COMPARISON OF EFFICACY OF POSTOPERATIVE RADIOTHERAPY AND CHEMO-RADIOTHERAPY IN LOCALLY ADVANCED ORAL CARCINOMA (T3 AND T4A)

By

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In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY IN OTORHINOLARYNGOLOGY

Under the guidance of

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LIST OF ABBREVIATIONS

EORTC	⇨	European Organisation for Research and Treatment of Cancer
RTOG	⇨	Radiation Therapy Oncology Group
RCT	⇨	Randomized Control Trail
LET	⇨	Linear energy transfer
NHEJ	⇨	Non Homologous End Joining
HRR	⇨	Homologous Recombinant Repair
SDR	⇨	Single dose radiation
OER	⇨	Oxygen enhancement ratio
3D-CRT	⇨	Three-Dimensional Conformal Radiation Therapy
IMRT	⇨	Intensity-Modulated Radiation Therapy
IG-IMRT	⇨	Image-guided intensity-modulated radiotherapy
HDR	⇨	High-Dose Rate
MDR	⇨	Medium-Dose Rate
LDR	⇨	Low-dose rate
PDR	⇨	Pulsed-dose rate
5FU	⇨	5 Fluorouracil
BSA	⇨	Body Surface Area

TS ⇨ Thymidylate synthase

DPD ⇨ Dihydropyrimidine dehydrogenase

ABSTRACT

Background:

Most of the guidelines regarding the head and neck oncology state that resection of tumour is definitive treatment for locally advanced oral carcinoma regardless of the lymph node status. And in post operatively adjuvant radiotherapy or Chemoradiation is to be given within 6 to 8 weeks to improve chances of locoregional control. However, in achieving locoregional control, there are lacunae in knowledge on whether Chemoradiotherapy or Radiotherapy alone should be given post operatively and some studies done in Europe state that Chemoradiation gives better results in these patients.

Objectives:

To perform composite resection of the tumour in locally advanced oral carcinoma patients (T_3 and T_{4a}) and to randomize these postoperative patients and compare the efficacy and safety of Radiotherapy and Chemotherapy with Radiotherapy in them

Methods:

Patients with T_3 and T_{4a} stage oral carcinoma, after composite resection were randomized into two groups post operatively and either Chemoradiotherapy or Radiotherapy alone were given according to their group. Locoregional Recurrence, Overall Survival Rate, disease free survival rate and adverse events were documented and compared.

Results: The various adverse effects noted in the study include Mucositis, Agranulocytosis, Moist Desquamation, Fever, Nausea/Vomiting, Pneumonia, Elevated Serum Creatinine, Trismus, Osteoradionecrosis and Toxicity related treatment delay. There were no treatment related deaths encountered in the study. Trismus and Mucositis is most commonly encountered adverse effects. About 23.3% (7) of patients in radiotherapy group developed trismus and 33.3% (10) of patients in Chemoradiotherapy group developed trismus. The grade of trismus is also more in chemo radiotherapy group compared to radiotherapy group. There were total 8 Recurrences noted in the study at various follow up times. 16.7% (5) of patients in radiotherapy group had locoregional recurrence compared to 10% (3) patients in Chemoradiation group

Conclusion:

Addition of chemotherapy (Cisplatin 100mg/m2 BSA once in 3 weeks) to post op adjuvant radiotherapy improves locoregional control in patients with adverse factors on histopathological examination of specimen like multiple lymph nodes showing metastasis, metastatic Lymph Node more than 3cm in diameter, perineural invasion and T4a ¬disease due to skin or bone involvement.

The complications encountered in patients receiving post-operative chemotherapy with radiotherapy compared to post-operative radiotherapy alone were almost similar. However significant agranulocytosis can occur in some patients receiving post-operative chemotherapy with radiotherapy and severity of trismus and mucositis in patients receiving post-operative chemotherapy with radiotherapy is more than their counterparts receiving post-operative radiotherapy alone.

KEYWORDS:

Buccal mucosa carcinoma, Locally Advanced, Post-Operative, Radiotherapy, Chemotherapy.

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INTRODUCTION

INTRODUCTION

Oral Carcinomas are very common in Kolar region.[1] There are many studies on advanced stage of oral Carcinoma and protocols in treating them. National Comprehensive cancer Network NCCN Guidelines state that all patients with T3 and T4a should undergo primary tumour resection with ipsilateral or bilateral neck dissection depending on extent of primary tumour. Majority of these patients receive post-operative Radiotherapy. In case of extracapsular spread from lymph nodes or positive margins of resection, Chemoradiotherapy is preferred. In the literature post-operative Chemoradiotherapy gives 10-15% better locoregional control compared to post-operative radiotherapy alone, but increases morbidity. There is a lacuna in the knowledge on whether post-operative Chemoradiotherapy benefits a patient with locally advanced oral Carcinoma, when there are no positive margins or extracapsular spread and Indian literature is inadequate. We would like to find out whether post-operative Chemoradiotherapy would improve locoregional control in patients with locally advanced oral Carcinoma and whether it increases morbidity in these patients when compared to post-operative radiotherapy alone.

REVIEW OF LITERATURE

Review of Literature

In 1992, intergroup study stated that the locoregional control is good with adjuvant chemo-radiotherapy.[2] In 1996, a study was reported on the results of their RCT that concomitant use of 50 mg weekly Cisplatin infusion in addition to post-operative radiotherapy improved loco-regional control and survival without significant increase of late radiation complications.[3]Two more studies also reported similar results, but with Mitomycin C and bleomycin.[4,5] Later many studies have been done and Chemoradiotherapy is included in various guidelines for the head and neck surgery, especially in locally advanced oral cancers with positive margins and extracapsular spread. Later many studies were conducted by RTOG and EORTC, which included two land mark studies and concluded that Chemoradiotherapy is superior in giving locoregional control, overall survival and Disease free survival.[6,7,8] In 2004, it was found that Chemoradiotherapy in these patients give a 10 – 15% better locoregional control, but has more morbidity compared to Radiotherapy alone.[9] In 2005, EORTC and RTOG conducted studies on locally advanced oral cancer and found that Chemotherapy when combined with radiotherapy in post-operative cases gave a very good control in containing the disease.[10,11] The control was even better in HPV/p16 positive cases.[12] But Chemoradiotherapy is associated with more morbidity compared to radiation alone in these patients.[10, 13] Similar results were replicated in a German study.[14] EORTC and another RCT has reported almost equivalent toxicity with radiation alone, but RTOG reported more toxicity.[8, 15] Though many platinums came, cisplatin gave better results as an adjuvant agent.[16] After a meta-analysis of both their data, oncology groups had come to a consensus that extracapsular spread and Positive margins are a definitive indications for Chemoradiation.[8, 17] But a grey area was still remaining as other papers identifying locoregional control, vascular invasion, perineural invasion, and advanced T stage also as various other indications.[18, 19]

A recent retrospective study done in Taiwan with similar inclusion and exclusion criteria as our study has concluded that multiple lymph node metastasis patients had a better outcome with Concurrent Chemoradiation with respect overall survival and recurrence.[18]

Osteoradionecrosis risk is not associated with the number of fractions patient receives but is associated with the dose of radiation patient receives per fraction [20] and Xerostomia appears to be a long-term complication of radiotherapy.[21] Old age, Advanced T stage and larynx-pharynx are identified as independent risk factors for severe late toxicities due to concurrent Chemoradiotherapy by a study that analyzed the patients from various RTOG studies.[22]

ANATOMY AND PATHOLOGY

Anatomy of Oral Cavity:

Development:[23]

The primitive oral cavity or *stomatodaeum* is seen as a slit-like space in the embryo of 4-weeks. A thin septum is present between the stomatodaeum and the foregut called *buccopharyngeal membrane.* It later breaks down making oral cavity continuous with the pharynx. Mesodermal condensations occur in the lateral wall and floor of the pharynx which gives rise to the branchial arches. These arches on differentiation, form cartilages, muscles and an arch artery. Each arch receives both afferent and efferent nerve supply, the skin, muscles and the endodermal lining of the arch concerned. There are two branches - The branch coming from same arch, *post-trematic branch and from succeeding arch, pretrematic branch.*

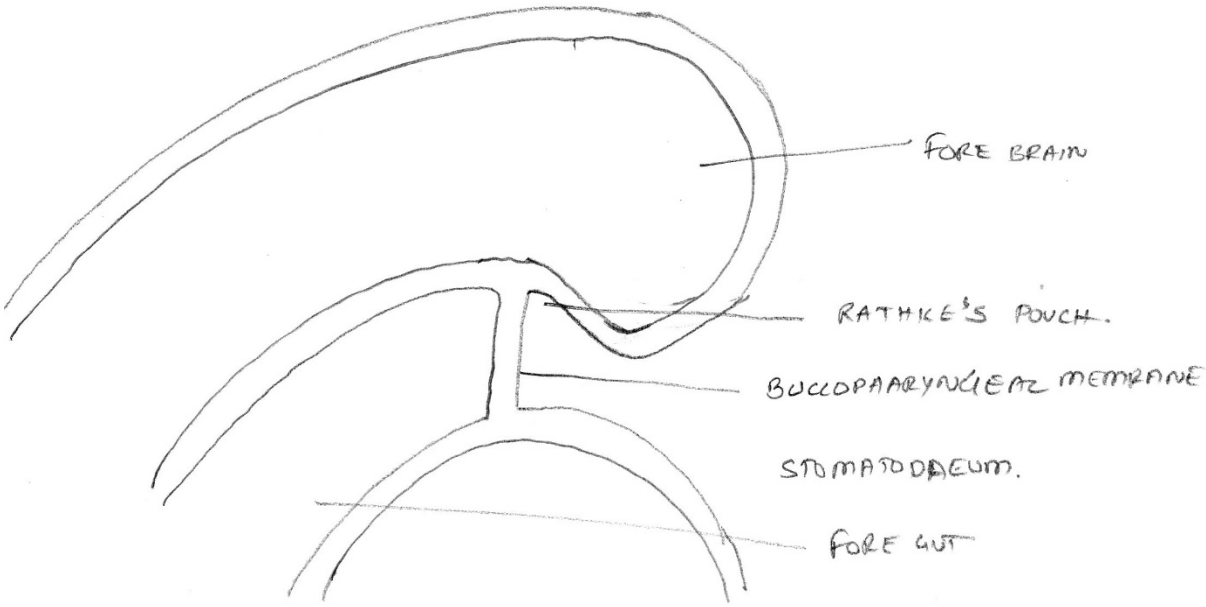


Illustration 01 - Sagittal section of human embryo showing early development of oral cavity

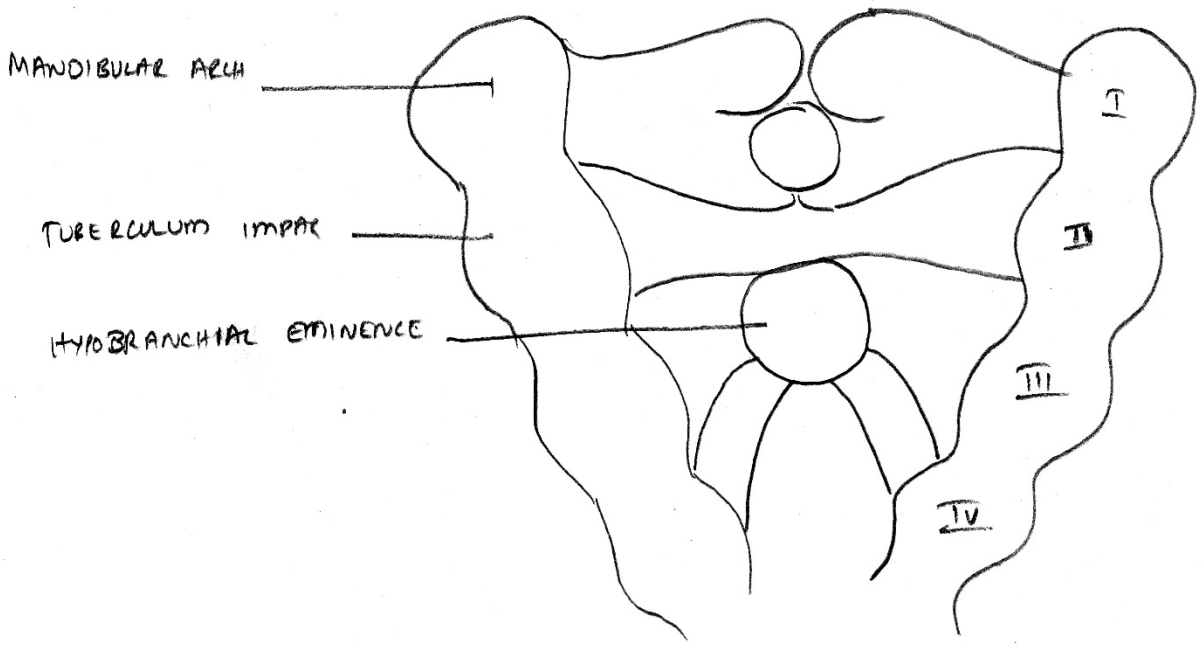


Illustration 02: Development of the tongue. Floor of the mouth in 9-mm fetus

Lateral aspect of the developing head gives rise to two mandibular processes which unite in the midline by the sixth week of embryonic life and forms the tissue of the lower jaw. From the mandibular process, Maxillary processes develop as buds, and grow forward on each side and fuse with the lower ends of the descending nasal processes. Primary palate is formed by fusion of the maxillary processes. It separates the primitive nasal cavity and primitive oral cavity. Following the descent of the developing tongue inwardly directed extensions of maxillary process fuse to form secondary palate and the tissues of nasal septum.

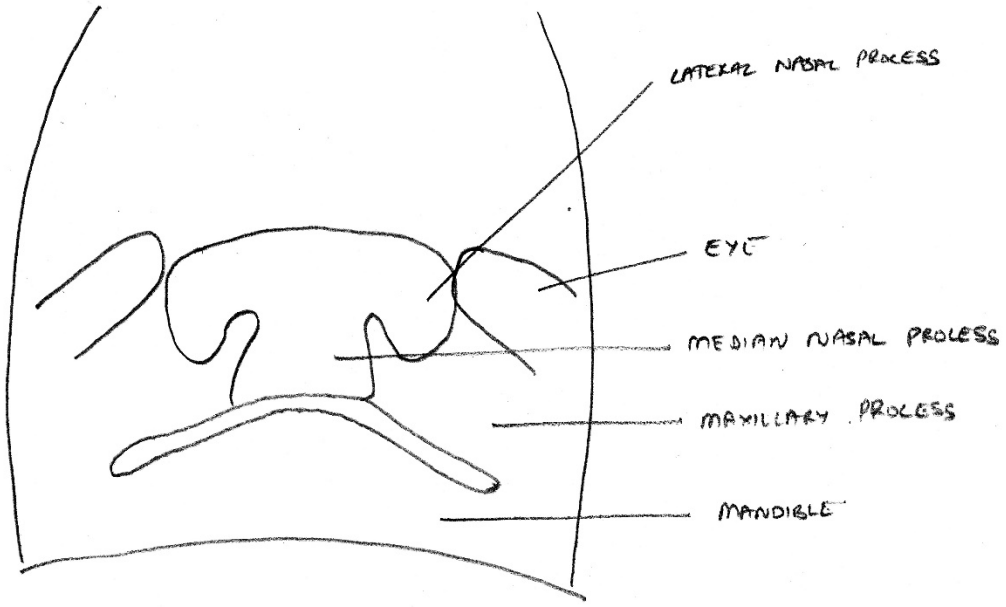


Illustration 03: Development of the face in 7-week-old fetus

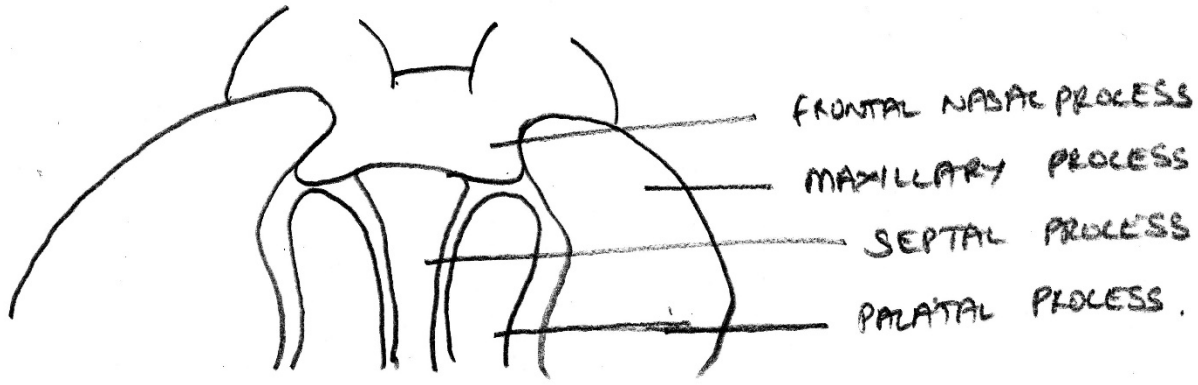


Illustration 04: View from below of developing palate in 6- week-old embryo

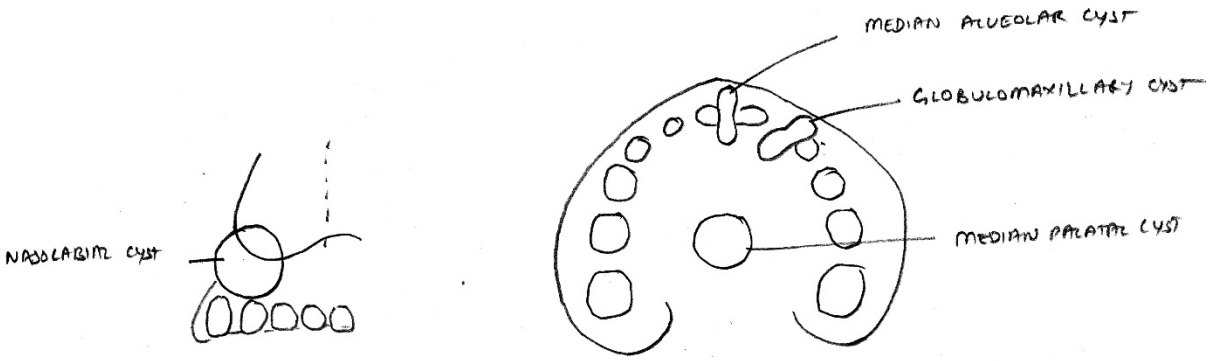


Illustration 05 and 06: Developmental cysts of the maxilla

The anterior part of tongue arises from paired eminences of the mandibular arches and the tuberculum impar, a midline structure, in the floor of the mouth. The posterior part of tongue is formed by the *hypobranchial eminence* of the third visceral arch. *Hypobranchial eminence* becomes continuous with the anterior part of the tongue by growing forward over the second. Just posterior to the site of fusion of the anterior and posterior parts the V-shaped *sulcus terminalis* is found. The tongue, partly, is in the nasal cavity during the early stages of development. Delay in its descent impedes the fusion of the palatal folds and the result is formation of palatal clefts.

Lips:[24]

The lips are made of the orbicularis oris muscle with skin on the outer surface and mucous membrane on the inner surface. The transitional area of skin to mucous membrane is called lip vermilion. Labial artery, a branch of the facial artery gives the blood supply. The motor nerve sypply is given by branches of the seventh cranial nerve and the sensory nerve supply by infraorbital branch of the fifth cranial nerve (V 2) to the upper lip, and the mental nerve (V 3) to the lower lip.

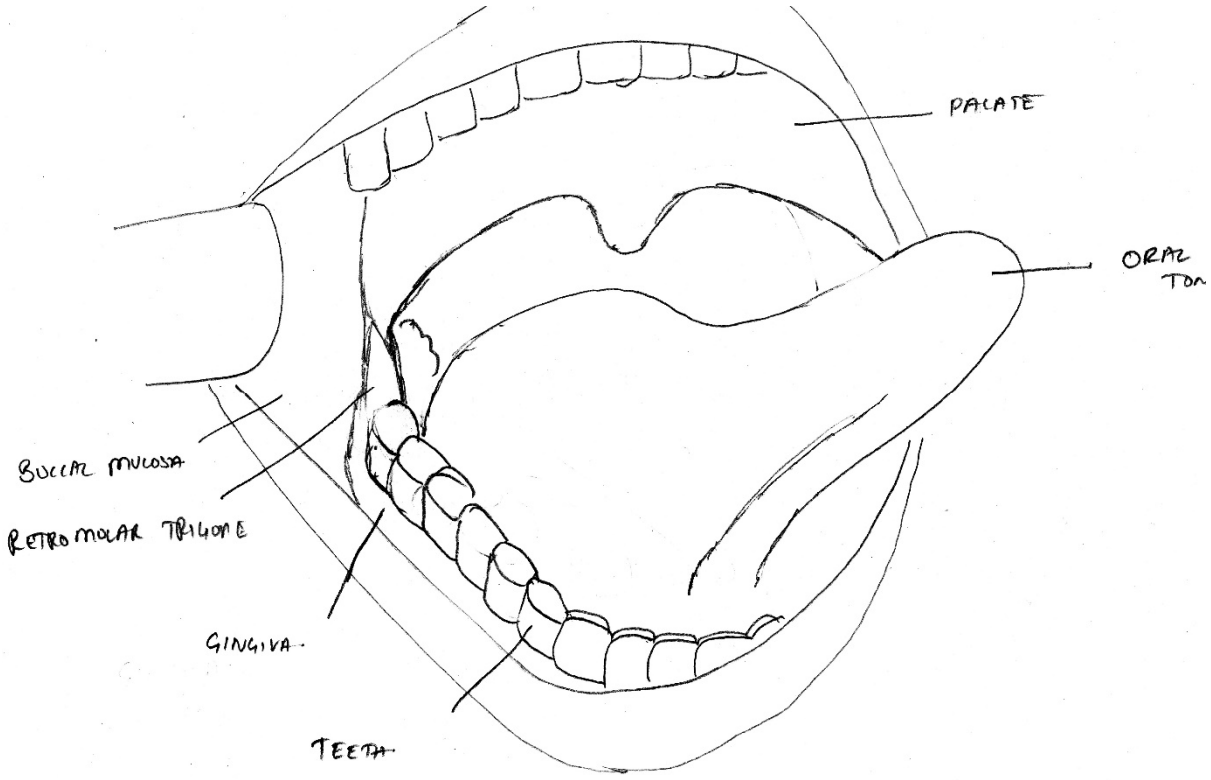


Illustration 07: Anatomy of Oral Cavity

Floor of Mouth:[24]

The U-shaped area bounded by the lower gum and oral tongue from the point of insertion of one anterior tonsillar pillar into the tongue to other is the floor of mouth. Just below the mucous membrane lie two sublingual glands separated by paired genioglossus and geniohyoid muscles. Genioglossus and geniohyoid muscles get inserted into the bony protuberances called genial tubercles at mental symphysis. The muscular floor is formed by mylohyoid muscle which arises from the mylohyoid ridge of the mandible and ends at the level of the third molars posteriorly. Between the mandible and the insertion of the mylohyoid on the external surface of the mylohyoid lies the submandibular gland. Its duct, Wharton's duct, traverses between the sublingual gland and the genioglossus muscle to exit in the anterior part of the floor of the mouth paramedially. It is about 5cm in length.

Tongue (Oral Part): Tongue can be divided as anterior 2/3rd (oral) and posterior 1/3rd (oropharyngeal).

The circumvallate papillae mark the division between oral tongue and oropharyngeal (base) of tongue. The arterial supply is mainly given by paired lingual arteries that are branches of the external carotid. The sensory innervation is given by the lingual nerve to the Gasserian ganglion (anterior 2/3) and Glossopharyngeal Nerve (Posterior 1/3).

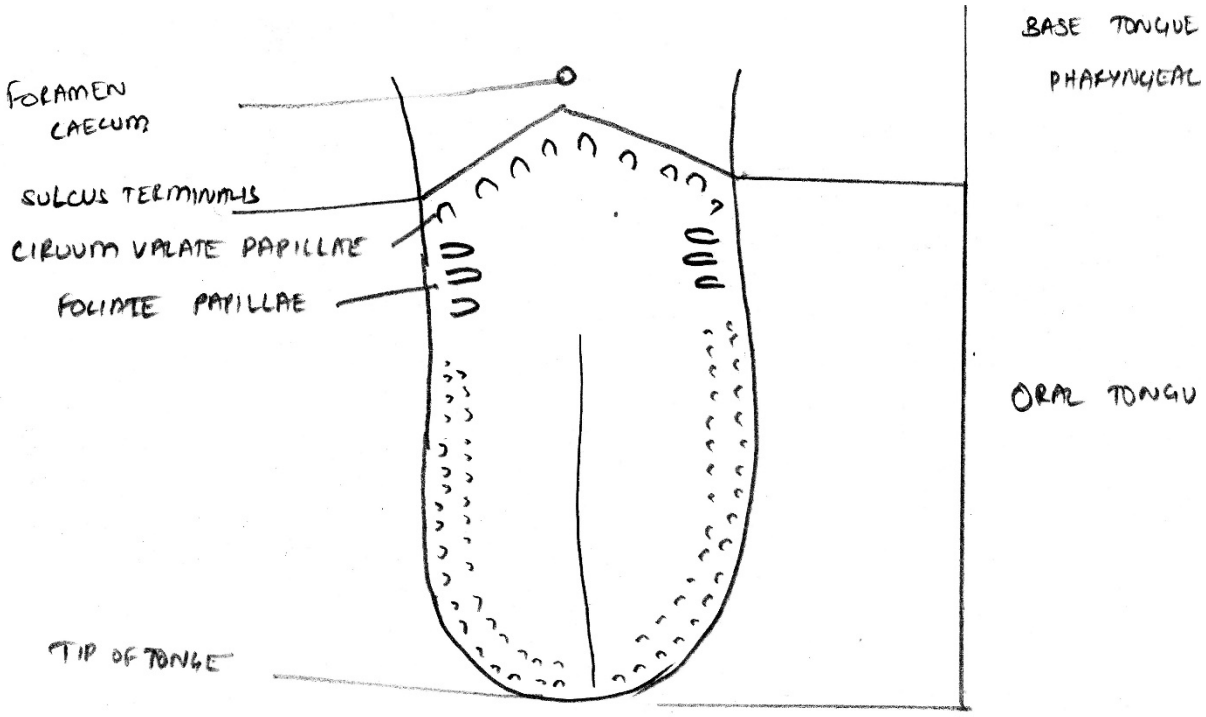


Illustration 08: Anatomy of tongue

Buccal Mucosa:[24]

It is the mucous membrane covering the inner surface of the lips and cheeks, extending from gingiva both above and below, anteriorly from vermilion to retromolar trigone posteriorly. Opposite to second upper molar on either side parotid duct opens. Mandibular nerve branches give sensory innervation to the buccal mucosa and a part of the cheek skin.

Gingiva and Hard Palate:[24]

The lower gingiva is made of keratinized mucosa covering the mandible extending from gingivobuccal sulcus to the starting of nonkeratinized mucosa of the floor of mouth.

The retromolar trigone: The triangular area behind the third molar tooth bounded by maxillary tuberosity superiorly, Anterior tonsillar pillar medially, buccal mucosa laterally and Third molar tooth inferiorly. It is covered by keratinized mucosa. It has tendinous pterygomandibular raphe, attached to the pterygoid hamulus and the posterior mylohyoid ridge of the mandible where buccinator, orbicular oris, and superior pharyngeal constrictor muscles get inserted. Pterygomandibular space is a space present just behind the pterygomandibular raphe, between the medial pterygoid muscle and the ascending ramus posterior to the deep lobe of the parotid and the parapharyngeal space. It contains lingual and dental nerves. In contrast to rest of oral mucosa, mucosa of alveolar ridges has no minor salivary glands.

ORAL CANCER

Pathology:

Most common malignancy seen in oral cavity is Squamous Cell Carcinoma. Leukoplakia and Carcinoma in Situ are also the common lesions in Oral Cavity. In addition to these Basal cell carcinomas and Keratoacanthoma occur on the skin surface of the lips. Minor salivary gland tumors are seen in the floor of mouth and upper alveolar ridge. In upper alveolar ridge adenoid cysctic carcinomas are common.[25]

Epidemology:

Cancer remains a major cause of both morbidity and mortality in the whole world with an estimated nine million new cases detected every year, of which oral cancers contribute to about 4lakh new cases ever year with 2/3rd occurring from developing countries. India, Sri Lanka, Bangladesh and Pakistan together make up to 30% of the newly detected oral cancer cases and men being commonly affected.[26] In India, every year about 7lakh people are newly being diagnosed with cancer and about 3.5 lakh are dying due to cancer.[27] Kidwai memorial institute of oncology in Bangalore, Karnataka has reported that every year an average of 5 thousand patients are getting registered in their cancer registry.[28] Head and Neck cancers account for more than 30% of all cancers in India and 40 to 50% of them are oral cancers and with an age adjusted rate of 20 per 1,00,000 population.[29] Here buccal mucosa is most commonly affected in contrast to the western countries where tongue and floor of mouth cancers predominate among oral cancers.[30] About 40% of oral cancers in south east Asia are of buccal mucosa.[31] Most of these cases occur in patients who are above 50 years age, but it is affecting younger patients of late in the developing countries due to the tobacco chewing habits. In India, males are almost four times more affected. Among oral cancers 18-33% are Floor of mouth cancers occurring more in men in 60s and 70s. Tongue cancers account for

22-39% of oral cancers occurring in more than 40yrs of age and male - female ratio is reducing for tongue cancers.[31]

Retromolar trigone accounts for 6 - 7% of oral cancers and is more common in males than females. Incidence of Maxillary (upper) alveolus cancer is 3.5 - 6.5% & hard palate is 1 - 3%. Hard palate cancers in contrast to other Oral cancers are seen more in females and is more due to reverse smoking habit. Mandibular cancers are about 7.5 - 17.5 % of all oral cancers. Ratio for mandibular: maxillary alveolus cancers is about 3:1.[31]

Etiology:

Exact cause is still not known. But various risk factors have been identified.

Tobacco is consumed in form smoking and in form chewing.

Smoking: Cigarettes, Cigars, Beedi, tobacco powder in pipes and Hookah are the various forms of smoking tobacco. Reverse smoking is the term used when tobacco is smoked by keeping the burning end inside the oral cavity. Repeated thermal injury and the Chemical carcinogens are the risk factors that cause cancer. The number of cigarettes smoked per day and the duration of smoking directly influence the risk involved. The risk increases with the increase in the number of cigarettes smoked and the total number of years smoked. The commonest forms used to smoke are cigarettes and beedi. Among them beedi poses more harm as it contains high content and more toxic agents like carbon monoxide, ammonia, hydrogen cyanide, phenol and carcinogenic hydrocarbons.

Chewing: Raw tobacco, processed mixtures and pyrolised forms of tobacco are used to chew. The raw tobacco is used with lime and areca nut. Freshly powdered tobacco mixed with slaked lime is called Khaini. This mixture is kept in lower gingivolabial sulcus in form of

quid for hours together and sucked. This causes khaini cancer (squamous cell carcinoma of the lower lip) and lower alveolar cancer. An oral quid made of betel leaf wrapped around areca nut, quick lime and tobacco is also used. It acts as a risk factor for causing squamous cell carcinoma of the sites where it is usually kept. Zarda, Gutkha, and Manipuri tobacco are various forms of processed tobacco. The pyrolised (roasted) forms of tobacco include mishri, bajjar, etc. Some even use snuff orally in specific areas.[32] When this chewing habit is combined with the smoking habit, the risk increases by 20 to 30 times.

Photo – 01: Cigarette and Beedi

Photo – 02: Tobacco leaf unprocessed with arrack nuts

Photo – 03: Unprocessed chewing tobacco

Photo – 04: Chewing tobacco with lime

Photo – 05: Khaini (Processed form of chewing tobacco)

Alcohol Consumption: Alcohol has a synergistic local effect by dissolving the carcinogens and help in their absorption in the sump area of the mouth. It also has a systemic negative effect on the immune system as most alcoholics have nutritional deficiency.[33]

Genetic factors: - Most sporadic tumors are caused by accumulated genetic mutations that are a result of multi-step process. These mutations results in loss of chromosomal heterozygosity, leading to a series of events that progresses into squamous cell carcinoma. The clinical and microscopic pathology from hyperplasia to invasiveness of the tumor are a result of these genetic mutations. Changes in expression p53 and other genes may predispose to cancer development and recurrence. p16 mutation causes cancer and its overexpression indicates good prognosis. c-erbB-2 overexpression shows correlation with nodal disease, metastasis and has poor prognosis. Xeroderma pigmentosum, Fanconi's anemia and Ataxic telangiectasia are some of the syndromes characterized by mutagen sensitivity, and all have been associated with oral cancers.[34] Ability to induce cytochrome p450 enzyme ecosystem is another good genetic marker.[35]

Other risk factors include spice rich diet, Occupation in carcinogenic environment like textile industry, Low cell mediated immunity, Viruses like Herpes Simplex and Human Papilloma Viruses (especially type 16)n, Syphilis, Sepsis due to dental infections, consumption of pot distilled spirits and chronic irritation by sharp tooth.

Tumor Biology:

The development of a tumor involves three phases:

a) Initiation

b) Promotion

c) Progression

The initiation phase: Series of mutations that occur in sequence that can lead to tumor genesis characterizes this stage.

The Promotion Phase: Exposures to promoting agents or conditions leads the initiated cells to become tumor cells, are required. This leads to the appearance of the abnormal cells are called preneoplastic or premalignant cells. The appearance of the first neoplastic cells indicate the end of the promotion phase.

The progression phase: The transformed cells show invasive growth and progression to form a tumor lesion and further into a highly metastatic tumor in this phase.[36]

Tumor Escape Pathways:[36]

Tumor related:

a) inadequate immunosensitivity

1) Tumor-specific antigens are not expressed

2) Low expression of major histocompatibility complex molecules in relation with tumor aggressiveness and metastatic potential

3) Masked/modulated antigen presention or processing

4) Resistance to cell-mediated immunity. Cell-mediated immunity kills tumor cells by processes like induction of apoptosis via apoptosis-inducing molecule F_{as}

b) Tumor is not immunogenic

1) Lack of co-stimulatory molecules, and hence no induction of any immune response

2) Secretion of immunosuppressive agents that inhibit T-cell functions

3) Losing of tumor antigens that down regulate T-cell molecules

4) Induction of T-cell tolerance

5) Failure of Programmed cell death (induced by T Lymphocytes)

B) Host related:

1) Tumor growth rate too exponential for the immune system to act on.

2) Inherited or acquired immunodeficiency/immunosuppression in the patients (Infectious or Iatrogenic)

3) Deficiency in antigen presentation by antigen-presenting cells.

4) Lack of access of effector cells to the tumor

6) Expression of immunodominant antigens on parental tumor and thus prevention of stimulation by other tumor antigens

7) Long latent period of carcinogens due to the failure of antitumor immune response due to age

Carcinogenesis:[37]

The loss of the normal signaling mechanisms involved in controlled cell growth leads to the tumor formation. Loss of apoptosis (programmed cell death) in tumor cells allows the accumulation and clonal expansion of cells. If the cell death machinery were preserved and functional, these cells would have died before clonal expansion. Tumor growth is the sum of cell proliferation minus cell death. Carcinogenesis as explained earlier in tumor biology involves DNA damage and the progression of mutated cells through the cell cycle via various phases. It is found that around 6-10 independent mutations are needed for the formation of

head and neck tumors. Overexpression or underexpression due to these mutations cause increased mitogenic receptors, loss of tumor suppressor proteins and expression of oncogene-derived proteins. These in turn inhibit apoptosis and increased production of proteins that derive the cell cycle. Genetic mutation occurring at 9p, 3p, 11 q, 8p, and 17p region are found to be carcinogenic. In smokers, rate of p53, p16 mutation is high, which cause oral cancer and high rate of recurrence post treatment.

Staging:

TNM:

American Joint Committee on Cancer 2010 TNM Staging[38]

Tumor staging:

T_x- Primary tumor can't be assessed.

T_0- No evidence of primary tumor

T_{is}- Carcinoma In Situ

T_1- Tumor < 2cm in its greatest dimension

T_2- Tumor > 2cm and < 4cm in its greatest dimension

T_3- Tumor > 4cm in its greatest dimension. In gingiva/alveous, superficial erosion of bone or tooth socket is also T_3

T_{4a}- Lip, Vermilion Border – Tumor invades through cortical bone, Floor of mouth, Inferior alveolar nerve or Skin of the face

T_{4a}- Oral Cavity: Tumor invades deep muscles of tongue, cortical bone, Maxillary sinus or skin of the face

T_{4b}- Tumor invading masticator space, pterygoid plates, skull base or encases internal carotid artery.

Nodal staging:

N_x- Lymph nodes can't be assessed.

N_0- No clinically palpable Lymph nodes

N_1- Single Ipsilateral node of <3cm in its greatest dimension

N_{2a}- Single Ipsilateral node of >3cm and <6cm in its greatest dimension

N_{2b}- Multiple Ipsilateral nodes of <6cm in its greatest dimension

N_{2c}- Contralateral node of <6cm in its greatest dimension

N_3- Node of >6cm

Metastasis Staging:

M_x- Distant metastasis can't be assessed

M_0- No distant metastasis found

M_1- Distant metastasis found

American Joint Committee on Cancer 2010 Overall Stage Grouping[39]

Stage 0-	T_{is}	N_0	M_0
Stage I-	T_1	N_0	M_0
Stage II-	T_2	N_0	M_0
Stage III-	T_3	N_0	M_0
	T_{1-3}	N_1	M_0

Stage IVA-	T_{4a}	N_{0-1}	M_0
	T_{1-4a}	N_2	M_0
Stage IVB-	$_{any}T$	N_3	M_0
	T_{4b}	$_{any}N$	M_0
Stage IVC-	$_{any}T$	$_{any}N$	M_1

Histological Grade:

G_X- Grade can't be assessed

G_1- Well differentiated

G_2- Moderately differentiated

G_3- Poorly differentiated

PRINCIPLES OF CANCER TREATMENT

Principles of Cancer Treatment

Surgical Treatment for Oral Cancer:

Surgery (Wide exciscion of tumor with or without and reconstruction if required) with Post-Operative adjuvant Radiotherapy for selected patients has been the treatment of choice from past several years.[40, 41]

T_3 or T_4 tumors due to their size require facial access incisions and bony resection of the maxilla or mandible (partial or total) depending on the distance between the tumor and the bones and their involvement. 1 cm margin should be kept around the tumor while resecting[42] and in cases with skin involvement it is advisable to have up to 2 with buccinator muscle included as the deep margin, along with skin.[43] Repositioning or ligation of parotid duct is done by some surgeons.[44]

Small tumours ($T_{1/2}$) can be resected perorally or by facial access incision and can be reconstructed by primary closure, buccal fat pad, temporoparietal fascial flap or Split thickness skin grafts with silicone sheets stabilizing graft[45]. In case of a deeper defect and in cases requiring partial or total mandibular resection as in case of some T_4, Deltopectoral Myocutaneous Flap, Pectoralis major Myocutaneous Flap, Microvascular free flap reconstruction with a radial free forearm flap or anterolateral thigh flap or composite free flaps can be used.[46]. In small tumors radial free forearm flap reconstruction has shown better mouth opening postoperatively compared to local flap like buccal fat pad or split skin graft.[47]Some studies has suggested Radiotherapy as a single modality treatment for $T_{1/2}$ tumours.[48, 49] A study at Memorial Sloan Kettering showed that surgery has better prognosis.[50]

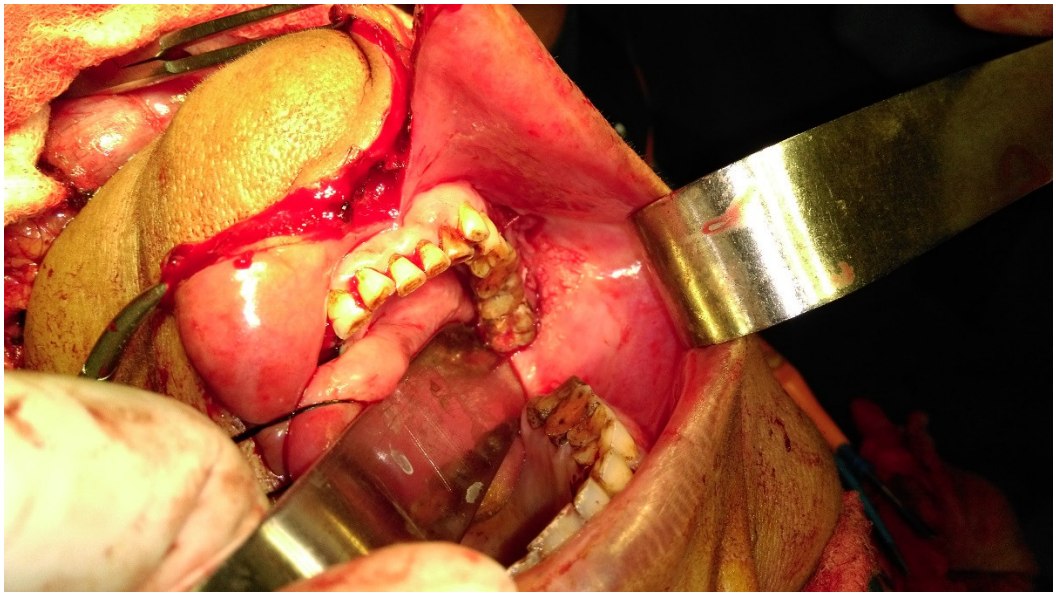


Photo - 06: Facial access flap raising in progress to excise the tumour

Neck:

Usually buccal cancers spread to level I and II lymph nodes of same side.[51, 52] Patients with clinical or radiological N_+ status should undergo comprehensive neck dissection. Selective neck dissection can be considered if nodes are present in only level 1.[53]In an N_0 neck, patients with tumors T_2 or more benefits from an elective neck dissection.[40, 54]

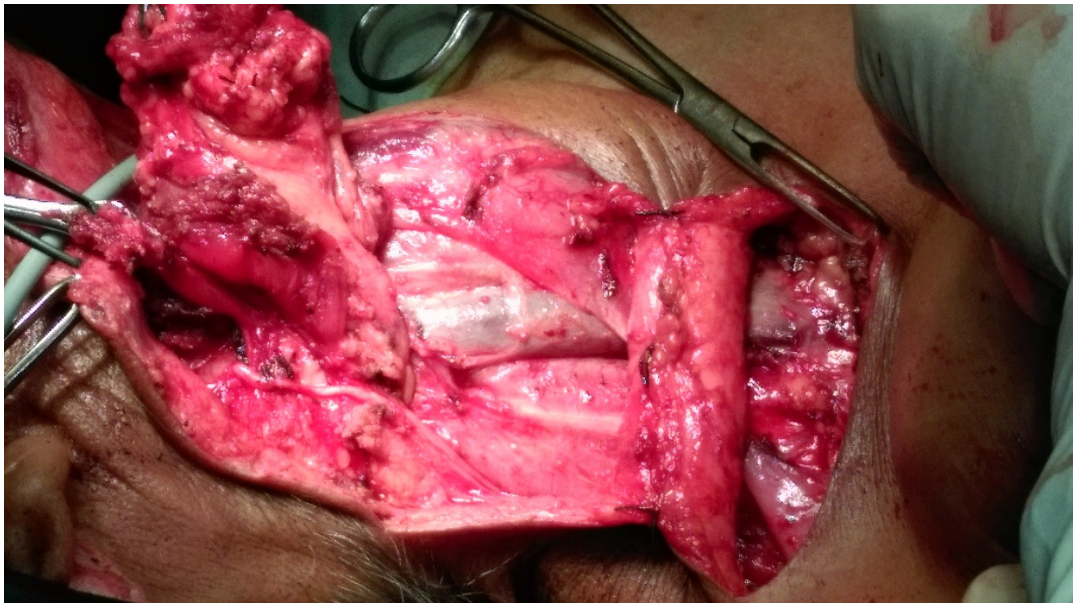


Photo - 07: Neck dissection in progress

Principles of Radiotherapy:

Radiotherapy is defined as the use ionizing radiation for the treatment of malignant and certain benign conditions.

Radiation has been available as a treatment for cancer for over 100 years. Ionizing radiation is a type of energy found within the electromagnetic spectrum (which also includes microwaves, radio waves and visible light). The goal of radiation treatment is to deliver a precisely measured lethal dose of radiation to a target (tumour) with minimal damage to the surrounding normal tissue.

Types of Radiation:

- Non Ionizing: Ultra Violet, Visible Light, Infra-Red
- Ionizing
    - Direct: Charged Particles (Protons, Neutrons and Electrons)
    - Indirect: Photons: X-rays, Gamma Rays

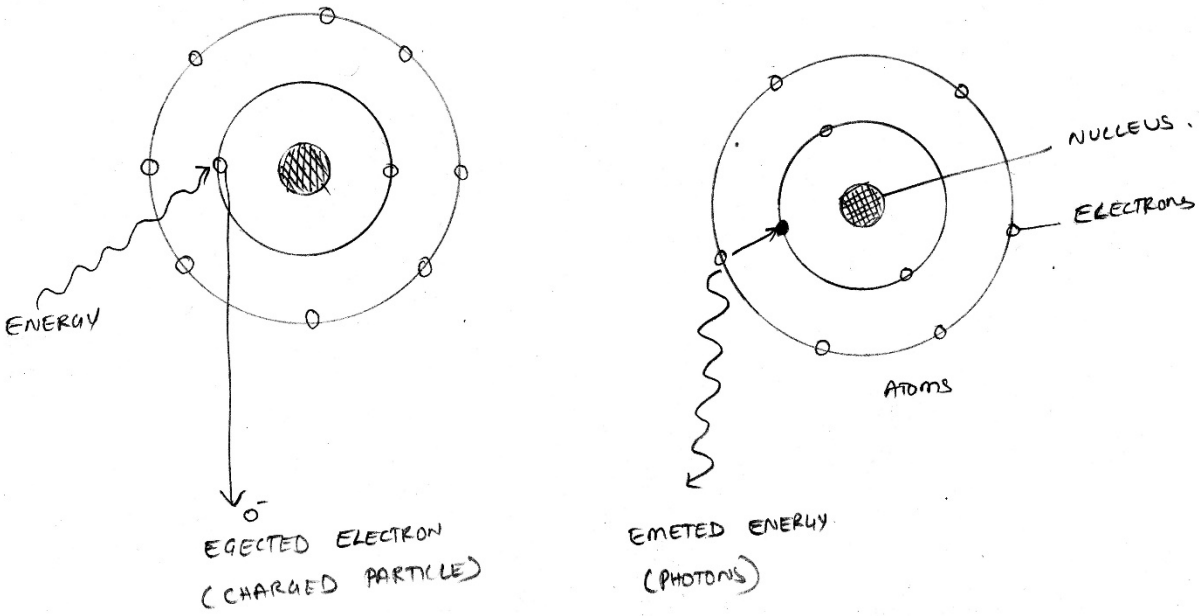


Illustration 09: Emission of charged particles and photons

Ionizing radiation is used in cancer therapy. They are in form of charged particles which directly interact with subcellular structures and cause DNA damage whereas the photons interact with water molecules and cause free radical formation which cause DNA damage. Charged particles lead to direct absorption of energy by the DNA resulting in ionization and thus DNA damage. This is termed as High linear energy transfer. Photons as mentioned above react with water and cause free radical formation which enter the nucleus and cause DNA damage. This is termed as Low LET.[55] The photons induced damage is variable as the cell having free radical scavengers have less DNA effect and even the presence of oxygen in cells effect the free radical formation compared to the charged particles.[56]

$H20 + PHOTON \rightarrow H20^{+} + e^{-}$

$H2O^{+} + H2O \rightarrow H30^{+} + OH^{\cdot}$

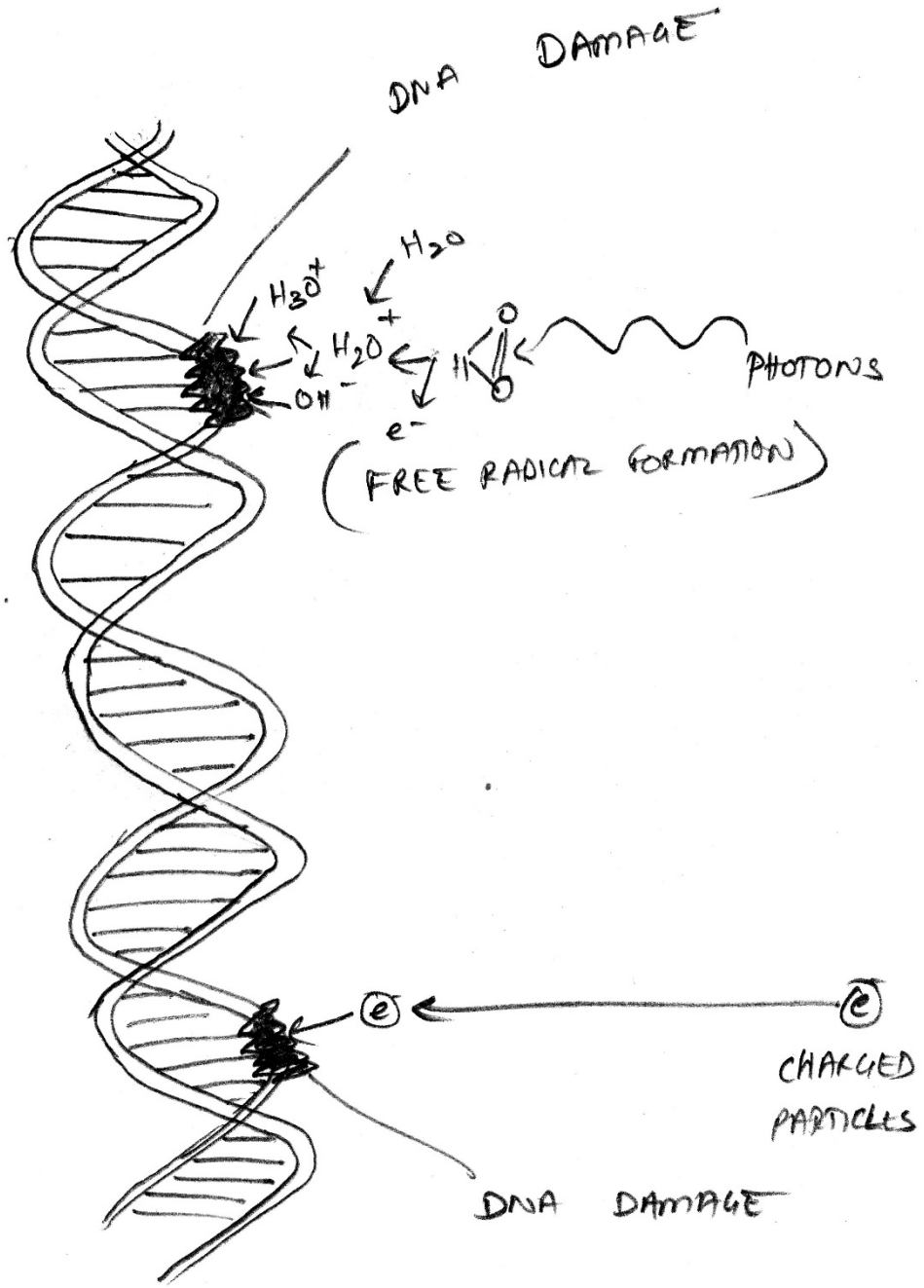


Illustration 10: Direct and Indirect damage

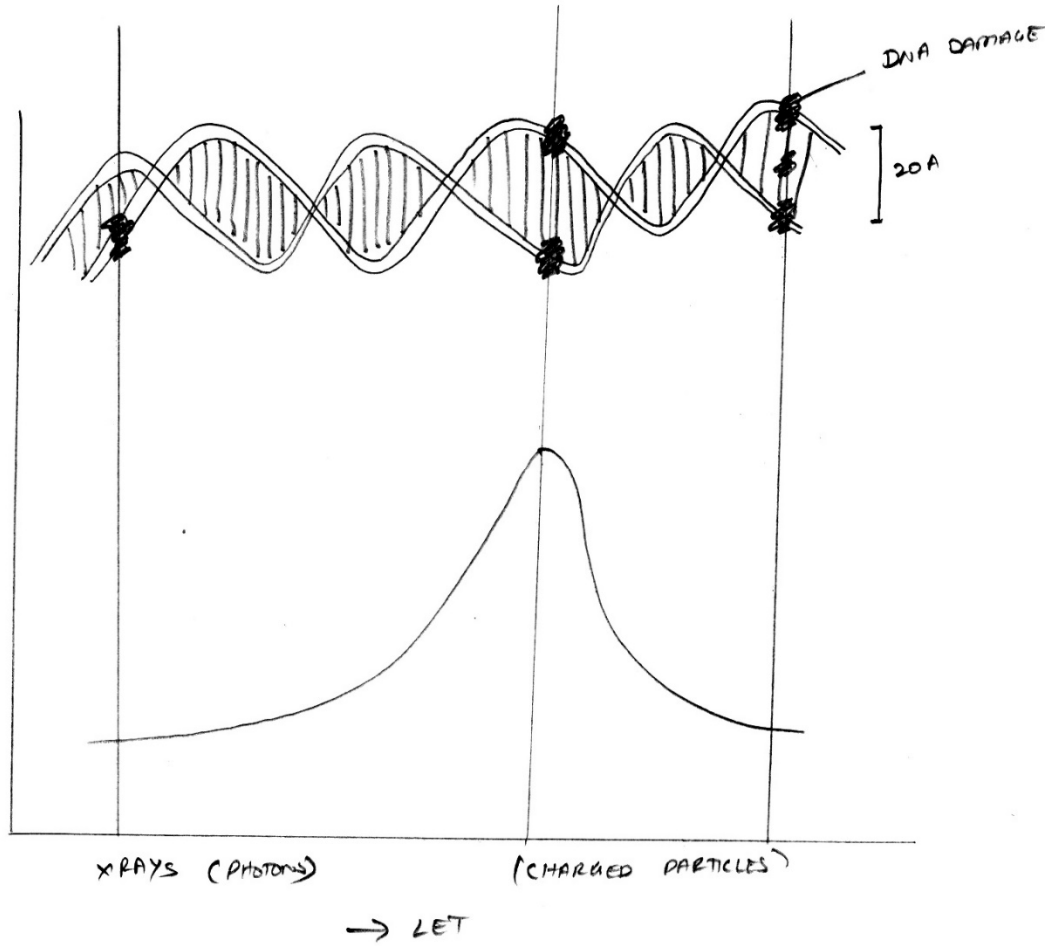


Illustration 11:Linear energy transfer and DNA damage.

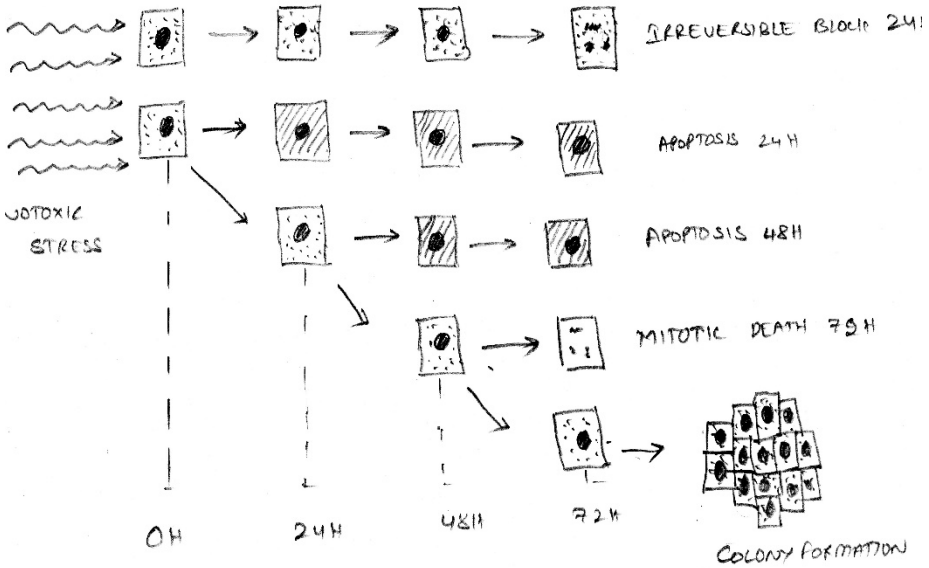


Illustration 12: Consequences of exposure to ionizing radiation at the cellular level.

RADIATION AND THE CELL CYCLE

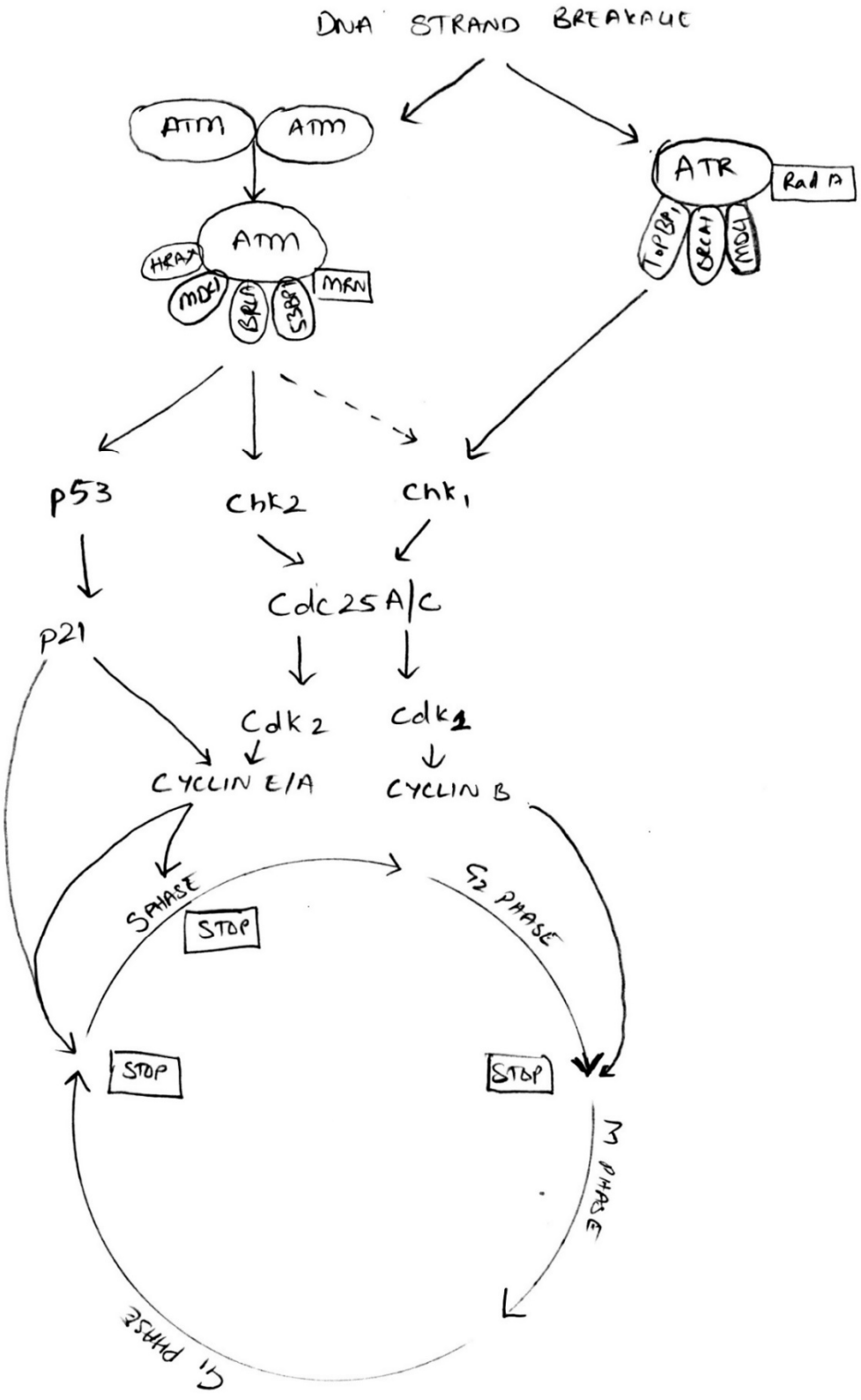


Illustration 13: Radiation effects at various stages of cell cycle

Cellular response to genotoxic stress: Cells must progress in a specific order in the cell cycle via the checkpoints that make sure that the damaged DNA is not transferred to the progeny. The three main places these check points act is at the end of G_1 phase, S phase. End of G_2 phase. The initial response to the radiation will be activation of ataxiatelangectasia mutation which phosphorylates many intermediate proteins that mediate the DNA repair process and localization of DNA double strand breaks and recruiting more ATM molecules thus creating a positive feedback loop.[57-61] End of G_1 phase checkpoint is most studied. Activated ATM works via p53 and p21 and results in inhibition of G_1 cyclin and prevents progression to S phase. Checkpoint Kinase 1 (Chk1) also causes arrest of cell cycle at this stage via Cdc25A but its action is rapid and short.[62] S phase checkpoint is controlled by Cdc25A, ATM and ATR. Cdc25A inhibits the Cdk2 and binding of the Cdc45 to chromatin. This prevents DNA polymerase-α recruiting and thus prevents initiation of DNA replication.[62] ATM via MRN complex cohesion protein SMC1 arrests the S phase. Loss of these leads to increased sensitivity to radiation as the positive feedback loop is broken.[60] Though ATR (Ataxia Telangiectasia and rad3-related) plays role in S phase check point its activity is more constitutive and doesn't change much with the radiation.[63] Checkpoint at G_2stops cells with damaged DNA from entering the mitosis. When this is missing, cells with damaged DNA enter the mitosis but the chromosomes can't be aligned properly at metaphase. Hence the cells that lack this checkpoint are more radiosensitive. DNA damage activates ATM and Chk which inhibits Cdc25A activation. Cdc25A is required for activation of Cyclin B/cdk1 which is the critical step at this Checkpoint[64,65] Polo like kinase (Plk) 1 and 3 also inhibit Cdc25A in response to DNA damage.[66] A lot of research is done to develop drugs that can inhibit checkpoint response proteins as this would inhibit radiation induced G_2 arrest and cause radiosensitization.[67]

DNA Repair:

Radiation causes various types of DNA damage that include base damage, double strand break, single strand break, sugar damage, DNA-DNA and DNA-Protein crosslinks. Among these the most critical damage caused is the double strand break.[68,69] Double-strand breaks are repaired by two processes in mammalian cells, nonhomologous end joining (NHEJ) which cause end to end joining and homologous recombination repair (HRR) which need undamaged DNA as template depending on which phase of the cell cycle and by the abundance of repetitive DNA.[70] HRR is seen more in late S and G_2 phases and NHEJ in G_1 phase but their activity is seen in other phases of cell cycle indicating that they are not exclusive to their phases and that there are other factors influencing them.

Nonhomologous End Joining:

Due to the unavailability of sister chromatid to act as a template NHEJ predominates G_1 phase. It occurs in steps: synapsis, end processing, fill-in synthesis, and ligation.[71] Synapsis is the first step. Ku heterodimer bind to the ends of the DNA double strand break and recruits DNA-dependent protein kinase catalytic subunit DNA-PKcs, artemis, a protein with endonuclease activity for 5′ and 3′ and hairpins to the DNA ends.[72] DNA-PKcs activates artemis's endonuclease activity for end processing. This role of artemis's endonuclease in NHEJ may not be required in this process as DNA polymerase-μ is associated with the Ku/DNA/XRCC4/DNA ligase IV complex is used in the fill-in reaction. Ku heterodimer may also recruit XRCC4/DNA ligase IV complex, which rejoins the DNA ends.[73,74] NHEJ, though effective is highly error prone as the main physiologic function of NHEJ is to produce antibodies and this very nature is essential for creating diversity.

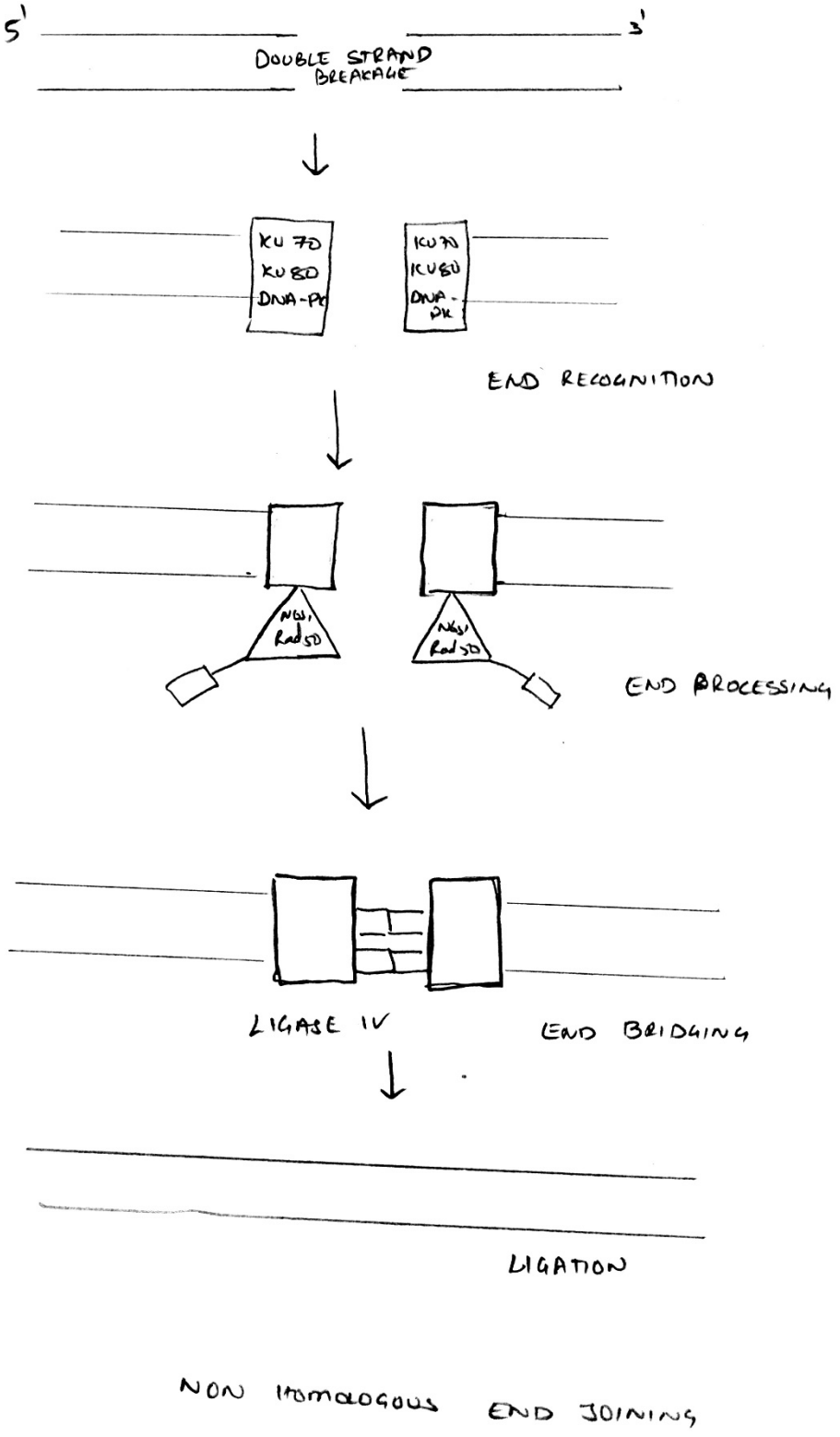


Illustration 14: Non homologues end joining

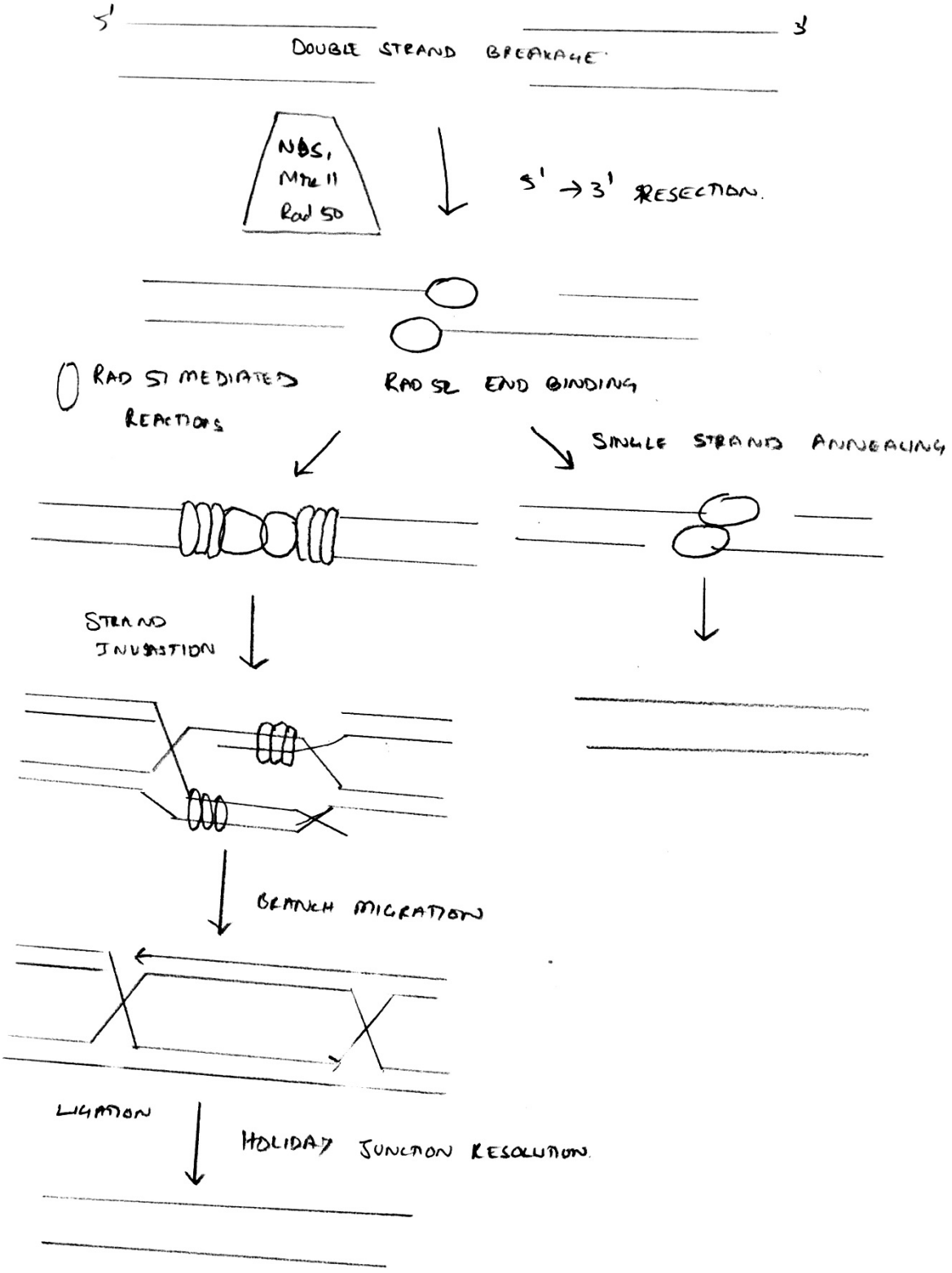


Illustration 15: Homologous Recombination:

Homologous Recombination: This is a highly accurate DNA repair pathway and requires undamaged DNA template for its function. ATM and MRN complex proteins are recruited to the sites of DNA double strand damage.[75] These MRN complexes recruit breast cancer tumor suppressor gene *BRCA1*[76] and Mre11 and some endonucleases that resect DNA and give 3' single strand DNA to act as a template. BRCA1 recruits BRCA2 which helps attaching Rad51 protein onto replication-protein A (RPA)-coated single-strand overhangs produced due to the action of endonucleases.[77] Rad51 forms nucleofilaments and catalyze strand exchange with the template strand. An important step in this process. It also recruits Rad52 which attaches to DNA and protects it against exonucleolytic degradation.[78] ATPase activity of Rad52 unwinds the double stranded DNA leaving the two invading ends which serve as primers and results in structures called Holiday Junctions. These junctions resolve by crossing over or by non-crossing over and gap filling. These genes create an important link between the HRR and chromosome stability and their inactivation leaves radiosensitivity and genomic instability.

RADIATION INDUCED CELL KILL

Radiation kills cells that are actively dividing. It may take days/weeks of treatment for cells to start dying

The potential consequences of cells exposed to ionizing radiation:

Normal cell division

DNA damage-induced senescence (reproductively inactive but metabolically active),

DNA damage induced apoptosis,

Mitotic-linked cell death

The effects of DNA damage can manifest within one or two cell divisions or after many cell divisions.[79] The late effects have been termed *delayed reproductive cell death.* The delayed reproductive cell death may also be effected by secreted factors that are induced after radiation exposure.[80] Survival curves of the tumor cells at low radiation doses and high doses show some differences.

Survival curves of tumor cells at low doses:

They possess a shouldered region at low doses. It becomes shallower with increase in dose and becomes exponential. It is thought that the cells are efficient in repairing DNA strand breaks and hence the low doses are less efficient in killing cells.[68,69]

Linear quadratic equation: $S = e^{-\alpha D - \beta}$ describes killing at low doses of radiation.[81]

S: fraction of cells that survive

D: dose of radiation

α and β are constants

When $\alpha D = \beta D2$ or $D = \alpha/\beta$, Cell killing by the linear and quadratic components will be equal.

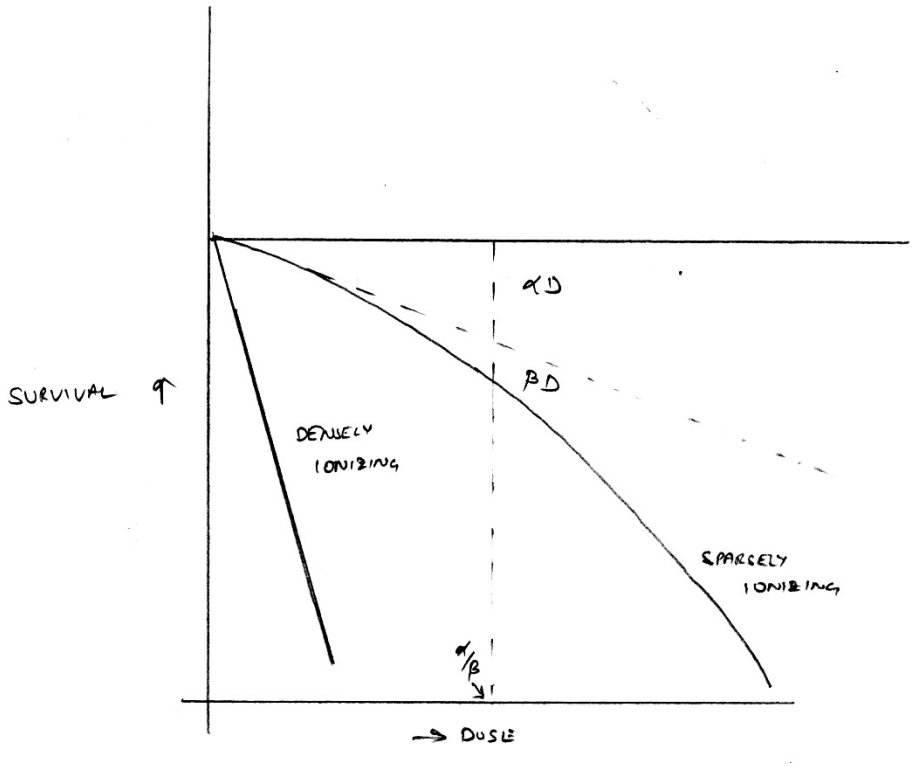


Illustration 16: Analysis of survival curves for mammalian cells exposed to radiation by the linear quadratic model.

Survival curves of tumor cells at high doses:

In high doses, the survival curves are more complex. They are described by three different components:

D1: an initial slope

D0: a final slope

Width of the shoulder

n: extrapolation number or

Dq: quasi-threshold dose.

Extrapolation number: The point where the shoulder intersects the ordinate when the dose is extrapolated to zero

Quasi-threshold dose: The width of the shoulder by cutting the dose axis when the survival fraction is unity

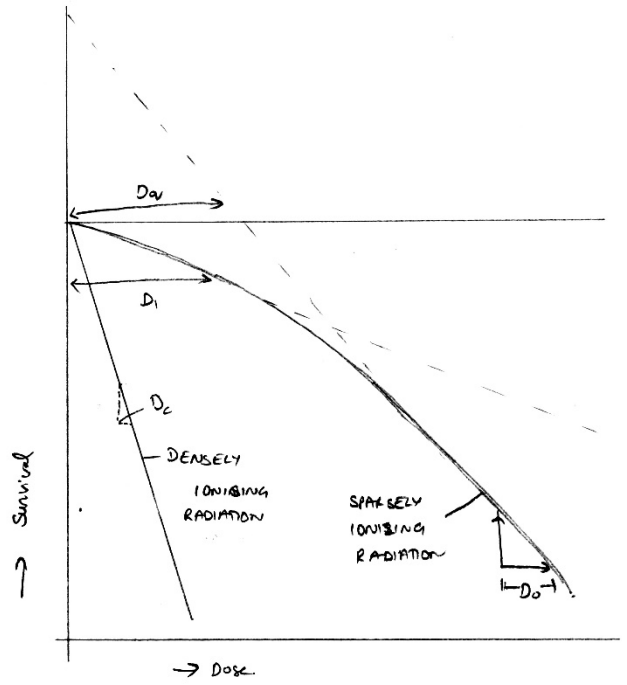


Illustration 17: analysis of survival curves for mammalian cells exposed to radiation by the multitarget model.

When cells are exposed to densely ionizing radiation via charged particles the shoulder on the survival curve disappears showing their high effectiveness in killing cells at both low and high doses.

Factors Effecting Response to Radiation:

Dose-Rate Effects

In case of weak ionizing radiation like X rays, dose rate plays an important role in cell killing. Reducing the dose rate increases exposure time and reduces the total effectiveness of

killing by x-rays as the SDR is raised and reduces the shoulder of the survival curve. On plotting the survival for individual doses in a multifraction experiment with enough time for SDR to occur, the resulting curve would appear almost linear with little or no shoulder.[83] This is again depends on cell types, as there are cell types with threshold to the lowering of dose rate, and in those cell types there will be an increase in cell killing due to accumulation of cells in a radiosensitive phase of the cell cycle. To conclude, the magnitude of the dose-rate effect changes among the cell types due to SDR, the redistribution of cells in the cell cycle, and total time taken for cell cycle.

Cell Cycle

The phase of the cell in the cell cycle at the time of radiation changes its sensitivity to radiation. Most Sensitive phases are late-G1 to early-S and G2 or M phases and most resistive phases are G1 and mid- to late-S phases.[55] Hence chemotherapeutic agents that delay the cell cycle in these specific phases are used to make tumor more sensitive to the radiation. In fractionation of radiotherapy this concept is used and a gap between the fractions is given to allow cells in resistant phases to get to sensitive phase.

Tumor Oxygenation

Oxygen has major influence on tumor response to radiation.[84] Tissue hypoxia result in decrease in killing effect of radiation, which is expressed as an oxygen enhancement ratio (OER).[85] OER is the ratio of radiotherapy doses needed to achieve same achieve effect under hypoxic and normoxic conditions. At high doses of radiation, the OER is approximately 3. At low doses it is appoximately 2.[86]. In hypoxia, DNA damage is readily repaired. In oxygenated conditions DNA damage is “fixed” because of oxygen’s interaction with free radicals formed due to radiation effects. The presence of oxygen is very important has for single-dose radiotherapy than fractionated radiotherapy as reoxygenation occurs between fractions. Hypoxic cells are not in active cell division and radiotherapy and radiosensitizing agents

work on actively dividing cells.

Survival difference is exhibited by many tumor cells halfway between fully aerobic and fully anoxic cells when exposed to a partial pressures between 3 and 10 mm Hg.[1] Only tumors possess levels of oxygen so low enough to influence the effectiveness of radiation killing compared to normal cells. In normal tissue oxygenation variations are mainly due to physiology changes compared to tumors whose variations are due to abnormal vasculature resulting in a more chronic condition. Thomlinson and Gray[87] observed that insufficiency in vasculature to provide oxygen to all tumor cells evenly is the cause for variations and hypothesized that oxygen can't reach tumor cells beyond 10 to 12 cell diameters from the lumen due to high metabolic consumption by respiring tumor cells. This type of hypoxia is termed as *chronic* or *diffusionmediated hypoxia*. In fractionated Radiotherapy tumor size reduces and reoxigentaion occurs in the deeper tumor cells. Hyperbaric Oxygen therapy is tried to increase the overall oxygen flow so as to increase the oxygen that is available for diffusion into the tumor cells. Experiments showed increased radiosensitiveity but clinical trials have shown that it increases sensitivity only in Head and Neck Cancers and Cervix cancers.[88] Erythropoietin in theory should increase the RBC production and thereby increase tumor oxygenation by increasing Hb bound Oxygen. But it was not successful in control of head and neck cancers when combined with radiotherapy, though it controlled anemia it may have also stimulated tumor growth.[89,90]

Clinical studies have been conducted using nicotinamide and carbogen combination and using Anti Vascular endothelial growth factor therapy have shown positive results in increasing tumor oxygenation.[91,92.] But they still need further evaluation to be used.

Imaging of hypoxia is also tried with the intention to alter the radiation doses according to the hypoxia maping as hypoxia has both prognostic and therapeutic implications but changes

being dynamic, it has not been successful yet.[93-95]

PHOTONS

- Neutral packets of energy not containing mass
- Most commonly used
- Could be obtained from radioactive sources or from linear acclerators(LA)
- Intranuclear: gamma rays
- Extranuclear: X-Rays

ELECTRONS

- Negatively charged particles
- Produced from Linear Accelerators.
- Do not penetrate into the deep tissues
- Clinically used for skin and superficial tumours

PROTONS

- Positively charged particles of atoms
- Causes cell damage by direct ionization
- Specific deposition of energy at the end of its path

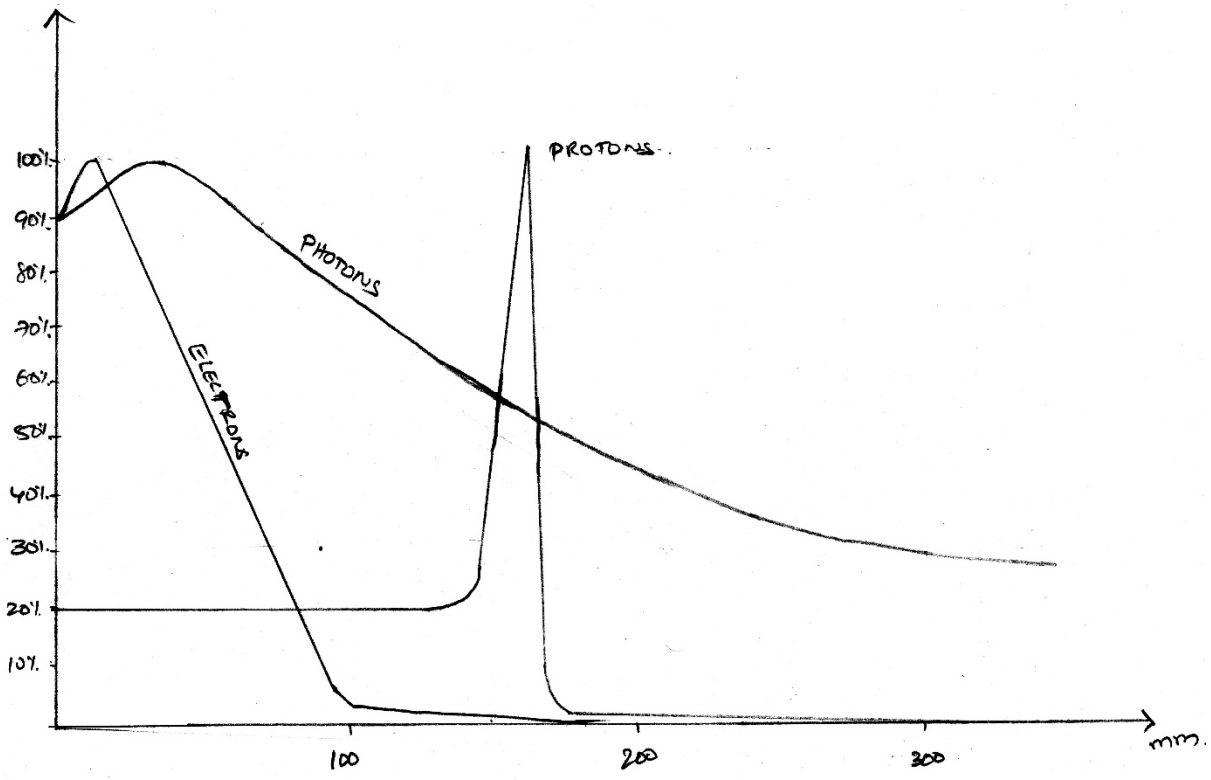


Illustration 18: Various radiations and their dose depth

NEUTRONS

- Particle with mass and no charge
- Causes more damages to the cells(normal and malignant) due to high LET
- Used mostly in certain salivary gland tumours, prostatic malignancies

ALPHA PARTICLES AND HEAVY IONS

- Cause cell damage by direct ionization
- Causes more damage to the cell(normal and malignant)
- Can be used for malignancies that do not respond well to photons

INTENT OF RADIOTHERAPY

- CURATIVE: Radiation given with an intention to cure the disease.

- DEFINITIVE
- ADJUVANT: Given postoperatively to reduce the chances of recurrence.
- NEO-ADJUVANT: Given prior to the definitive treatment to reduce the tumour burden.
- PROPHYLACTIC: To reduce the chances of tumour from occurring in high risk patients
- PALLIATIVE - To relieve the symptoms without the intent of eradicating the disease.

MODES OF RADIATION DELIVERY

- EXTERNAL / TELETHERAPY
- INTERNAL / BRACHYTHERAPY: intracavitary, interstitial, intraluminal
- RADIOPHARMACEUTICALS
- INTRAOPERATIVE RADIOTHERAPY

EXTERNAL IRRADIATION

- Given using Cobalt-60 or Linear Accelerators
- Used to treat large area of the body to include the primary and the regional (draining) lymphnodal sites.
- Treated on an outpatient basis

MODES OF EBRT DELIVERY

- CONVENTIONAL
- 3D-CRT

- IMRT
- IG-IMRT
- RAPID-ARC/ VMAT
- TRUEBEAM (FFF PHOTONS)
- CYBERKNIFE, TRUEBEAM

DOSING AND TREATMENT

- SI unit for absorbed dose is Gray (Gy)
- 1 Gy = 1 J/kg =100cGy
- Older term ‘rad’ is no longer used

DOSE FRACTIONATION:

- Curative – Usually delivered as 1.8-2 Gy once daily, but there can be smaller fraction sizes (1.2-1.8 Gy) or slightly larger fraction sizes (2.2 Gy).
- Adjuvant – Also usually delivered as 1.8-2 Gy once daily, but there can be the same variations as for curative.
- Palliative – Much larger fraction size (3-8 Gy)

WHY FRACTIONATION?

- REPAIR
- REASSORTMENT
- REPOPULATION
- REOXYGENATION

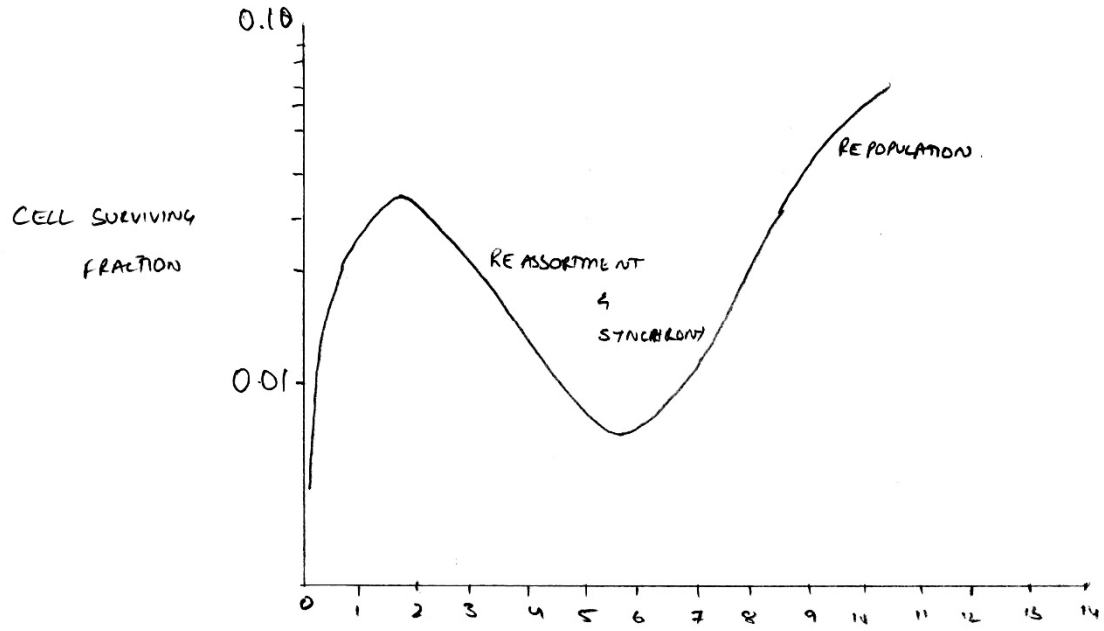


Illustration 19: Idealized survival curve of rodent cells exposed to two fractions of x-rays.

ALTERED FRACTIONATION

- **HYPERFRACTIONATION**: increased no. of fractions keeping the effective dose and the total duration the same. Dose of each fraction is reduced. Each fraction is given at interval of minimum 6 hours. More than one fraction per day is administered.
- **ACCELERATED FRACTIONATION:** Shortened duration with same total effective dose. Standard dose of each fraction with multiple fractions per day.
- **CHART (** Continuous Hyperfractionated Accelerated Radiotherapy)
- **HYPOFRACTIONATION:** Reduced no. of fractions with higher doses. Generally given in palliation.

Both hyperfractionation and accelerated fractionation have been found to be superior than the standard radiation fractionation in treating head and neck cancers when radiation is given alone.[96]

Concurrent Chemotherapy

It is given for Radiosensitization and synergistic effect for tumour damage. Chemotherapeutic agents that give these effects are:

- Antimetabolites
- Platinums
- Taxanes
- Molucularly Targeted Agents
- Other agents

Antimetabolites

Most commonly used chemotherapeutic agent. Used in almost all cancers, alone or in combinations. In head and neck cancers it is used in combination with cisplatin or Mitomycin C.

5Flurouracil is an analogue of uracil and hence it miss-incorporates itself into DNA and RNA. But the inhibition of Thymidine synthase which Leads to depletion of dTTP and inhibition of DNA synthesis slowing down progress through S Phase is thought to cause radiosensitization[97]

Gemcitabine (2,2Deoxyflurocytdine) is another molecule which acts via depletion of dATP, shows radiosensitization but with more complications.[98-101] It is still under trails.

Platinums

Cisplatin and Carboplatin are most commonly used either alone or in combinations. In head and neck they are usually used in combination with 5FU. They act by causing Inter and Intrastrand DNA Crosslinking which cause breakage of DNA strands at repair when these are removed. Its radiosensitizer actions are thought to be due to its inhibition of both Homologous and Non-Homologous repair mechanisms or by increasing the no. of lethal DNA double strand breaks induced by radiation.[102]

Taxanes

Paclitaxel and Docetaxel are the common molecules used in this group. They stabilize microtubules and thus result in redistribution of cells in G2 or M phase. In combination with platinum drugs they showed a significant clinical benefit in some unresectable cancers.[103,104]

Molecularly Targeted Agents

These are less toxic agents. They are ineffective as single agents, always used in combination with other agents. EGFR is most common target. Both Antibodies (Cetuximab) and Small Molecule EGFR inhibitors (Erlotinib) have evolved. Their mechanism not properly understood. Erlotinib is a tyrosine kinase inhibitor. Presently they show promising radiosensitization effects in Phase 3 trails in head and neck cancers.[105]

Chk1 inhibitors and Poly Adenosine diphosphate Ribose Polymerase are other molecules in clinical development.[106,107]

Other Agents

Vinka Alkaloids (Vincrystine) blocks Mitotic Spindle Arrest and attests the cells in M Phase and thus has radiosensitizing effects. It is being used in only few cancers like medulloblastoma, rhabdomyosarcoma, and brainstem glioma, as it doesn't exhibit the myelosuppressive side effects.

Capicitabine is Oral Thymidine synthase inhibitor under trails

Amifostine is a free radical Scavenger with selectivity towards normal tissues and hence give radioprotection to normal cells. Normal tissues have more Alkaline phosphatase which it converts into free thiol metabolite. Few studies report reduction of radiation indused toxicity in head and neck cancers but still needs further investigation.[108,109]

BRACHYTHERAPY

- PERMANENT – placement of radioactive pellets or seeds into the tumour tissue for an indefinite period of time
- TEMPORARY – placement of radioactive pellets or seeds into the tumour tissue for a specified period of time

TEMPORARY BRACHYTHERAPY

- **DOSE RATE:**
    - HDR
    - MDR
    - LDR
    - PDR
- **INTERSTITIAL**
- **INTRACAVITARY**

- **INTRALUMINAL**

SAFETY FOR PATIENT AND FAMILY: No need for special precautions for any of the family members

SIDE EFFECTS OF RADIOTHERAPY:

SITE SPECIFIC

- Skin Changes
- Mucositis
- Fatigue
- Xerostomia
- Dysphagia
- Trismus
- Osteoradionecrosis , Osteomyelitis

SECOND MALIGNANCIES

- Overall risk is low
- most develop within few yrs, peaking at 5-9 yrs
- some are diagnosed even after 10-15 yrs

Platinum Chemotherapy Agents:

The various platinum based chemotherapeutic agents make the most broadly used anti-cancer drug class since their introduction in 1970.[110,111] They are Cisplatin, Carboplatin and Oxaliplatin, etc. They are used as mainstay systemic treatment in lung malignancies,

Aerodigestive malignancies, Lower Gastrointestinal malignancies and Gynecological and Genitourinary malignancies. They are either used alone or in combination with other drugs. Among them Cisplatin (***cis*-diamminedichloroplatinum(II)** (**CDDP**)) and Carboplatin are used widely. Oxaliplatin is used for colorectal malignancies. Satraplatin is a new platinum drug under trails which is active orally and shows activity against cisplatin and taxane resistant tumor cell lines.[112-115] Core element in all the above mentioned agents is platinum and all show common traits in the chemistry and pharmacological properties.[110-112,116,117] Recently more cytotoxic Cisplatin and Carboplatin nanoparticles have been developed.[118-121]

These are atypical alkylating agents. Damage by these drugs on DNA is almost similar. However this damage is are different from other classes of alkylating agents.[3,8] The bifunctional alkylating agents have movable reactive arms around the carbon core which results in DNA that is spatially flexible relative to covalent bonds formed by the agents. In platinums, reactive groups are fixed and hence the DNA covalently bound to Platinums is also fixed. The DNA formed after platinum adduct is repaired by nucleotide excision repair pathway.

Cisplatin is administered IV diluted in 250 to 500ml of Normal Saline infused without cations over 1 to 4hrs. Shorter the infusion time, greater is the toxicity. Its dose in Head and Neck cancers is 100mg/m^2 body surface area (BSA) given over 2days 3 weekly. Good urine flow should be ensured. Patient should be prehydrated and posthydrated with 2 liters of IV Fluids, Loop diuretics should be avoided and Mannitol 125mg should be infused along with cisplatin to avoid renal complications.

Renal insufficiency with cation wasting, nausea and vomiting, peripheral neuropathy, auditory impairment, and myelosuppression with thrombocytopenia are common toxic effects. Uncommon serious toxic effects include hypersensitivity, visual impairment,

seizures, and late leukemia. Appropriate bone marrow cytokines should be used to control Myelosuppression. Adequate prevention of nausea and vomiting can be ensured by 2004 Perugia International Antiemesis Consensus Conference Guidelines.[123] Generally level 4 antiemesis regimens are used for cisplatin regimens. According to Level 4 anti-emesis regimen, before chemotherapy, a serotonin 5-hydroxy tryptamine type 3 receptor antagonist, dexamethasone, and aprepitant and after chemotherapy, dexamethasone on days 2, 3, and 4, and aprepitant on days 2 and 3 should be administered.

Photo - 08: Cisplatin vial

Antimetabolite Chemotherapy Agents:

5 Fluropyrimidines 5Flurouracil remains to be one of the most widely used anti-cancer agent since its introduction in 1950s. It is used in a wide range of malignancies including Head and Neck malignancies, Gastro intestinal Malignancies, Breast and Ovarian malignancies.[124] It is still used widely in combination regimens. In body, 5FU enters cells through facilitated

transport system which is then anabolized to active metabolites which act via inhibition of TS and incorporation into RNA and DNA. 5FU is actively catabolized by DPD enzyme in the body and excreted within 8 to 14 min following an IV bolus and. Complications include mucositis, myelosuppression, diarrhea and nuerotoxicity.[125] Resistance is commonly developed against 5FU via over expression of DPD enzyme and alteration of TS enzyme. Various agents have been tried to increase the anti-tumor effects of 5FU.[126,127] Reduced folate LV being used as the main biomodulator for past two decades. As this drug acts only in S phase in recent years continuous infusion of the 5FU is being used to increase the anticancer effect by increasing the fraction of the cells that are exposed. 5FU toxicity is dose and schedule dependent. Longer the duration of infusion and higher the dose, more are the side effects which include the most common effects like diarrhea, mucositis and myelosuppression to less common hand foot syndrome and acute neurological symptoms. Coronary vasospasm has also been reported.

Various chemotherapy with radiotherapy Protocols using Cisplatin:

Cisplatin + infusional 5-FU[128]

Day 1: Cisplatin 60mg/m2 over 15 minutes; plus

Days 1–5: 5-FU 800mg/m2 by continuous infusion; plus

Days 1–5: Radiotherapy: 2Gy repeated every other week for

7 cycles.

Weekly cisplatin [129,130]

Day 1–28: Cisplatin 40mg/mg2 IV over 30 minutes weekly; plus

Days 1–38: Radiotherapy (5 fractions/week): 1.8Gy single dose (up to total dose of 50.4Gy); plus

Days 22–38: Boost radiotherapy: 1.5Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose (total tumor dose of 69.9Gy.) OR

Day 1–28: Cisplatin 40mg/mg2 IV weekly; plus

Days 1–40: Radiotherapy: five fractions of 1.8Gy/week (up to total dose of 54Gy); plus Days 25–40: Boost radiotherapy: 1.5Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose.

Cisplatin[3,6,9,10]:

Days 1, 22 and 43: Cisplatin 100mg/m2 IV + radiotherapy.

RESEARCH HYPOTHESIS AND QUESTION

Research Hypothesis

- Postoperative chemotherapy with radiotherapy gives better loco-regional control in locally advanced Oral cancers compared to postoperative radiotherapy alone.

Research Question

- Does postoperative Chemotherapy with radiotherapy give better loco-regional control in locally advanced Oral cancers compared to postoperative radiotherapy alone?

OBJECTIVES OF THE STUDY

Objectives of the study

- To perform composite resection of the tumour in locally advanced oral carcinoma patients (T_3 and T_{4a}) and to randomize these postoperative patients and compare the efficacy and safety of Radiotherapy and Chemoradiotherapy in them.

MATERIALS AND METHODS

Materials and Methods:

Study Period: December 2013 to November 2015

Source of the data

Ours is a time bound study. All the Locally advanced oral Carcinoma (T_3 and T_{4a}) patients who underwent surgery and falling under the below mentioned criteria between December 2013 and May 2015 in R L Jalappa Hospital and Research Centre are randomized by simple randomization technique. Every alternate patient to the other group.

- **Inclusion Criteria:**
    - Locally advanced Oral cancer patients (T_3 and T_{4a}) who underwent surgery with curative intent and planned for adjuvant therapy.
- **Exclusion Criteria:**
    - Patients with extracapsular spread of tumor from lymph nodes
    - Positive tumor margins
    - Patients with poor renal function
    - Patients who received prior Radiotherapy
    - Debilitated patients

Materials and Methods

- Patients with T_3 and T_{4a} stage oral carcinoma, undergoing composite resection are randomized into two groups postoperatively: Radiotherapy Group (Group 1) and Chemoradiation Group (Group 2)
- Chemoradiotherapy or radiotherapy alone is given according to their group

- Chemoradiotherapy involves Chemotherapy and Radiotherapy administered to the patient concurrently.
- Chemotherapy: 100mg/m2 BSA over 2days and 1500mg 5FU over 3 days; once in 21days; 3 cycles.
- Radiotherapy: 1.8 to 2 Gy/Fraction, 33 fractions over 6-7 weeks (Normal Fractionation)
- Overall survival rate, disease free survival rate, Recurrence (Local, Regional and Loco-regional) and adverse events were documented and compared between both the groups.

Photo - 09: T_{4a} Buccal Carcinoma with fungation

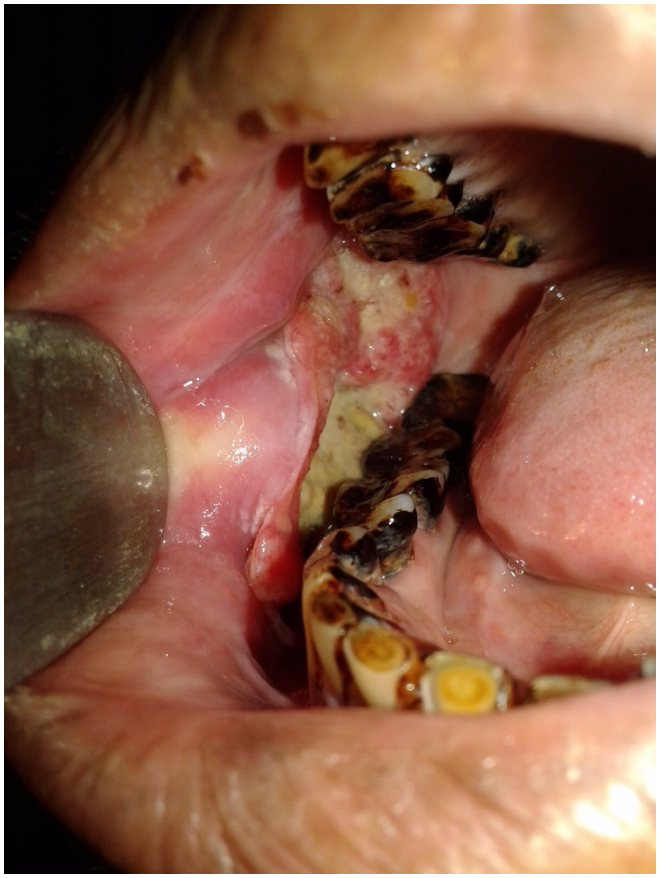


Photo - 10: Buccal Mucosa Ca involving RMT

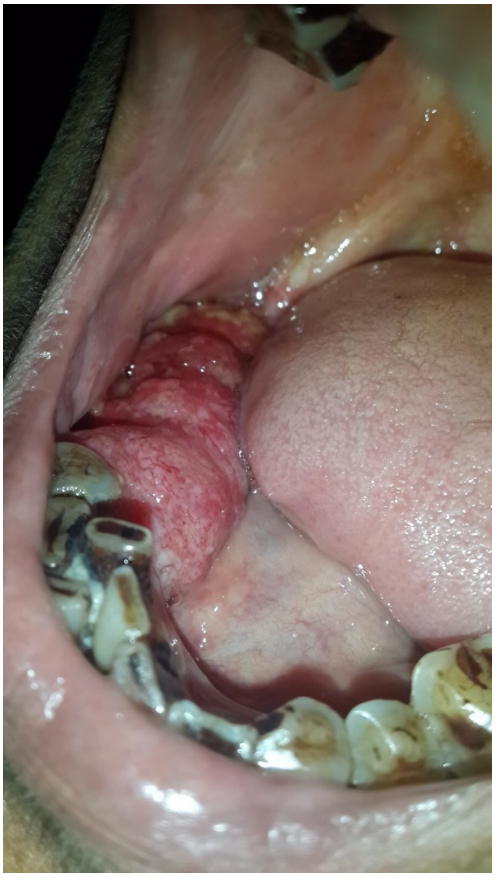
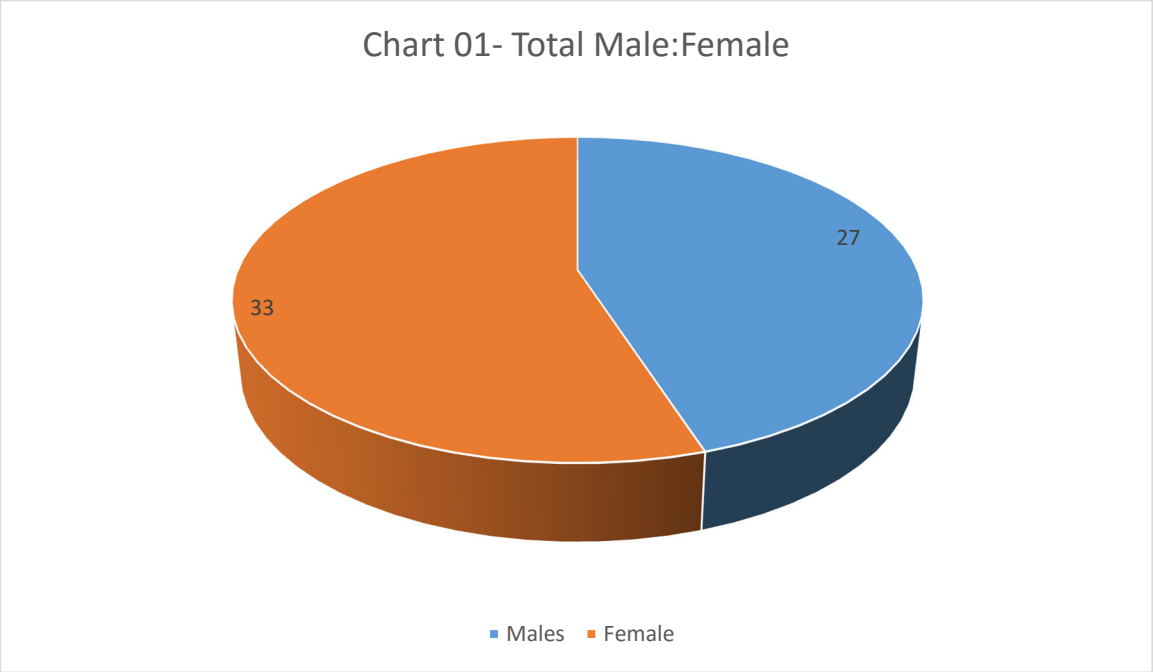


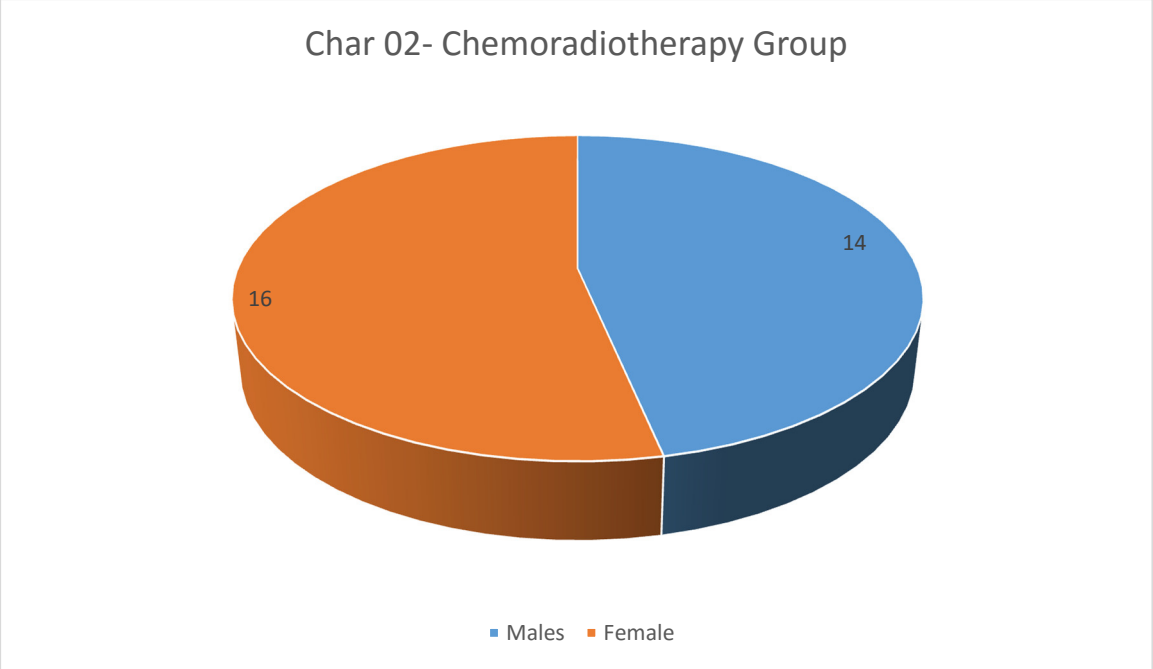
Photo -11: Lower alveolus Carcinoma

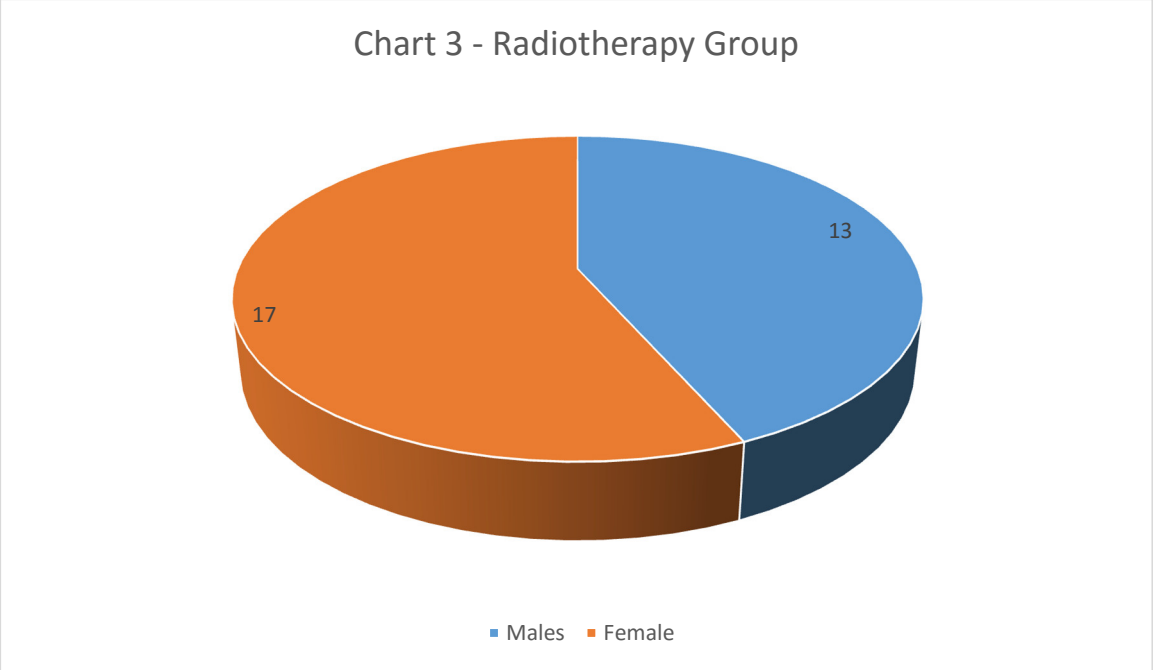
OBSERVATIONS AND RESULTS

Observations and Results

We have got a total number of 60 patients in the study. 30 patients falling in Postoperative Radiotherapy group and 30 into Postoperative Chemotherapy with Radiotherapy group. The age of the patients ranged from 43 to 72 years with mean age of 56.23years. In Radiotherapy group it ranged from 43 to 72 years with mean age 56years and in Chemoradiotherapy group 45 – 71 with mean age 56.5years. We got a male to female ratio of 9:11 (0.81) in the study with male to female ratio in Radiotherapy group 13:17 (0.76) and Chemoradiotherapy group 7:8 (0.87) Follow up period is for minimum 6 months. All the patients in both the groups have finished 6 months of follow-up. Follow up was continued till the end of study period. 46 (24 in Radiotherapy group and 22 in Chemoradiotherapy group) patients have completed 1 years follow up and 39 (20 in Radiotherapy group and 19 in Chemoradiotherapy group) patients completed 1year 6 months of follow up.







27 patients had locally advanced buccal mucosa with lower alveolus cancers in post-operative chemotherapy with radiotherapy group and 28 patients in post-operative Radiotherapy group. Rest of the patients had anterior 2/3rd of tongue carcinoma.

36 nodal positive cases are found to be N_0 on histopathological examination

. In three patients treatment delay due to the toxicity occurred in Chemoradiotherapy group as these patients developed agranulocytosis. Out of these three two patients required Granulocyte Stimulating Factors. In 5 Patients agranulocytosis occurred in Chemotherapy with Radiotherapy group.. Among them 3 required granulocyte stimulating factors. Out of these 3, two had treatment delay. The other patient in whom treatment delay occurred due to the same factor recovered spontaneously.

Table 01: Agranulocytosis

Agranulocytosis in Chemoradiation Group	5
Spontaneous Recovery	2
Granulocyte Stimulating Factors used	3

The various adverse effects noted in the study include Mucositis, Agranulocytosis, Moist Desquamation, Fever, Nausea/Vomiting, Pneumonia, Elevated Serum Creatinine, Trismus, Osteoradionecrosis and Toxicity related treatment delay. There were no treatment related deaths encountered in the study. Though dehydration was encountered it didn't progress to severe dehydration due to adequate management with plenty of oral fluids and Intravenous fluids immediately.

Two patients, one in each group developed osteoradionecrosis. Trismus and Mucositis is most commonly encountered adverse effects. About 23.3% (7) of patients in radiotherapy group developed trismus and 33.3% (10) of patients in Chemoradiotherapy group developed trismus. The grade of trismus is also more in chemo radiotherapy group compared to radiotherapy group. In radiotherapy group all the patients had grade II trismus where as in Chemoradiotherapy group half the patients who developed trismus had grade III trismus.

Table 02: Adverse Effects

Adverse effects	**Radiotherapy**	**Chemoradiotherapy**
Mucositis	25	27
Agranulocytosis	0	5 (2 Spontaneous Recovery, 3 Granulocyte Stimulating Factors)
Moist Desquamation	4	3
Ototoxicity	0	0
Fever	7	6
Nausea/Vomiting	0	14
Severe Dehydration	0	0
Pneumonia	3	5
Elevated Sr. Cr.	0	0
Trismus	7	10
Osteoradionecrosis	1	1
Toxicity related treatment delay	0	5
Treatment Related Death	0	0

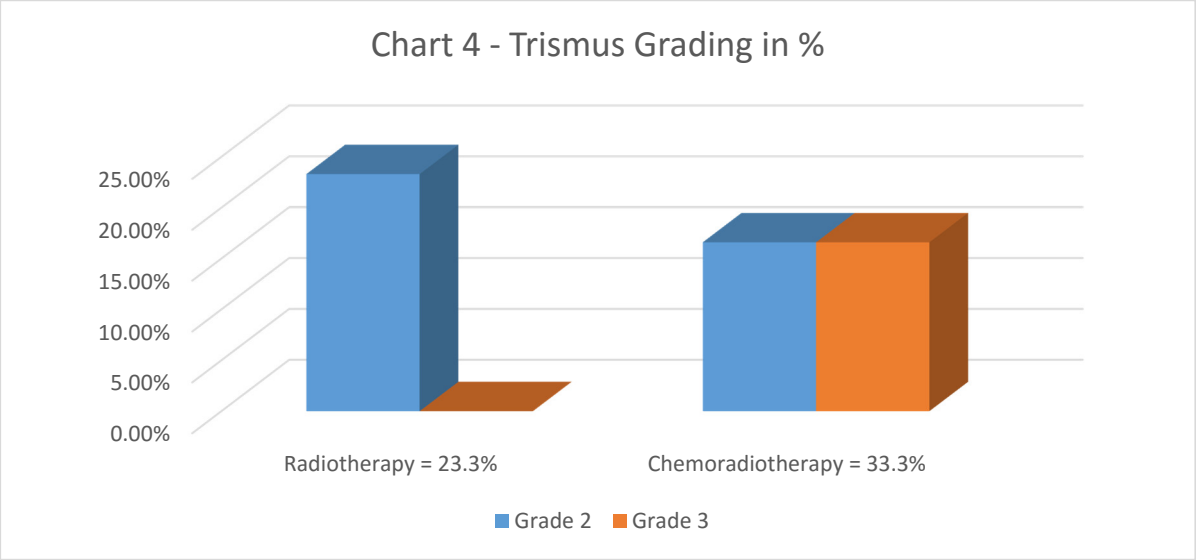
Risk Estimation: Incidence among exposed/Incidence among non exposed.

Risk of Mucocitis: 10.8% more in chemotherapy with radiotherapy

Risk of Trismus: 14.2% more in chemotherapy with radiotherapy

Table 03: Trismus

Trismus	Radiotherapy	Chemoradiation
Grade 2	7	5
Grade 3	0	5



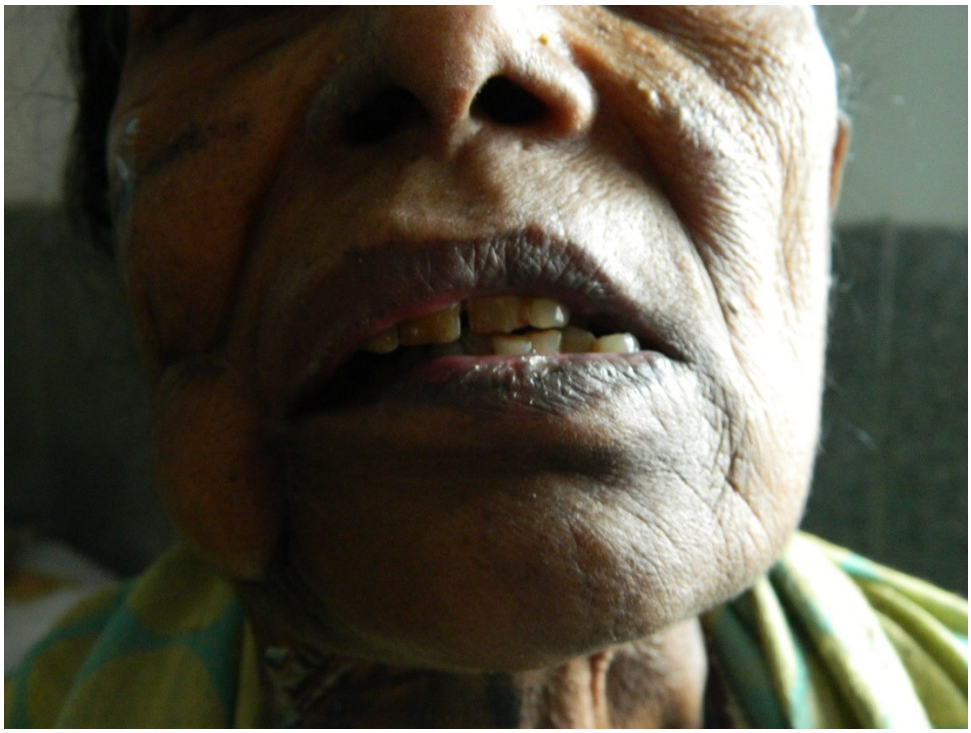


Photo - 12: Trismus

Mucositis is widely seen adverse effect with 83.3% in radiotherapy group and 90% in Chemoradiotherapy group with more severity in the chemoradiotherapy group compared to radiotherapy group.

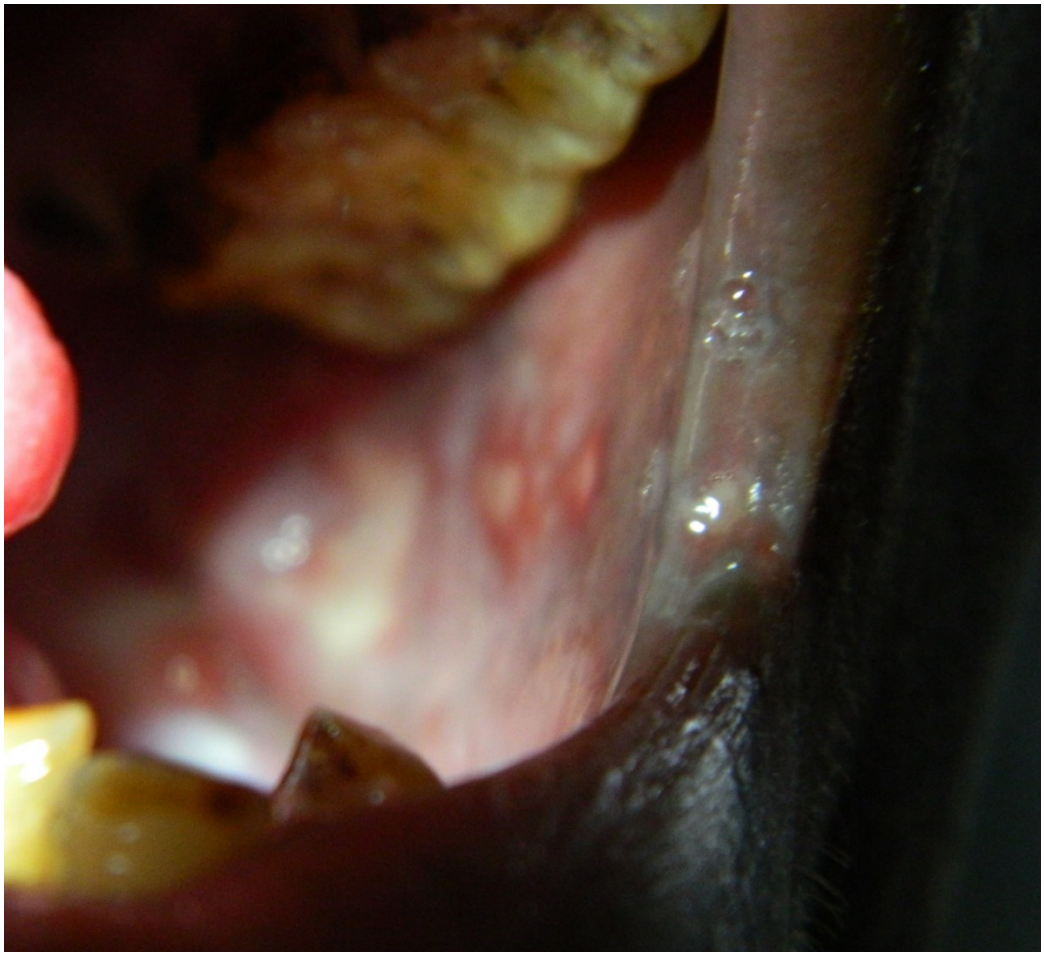
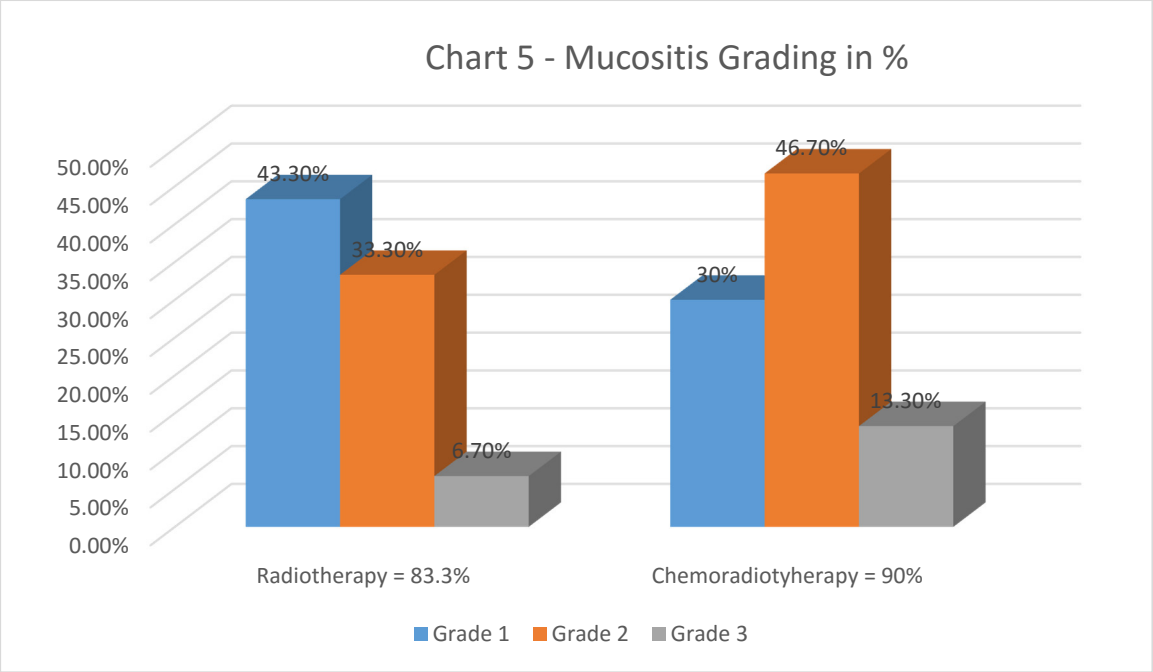


Photo -13: Mucositis

Table 04: Mucocitis

Mucositis	Radiotherapy	Chemoradiation
Grade 1	13	9
Grade 2	10	14
Grade 3	2	4

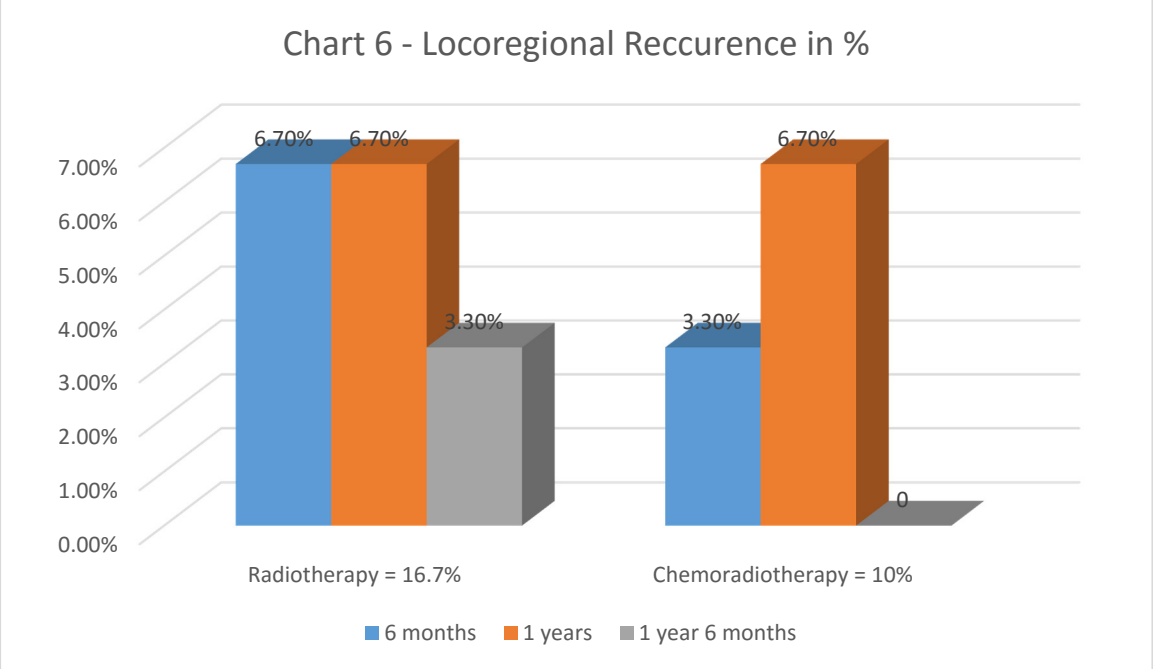


There were total 8 Recurrences noted in the study at various follow up times. 16.7% (5) of patients in radiotherapy group had locoregional recurrence compared to 10% (3) patients in Chemoradiation group. At 6 months of follow up 6.7% (2) of radiotherapy group and 3.3% (1) of Chemoradiotherapy group patients presented with locoregional recurrence. At one year follow up 6.7% (2) more patients in each group presented locoregional recurrence making a total of 13.4% and 10% of patients in the respective groups. Another 3.3% (1) of patients in radiotherapy group presented with locoregional recurrence at 1year 6 months follow up period. None of the patients had distant metastasis

Risk of recurrence: 16.6% more with post-operative radiotherapy compared to chemotherapy with radiotherapy groups

Table 05: No. of patients disease free

Disease free	6 weeks	3 months	6 months	1 Year	1 Year 6 months
Total	**60/60**	**60/60**	**57/60**	**39/46**	**31/39**
RT	**30/30**	**30/30**	**28/30**	**20/24**	**15/20**
CT-RT	**30/30**	**30/30**	**29/30**	**19/22**	**16/19**



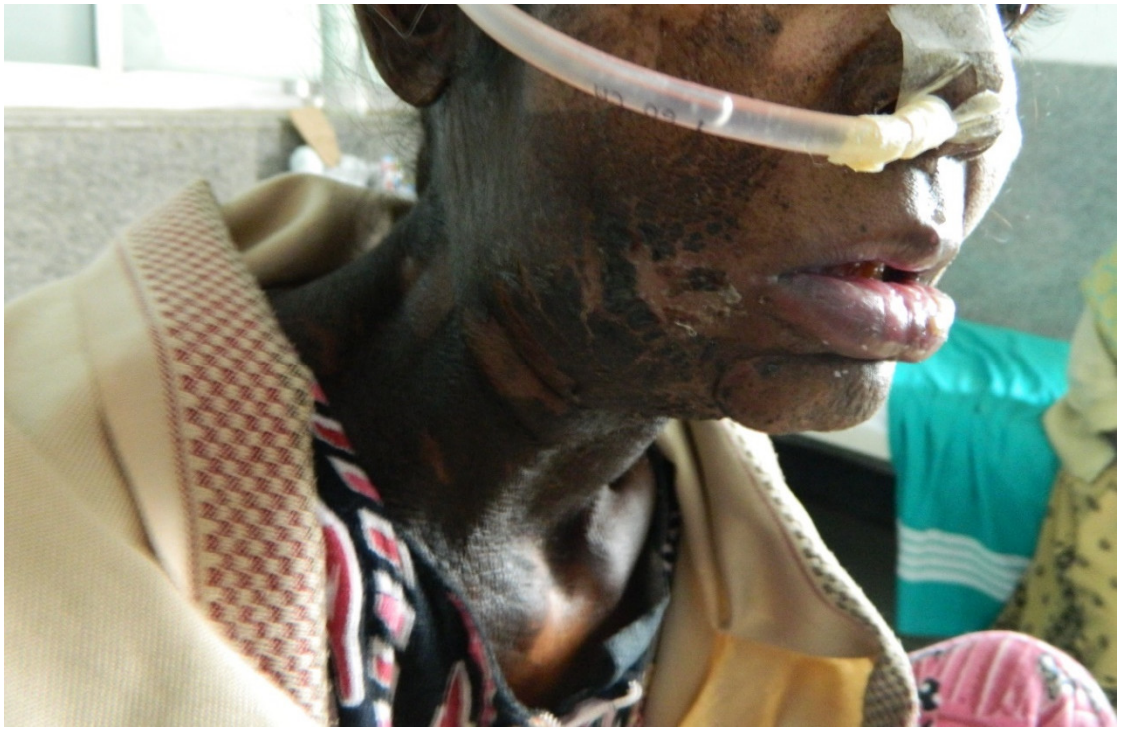


Photo - 14: Moist desquamation

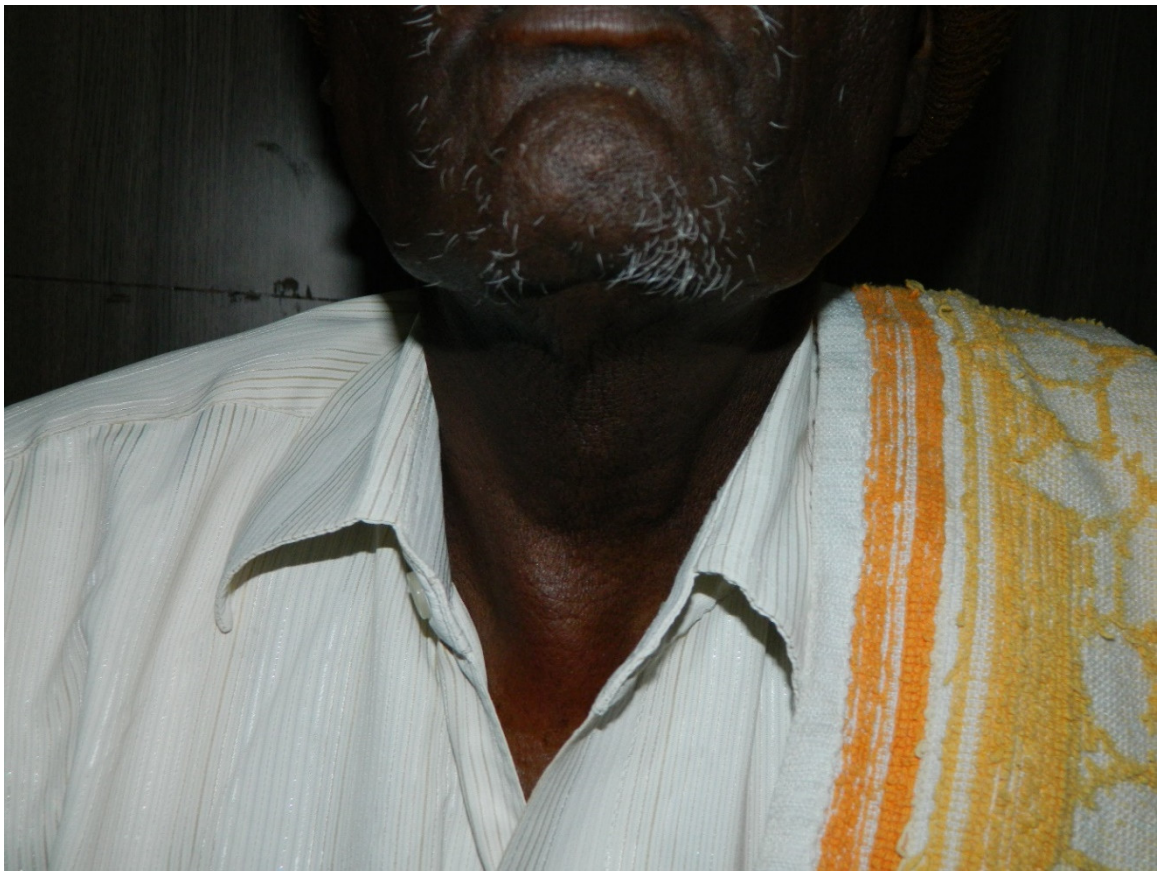


Photo -15: Post radiated neck

Table 06: Various factors in patients with recurrence.

Recurrences in Chemotherapy with Radiotherapy Group						
Stage	**Grade**	**Margin**	**Positive Nodes**	**Perineural Invasion**	**Recurrence Time**	**Type of recurrence**
T4aN2aMx	**Poorly differentiated**	**1.2cm**	**Multiple**	**No**	**1 year**	**Locoregional**
T4aN1MX	**Moderately differentiated**	**0.3cm**	**No**	**No**	**1 Year**	**Local**
T4aN2aMx	**Moderately differentiated**	**0.9cm**	**Multiple**	**No**	**6months**	**regional**
Recurrences in Radiotherapy Group						
T4aN2bMx	**Moderately differentiated**	**0.5cm**	**Multiple**	**Yes**	**6Months**	**Regional**
T3N1Mx	**Moderately differentiated**	**0.7cm**	**No**	**No**	**1Year**	**Local**
T4aN1Mx	**Poorly differentiated**	**0.8cm**	**single**	**yes**	**1year 6months**	**Regional**
T4aN2bMx	**Poorly differentiated**	**1.2cm**	**Multiple**	**No**	**1 year**	**Regional**
T4aN2aMx	**moderately differentiated**	**0.3**	**Single**	**No**	**6 months**	**Local**

Table 07: Disease grading in both the groups.

CT-RT	N0	N1	N2a	N2b
T3	**2**	**6**	**5**	**1**
T4a	**1**	**7**	**5**	**3**
RT				
T3	**3**	**8**	**5**	**0**
T4a	**2**	**5**	**4**	**3**

There are 6 patients with multiple positive lymph nodes in post-operative chemotherapy with radiotherapy group, 2 out of 6 (33%) recurred and 2 (50%) out of 4 patients recurred in post-operative radiotherapy group. Among the patients with positive nodes, 3 out of 7 recurred when post-operative radiotherapy alone was given. In post-operative chemotherapy with radiotherapy, 2 out of 9 recurred.

DISCUSSION

Discussion

From the past 30 years a lot of effort was made to identify the prognostic factors in the postoperative patients with locally advanced oral carcinoma as there are high rates of locoregional failures and distant metastasis. [131-134] Various risk factors identified included two or more resected lymph nodes with tumour deposits, extracapsular spread, and largest node of more than 3 cms, mucosal margins of resected specimen with tumour deposits, perineural invasion and treatment delay of more than 6 weeks. Post-operative adjuvant radiotherapy was recommended for these patients.[135] Both European and American retrospective studies have showed significant reduction in the locoregional failure rates with the introduction of postoperative radiotherapy[131,132,136] But many studies reported a wide range in the locoregional control rate.[133,134,137]

Intergroup study, in 1992 stated that the locoregional control is good with adjuvant Chemotherapy with radiotherapy.[2] Many studies followed it using Cisplatin, Mitomycin and Bleomycin which showed an improvement in locoregional control without significant late radiotherapy complications.[3,4,5] RTOG and EORTC in 2004 has conducted land mark studies which showed almost 10to15% better locoregional control, overall survival rates and disease free survival rates, compared to Postoperative radiotherapy alone.[6,7,8,9] RTOG and another German study has reported more morbidity[10,13,14] EORTC and another RCT has reported almost equivalent toxicity with postoperative concurrent chemotherapy with radiotherapy compared to post-operative radiotherapy alone.[8, 15] After a meta-analysis of both EORTC and RTOG data, oncology groups had come to a consensus that extracapsular spread and Positive margins were definitive indications for Chemotherapy with radiotherapy.[8, 17] leaving a grey area as there are other studies reporting vascular invasion, perineural invasion, multiple lymph nodes with metastatic deposits and advanced T stage also as various other indications. [18,19]

This study included 60 patients with locally advanced oral squamous cell carcinoma ($30T_3$ and $30T_{4a}$) who were alternatively taken up for post-operative radiotherapy or post-operative chemotherapy with radiotherapy. Therefore there were 30 patients who received post-operative radiotherapy and 30 patients who received post-operative chemotherapy with radiotherapy. Patients with tumor deposits in the resected margins and extra capsular spread were excluded from the study. According to the literature it is mandatory to subject them to post-operative chemotherapy with radiotherapy.[10]

Patient's age ranged from 42yrs to 72 yrs with a mean age of 56yrs. The age distribution was almost similar in both the groups. Male to female ratio in the study was 9:11. In post-operative radiotherapy arm it was 13:17 and post-operative chemotherapy with radiotherapy where it was 7:8. The female predominance in our study can be attributed to the habit of having tobacco quid in cheek among the women of this region.

The patients were followed up for a minimum period of 6 months after completing the treatment. 24 of 30 patients in post-operative radiotherapy group and 22of 30 patients in post-operative chemotherapy with radiotherapy group completed 1 year follow-up and 20 of 30 and 19of 30 patients completed 1and half years of follow up respectively after completing post-operative adjuvant treatment.

27 patients had locally advanced buccal mucosa with lower alveolus cancers in post-operative chemotherapy with radiotherapy group and 28 patients in post-operative Radiotherapy group. Rest of the patients had anterior $2/3^{rd}$ of tongue carcinoma. The predominance of buccal mucosa and lower alveolus carcinoma can again be attributed to the tobacco chewing habits in form of quid among the villagers particularly ladies in this region. A study done here had shown high prevalence of oral cancer (particularly buccal mucosa) in this region.[1]

T_3 and T_{4a} with nodal staging ranging from N_0 to N_{2b} are in the study as shown in the table no__. 36 nodal positive cases are found to be N_0 on histopathological examination showing high prevalence of reactive lymph nodes due to poor oral hygiene. Which is in accordance with the other studies.[138,139]

During the course of adjuvant treatment various complications were seen in both the arms of study. 3 patients in post-operative chemotherapy with radiotherapy group had a treatment delay due to significant agranulocytosis and two of these patients required granulocyte stimulating factors. 16.7% of patients had significant agranulocytosis in post-operative chemotherapy with radiotherapy group and 10% had treatment delay. Other studies have also reported treatment delay due to adverse effects of cisplatin.[9,140]

Mucositis was seen in both the groups. 25 0f 30 in post-operative radiotherapy and 27 of 30 in post-operative chemotherapy with radiotherapy. However the severity of mucositis was more in post-operative chemotherapy with radiotherapy compared to post-operative radiotherapy alone. Grade I -13, II-10 and III-2 in post-operative Radiotherapy group and 9 grade I, 14 grade II and 2 grade III in post-operative chemotherapy with radiotherapy. This was similar to the findings in other studies.[9,140]

Moist desquamation was almost similar in both groups with 4 and 3 in post-operative radiotherapy and chemotherapy with radiotherapy respectively. This is in spite of non-escalation of dose in post-operative radiotherapy group. 7 patients in post-operative radiotherapy and 6 in post-operative chemotherapy with radiotherapy had fever during the course of treatment which was statistically insignificant.

14 of 30 patients receiving post-operative chemotherapy with radiotherapy had significant nausea/vomiting which was Cisplatin induced. This was similar to another study in which reported nausea and vomiting as one of the common adverse effects of cisplatin and 5FU

regimen like in ours.[140] However none had severe dehydration or elevation in serum creatinine.

Trismus was seen in 7 patients receiving post-operative Radiotherapy and 10 in post-operative chemotherapy with radiotherapy. All 7 patients in post-operative radiotherapy had grade II trismus. However it was more severe in post-operative chemotherapy with radiotherapy with 5 patients with grade III. 3 patients (10%) receiving post-operative radiotherapy has pneumonia secondary to aspiration compared to 5 (16.7%) in post-operative chemotherapy with radiotherapy. This results are similar to a study that reported aspiration pneumonia in patients receiving chemotherapy and radiotherapy and is attributed to swallowing dysfunction secondary to the treatment.[141]

The above results of the complications appear to be almost similar in both post-operative Radiotherapy and post-operative chemotherapy with radiotherapy groups with only minor differences showing marginally more toxicity in post-operative chemotherapy with radiotherapy group. This was similar to the large study done by EORTC in 2004 where they found toxicity to be almost similar in both groups. However RTOG done at san\me time showed higher toxicityin post-operative chemotherapy with radiotherapy group.[6,9]

There was no treatment related death in either of the two groups in this study.

The causes of increased severity of mucositis and trismus in post-operative chemotherapy with radiotherapy can be attributed to cisplatin induced mucositis in addition to radiation mucositis and resultant fibrosis.

8 patients in this study had recurrence. 3(10%) in post-operative chemotherapy with radiotherapy group and 5 (16.7%) in post-operative radiotherapy group. 4Regional and 3 Local and 1 locoregional recurrences. 3,1 regional, 2,1 local and 0,1 locoregional recurrences in post-operative Radiotherapy and chemotherapy with radiotherapy respectively. This shows

relatively better locoregional control in patients receiving post-operative chemotherapy with radiotherapy. In literature various studies like the two significantly large studies by EORTC and RTOG have shown significantly better locoregional control in advanced head and neck carcinomas receiving post-operative chemotherapy with radiotherapy compared to those receiving post-operative radiotherapy alone. However these two studies have recommended post-operative chemotherapy with radiotherapy whenever the adverse factors included positive margins and extra capsular spread.[10] The inclusion of chemotherapy in addition to post-operative radiotherapy in other adverse factors like perineural invasion multiple positive lymph nodes, lymphovascular emboli, bone erosion etc. was optional but not mandatory by these studies. A Taiwanese study published in 2014 found better regional control rates when patients having multiple lymph nodes without extra capsular spread.[18]

In our study out of 6 patients with multiple positive lymph nodes 2 out of 6 (33%) recurred in post-operative chemotherapy with radiotherapy group and 2 (50%) out of 4 patients recurred in post-operative radiotherapy group. Though the number of patients with multiple lymph nodes is less, the recurrence pattern shows better results with post-operative chemotherapy with radiotherapy similar to Taiwanese study.[18] Among the 5 patients out of 8 who recurred in post-operative Radiotherapy arm 4T_{4a} and 1 T_3, 2 N_1, 1 N_{2a}, and 2 N_{2b}. Among the 3 patients out of 8 who recurred in post-operative chemotherapy with radiotherapy arm all 3 had tumors with T_{4a}, 1 N_1, and 2 N_{2a}. Two patients staged N_{2a} preoperatively were upstaged postoperatively and two patients staged N_1 preoperatively was found to be reactive on histopathological examination of resected specimen.

In post-operative chemotherapy with radiotherapy group all three patients were T_{4a} in view of skin and bone involvement. The 1 patient with poorly differentiated Squamous Cell Carcinoma had locoregional recurrence showing that higher grading is a poor prognostic factor.

Among the patients with positive nodes, 3 out of 7 recurred when post-operative radiotherapy alone was given. In post-operative chemotherapy with radiotherapy, 2 out of 9 recurred. This shows better regional control with post-operative chemotherapy with radiotherapy compared with post-operative radiotherapy alone. Similar benefit with post-operative chemotherapy with radiotherapy was noted in both EORTC and RTOG studies.[6,9]

Perineural invasion cases, 1 out of 3 recurred in post-operative radiotherapy group and in post-operative chemotherapy with radiotherapy none of 4 recurred showing it gives better locoregional control when perineural invasion is seen, this is similar to EORTC and RTOG studies.[6,9]

The analysis of recurrences shows that majority of recurrences occur during 6 months to 1 year after completing the treatment.

Due to small numbers we have not been able to analyze the risk due to bone involvement and skin involvement in recurrence and role of post-operative chemotherapy with radiotherapy in preventing them. In our study post-operative chemotherapy with radiotherapy gave better locoregional control when compared to post-operative radiotherapy alone in presence of adverse factors like T_4 disease, perineural invasion, multiple positive lymph nodes and single positive lymph nodes especially when node was larger than 3cms.

Larger multicentric studies involving bigger sample size and longer follow up period are required to document and mandate chemotherapy in addition to post-operative radiotherapy in patients with adverse factors after composite resection.

CONCLUSION

Conclusion

1. There is a high prevalence of oral carcinoma particularly buccal mucosa carcinoma in the Kolar region due to the habit of chewing tobacco quid.
2. Most of patients present with locoregionally advanced disease.
3. Addition of chemotherapy (Cisplatin 100mg/m^2 BSA once in 3 weeks) to post op adjuvant radiotherapy improves locoregional control in patients with adverse factors on histopathological examination of specimen like multiple lymph nodes showing metastasis, metastatic Lymph Node more than 3cm in diameter, perineural invasion and T_{4a} disease due to skin or bone involvement.
4. The complications encountered in patients receiving post-operative chemotherapy with radiotherapy compared to post-operative radiotherapy alone were almost similar. However significant agranulocytosis can occur in some patients receiving post-operative chemotherapy with radiotherapy and severity of trismus and mucositis in patients receiving post-operative chemotherapy with radiotherapy is more than their counterparts receiving post-operative radiotherapy alone.
5. There can be treatment delay in few patients when chemotherapy is added to post-operative radiotherapy due to toxicity like agranulocytosis.
6. Patients found to have positive margins or extracapsular spread of tumor should receive post-operative chemotherapy with radiotherapy as recommended by various studies in literature.
7. More multi-institutional studies with larger sample size and longer follow up are required to prove the definite advantage of chemotherapy with radiotherapy in locally advanced oral carcinoma having adverse factors like multiple lymph nodes showing metastasis, metastatic Lymph Node more than 3cm in diameter, perineural invasion and T_{4a} disease due to skin or bone involvement.

SUMMARY

Summary

Oral Carcinomas are very common in Kolar region. And most of them present at an advanced stage.[1] Combined modality approach for the locally advanced oral Squamous Cell Carcinoma is advocated from the past two decades. Though the outcome was significantly improved compared to surgery alone, the locoregional recurrence and overall survival hasn't improved much.

Most of the guidelines regarding the head and neck oncology state that resection of tumour is definitive treatment for locally advanced oral carcinoma regardless of the lymph node status. And in post operatively adjuvant radiotherapy or Chemoradiation is to be given within 6 to 8 weeks to improve chances of locoregional control. However, in achieving locoregional control, there are lacunae in knowledge on whether Chemoradiotherapy or Radiotherapy alone should be given post operatively and some studies done in Europe and Taiwan state that Chemoradiation gives better results in these patients.[6,9,18]

Patients with T_3 and (locally advanced) T_{4a} stage oral carcinoma, after composite resection were randomized into two groups post operatively and either Chemoradiotherapy or Radiotherapy alone were given according to their group. Locoregional Recurrence, Overall Survival Rate, disease free survival rate and adverse events were documented and compared.

The various adverse effects noted in the study include Mucositis, Agranulocytosis, Moist Desquamation, Fever, Nausea/Vomiting, Pneumonia, Elevated Serum Creatinine, Trismus, Osteoradionecrosis and Toxicity related treatment delay. There were no treatment related deaths encountered in the study. Trismus and Mucositis is most commonly encountered adverse effects. About 23.3% (7) of patients in radiotherapy group developed trismus and 33.3% (10) of patients in Chemoradiotherapy group developed trismus. The grade of trismus is also more in chemo radiotherapy group compared to radiotherapy group. There were total 8 Recurrences

noted in the study at various follow up times. 16.7% (5) of patients in radiotherapy group had locoregional recurrence compared to 10% (3) patients in Chemoradiation group. Of the patients who recurred, multiple lymphnodes showing metastasis, poorly differentiated carcinoma, higher stage and perineural invasion acted as risk factors.

We can conclude that addition of chemotherapy (Cisplatin 100mg/m2 BSA once in 3 weeks) to post op adjuvant radiotherapy improves locoregional control in patients with adverse factors on histopathological examination of specimen like multiple lymph nodes showing metastasis, metastatic Lymph Node more than 3cm in diameter, perineural invasion and T4a ¬disease due to skin or bone involvement.

The complications encountered in patients receiving post-operative chemotherapy with radiotherapy compared to post-operative radiotherapy alone were almost similar. However significant agranulocytosis can occur in some patients receiving post-operative chemotherapy with radiotherapy and severity of trismus and mucositis in patients receiving post-operative chemotherapy with radiotherapy is more than their counterparts receiving post-operative radiotherapy alone.

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ANNEXURE I

Case No.: Group: Sr. No.:

COMPARISON OF EFFICACY OF POSTOPERATIVE RADIOTHERAPY AND CHEMORADIOTHERAPY IN LOCALLY ADVANCED ORAL CARCINOMA (T_3 AND T_{4A})

Proforma

Case No.: **Group:** **Hospital No.:** **DOA:**

Name of the patient: **Age:** **Sex: M/F**

Occupation: **Phone No.:**

Address:

Complaints of	Yes/no	Since
Ulcer/mass in oral cavity		
Mass/swelling in neck		
Restricted mouth opening		
Excessive salivation		
Difficulty in swallowing		
Voice change		
Loss of appetite		
Weight loss		
Generalized weakness		
Pain in Cheek (Side:)		
Loose Tooth		
Others (Specify) • • •		

Co-morbidities	Yes/no	Since
Hypertension		
Diabetes Mellitus		
Pulmonary Tuberculosis		
Acid Peptic Disease		
Others (Specify) • • •		

Case No.: Group: Sr. No.:

Family History: ☐ Contributory ☐ Not contributory

Personal history	
Sleep, bowel, bladder habits	
Appetite	

Habits	**Yes/no**	**Quantity/day**	**Since**
Tobacco chewing			
Bidi			
Cigarette			
Alcohol			
Others (Specify) • • •			

General physical examination:

Built: Nourishment: Pallor:

Icterus: Pulse: Blood pressure:

Weight:

Local examination:

Oral cavity:

Orodental hygiene:

Lips:

Mouth opening: Trismus: ☐ Present ☐ Absent

Lesion	Site	Greatest Antero Posterior diameter in cms	Greatest Transverse diameter in cms	Type of growth

Neck nodes:

Number: Level of node:

Size: Consistency:

Tendernes: Mobility:

Skin over the node:

Clinical diagnosis with TNM Staging:

Investigations:

Hb: **RBC:** **TC:** **Platelets:**

BT: **CT:** **HIV:** **HBsAg:**

DC: N: L: M: E: B: Others: **RBS:**

CT SCAN/USG Neck:

FNAC:

Biopsy Report:

Case No.: Group: Sr. No.:

Treatment:

Operation done:

- ☐ Wide excision
- ☐ Hemimanibulectomy
- ☐ Marginal mandibulectomy
- ☐ SOND ☐ MRND ☐ RND

Date of surgery:

Intra-operative findings:

Cervical facial lymph nodes: ☐ Present ☐ Absent

Number:

Size of the biggest node:

Extracapsular spread: ☐ Present ☐ Absent

Mobility:

Histo-pathological report:

Of the primary tumour:

Histological type: Squamous cell carcinoma

☐ Conventional ☐ Verrucous ☐ Papillary ☐ Acantholytic

Differentiation:

- ☐ well
- ☐ Moderately
- ☐ Poor

Margins: ☐ Positive ☐ Negative

Lymph node status

Total number of lymph nodes:

No. of positive nodes:

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

Extra-capsular spread: ☐ Present ☐ Not Identified

Neo-Adjuvant therapy prior to surgery:

☐ Given ☐ Not given

If Given:

☐ RT ☐ CT ☐ RT and CT

Postoperative adjuvant therapy:

☐ **Radiotherapy** ☐ **Chemo-radiotherapy**

Radiotherapy: From: To:

Mode: ☐ Conventional (Cobalt 60)

☐ IMRT

☐ Linear Acceleration

Dose: Fractions: Days:

Chemotherapy: Cycles: 1: 2: 3:

Dose per cycle: 1: 2: 3:

Adverse Events:

Adverse event (Please Tick)	**At 6 Weeks**		**At 3 Months**		**At 6 Months**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
Mucositis						
Hematologic Toxicity						
Moist Desquamation						
Neurotoxicity						
Ototoxicity						
Fever						
Nausea/Vomiting						
Severe Dehydration						
Malnutrition						

Pneumonia						
Elevated Serum Creatinine						
Trismus						
Osteoradionecrosis						
Toxicity related treatment delay						
Treatment related Death						

Follow up:

	At 6 weeks	**At 3 months**	**At 6 months**
Disease free			
Local recurrence			
Regional recurrence			
Locoregional recurrence			
Distant metastasis			

Last Date of Follow-up:

ANNEXURE II

Case No.: Group: Sr. No.:

COMPARISON OF EFFICACY OF POSTOPERATIVE RADIOTHERAPY AND CHEMORADIOTHERAPY IN LOCALLY ADVANCED ORAL CARCINOMA (T_3 AND T_{4A}).

Informed Consent Form:

I, Mr./Mrs. have been explained in a language I can understand, that I will be included in a study which is comparing the efficacy of chemotherapy plus Radiotherapy and Radiotherapy alone in post operative patients of locally advanced oral cancer.

I've been explained that there are two different treatments modalities being given to the patients in the study, i.e., chemotherapy plus radiotherapy and radiotherapy alone, and the complications associated as given in the information sheet.

I've been explained that my participation in this study is entirely voluntary and any complications due to the treatment will be attended to promptly. I can withdraw from the study anytime and this will not affect my relation with my doctor or the treatment for my ailment.

I've been explained that this study requires a fallow up of 6 moths that contain regular clinical examination and Ultrasound scan of the neck. and that there is no additional cost involved. And in case any additional cost, it will be reimbursed.

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

I, in my sound mind give consent to be added in the study.

Signature of the Patient Signature of the Witness

Name: Name:

Date: Place:

ANNEXURE III

RTOG Scoring Criteria

Grade	Description
0 (none)	No change over baseline
I (mild)	Irritation, may experience slight pain, not requiring analgesic
II (moderate)	Patchy mucositis that may produce inflammatory serosanguinitis discharge; may experience moderate pain requiring analgesia
III (severe)	Confluent, fibrinous mucositis, may include severe pain requiring narcotic
IV(life-threatening)	Ulceration, hemorrhage, or necrosis

- Trotti et al. Int J Radiat Oncol Biol Phys 2000; 47:13-47.
- Sonis et al. Cancer 2004; 100(9 Suppl):1995-2025.

Trismus grading used

Stage I: Mouth opening > 3 cm

Stage II: Mouth opening 2–3 cm

Stage III: Mouth opening <2 cm

ANNEXURE IV

Master Chart Post-Operative Radiotherapy Group

Sr. No (RTX)	Site	Clinical Staging	Age	Sex	Comorbidities	Habit duration	Mucositis	Agranulocytosis	Moist Desquamation	Ototoxicity	Fever	Nausea/ Vomiting	Severe Dehydration	Pneumonia	Trismus	Osteoradionecrosis	Toxicity related treatment delay	Recurrence at 6 Week	At 3 months	At 6 months	at 1 year	At 1 Year 6 months	Grade of tumor	Closest margin	Skin Involvement	Bone Involvement	Nodes	Perineural Invasion
1	B	$T_3N_1M_X$	52	F	-	35	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	1	-	-	-	-
2	B	$T_{4a}N_1M_X$	60	M	D	30,A	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	1.4	-	-	-	-
3	T	$T_3N_{2a}M_X$	65	F	-	35	2	-	-	-	+	-	-	-	2	-	-	-	-	-	-	-	W	1.6	-	-	++	-
4	B	$T_{4a}N_{2a}M_X$	45	M	-	25	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	0.8	+	-	-	-
5	L	$T_{4a}N_{2b}M_X$	55	F	-	30	1	-	+	-	-	-	-	+	-	-	-	-	-	+			M	0.5	-	-	++	+
6	B	$T_{4a}N_1M_X$	60	F	D	30	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	M	0.9	-	-	-	-
7	T	$T_3N_{2a}M_X$	58	M	H	30,A	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	1.1	-	-	-	-
8	B	$T_3N_1M_X$	48	F	-	20	2	-	-	-	+	-	-	-	-	-	-	-	-	-	+		M	0.7	-	-	-	-
9	L	$T_{4a}N_1M_X$	50	F	-	20	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	1.2	-	-	-	-
10	L	$T_3N_1M_X$	45	F	-	20	1	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	W	1.2	-	-	-	-
11	L	$T_{4a}N_{2a}M_X$	58	F	-	30	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	0.9	+	+	-	-
12	B	$T_{4a}N_1M_X$	63	F	-	35	3	-	+	-	+	-	-	+	-	-	-	-	-	-	-	+	P	0.8	-	-	+	+
13	B	$T_3N_1M_X$	66	M	H	30	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	M	1.4	-	-	-	-
14	B	$T_3N_{2a}M_X$	54	M	D,H	25	1	-	-	-	+	-	-	-	2	-	-	-	-	-	-	-	P	1.3	-	-	-	-
15	B	$T_{4a}N_{2b}M_X$	72	M	-	40	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	1.5	+	-	-	-
16	B	$T_3N_1M_X$	44	M	-	20	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	M	1.7	-	-	-	-
17	B	$T_3N_1M_X$	47	M	-	30	1	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	P	1.4	-	-	-	-
18	B	$T_{4a}N_1\ M_X$	57	F	H	30	2	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	M	1.5	+	-	-	+
19	B	$T_{4a}N_{2b}M_X$	62	F	-	40	1	-	-	-	-	-	-	-	-	-	-	-	-	-	+		P	1.2	-	-	++	-
20	L	$T_{4a}N_{2a}M_X$	69	F	H	45	1	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	W	0.9	-	+	-	-
21	B	$T_3N_1M_X$	63	M	-	35,A	1	-	-	-	+	-	-	-	-	-	-	-	-	-	-	NA	W	0.8	-	-	-	-
22	B	$T_3N_1M_X$	55	F	-	20	2	-	-	-	-	-	-	+	2	-	-	-	-	-	-	NA	M	1.3	-	-	+	-
23	L	$T_3N_{2a}M_X$	60	M	-	30	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	W	0.7	-	-	++	-
24	B	$T_3N_1M_X$	65	F	D,H	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	W	1.5	-	-	-	-
25	B	$T_{4a}N_{2a}M_X$	60	F	-	35	3	-	+	-	-	-	-	-	-	-	-	-	-	+		NA	M	0.3	-	+	-	-
26	L	$T_{4a}N_1M_X$	48	M	-	25,A	2	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	M	1.2	-	-	-	-
27	L	$T_3N_1M_X$	40	F	-	20	2	-	-	-	+	-	-	-	2	-	-	-	-	-	NA	NA	W	0.7	-	-	-	-
28	B	$T_{4a}N_1M_X$	56	M	-	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	M	1.3	-		-	-
29	B	$T_3N_{2a}M_X$	54	M	-	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	W	1.1	-		+	-
30	B	$T_3N_1M_X$	48	F	-	20	2	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	W	0.9	-		-	-

Legend:

B = Buccal Mucosa

L = Lower Alveolus

T = Anterior 2/3rd of Tongue

M = Male (in Sex)

F = Female

D = Diabetes Mellitus

H = Hypertensive

A = Alcoholic

+ = Present/Positive

- = Absent/Negative

W = Well Differentiated

M = Moderately differentiated (in Grade of tumor)

P = Poorly Differentiated

++ = Multiple nodes positive

NA = Not Available

Master Chart Post-Operative Chemotherapy with Radiotherapy Group

Sr. No(CRTX)	Site	Clinical Staging	Age	Sex	Comorbidities	Habit duration	Mucositis	Agranulocytosis	Moist Desquamation	Ototoxicity	Fever	Nausea/ Vomiting	Severe Dehydration	Pneumonia	Trismus	Osteoradionecrosis	Toxicity related treatment delay	Recurrence at 6 Week	At 3 months	At 6 months	at 1 year	At 1 Year 6 months	Grade of tumor	Closest margin	Skin Involvement	Bone Involvement	Nodes	Perineural Invasion
1	B	$T_3N_1M_X$	49	M	-	30	2	-	-	-	+	+	-	+	-	-	-	-	-	-	-	-	W	1.6	-	-	-	-
2	B	$T_{4a}N_{2b}M_X$	64	F	H	35	1	-	-	-	-	+	-	-	2	-	-	-	-	-	-	-	W	1.2	-	-	-	-
3	B	$T_{4a}N_{2a}M_X$	69	F	D, H	40	3	-	-	-	-	+	-	-	-	-	-	-	-	-	+		P	1.2	+	-	++	-
4	L	$T_3N_{2a}M_X$	63	M	-	35	3	+*	-	-	+	-	-	+	-	-	+	-	-	-	-	-	W	1.7	-	-	-	-
5	B	$T_3N_{2a}M_X$	45	M	-	20,A	2	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	M	1.4	-	-	-	-
6	L	$T_3N_{2b}M_X$	52	M	-	30	2	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	W	1.3	-	+	-	-
7	B	$T_{4a}N_1M_X$	58	F	-	35	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	P	1.6	+	-	++	+
8	B	$T_{4a}N_{2a}M_X$	55	F	D	35	1	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	M	0.9	-	-	+	+
9	T	$T_3N_1M_X$	48	M	-	25	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	0.7	-	-	-	-
10	L	$T_3N_1M_X$	58	F	-	30	2	+*	-	-	+	+	-	+	-	-	+	-	-	-	-	-	W	0.9	-	-	-	-
11	B	$T_{4a}N_1M_X$	62	M	-	35	1	-	-	-	-	+	-	-	-	-	-	-	-	-	+		M	0.3	-	-	-	-
12	B	$T_3N_{2a}M_X$	63	F	D	40	2	-	+	-	-	+	-	-	2	-	-	-	-	-	-	-	W	1.3	-	-	+	-
13	L	$T_3N_{2a}M_X$	57	F	-	30	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	W	1.4	-	-	-	-
14	L	$T_{4a}N_{2a}M_X$	71	M	H	45	1	-	-	-	-	-	-	-	-	-	-	-	-	+			M	0.9	+	+	++	-
15	T	$T_{4a}N_1M_X$	50	F	-	30	1	+	-	-	-	-	-	-	3	-	-	-	-	-	-	-	W	0.9	-	-	++	-
16	B	$T_{4a}N_{2b}M_X$	54	F	-	30	2	-	-	-	+	-	-	+	3	-	-	-	-	-	-	-	W	1.4	-	-	-	-
17	L	$T_3N_1M_X$	62	M	H	35	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	M	1.6	-	-	-	-
18	B	$T_3N_1 M_X$	68	M	-	40	2	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	M	0.8	-	-	-	-
19	B	$T_{4a}N_1M_X$	66	F	D	40	3	-	-	-	+	-	-	-	2	+	-	-	-	-	-	-	W	0.6	-	-	-	-
20	B	$T_{4a}N_{2a}M_X$	53	M	-	20,A	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	W	0.5	+	-	+	+
21	T	$T_3N_1M_X$	40	F	-	15	2	+*	-	-	-	+	-	-	-	-	+	-	-	-	-	NA	M	0.9	-	-	-	-
22	B	$T_{4a}N_1M_X$	45	F	-	20	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	W	0.8	+	-	++	-
23	B	$T_{4a}N_{2a}M_X$	52	M	D,H	30	1	-	+	-	-	-	-	-	3	-	-	-	-	-	NA	NA	W	0.4	-	-	-	-
24	B	$T_{4a}N_{2b}M_X$	56	F	-	25	2	-	-	-	-	+	-	-	-	-	-	-	-	-	NA	NA	P	1.3	-	+	++	-
25	L	$T_{4a}N_1M_X$	47	M	-	25,A	2	-	-	-	+	-	-	+	2	-	-	-	-	-	NA	NA	M	1	-	-	-	+
26	L	$T_3N_{2a}M_X$	48	F	-	25	-	+	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	M	1.3	-	-	-	-
27	B	$T_3N_1M_X$	48	M	-	15	3	-	-	-	-	+	-	-	-	-	-	-	-	-	NA	NA	M	1.8	-	-	-	-
28	L	$T_3N_1M_X$	63	F	-	25	2	-	-	-	+	+	-	-	-	-	-	-	-	-	NA	NA	W	0.5	-	-	-	-
29	B	$T_{4a}N_1M_X$	67	M	H	40	2	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	W	1.1	-	-	-	-
30	B	$T_{4a}N_1M_X$	59	F	-	35	1	-	-	-	-	-	-	-	2	-	-	-	-	-	NA	NA	W	1	-	-	-	-

Legend:

B = Buccal Mucosa

L = Lower Alveolus

T = Anterior 2/3rd of Tongue

M = Male (in Sex)

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+ = Present/Positive

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W = Well Differentiated

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P = Poorly Differentiated

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NA = Not Available