival in

oral cancer. However, the overall usefulness of neoadjuvant chemotherapy is still controversial and being debated.[41,49,50] Most of the above studies have also shown a better outcome in patients who had good or partial response to neoadjuvant chemotherapy compared to those who had progressive disease. However, all these studies included locally advanced resectable tumours and none of them had T4b patients. In contrast, our study which had only T4 (T4a & T4b) patients also showed that the outcome in partial responders to neoadjuvant chemotherapy was better when compared to patients who did not receive neoadjuvant chemotherapy. However, this observation has to be taken with caution as 30% of the patients in the neoadjuvant arm had progressive disease and the overall outcome did not show survival benefit. In our study, the local and locoregional recurrences were less frequent among the partial responders and stable disease to neoadjuvant chemotherapy (control rates 70%) when compared to patients who didn't receive neoadjuvant chemotherapy or those who did not respond to it. Similar results have been documented in a study published in 2019 in China.[45]

In our study, the nodal recurrences (regional) were more frequent in patients staged T4b compared to those staged T4a in both the groups. This observation is similar to findings in literature which show that number of metastatic lymph nodes and extra nodal spread is higher in very advanced disease. Though the mean follow up period in our study was 18 months which is relatively shorter follow up, we observed that most of the recurrences were locoregional. This is because all our patients were staged T4. The maximum number of recurrences in our study were between 6 months to 12 months. Similar observations have been made in other studies in literature and show that majority of their recurrences are within first 18 months of their treatment.

The same holds good for advanced malignancies. Various studies in literature have shown that the outcome is better with upfront surgery compared to neoadjuvant chemotherapy followed by surgery. Our results differ from the above observations as the overall outcome was almost similar in both groups in this study. This can be explained the fact that other comparative studies included only locally advanced resectable tumours(T3 and T4) unlike particularly T4b in our study.

The other studies in literature attempted conservation in the extent of resection and some studies also tried only chemo-radiation in good responders to neoadjuvant chemotherapy. Our resection did not have conservative aims unlike the above studies.[41,46,47,48]

Our study differed from other studies in literature which compared neoadjuvant chemotherapy followed by surgery and surgery alone followed by adjuvant treatment in both the groups. This was because 40% of subjects in our study were staged T4b with extension to infratemporal fossa. The small inequality in T4b patients between the 2 groups was mainly because some patients staged T4a clinically and on imaging turned out to be T4b on histopathological examination due to extension of disease into the infratemporal fossa along the muscles of mastication. In literature, infratemporal fossa spread was seen as a factor for inoperability till 2007. It was only in the last 12-14 years that surgeons ventured into oral squamous cell carcinoma with infratemporal fossa involvement with a curative intent. The patients staged T4b in both groups in our study had reasonably good outcome because they only had tumour below the upper margin of lateral pterygoid on imaging. Studies in India and Taiwan have shown that infratemporal fossa involvement till the level of sigmoid notch of

mandible has an outcome similar to T4a disease when compartment resection is done.[38,39] Studies have also shown that the oncological outcome is reasonably good when the disease in infratemporal fossa does not extend to pterygoid plates or roof of infratemporal fossa. However, as mentioned earlier the locoregional recurrences in both group A and Group B in our study were more frequent in subjects staged T4b in comparison to subjects stage T4a. Studies from Tata Memorial Hospital, India, have shown reasonably good locoregional control rates in advanced oral cancers when neoadjuvant chemotherapy was used.[48] Literature also shows 6-10% benefit when chemotherapy (preferably Taxane based) is used in neoadjuvant as well as adjuvant settings in locally advanced oral cancers.[50]

The risk factors for poor outcome in our study included close superior margin of resection (less than 5mm after formalin fixation), positive margins (1 patient in each group), extra nodal spread in lymph nodes, perineural invasion and lymphovascular invasion. Other studies in literature as well as various oncology groups have also implicated positive margins and extra nodal spread from lymph nodes as poor prognostic factors.[46] This can also be seen in the 8th edition of the AJCC staging where extra nodal spread from a lymph node irrespective of its size stages the patient as N3b.

The locoregional control in our study was similar to that seen in other studies on locally advanced oral cancers. Some studies using neoadjuvant chemotherapy included the response to neoadjuvant chemotherapy, p53 mutation and depth of invasion more than 5mm as poor prognostic factors.[50,51,52] In our study, almost all patients had depth of invasion more than 5mm. We did not consider p53 mutation in

this study and the response to neoadjuvant chemotherapy (except in those who had progressive disease) did not have a significant impact in the overall locoregional control. However, the partial responders to neoadjuvant chemotherapy had a far better outcome. The use of adjuvant chemotherapy with radiotherapy in our study was similar to that seen in Tata Memorial study on locally advanced oral cancers.

The disease free survival rates observed in our study were 50% in the neoadjuvant followed by surgery arm and 43.33% in the surgery alone arm over a minimum period of 1 year. Hence, neoadjuvant chemotherapy does provide benefit in patients having locally advanced oral cancer. This trend was also seen in European studies where the overall survival and time for disease recurrence was found to be better with neoadjuvant chemotherapy.

SUMMARY

Prevalence of Oral cancers has been increasing across the globe. Oral squamous cell carcinoma is the 6th most common malignancy in the world. Majority of these cancers are from South East Asia. In India, oral malignancies account for maximum number of cancers in males and second highest number of cancer in females. The main cause of this high prevalence in India is addiction to chewable tobacco, areca nut and betel leaves.

Oral cancers affect quality of life and aesthetics and are aggressive with a tendency towards rapid infiltration into adjoining tissues and lymph node metastasis.
80 % of our patients present in a locally advanced stage making them inoperable or difficult to resect with post operative morbidity involving loss of structure and function. Neoadjuvant Chemotherapy in such cancers may be necessary in order to control its progression till definitive treatment (surgery) is done or to down stage the tumor prior to surgery.

Our study was a randomized comparative study done between December 2018 to November 2020 and included 60 patients who were all staged T4, with 40% of the subjects staged T4b. These were selected T4b tumours having extension to infratemporal fossa but were operable. Patients having Recurrent Tumors, extension to skull base or prevertebral space, encasement of Carotids or past history of Anti malignant chemotherapy were excluded from this study.

The study subjects were randomized into 2 groups (Group A- Neoadjuvant

Chemotherapy followed by surgery and adjuvant treatment and Group B – surgery alone followed by adjuvant treatment). The objectives of our study were:-

1. To document the oncological outcome of surgery followed by adjuvant treatment in locally advanced oral cancers.
2. To document the oncological outcome of Paclitaxel based Neoadjuvant Chemotherapy followed by surgery and adjuvant treatment in locally advanced oral cancers.
3. To compare the oncological outcome and surgical complications in the above mentioned 2 groups.

The Group A which was subjected to Neoadjuvant chemotherapy was subjected to 2 cycles of Paclitaxel and Carboplatin given at 3 weekly intervals. This was followed by surgery in the form of Composite Resection and Neck Dissection with Reconstruction and adjuvant Radiotherapy or Radiotherapy with Chemotherapy.

The Group B had patients undergoing Surgery alone in the form of Composite Resection and Neck Dissection with Reconstruction and adjuvant Radiotherapy or Radiotherapy with Chemotherapy.

The main end points in our study were loco-regional control and complications of treatment.

The patients were followed up for a minimum of 1 year after completion of treatment having a mean follow up of 18 months.

The complications and recurrences were documented and analysed by descriptive

statistics and compared between the 2 groups.

During the post-operative period, there was marginally higher tendency towards reconstructive flap necrosis in Neoadjuvant chemotherapy group and a marginal increase in number of orocutaneous fistulas in surgery alone group. However, the difference in rate of complications between the 2 groups was not statistically significant. Other surgical complications were similar both the groups.

In our study the mean depth of invasion in group A was 7mm and Group B was 6.2 mm. There was no statistically significant difference between the 2 groups with regard to depth of invasion.

The other adverse histopathological risk factors like perineural spread and lymphovascular invasion were also similar in both the groups in our study. All patients in both the groups were found to have atleast 1 metastatic lymph node. However, there was a marginally higher frequency of N2 nodal status in the neoadjuvant chemotherapy group compared to surgery alone group.

In the neoadjuvant group 30% of the patients had progressive disease and had a poor outcome.

Our study which had only T4 (T4a & T4b) patients also showed that the outcome in partial responders to neoadjuvant chemotherapy was better when compared to patients who did not receive neoadjuvant chemotherapy. However, this observation has to be taken with caution as 30% of the patients in the neoadjuvant arm had progressive disease and the overall outcome did not show survival benefit. In our study, the local

and locoregional recurrences were less frequent among the partial responders to neoadjuvant chemotherapy when compared to patients who didn't receive neoadjuvant chemotherapy or those who did not respond to it.

Though the mean follow up period in our study was 18 months which is relatively shorter follow up, we observed that most of the recurrences were locoregional. This is because all our patients were staged T4. The maximum number of recurrences in our study were between 6 months to 12 months.

The locoregional recurrences in both group A and Group B in our study were more frequent in subjects staged T4b in comparison to subjects stage T4a. The regional recurrences were similar in both the groups.

The risk factors for poor outcome in our study included close superior margin of resection (less than 5mm after formalin fixation), positive margins (1 patient in each group), extra nodal spread in lymph nodes, perineural invasion and lymphovascular invasion. The superior margin was found to be the closest margin in both the groups.

The disease free survival rates observed in our study were 50% in the neoadjuvant followed by surgery arm and 43.33% in the surgery alone arm over a minimum period of 1 year. Hence, neoadjuvant chemotherapy does provide benefit in patients having locally advanced oral cancer.

CONCLUSIONS

1. There is high prevalence of oral squamous cell carcinoma in Kolar region and majority of the patients are elderly females. 80% of patients present with locally advanced disease requiring aggressive multimodality treatment.
2. Properly selected T4b tumours which were considered inoperable till 2007 are resectable and carry reasonably good outcome when infratemporal fossa compartment clearance is done.
3. Neoadjuvant chemotherapy in locally advanced oral squamous cell carcinoma holds promise as an important part of multimodality treatment and requires large multi centric trials in near future.
4. There is no significant difference in overall survival and disease free survival after treatment by surgery alone followed adjuvant treatment and neoadjuvant chemotherapy followed by surgery and adjuvant treatment.
5. The resectable locally advanced oral squamous cell carcinoma is better treated by surgery alone followed by adjuvant treatment. The survival rates are marginally better when compared to neoadjuvant chemotherapy group.
6. 30% of locally advanced oral cancers do not respond to neoadjuvant chemotherapy and progress resulting in inoperability in some of these patients.
7. Patients with partial response and stable disease following 2 cycles of Taxane based neoadjuvant chemotherapy and later by surgery and adjuvant treatment carry better outcome and prognosis when compared to those treated by surgery alone and adjuvant treatment, when it comes to locally advanced (T4) oral squamous cell carcinoma.
8. Neoadjuvant chemotherapy provides significant improvement in outcome

when regional lymph nodes have advanced disease. It also reduces the chances of distant metastasis.

9. Neoadjuvant chemotherapy makes resection easier in locally advanced oral cancers by reducing the tumor volume. However, it does not help to reduce the magnitude and extent of resection.
10. There is no statistically significant difference in complications after surgery and time taken for recovery in patients with locally advanced oral cancer treated by surgery alone followed by adjuvant treatment or by neoadjuvant chemotherapy followed by surgery and adjuvant treatment.
11. Chemotherapy in both neoadjuvant as well as adjuvant settings helps to improve the outcome marginally in locally very advanced oral squamous cell carcinoma.

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ANNEXURES

STUDY PROFORMA

PATIENT DETAIL

Name:

Age:

Sex:

Address :

Date:

Occupation:

Telephone no.:

Hospital no:

E-mail ID:

PRESENTING COMPLAINT

CHIEF COMPLAINTS	**YES/NO**	**SINCE**
Presence of ulcer/mass in oral cavity		
Presence of mass/ swelling in neck		
Restricted mouth opening		
Excessive salivation		
Difficulty in swallowing		

Change in voice		
Loss of appetite		
Weight loss		
Generalized weakness		
Difficulty in speech		
Loosening of teeth		
Earache		

HISTORY OF PRESENT ILLNESS

Onset:

Duration:

Progression:

Aggravating factors:

Relieving factors:

H/O trauma:Y/N

H/O difficulty in swallowing: Y/N

H/O difficulty in breathing: Y/N

H/O change in voice: Y/ N

H/O weight loss: Y/N

PAST HISTORY

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

H/O previous surgery: Y/N

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

FAMILY HISTORY

Contributory Not contributory

PERSONAL HISTORY

Loss of appetite: Y/N

Disturbed sleep: Y/N

Bowel and bladder disturbances: Y/N

Habits –

Tobacco chewing :

Gutka

Tobacco – Y/N Lime – Y/N

Duration - Frequency –

Side – Right/ Left/ Both

Leaves overnight – Y/N

Stopped since (if stopped)

Smoking :

Pipe

Duration - Packs/Day -

Alcohol :

Duration -

Type -

Amount/day -

Stopped since (if stopped):

GENERAL PHYSICAL EXAMINATION

Built:

Nutrition:

Temperature:

Pulse:

BP:

RR:

Pallor: Y/N

Icterus: Y/N

Cyanosis Y/N

Clubbing: Y/N

Lymphadenopathy: Y/N

Edema: Y/N

LOCAL EXAMINATION

Oral Cavity :

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

Oro-dental Hygiene: Poor/ Satisfactory

Nicotine stains: Y/ N Site: Buccal mucosa

Retromolar Trigone

Lower alveolus

Upper alveolus

Hard palate

Tongue

Floor of mouth

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 :

TNM STAGING:

INVESTIGATIONS :

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

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

CT SCAN

DIMENSIONS

VOLUME

BIOPSY REPORT:

CLINICAL DIAGNOSIS:

NEOADJUVANT CHEMOTHERAPY :

DOSE:

CYLCLES:

DURATION:

DRUG REACTION:

COMPLICATIONS:

Difficulty In swallowing: Y/N

Difficulty in breathing: Y/N

Pain in swallowing: Y/N

Difficulty in closing mouth: Y/N

Headache: Y/N

Giddiness, Vertigo: Y/N

RESPONSE: Partial / Stable / Progressive

SURGERY:

NECK: SOND/MRND/RND

RECONSTRUCTION: PMMC/forehead flap/deltopectoral flap/supraclavicular flap/submental flap/ radial forearm free flap/bipaddle PMMC/ buccal pad of fat/ skin graft

TIME TAKEN FOR SURGERY:

ADEQUACY OF EXPOSURE:

FARTHEST MARGIN OF RESECTION:

CLOSEST MARGIN OF RESECTION:

COMPLICATIONS:

Flap Necrosis

Orocutaneous Fistula

HISTOPATHOLOGY REPORT:

Tumour size:

Tumour grade:

Resected margin of tumour:

Lymphovascular invasion: Y/N

Perineural invasion: Y/N

Bone invasion: Y/N

Metastatic lymph nodes: Y/N

Number:

Level :

Size of the biggest node:

Extra capsular spread:

RADIOTHERAPY: DOSE: Gy

FRACTIONS: #

DAYS:

FOLLOW UP: months

LOCAL RECURRENCE

REGIONAL RECURRENCE

LOCO REGIONAL RECURRENCE

DISTANT METASTASIS

DIED DUE TO OTHER CAUSE:

DIED DUE TO DISEASE:

LOST TO FOLLOW UP:

SYSTEMIC EXAMINATION:

CARDIO VASCULAR SYSTEM:

RESPIRATORY SYSTEM:

ABDOMEN:

CENTRAL NERVOUS SYSTEM:

INFORMED CONSENT FORM

I Mr./Mrs._____have been explained in a language I understand, that I will be included in a study which is A COMPARATIVE STUDY OF ONCOLOGICAL OUTCOME BETWEEN SURGERY ALONE AND NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED ORAL CANCERS**,** being conducted in RL JALAPPA HOSPITAL.

I have been explained that my clinical findings, investigations, possibility of neoadjuvant chemotherapy (Paclitaxel 175mg/m^2 + Carboplatin), surgery to be performed (Composite Resection + Neck Dissection + Reconstruction), 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 personal and clinical details will be kept confidential and my photograph if any will not reveal my identity.
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.

Caretaker's name:

Signature/Thumb impression:
DATE:

PATIENT INFORMATION SHEET

Study title: A COMPARATIVE STUDY OF ONCOLOGICAL OUTCOME BETWEEN SURGERY ALONE AND NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED ORAL CANCERS

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

Details-

Patients diagnosed having locally advanced oral cancer and admitted to R.L.Jalappa Hospital will be included in this study. Patients are explained regarding the severity and gravity of the disease and will undergo treatment specified for them.

Patients in this study will have to undergo pre and postoperative blood investigations along with sequential imaging. Patients will also undergo treatment by surgery (Composite Resection + Neck Dissection + Reconstruction) or Neoadjuvant Chemotherapy with Paclitaxel 175mg/m^2 + Carboplatin followed by above mentioned surgical procedure.

All patients will undergo surgery for the removal of the disease. There will be no compromise on the treatment plan. Patients receiving Neoadjuvant Chemotherapy will undergo 2 cycles. This is being given to assess the benefits of Neoadjuvant Chemotherapy like downgrading the tumor, making defined surgical margins etc.

Patients will undergo the same type of surgery in both groups and extent of resection will depend on the disease. At no point with any patient in either group will treatment be compromised.

Please read the above 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.

WHO TO CONTACT**?**

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S No.	name	uhid	age/sex	date of admission	date of surgery	staging	tumor site	nact +/-	date of last nact	radiological dimensions	response to NACT	Post 2 cycles NACT radiological dimensions	surgery	surgical findings	dimension of lesion	skin involvement	bone involvement	depth of invasion	perineural involvement	lymphovascular spread
1	VENKATAMMA	646908	60/F	6/10/2018	6/12/2018	T4bN2aM0	Left Lower Gingivobuccal sulcus	given	14/11/18	12x8.2x5.2	stable	11x7.5x5	CR+ITF clearance +HM+PMMC	infratemporal extent	10x6.5x4	Present	Present	6mm	None	None
2	MUNINARAYAMMA	649901	60/F	20/11/2018	11/12/2018	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	4.5x3x1.6	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3.5x2.4x1	absent	present	6mm	None	None
3	SAMPOORNAMMA	656913	55/F	11/10/2018	20/12/18	T4bN1M0	Right Retromolar trigone	given	1/12/2018	7.6x6.2x4.8	partial	7x5.5x4.1	CR+ITF clearance +HM+PMMC	infratemporal extent	6x5x3.6	Present	Present	7mm	None	None
4	LAKSHMAMMA	602817	60/F	15/1/19	24/1/19	T4aN1M0	Right Lower Alveolus	NOT GIVEN	NONE	6x5.5x3.7	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	5.2x4.8x3.1	absent	Present	6mm	None	None
5	VENKATLAKSHMAMMA	655704	50/F	15/11/18	29/1/19	T4aN2aM0	Left Buccal mucosa	given	10/1/2019	4.5x3.1x2.2	partial	3.5x2.2x1.6	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.5x2x3.2	Present	Present	11mm	None	None
6	MANGAMMA	666223	65/F	20/1/19	5/2/2019	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	4.5x4x2.2	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	4x3.5x1.5	Present	Present	9mm	None	None
7	PUTTAMMA	688679	55/F	2/1/2019	5/3/2019	T4bN1M0	Left Lower Gingivobuccal sulcus	given	20/2/19	5.5x5.8x4.3	partial	4.5x5x3.6	CR+ITF clearance +HM+PMMC	infratemporal extent	4x4.2x3	Present	Present	7mm	None	None
8	LAKSHMAMMA	655458	62/F	26/2/19	7/3/2019	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	3.5x2.5x2	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3x2x1.5	absent	Present	9mm	None	None
9	BYRAMMA	686801	45/F	21/1/19	12/3/2019	T4aN1M0	Right Buccal mucosa	given	24/2/19	6x5x4	stable	6x4.4x4	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	5.2x4x3.5	Present	Present	6mm	None	None
10	MENASAMMA	684133	60/F	8/3/2019	14/3/19	T4bN2bM0	Right Lower Alveolus	NOT GIVEN	NONE	6x5.5x4.2	NOT GIVEN	NONE	CR+ITF clearance +HM+PMMC	infratemporal extent	5.5x4.8x3.5	Present	Present	6mm	None	None
11	YASHODAMMA	509800	55/F	12/2/2019	2/4/2019	T4aN1M0	Left Buccal mucosa	given	12/3/2019	4.8x3.6x3	stable	4.5x3.5x3	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3.6x3x2.5	Present	Present	8mm	None	None
12	PUTTAMMA	693468	55/F	25/3/19	4/4/2019	T4aN1M0	Right Lower Gingivobuccal sulcus	NOT GIVEN	NONE	3.5x2x1.5	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	3x1.5x0.5	absent	Present	5mm	None	None
13	VENKATLAKSHMAMMA	689893	54/F	20/2/19	23/4/19	T4aN2aM0	Left Buccal mucosa	given	1/4/2019	4.2x2.5x2.5	progressive	6x4x2.5	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
14	GOWRAMMA	692506	61/F	14/4/19	30/4/19	T4aN1M0	Left Lower Alveolus	NOT GIVEN	NONE	3x2x2	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.5x1.5x1.5	Present	Present	14mm	None	present
15	NARAYANAMMA	701074	50/F	26/3/19	7/5/2019	T4aN1M0	Right Buccal mucosa	given	15/4/19	4.5x2.2x1.6	progressive	6.5x3x2.2	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
16	VENKATLAKSHMAMMA	703101	45/F	1/5/2019	14/5/19	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	4.5x5x3.6	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	4x4.2x3	absent	Present	6mm	None	None
17	ANJINAMMA	709580	35/F	4/4/2019	23/5/19	T4bN1M0	Left Lower Gingivobuccal sulcus	given	6/5/2019	7x4.7x2	stable	6.5x4.5x2	CR+ITF clearance +HM+PMMC	infratemporal extent	6x4x1.5	Present	Present	2mm	None	None
18	NARASAMMA	712585	65/F	10/5/2019	23/5/19	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	2.5x2x1	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.3x4.1x3	absent	Present	4mm	None	None
19	CHIKKAMUNIYAMMA	714374	50/F	28/3/19	23/5/19	T4aN1M0	Left Lower Alveolus	given	5/5/2019	3.6x3.2x2.4	progressive	5.6x4.2x3.6	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
20	NARAYANAMMA	710243	52/F	10/5/2019	28/5/19	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	3.5x3.2x2.4	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3x2.6x2	absent	present	10mm	None	None
21	SHEIK IBRAHIM	709585	65/M	10/4/2019	28/5/19	T4bN1M0	Left Buccal mucosa	given	14/5/19	6.7x5.5x3	stable	6.5x5.2x3	CR+ITF clearance +HM+PMMC	infratemporal extent	6x4.8x2.6	Present	Present	8mm	Present	Present
22	YELLAMMA	712631	50/F	20/5/19	6/6/2019	T4aN1M0	Left Lower Alveolus	NOT GIVEN	NONE	4.2x2.8x3	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3.5x2.2x2.4	absent	Present	2mm	None	None
23	NARENDRA BABU	718623	46/M	20/4/19	4/6/2019	T4bN1M0	Right Buccal mucosa	given	20/5/19	6.5x5.1x3.6	partial	5.5x4.2x3	CR+ITF clearance +HM+PMMC	infratemporal extent	5x3.6x2.5	Present	Present	10mm	None	None
24	SAVITRAMMA	720440	45/M	30/5/19	18/6/19	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	4.8x3.2x1.6	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	3.8x2.5x1	Present	Present	6mm	Present	None
25	JAYAMMA	696880	48/F	1/5/2019	25/6/19	T4aN1M0	Right Buccal mucosa	given	8/6/2019	4.4x3.6x2.4	progressive	5.2x4.2x3	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
26	JAYAMMA	727843	65/F	1/6/2019	27/6/19	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	3.2x2.4x2	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.4x1.8x1.4	absent	Present	4mm	None	None
27	HOTTAPPA	730031	48/M	12/5/2019	29/6/19	T4bN1M0	Left Buccal mucosa	given	13/6/19	4.8x4.2x3.8	stable	4.5x4x3.6	CR+ITF clearance +HM+PMMC	infratemporal extent	4x3.6x3.1	Present	Present	8mm	None	None
28	JAYAMMA	727292	45/F	15/6/19	2/7/2019	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	3.6x2.6x1.6	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3x2x1.2	absent	Present	6mm	None	None
29	PADMAMMA	738384	40/F	20/5/19	9/7/2019	T4bN1M0	Left Buccal mucosa	given	20/6/19	4.5x5.2x3.5	progressive	5.5x4.4x3	CR+ITF clearance +HM+PMMC	infratemporal extent	5x4x2.5	Present	Present	10mm	None	Present
30	SARASWATHAMMA	732832	65/F	1/7/2019	11/7/2019	T4aN1M0	Right Buccal mucosa	NOT GIVEN	NONE	4.5x4x2.3	NOT GIVEN	NONE	BR+HM+PMMC	NO INFRATEMPORAL EXTENSION	4x3.5x2.5	absent	Present	6mm	None	None
31	RATHNAMMA	731263	45/F	1/6/2019	16/7/19	T4aN1M0	Left Buccal mucosa	given	1/7/2019	5.7x3.6x2.5	progressive	6.5x4.2x3.1	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
32	RAMAPPA	737762	45/M	10/7/2019	30/7/19	T4bN1M0	Right Buccal mucosa	NOT GIVEN	NONE	5.6x4.7x3.6	NOT GIVEN	NONE	CR+ITF clearance +HM+PMMC	infratemporal extent	5x4.1x2.8	Present	Present	5mm	none	none
33	VENKATARAYAPPA	677591	65/M	10/6/2019	25/7/19	T4bN1M0	Right Lower Alveolus	given	10/7/2019	5.5x4.5x5.5	partial	4.5x4x5	CR+ITF clearance +HM+PMMC	infratemporal extent	4x3.5x4.5	Present	Present	6mm	none	none
34	KALLAPPA	737116	65/M	14/7/19	1/8/2019	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	4.5x2.6x4	NOT GIVEN	NONE	WE+MM+PMMC	NO INFRATEMPORAL EXTENSION	3.5x2x3.5	absent	absent	5mm	none	none
35	GURAMMA	724221	61/F	15/6/19	13/8/19	T4aN1M0	Left Buccal mucosa	given	21/7/19	4.8x3.8x2.8	progressive	6x4.5x3.5	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
36	MANJUNATH	743116	42/M	1/8/2019	20/8/19	T4bN1M0	Right Lower Alveolus	NOT GIVEN	NONE	4.5x3.5x4	NOT GIVEN	NONE	CR+ITF clearance +HM+PMMC	infratemporal extent	4x3x3.5	absent	Present	4mm	none	none
37	MUNIYAMMA	742665	62/F	30/6/19	21/8/19	T4aN1M0	Right Buccal mucosa	given	1/8/2019	4.8x4.6x3	stable	4.3x4.1x2.7	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	3.8x3.5x2.4	absent	Present	6mm	none	none
38	GOWRAMMA	724221	48/F	5/8/2019	22/8/19	T4bN1M0	Left Buccal mucosa	NOT GIVEN	NONE	5x4.6x2.8	NOT GIVEN	NONE	CR+ITF clearance +HM+PMMC	infratemporal extent	4.6x3.1x1.8	Present	Present	8mm	None	None
39	BELLAMMA	751773	50/F	4/7/2019	29/8/19	T4aN1M0	Right Buccal mucosa	given	5/8/2019	3.2x3x2.4	stable	3x2.6x2	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.5x2x1.6	absent	absent	4mm	None	None
40	VENKATLAKSHMAMMA	756948	60/F	25/8/19	3/9/2019	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	3.5x2.4x1.6	NOT GIVEN	NONE	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	2.8x1.8x1	absent	Present	9mm	None	None
41	MUNIYAMMA	754134	60/F	15/7/19	10/9/2019	T4bN1M0	Left Buccal mucosa	given	20/8/19	5.8x4x3	progressive	6.3x4.5x3.5	CR+ITF clearance +HM+PMMC	infratemporal extent	5.5x4x3	Present	Present	8mm	None	None
42	SAVITRAMMA	755299	40/F	25/8/19	10/9/2019	T4aN1M0	Left Buccal mucosa	NOT GIVEN	NONE	3.5x2.6x2.1	NOT GIVEN	NONE	WE+MM+PMMC	NO INFRATEMPORAL EXTENSION	3x2.2x1.6	absent	absent	6mm	None	None
43	NARAYAMMA	764794	60/F	20/7/19	24/9/19	T4aN2aM0	Left Buccal mucosa	given	5/9/2019	4.8x3.8x2.8	stable	4.5x3.6x2.6	WE+HM+PMMC	NO INFRATEMPORAL EXTENSION	4x3.1x2.2	Present	Present	4mm	None	None
44	JAYAMMA	773656	60/F	1/10/2019	17/10/19	T4aN1M0	Left Lower Alveolus	NOT GIVEN	NONE	3.5x2.5x1.6	NOT GIVEN	NONE	WE+MM+PMMC	NO INFRATEMPORAL EXTENSION	3.1x2x1.2	absent	absent	2mm	None	None
45	VENKATAMMA	773362	60/F	4/9/2019	22/10/19	T4bN1M0	Right Buccal mucosa	given	3/9/2019	3.5x2.4x2.1	progressive	4.5x3.2x2.6	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED	NOT OPERATED
46	AKKAMMA	774216	60/F	1/10/2019	24/10/19	T4aN1M0	Left Lower Gingivobuccal sulcus	NOT GIVEN	NONE	3x2.1x2.2	NOT GIVEN	NONE	WE+MM+PMMC	NO INFRATEMPORAL EXTENSION	2.5x1.5x1.6	absent	absent	2mm	None	None
47	NAGARATHNAMMA	647532	55/F	15/9/19	31/10/19	T4bN1M0	Left Buccal mucosa	given	12/10/2019	6x4.2x3.2	partial	5.1x3.5x2.6	CR+ITF clearance +HM+PMMC	infratemporal extent	4.5x3.1x2.1	absent	Present	5mm	None	None
48	NARAYANASWAMY	773532	60/M	25/10/19	7/11/2019	T4bN2bM0	Right Buccal mucosa	NOT GIVEN	NONE	6X3.8X2.5	NOT GIVEN	NONE	CR+ITF clearance +HM+PMMC	infratemporal extent	5.2X3.2x1.7	Present	Present	8mm	None	None

S No.	closest margin	no. of lymph nodes	extranodal spread	adjuvant treatment	radiotherapy start date	radiotherapy end date	fraction	chemotherapy given	dose	cycles of chemo	complications	date of last follow up	status at last follow up	local recurrence	regional recurrence	locoregional recurrence	reason for recurrence	reason for chemotherapy
1	posteriorly 4mm	46	None	radiotherapy + chemotherapy	3/1/2019	10/2/2019	33	cisplatin	55mg	4	NONE	20/8/19	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
2	superiorly 4mm	24	present	radiotherapy + chemotherapy	10/1/2019	17/2/19	34	cisplatin	55mg	4	orocutaneous fistula	3/9/2019	unstable	absent	absent	present	extranodal spread	extranodal spread, close margin
3	posteriorly 3mm	40	present	radiotherapy + chemotherapy	2/2/2019	8/3/2019	34	cisplatin	55mg	4	orocutaneous fistula	10/12/2019	unstable	absent	LYMPH NODE METASTASIS	absent	extranodal spread	extranodal spread, close margin
4	superiorly 6mm	36	None	radiotherapy	20/2/19	26/3/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	6/10/2019	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
5	superiorly 1mm	21	present	radiotherapy + chemotherapy	20/3/2019	30/4/2019	33	cisplatin	50mg	4	orocutaneous fistula	2/1/2020	unstable	PRESENT	absent	absent	extranodal spread	extranodal spread, close margin
6	posteriorly 1mm	27	None	radiotherapy + chemotherapy	8/4/2019	12/5/2019	33	cisplatin	50mg	4	Flap necrosis	19/6/19	unstable	absent	LYMPH NODE METASTASIS	absent	close margin	close margin
7	superior 6mm	24	None	radiotherapy	8/4/2019	12/5/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	20/1/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
8	anteriorly 9mm	18	none	radiotherapy	10/4/2019	14/5/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	18/11/19	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
9	inferiorly 3mm	16	none	radiotherapy + chemotherapy	24/4/19	31/5/19	33	cisplatin	55mg	4	NONE	14/1/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
10	anteriorly 2mm	24	present	radiotherapy + chemotherapy	24/4/19	31/5/19	33	cisplatin	55mg	5	orocutaneous fistula	10/12/2019	unstable	absent	absent	present	extranodal spread	extranodal spread, close margin
11	inferiorly 5mm	28	none	radiotherapy	2/5/2019	6/6/2019	32	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	21/12/19	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
12	posteriorly 5mm	14	none	radiotherapy	2/5/2019	6/6/2019	32	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	5/1/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
13	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	18/6/19	24/7/19	34	cisplatin	55mg	4	NONE	15/12/19	unstable	absent	absent	present	progressive disease	progressive disease
14	inferiorly 1mm	28	present	radiotherapy + chemotherapy	6/6/2019	14/7/19	33	cisplatin	50mg	4	orocutaneous fistula	28/12/19	unstable	absent	LYMPH NODE METASTASIS	absent	lymphovascular spread	extranodal spread, close margin, lymphovascular spread
15	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	9/6/2019	14/7/19	32	cisplatin	55mg	4	NONE	20/1/20	unstable	PRESENT	absent	absent	progressive disease	progressive disease
16	superiorly 6mm	18	none	radiotherapy	20/6/19	28/7/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	14/2/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
17	superiorly 10mm	24	none	radiotherapy	20/6/19	28/7/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	31/1/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
18	superiorly 5mm	20	none	radiotherapy	28/6/19	1/8/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	2/2/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
19	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	24/6/19	31/7/19	32	cisplatin	50mg	4	NONE	DIED	DIED	DIED	DIED	DIED	DIED	DIED
20	superiorly 8mm	18	none	radiotherapy	1/7/2019	6/8/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	10/1/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
21	anteriorly 6mm	48	Present	radiotherapy + chemotherapy	18/7/19	26/8/19	33	cisplatin	60mg	4	Flap necrosis	12/3/2020	unstable	absent	absent	present	perineural invasion, lymphovascular spread, extranodal spread	perineural invasion, lymphovascular spread, extranodal spread
22	posteriorly 1mm	32	Present	radiotherapy + chemotherapy	28/7/19	3/9/2019	33	cisplatin	50mg	4	orocutaneous fistula	15/7/20	unstable	absent	LYMPH NODE METASTASIS	absent	extranodal spread	extranodal spread, close margin
23	superiorly 6mm	24	none	radiotherapy	20/7/19	30/8/19	34	NOT GIVEN	NOT GIVEN	NOT GIVEN	orocutaneous fistula	20/1/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
24	anteriorly 5mm	14	none	radiotherapy + chemotherapy	31/7/19	6/9/2019	33	cisplatin	50mg	5	NONE	15/5/20	unstable	absent	LYMPH NODE METASTASIS	absent	perineural invasion	perineural invasion
25	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	31/7/19	6/9/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	10/2/2020	unstable	absent	absent	present	progressive disease	NO CHEMOTHERAPY GIVEN
26	posteriorly 5mm	13	Present	radiotherapy + chemotherapy	2/8/2019	11/9/2019	33	cisplatin	50mg	5	NONE	20/7/20	unstable	PRESENT	absent	absent	extranodal spread	extranodal spread
27	superiorly 3mm	32	none	radiotherapy + chemotherapy	6/8/2019	14/9/19	33	cisplatin	60mg	4	NONE	6/6/2020	unstable	absent	absent	present	close margin	close margin
28	inferiorly 5mm	12	none	radiotherapy	6/8/2019	14/9/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	28/5/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
29	superiorly 3mm	25	Present	radiotherapy + chemotherapy	14/8/19	21/9/19	34	cisplatin	60mg	5	orocutaneous fistula	14/3/20	unstable	absent	absent	present	lymphovascular spread	lymphovascular spread, extranodal spread, close margin
30	superiorly 5mm	12	none	radiotherapy	14/8/19	21/9/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	12/2/2020	unstable	absent	absent	present	close margin	NO CHEMOTHERAPY GIVEN
31	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	20/8/19	28/9/19	34	cisplatin	55mg	5	NONE	14/3/20	unstable	absent	absent	present	progressive disease	NO CHEMOTHERAPY GIVEN
32	posteriorly 5mm	11	none	radiotherapy	4/9/2019	10/10/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE		stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
33	posteriorly 3mm	9	present	radiotherapy + chemotherapy	12/9/2019	18/10/19	34	cisplatin	60mg	5	Flap necrosis	15/7/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
34	posteriorly 5mm	29	present	radiotherapy + chemotherapy	30/8/19	5/10/2019	34	cisplatin	60mg	5	NONE	6/6/2020	unstable	PRESENT	absent	absent	extranodal spread	extranodal spread
35	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	1/10/2019	7/11/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	DIED	DIED	DIED	DIED	DIED	DIED	DIED
36	superiorly 5mm	14	none	radiotherapy	26/9/19	2/11/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	3/3/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
37	anteriorly 6mm	18	none	radiotherapy	30/9/19	7/11/2019	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	10/8/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
38	superiorly 4mm	20	None	radiotherapy + chemotherapy	30/9/19	7/11/2019	33	cisplatin	50mg	4	NONE	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up
39	anteriorly 6mm	12	None	radiotherapy	4/10/2019	12/11/2019	32	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	24/2/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
40	anteriorly 8mm	16	None	radiotherapy	8/10/2019	16/11/19	32	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	13/3/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
41	posteriorly 10mm	27	None	radiotherapy	22/10/19	30/11/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	orocutaneous fistula	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up	lost to follow up
42	superiorly 5mm	14	None	radiotherapy	15/10/19	24/11/19	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	15/5/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
43	anteriorly 6mm	16	None	radiotherapy	31/10/19	4/12/2020	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	31/5/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
44	superiorly 5mm	14	None	radiotherapy	22/11/19	28/12/19	32	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	16/7/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
45	NOT OPERATED	NOT OPERATED	NOT OPERATED	radiotherapy + chemotherapy	28/11/19	2/1/2020	33	cisplatin	55mg	4	NONE	4/8/2020	unstable	absent	absent	present	progressive disease	progressive disease
46	posteriorly5mm	18	present	radiotherapy + chemotherapy	28/11/19	2/1/2020	33	cisplatin	50mg	5	NONE	15/6/20	unstable	absent	absent	present	extranodal spread	extranodal spread
47	superiorly 4mm	21	None	radiotherapy + chemotherapy	14/12/19	21/1/20	33	cisplatin	50mg	4	orocutaneous fistula	10/5/2020	unstable	absent	LYMPH NODE METASTASIS	absent	close margins	close margins
48	superiorly 4mm	42	present	radiotherapy + chemotherapy	10/12/2019	15/1/20	34	cisplatin	60mg	4	NONE	15/6/20	unstable	PRESENT	absent	absent	extranodal spread	extranodal spread

S No.	name	UHID	age/sex	date of admission	date of surgery	biopsy	tumor site	ryct +/-	date of last ryct	radiological dimensions	response to NACT	Post 2 cycle NACT radiological dimension	surgery	surgical findings	dimension of lesion	skin involvement	bone involvement	perineural involvement	lymphovascular spread	depth of invasion	closest margin	no. of lymph nodes	extranodal spread	adjuvant treatment	radiotherapy start date	radiotherapy end date	fraction	chemotherapy given	dose	cycles of chemo	complications	date of last follow up	status at last follow up	local recurrence	regional recurrence	loc.reg&out recurrence	reason for recurrence	reason for chemotherapy
49	VENKATASWARY	780245	60/M	20/9/19	7/11/2019	8gyrt	Right Buccal mucosa	NOT GIVEN	15/10/19	5.6x4.1x2.8	partial	4.5x3.2x2.1	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	3.8x2.6x1.4	absent	Present	None	None	6mm	None	18	None	radiotherapy	10/12/2019	15/1/20	34	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	20/7/20	unstable	13/8/20	NAD	close margins, extranodal spread	extranodal spread
50	PILLAMMA	783082	50/F	31/10/19	19/11/19	14yrs	Left Buccal mucosa	NOT GIVEN	NONE	5.5x4.3.2	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	5.2x3.8x3	Present	Present	Present	Present	2mm	Present	17	present	radiotherapy + chemotherapy	2/1/2020	9/2/2020	34	NOT GIVEN	55mg	4	Flap necrosis	13/8/20	unstable	absent	absent	absent	DIED	close margins, extranodal spread
51	PARVATHAMMA	783246	50/F	12/10/2019	21/11/19	8gyrt	Left Lower Alveolus	NOT GIVEN	10/11/2019	4.2x2.6x1.6	progressive	4.5x3.2x2.1	CR+ITF clearance +HM+PM/MC	Intratemporal extent	4.1x2.6x1.8	Present	Present	Present	present	8mm	Present	18	present	radiotherapy + chemotherapy	20/1/20	26/2/20	33	cisplatin	55mg	4	Flap necrosis	DIED	DIED	DIED	DIED	DIED	DIED	DIED
52	LAKSHMAMMA	786325	60/F	1/1/2019	21/11/19	14yrs	Right Buccal mucosa	NOT GIVEN	NONE	4.2x2.4x2.6	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	3.5x2x2.1	Present	Present	Present	6MM	None	None	24	None	radiotherapy + chemotherapy				NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	DIED	DIED	DIED	DIED	DIED	DIED	DIED
53	NARAYAMMA	787789	50/F	12/10/2019	28/11/19	14yrs	Left Buccal mucosa	NOT GIVEN	14/11/19	4.2x2.7x1.9	partial	3.6x2.1x2.6	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	3.1x1.6x2.1	absent	Present	Present	None	6mm	None	21	None	radiotherapy	6/1/2020	12/2/2020	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	20/9/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
54	RATNHAMMA	786516	48/F	18/11/19	3/12/2019	14yrs	Right Buccal mucosa	NOT GIVEN	NONE	4.5x4.6x3	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	4.1x3.2x2.5	Present	Present	Present	None	4mm	None	11	present	radiotherapy + chemotherapy	8/1/2020	14/2/20	33	cisplatin	50mg	4	NONE	24/8/20	stable	absent	absent	LYMPH NODE METASTASIS	NAD	NO CHEMOTHERAPY GIVEN
55	VENKATAMMA	758962	60/F	30/10/19	26/11/19	8gyrt	Right Buccal mucosa	NOT GIVEN	8/12/2019	4x3.5x2.5	stable	3.6x3.1x2.1	CR+ITF clearance +HM+PM/MC	Intratemporal extent	3x2.5x1.5	Present	Present	Present	None	8mm	None	7	present	radiotherapy + chemotherapy	15/2/20	22/2/20	33	cisplatin	50mg	4	orocutaneous fistula			absent	LYMPH NODE METASTASIS	NAD	NO CHEMOTHERAPY GIVEN
56	CHANDRAMMA	792154	54/F	6/12/2019	31/12/19	14yrs	Left Buccal mucosa	NOT GIVEN	NONE	4.5x3.8x3	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	4x3.2x2.5	Present	Present	Present	None	7mm	None	18	None	radiotherapy	1/2/2020	8/3/2020	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	NONE	24/9/20	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
57	JAYALAKSHMAMMA	803043	54/F	5/11/2019	2/1/2020	8gyrt	Right Buccal mucosa	NOT GIVEN	15/12/19	5.9x4.7x4	partial	5.2x4x3.6	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	4.7x3.5x3.1	Present	Present	Present	None	9mm	None	14	None	radiotherapy	20/2/20	31/3/20	33	NOT GIVEN	NOT GIVEN	NOT GIVEN	orocutaneous fistula	4/9/2020	unstable	absent	absent	absent	present	close margins
58	KRISHNAMMA	799562	76/F	14/12/19	7/1/2020	14yrs	Left Lower Alveolus	NOT GIVEN	NONE	3.6x4.1x1.5	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	3x3.6x1	Present	Present	None	None	10mm	None	16	None	radiotherapy + chemotherapy	20/2/20	31/3/20	33	cisplatin	50mg	4	orocutaneous fistula	6/10/2020	unstable	PRESENT	absent	absent	absent	close margins, depth of invasion >1cm
59	RAGHUNATH	809355	55/M	16/11/19	9/1/2020	8gyrt	Left Buccal mucosa	given	21/12/19	4.4x4x2.8	stable	4.2x3.6x2.5	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	3.6x3x2.5	absent	Present	None	None	8mm	None	21	None	radiotherapy	1/1/2020	8/4/2020	32	NOT GIVEN	50mg	4	NONE	9/10/2020	stable	absent	absent	absent	NAD	NO CHEMOTHERAPY GIVEN
60	SANJAPPA	806140	65/M	3/1/2020	9/1/2020	14yrs	Right Buccal mucosa	NOT GIVEN	NONE	4.5x3.5x2.5	NOT GIVEN	NONE	WE+HM+PM/MC	NO INFRATEMPORAL EXTENSION	4x3x2	Present	Present	Present	None	8mm	None	16	present	radiotherapy + chemotherapy	5/3/2020	13/4/20	34	cisplatin	60mg	5	orocutaneous fistula	9/8/2020	unstable	absent	absent	absent	present	close margin	extranodal spread, close margin