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Research Article

An Evaluation of Intensity Modulated Radiotherapy (IMRT) versus Radical Brachytherapy in Early Stage Buccal Mucosal Cancers (T1N0M0)

Bhupen Prasad *

*Correspondence to: Bhupen Prasad, India.

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Introduction

Head and Neck squamous cell carcinoma is the sixth commonest cancer in the world.[1] Head and neck are one of the commonest sites for squamous cell carcinoma in our country accounting for 23% of all cancers in males and 6% in females.[2]

Oral cancer is a part of a group of head and neck cancer which arise as a primary lesion in any part of the oral cavity. Oral cancer (OC) is the commonest cancer in developing countries like India, accounting for 50–70% of total cancer mortality and accounts for the highest incidence among Asian countries. [3] Globally, oral cancer is the sixth most common cancer.[4] Worldwide, with an incidence of 300,000 cases in 2012, amounting for over 2% of the overall burden of cancer diagnosed globally.[5] It is estimated in the United States for 2017, about 49,670 new cases of oral and oropharyngeal cancers and about 9,700 people will die of these cancers.[6] The average age of most people diagnosed with these cancers is in the 6th-7th decade of life, but they can occur in young people.

Oral cancer is a major problem in the Indian subcontinent where it ranks among the top three types of cancer in the country.[7] Age-adjusted rates of oral cancer in India is high, that is, 20 per 100,000 population and accounts for over 30% of all cancers in the country.[8] A recent report prepared by experts of National Institute of Health and Family Welfare (NIHFW) to study the harmful effects of gutka specified clearly that India alone accounted for 86 percent of the total oral cancer figure across the world. The variation in incidence and pattern of the disease can be attributed to the combined effect of aging of the population, as well as regional differences in the prevalence of disease-specific risk factors.[9] The high incidence of carcinoma of the Buccal Mucosa in our country is attributable to the extensive use of tobacco in various forms and the locally advanced cancers account for about 70% of the cases at the time of presentation.

As per the hospital-based cancer registry of Kamala Nehru Memorial Hospital, Regional Cancer Centre, Allahabad, the hospital-based incidence of total head and neck cancer patients constitute 1301 cases of all cancer patients reported from 2016-2017. Among them 36.27 % are exclusively buccal mucosa cancers, accounting for 472 cases of all age groups including both the sexes. The ratio of male: female is 3:1.10 In 2017, total no. of cases of buccal mucosa cancers were 467 out of which 351 were males and 116 were females whereas, in 2018, total no. of cases of buccal mucosa cancers were 423 out of which 317 were males and 106 were females.[10] The registry shows strong male predominance. Among oral cavity cancers, the most common subsite is buccal mucosa and the present study aims at treatment profiles of these cancers.

The buccal mucosa is the mucosa that lines the inner surface of the lips and cheeks. From the back of the mouth to the front of the mouth, the buccal mucosa extends from the anterior tonsillar pillar (also called the palatoglossus muscle) and includes the innermost lining of the lips. The buccal mucosa includes the mucosal surfaces of the cheek and lips from the line of contact of the opposing lips to the pterygomandibular raphe posteriorly. This extends to the line of attachment of the mucosa of the upper and lower alveolar ridge superiorly and inferiorly. Sensation in this part of the mouth is provided by the third division of the fifth cranial nerve (called the trigeminal nerve). Innervation is supplied by the buccal nerve, a branch of the mandibular nerve.

Just underneath the buccal mucosa, in the inner cheek, are minor salivary glands, nerves, blood vessels, and tiny lymphatic channels. Also, the buccal fat pad and some important muscles of facial movement and chewing are located between the buccal mucosa and the cheek skin. Finally, the upper and lower jawbones are on the border of the buccal region. Because of these structures, buccal cancers can cause a number of different symptoms, depending on what neighboring structures they invade.

The regional lymph node anatomy of the head and neck contains lymph nodes that run parallel to the jugular veins, spinal accessory nerve, and facial artery and into the submandibular triangle; an understanding of this anatomy and the status of regional lymph nodes is critical to the care of head and neck cancer patients. The regions of the neck have been characterized by levels (I–VII) to facilitate communication regarding the lymph node anatomy:

- Level I: contains the submental and submandibular lymph nodes.
- Level II: contains the upper jugular lymph nodes, which are above the digastric muscle.
- Level III: contains the mid-jugular lymph nodes, which are between the omohyoid muscle and the digastric muscle.
- Level IV: contains the lower jugular lymph nodes.
- Level V: contains the lymph nodes of the posterior triangle.
- Level VI: lymph node of the anterior compartment. (Pre- and Paratracheal, the pre-cricoid node, and the perithyroidal nodes)
- Level VII: upper mediastinal nodes.

The risk of neck metastases depends on several factors including site and size of the primary tumor. Overall, for patients with squamous cell carcinoma of the oral cavity, cervical metastases occur in approximately 30% of cases.[11] For cancers of the buccal mucosa, the incidence of positive cervical lymph nodes at diagnosis is 10% to 30%; the incidence of pathologically positive nodes in a clinically negative neck is about 15%.[12]

The reported 5-year survival rates for Buccal Mucosa cancers in India ranges from 80% for stage I disease to 5-15% for locally advanced disease.[13,14] There is generally a lack of consensus over the use of surgery, radiotherapy and chemotherapy in the treatment of advanced Buccal Mucosa cancers in India. This includes sequence/combination of the different modalities and the use of concurrent chemo-radiotherapy. Recurrent disease after surgery and/or radiotherapy is difficult to salvage and therefore it is necessary to provide optimum, state of the art, evidence-based care to patients to improve cure rates with minimum morbidity and good quality of life. Providing treating doctors with uniform guidelines for the management of Buccal Mucosa cancer appears to be an appropriate step forward in achieving this goal.

Tobacco and alcohol have long been implicated as the traditional risk factors for HNSCC in adults, regardless of age. Individuals who smoke more than 20 cigarettes a day and consume more than 100 g of alcohol a day are believed to be at increased risk for oral epithelial dysplasia.[15] Chewing of the "betel quid' (also known as 'pan') is linked to the development of HNSCC of the buccal mucosa. The relative risk for OSCC was 7.74 for betel quid with tobacco whereas the relative risk reduces to 2.56 for betel quid without tobacco.[16] Although alcohol is not considered to be a carcinogen, excessive alcohol intake increases the risk of HNSCC most often acting synergistically with tobacco.[17]

The natural course of progression of the disease from pre-malignant lesions to the malignant transformation occurs with years of exposure. The different premalignant lesions associated with oral cancers are:

Leukoplakia: It is the most common precursor of oral cavity cancer. WHO defines as white patch or plaque that cannot be rubbed off or characterized clinically or pathologically as any other disease. The malignant transformation is 1-18%.[18]

Erythroplakia: It describes a chronic, red, generally asymptomatic lesion or patch on the mucosal surface that cannot be attributed to a traumatic, vascular, or inflammatory cause. It has a high malignant transformation with approximately 51% of histological specimens showing invasive carcinoma.[19]

Oral Submucosal Fibrosis: It describes generalized fibrosis of the oral cavity tissues resulting in marked

rigidity and trismus. Oral submucous fibrosis is associated with the use of betel quid (with or without tobacco) or pan masala. In India, it is estimated that as many as 5 million individuals are affected with oral submucous fibrosis.[20]

Squamous cell carcinomas (SCC) constitute more than 90% of all oral cancer. Buccal SCCs are usually low-grade cancers and are most commonly found in the lateral walls of the buccal cavity. These lesions spread along the submucosal surface and may eventually involve the skin. Advanced lesions may erode the adjacent alveolar margin.

Histological Classification

- Squamous cell Carcinoma (Predominant)
    - Basaloid variant (Worse Prognosis, Higher Grade)
    - Verrucous variant (Low Grade, Good Prognosis)
- Non-Squamous type (10%)
    - Adenocarcinomas,
    - Melanoma (0.8-2% Of All Melanomas)
    - Ameloblastoma,
    - Lymphoma (2% of all lymphomas)
    - Kaposi sarcoma

Prognostic Factors

Host and tumor factors have been correlated with survival but not consistently with primary, nodal, and distant relapses. Age and gender are host characteristics that may have prognostic significance. Although the TNM system is the accepted standard for head and neck tumor classification, there are often discrepancies between tumor size and survival. Recurrence rates increased with tumor size, clinical stage, thickness, and depth of invasion. Measurement of tumor thickness should be included in estimating prognosis, planning therapy, and comparing results in patients with squamous cell carcinoma of the buccal mucosa.[21]

Diagnostic Workup

A comprehensive head and neck examination is mandatory in patients with suspected oral/buccal mucosa cancers. Visual inspection and palpation allow an accurate impression of the extent of the disease, the presence of bone invasion, or skin breakdown. Appropriate documentation with drawings and photographic records of the tumor are useful in staging, decision-making and further follow up.

The choice of imaging modality is often determined by clinical findings. CT is adequate for early mucosal lesions and the staging for lymph node metastasis. MRI provides complementary information about soft tissue extent and perineural invasion and is also helpful for evaluating the extent of medullary bone involvement because adult marrow is normally replaced by fat. The initial workup consists of diagnosis by biopsy.

Staging

The TNM classification laid down by the American Joint Commission on Cancer (AJCC 2010) is universally accepted for staging buccal mucosa cancer.**[**22**]**(ANNEXURE I)

Treatment

The goals of treatment of stage I buccal mucosa cancers are the eradication of tumor, preservation of organ function, enhance the quality of life, improve overall survival and decrease the incidence of second malignancies. Both surgery and irradiation are equally effective at treating early-stage buccal mucosa cancers. Tumor factors, patient factors, and physician and patient preferences should dictate the choice of therapy.

Surgery is the most common and gold standard treatment employed in early stage buccal mucosa cancer, which results in a cure for most of the patients. In some cases, patients are unable to tolerate surgery or unwilling to undergo surgery due to cosmesis and functional morbidity, radiation becomes the cornerstone of the treatment.

Teletherapy is the general term applied to the treatment when an external source of radiation is at an appreciable distance {generally 80-100 cm} from the part being treated. Radiation beams used are high energy x-ray {linear accelerator}/ gamma rays{co60}. The radiotherapy practice in head and neck cancer is immensely benefitted by the advanced modalities like Intensity Modulated Radiotherapy **[**IMRT**]**&

Image-Guided Radiotherapy **[**IGRT**]**. The judicious combination of beam portal, a beam modification device is capable of providing better dose homogeneity in tumor volume and enhancing the doses accordingly.

In the 1990s, technological and computer treatment planning advances led to the development of Intensity-modulated radiotherapy {IMRT}. The technique of IMRT is more complex and resource-intensive than 3DCRT. It uses a CT-based inverse planning process to deliver ionizing radiation conformally to the target by altering the beam intensity using tungsten-based multi-leaf collimators. Standard IMRT techniques are referred to as sliding window, step, and shoot.

IMRT is a specialized form of 3D-CRT that allows radiation to be more exactly shaped to fit the tumor. The radiation beam in IMRT can be split into many tiny beamlets and the intensity of each beamlet can be modulated. Using IMRT it is possible to further limit the amount of radiation received by normal tissue located in the close proximity of the tumor. The ability to optimize the intensities of each beamlet leads to attaining desired tumor control and minimal toxicity to normal tissues. With respect to oral cavity cancer, IMRT offers the opportunity to diminish normal tissue toxicities, including damage to major salivary glands (xerostomia), to the mandible (osteoradionecrosis) and to the spinal cord(myelopathy).**[**23,24**]**

IMRT requires an exact determination of the tumor location and a thorough knowledge of the processes of likely infiltration and spread.**[**25**]** International Commission on Radiation Units and Measurements created terminology for use across institutions. Definitions include gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV).26 The GTV pertains to gross disease identified by clinical workup (physical examination and imaging), CTV includes the GTV and any areas at risk for microscopic disease, and PTV is an expansion of the CTV by a margin to account for patient or organ motion and day to day set up variation. ICRU 83 (Annexure VI) presents updated definitions for IMRT and assorted volumes that will form the skeleton of the treatment plan.**[**27**]**

IMRT has many potential advantages. It can be used to produce dose distributions that are more conformal than those possible with standard 3DCRT. Dose distributions within the PTV can be made more homogenous, and a sharper fall off of dose at the PTV boundary can be achieved. This may reduce the volume of normal tissues to be exposed to a high dose and may allow escalation of tumor dose, reduction of normal tissue dose, leading to an improved outcome, including lower morbidity. A lower rate of complications also may result in a lower cost of patient care following the treatment.

An integrated boost treatment may offer an additional radiobiologic advantage28 in terms of lower dose per fraction to normal tissues while delivering a higher dose per fraction to the target volume. Higher dose per fraction also reduces the number of fractions and hence lowers the cost and burden to the patient for a treatment course. IMRT also offers the potential of adaptive therapy- revision of the treatment plan according to imaging of tumor reduction and organ movement during the course of radiation therapy.

By modulating photon beam, it is possible to obtain concave and convex shape dose distributions with IMRT, and it has the ability to conform radiation dose to irregular target volumes sparing the underlying critical structures resulting in better tumor control probability (TCP) and reduced normal tissue complication probability (NTCP).

IMRT theoretically reduces radiation dose to adjacent organs or tissues at risk. However, with IMRT a larger volume of uninvolved adjacent tissues may be exposed to low-intensity ionizing radiation than 3DCRT. There is also an increased probability of missing out areas of the microscopic spread of tumor due to tighter margins which result in recurrences leading to treatment failure. Other limitations of IMRT include high cost, complex and time-consuming planning procedures, etc compared to earlier modalities of EBRT.

Brachytherapy (BRT) is an invasive technique that was the first form of irradiation in clinical use, dating back to 1901 with the use of radium. Historically, it has been used extensively in many tumor types, including head and neck cancers and skin cancers. Brachytherapy is the best form of conformal radiotherapy. ICRU 38 defined three categories of brachytherapy:

- Low dose rate (LDR)—a range of 0.4 to 2 Gy per hour.
- Medium dose rate (MDR) a range of 2 to 12 Gy per hour.
- High dose rate (HDR) over 12 Gy per hour, which must be delivered by automatic after-loading.

With the development of high-dose-rate brachytherapy (HDR-BRT), having an advantage of avoiding radiation exposure to health care providers and with fractionated radiation scheme, HDR-BRT has replaced low-dose-rate (LDR) where BRT is commonly used, as sole or adjunct therapeutic measure which has been proven in various other sites such as gynecological malignancies, prostate carcinoma.**[**29-30**]**

In external beam radiotherapy (EBRT), a relatively large volume is treated with a relatively homogeneous distribution of dose such that deviations of dose within the volume typically can range from 95% to 107% of the dose. In contrast, brachytherapy treats a smaller volume with an extremely heterogeneous dose distribution. The average dose within the prescribed volume is usually far higher than the prescribed dose

at the reference isodose on the periphery of the implant. This is tolerated due to the volume–effect relationship: very small normal tissue volumes (e.g., 1 to 2 cm3) can tolerate very high doses that larger volumes would not tolerate. This is probably due to the three-dimensional arrangement of vascular supply within normal tissues.

The advantage of BRT is that it provides a localized high dose of radiation, with rapid fall-off beyond planning treatment volume or implant treatment volume (PTV/ITV), sparing normal surrounding tissue, and short overall treatment time.[31] Brachytherapy is an important alternative to conventional EBRT which is known to have a detrimental effect on adjacent normal tissues, such as the parotids, salivary glands, mandible, spinal cord and muscles of mastication.

With advent of stepping source technology, there is an advantage of optimizing dose distribution by varying dwell times and dwell positions with graphical representation of dose volume histogram (DVH), which has been able to help us know the dose received by clinical target volume (CTV) and organs at risk (OAR), and has resolved the complicated dosimetry concerns. The other advantage of Brachytherapy over IMRT is the short duration of treatment which confers a superior radiobiological advantage by addressing the concept of Re-population of tumor cells which is countered during the prolonged duration of treatment.

There has been a rise in use of HDR-BRT in other forms of cancers, especially gynecological malignancies, prostate cancer, etc; however, BRT usage for HNC has been showing a declining trend because of the low incidence of HNC in western countries. Other limitations include lack of availability of appropriate infrastructure, cost of isotope, expertise, etc. The other reasons for reduced acceptability are lack of experience/expertise, complex application fear of injuring close vital vessels, and anatomical structure or shape, complicated dosimetry, and biological concerns of HDR[31]. Patient factors such as coexisting trismus, medical co-morbidities which are considered contraindications for anesthesia are also other major limitations.

Advances in HDR brachytherapy with the integration of imaging CT, magnetic resonance imaging (MRI), intraoperative ultrasonography, positron-emission tomography, and functional imaging] has led to better optimization of dose distribution with improved outcome. Better tumor localization and improved normal tissue definition will help to optimize dose distribution to the tumor and reduce normal tissue exposure.[35] With recent advancements and innovations in brachytherapy such as image-based / guided brachytherapy; HDR and PDR brachytherapy, its status has been redefined and glorified. It has a special mentioning in the era of precision oncology and desirable treatment outcomes can be fetched with a meticulous

multidisciplinary team.

Several international consensus guidelines are available for the management of oral cavity cancers, but none of them addresses Buccal Mucosa cancers in particular. Therefore, formulating reliable guidelines based on western data is questionable given the fact that buccal mucosa tumors are quite rare in the developed countries. There is obviously an urgent need to formulate consensus statement for the management of carcinoma of Buccal Mucosa based on Indian data and experience which would not only incorporate the evidence available but would also be feasible to be practiced in the hospitals of India.

The present study is an attempt to determine the efficacy and clinical outcome with the sophisticated technique IMRT which deliver high conformal dose to the tumor, sparing normal structures versus the HDR Brachytherapy which targets only the tumor with negligible dose to normal structures adjacent to tumor in stage I carcinoma of the buccal mucosa.

Aims and Objectives

To evaluate the responses & toxicities of treatment with Intensity Modulated Radio Therapy (IMRT) versus Radical Brachytherapy in Early Stage(T1N0MO) Carcinoma of Buccal Mucosa with regards to:

- Loco-regional response.
- Acute toxicities as per RTOG criteria.
- Late toxicities as per RTOG Criteria.
- Loco-regional control (LRC), Overall survival (OS) and Disease-free survival (DFS).

Material And Methods

Study Site

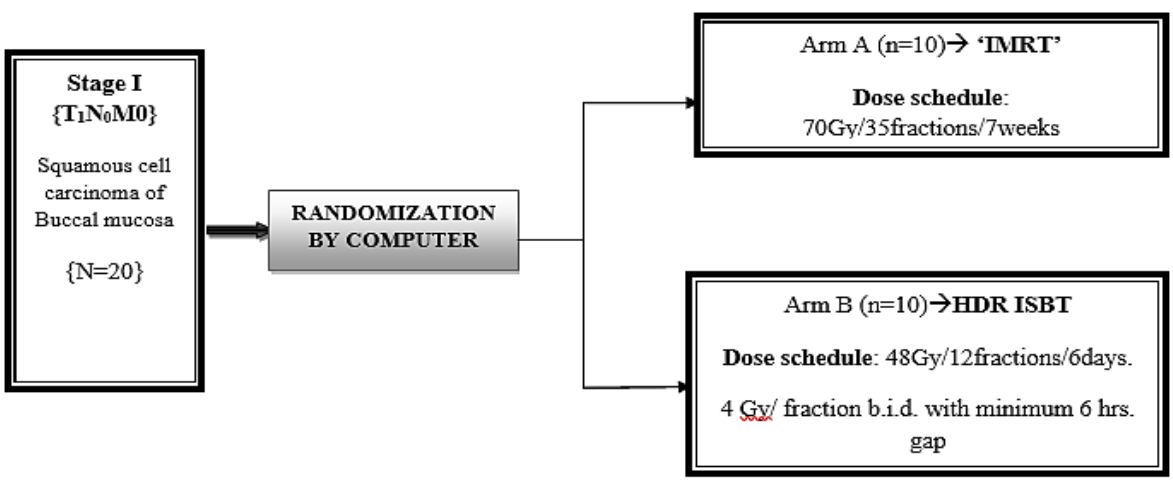
The present study has been conducted in the Department of Radiation Oncology, Kamala Nehru Memorial Hospital, Regional Cancer Centre (RCC), Allahabad, Uttar Pradesh. The institute is recognized by the Ministry of Health and Family Welfare, Department of Science and Technology, and Department of Atomic Energy of Regulatory Board, Government of India as a research institute. The institute provides comprehensive facilities for diagnosis, treatment and patient monitoring under one roof.

Study Population

The institute being Regional Cancer Centre caters to the needs of the cancer patients from the neighboring districts of Allahabad and the adjacent states of Uttar Pradesh i.e. western parts of Bihar, Northern parts of Madhya Pradesh. Patients of early stages of buccal mucosa cancer of various age groups of both sexes reported to our institute during the period of 2017-2018 have been included in the present study.

Study Design

The present study is a prospective, randomized, comparative double arm study involving patients of all age groups of both the sexes, T1N0M0 buccal mucosa cancers with biopsy-proven squamous cell carcinoma reporting to Kamala Nehru Memorial Hospital, RCC, Allahabad. On the basis of the inclusion and exclusion criteria, the patients were selected and enrolled in the study. The patients were randomized into 2 arms by computer viz., Arm A(n=10) and Arm B (n=10). The patients in Arm A received locoregional therapy in the form of Intensity Modulated Radiotherapy (IMRT) and that of in Arm B received locoregional therapy in the form of Radical Interstitial Brachytherapy.



Sample Size

Patients reporting for treatment of early staged buccal mucosa i.e. T1N0M0 with proved squamous cell histology of age groups 21-70 years were enrolled.

The formula for sample size calculation:

$$n = \frac{2(Z\alpha + Z1\text{-}\beta)2\ \sigma\ 2}{\phi 2}$$

Zα, Z is a constant (set by convention according to the accepted α error). Usually for 2 sided it is 1.96 at 5%.

Z1-β, Z is a constant set by convention according to the power of the study. Power of the study at 80% is 0.8146.

σ is the standard deviation based on the data in the published paper.

Φ is the effect size of the treatments compared.

The study was for the limited period and time-bound, the above formula may not be feasible in estimating the sample size. The above formula is employed for studies/research for a longer period and landmark trials where the time span is not a limiting factor.

As per hospital-based registry, the no. of buccal mucosa cancers including all subsites of both the sexes of all age groups are 472 cases reported to the hospital. Taking into consideration of inclusion and exclusion criteria such as early stage, buccal mucosa cancers exclusively, all age groups between 21 and 70 years, patient KPS score ≥ 70, histologically proven squamous cell carcinoma, no previous chemotherapy infusions and willing to participate in the study, 20 cases were enrolled for the research purpose.

The sample consisted of 20 patients including both sexes on the basis of inclusion and exclusion criteria, with written consent for participation in the study. Computer randomization divided the sample into two treatment arms viz. Arm A (n=10) and Arm B (n=10).

Study Period

The study was conducted from August 2017 to June 2019 with a minimum of 6 months follow up. The patients were assessed and monitored during treatment and follow up phases.

ELIGIBILITY CRITERIA

Inclusion criteria:

- Age groups 21-70 of both sexes.
- Histologically proven Stage I Squamous cell carcinoma histology.
- Karnofsky performance status (KPS) ≥ 70%.
- No prior systemic chemotherapy/radiotherapy.
- Granulocyte count ≥ 4,000/mL.
- Platelet count ≥ 1,50,000/mL.
- Haemoglobin ≥10mg/dL.
- Bilirubin less than 1.5x normal.
- Creatinine clearance ≥50 mL/min

Exclusion criteria:

- Age > 70 years.
- T2-4, N1-3
- Previous systemic chemotherapy.
- Metastatic disease.
- Other than squamous cell carcinoma histologies.
- Patient with second malignancies, serious medical/psychiatric illness.
- Unwilling to participate in the study protocol.

Sampling Technique

Patients enrolled in the present study were randomized by computer into Arm A and Arm B after careful assessment. Consent of all the patients of stage I squamous cell carcinoma of buccal mucosa was obtained in the prescribed consent form(Annexure XVI - A&B), and a questionnaire form (Annexure IX), which

included all information about symptoms, history of present illness, addictions, past history, general examinations, KPS status(Annexure V), investigations, treatment modalities , responses (Annexure VI)and their accepted side effects and toxicity and long-term survival in each arm (Annexure III &IV).

Statistical Methods

- Statistical analysis was performed using SPSS, Version 14
- Patients and tumor-related characteristics were observed and analyzed using Chi-Square Test
- For Chi-Square calculation, the null hypothesis was made for each observation- to be tested is that "type of treatment given to the patients did not depend upon the observation" e.g., socio-economic status
- If Chi-Square calculated is less than chi-square tabulated then the null hypothesis may be accepted.

i.e. $\chi_2$calculated < χ_2 tabulated, hypothesis accepted.

e.g. Type of treatment did not depend upon the socio-economic status.

Loco-regional recurrences, distant metastasis, disease-free survival, overall survival and skin reactions, analysis between two arms was done using the test of significance for proportion.

Methodology:

Data Collection

A mandatory workup of each patient included in the study was carried out prior to the commencement of treatment. It assisted in staging the disease, evaluation of performance status and the eligibility of the patient to undergo the proposed treatment.

The Questionnaire Form (Annexure-IX) of every patient was filled at the time of enrolment of study which includes:

I. Case number

II. Registration number

III. Age/sex of the patient

IV. Occupation

V. Marital status

VI. Socio-economic status

VII. Education

VIII. Addictions if any

IX. A brief history of the case:

a) Presenting complaints: the complaint of the patient at the time of the first consultation regarding the duration and symptoms of the disease.

b) Past history: regarding tuberculosis, diabetes, hypertension, asthma and any other chronic illness.

c) Family history: regarding the history of cancers/similar type of illness/systemic illness among family members.

d) Previous treatment history: especially for present illness.

e) Personal history: regarding bladder and bowel habits, diet appetite, sexual history and rule out any serious medical illness.

X. General examination –

a) General condition

b) Karnofsky performance status

c) Height

d) Weight

e) BMI

f) Pallor

g) Icterus

h) Cyanosis

i) Edema

j) Cervical Lymph Node Examination

k) Neck vein

l) Jugular venous pressure

m) Vital signs (Pulse, Blood Pressure, Respiratory rate, Temperature)

XI. Systemic examination –

a) Respiratory system

b) Cardiovascular system

c) Abdominal examination

d) Genitourinary system

e) Skeleto-motor system

f) Central nervous system

XII. Local examination –

a) Oro –dental hygiene:

i. Teeth – edentulous /with some or all teeth present/ any metallic tooth/ delicate tooth.

ii. Condition of teeth-root canal treatment/ caries teeth/ oral sepsis/mobility of teeth/ presence of any metallic teeth.

iii. Condition of oral mucosa- leukoplakia/erythroplakia

iv. Gingival tissue

v. Prosthesis

b) Presence or absence of trismus:

c) Local examination of the oral cavity

d) Examination of the oropharynx by direct inspection and palpation for any other lesion

XIII. Examination of regional lymph nodes under the following heading:

a) Site of nodes – level I, II, II, IV, V.

b) Laterality of nodes- unilateral/bilateral/contralateral

c) Number of nodes

d) Size of nodes

e) Consistency of nodes

f) Fixity/mobility of nodes.

Staging Of The Disease

After a thorough clinical examination of the patient, their disease was staged according to the TNM staging system of AJCC 2010 (Annexure I).

Pretreatment Diagnostic Work Up

I. Routine blood profile – Hb, TLC, DLC, Platelets, BUN, Serum creatinine, random blood sugar, LFT, Serum electrolytes and a baseline ECG.

II. Radiological examination –

a) X-ray soft tissue neck lateral view

b) Chest X-ray P/A view

c) CT scan with i.v contrast of primary site and neck for nodal status

d) MRI –T1/T2 images

III. Histopathological investigation –

a) Direct Biopsy from the primary site for cellular classification and grade of the tumor.

IV. Metastatic work up-

a) Bone scan whenever indicated

b) USG abdomen and pelvis whenever indicated

c) FDG-PET whenever indicated.

Pretreatment Dental Evaluation

Dentulous patients are at increased risk for caries and osteoradionecrosis from the reduction and qualitative change of salivary flow, change in Ph, and proliferation of bacteria. Panorex X-ray films, identification of non-restorable teeth for pre-treatment extraction, dental trays for a fluoride rinse, protection against scatter radiation, as well as education about long term oro-dental hygiene should be strongly advocated before radiation therapy is employed.

1. Complete clinical examination about the status of teeth, condition of the mucosa, gingival tissue, prosthesis
2. Complete charting of all dental findings like caries tooth, root canal treatment, oral sepsis, metallic tooth
3. Complete hygiene instructions and precautions about trauma and premature use of a prosthesis
4. Removal of teeth which are non-viable
5. Antibiotic coverage during the healing stage if teeth are extracted
6. Dental prophylaxis of remaining teeth should be encouraged

Treatment Procedure

In our study, we enrolled squamous cell buccal mucosa carcinoma patients reporting to Kamala Nehru Hospital with T1N0M0 stage (AJCC 2010). The patients based on the eligibility criteria were randomized by computer into two arms each arm comprising 10 patients. Arm A & Arm B received locoregional therapy in the form of IMRT and HDR Interstitial Brachytherapy **[**HDR ISBT**]** respectively.

ARM A: - 'IMRT'

RADIOTHERAPY TECHNIQUE:

- Simulation Protocol:

All patients having radiotherapy should be immobilized in a Perspex or thermoplastic cast fixed to the couch in at least five places. The spine should be straight. The shoulders are immobilized in the shell as inferiorly as possible so that the shoulder tips are inferior to the lower border of the cricoid cartilage thus permitting lateral radiation beams to treat the buccal mucosa without the need to angle them inferiorly. CT slices 3 mm thick are obtained from the base of the skull to the carina with the patient immobilized in the treatment position.

- Energy: 6 MV Photons
- Machine: Siemens – Artiste (LINAC)
- Target Volume Definition:
    - Gross tumor volume (GTV): The GTV is the gross demonstrable extent and location of the tumor. The GTV may consist of a primary tumor (primary tumor GTV or GTV-T), metastatic regional node(s) (nodal GTV or GTV-N), or distant metastasis (metastatic GTV, or GTV-M).
    - Clinical target volume (CTV): The CTV is a volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy. There is no general consensus on what probability is considered relevant for therapy, but typically a probability of occult disease higher than from 5% to 10% is assumed to require treatment.
    - Planning target volume (PTV): The PTV is a geometrical concept introduced for treatment planning and evaluation. It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability, despite geometrical uncertainties such as organ motion and setup variations.
    - Organ at risk (OAR): The OAR or critical normal structures are tissues that if irradiated could suffer significant morbidity and thus might influence the treatment planning and/or the

absorbed dose prescription. In principle, all non-target tissues could be OARs. However, normal tissues considered as OARs typically depend on the location of the CTV and/or the prescribed absorbed dose. Historically, OARs have been loosely grouped into "serial" or "parallel" organs or a combination of the two.

- Planning organ at risk volume (PRV): As is the case with the PTV, uncertainties, and variations in the position of the OAR during treatment must be considered to avoid serious complications. For this reason, margins have to be added to the OARs to compensate for these uncertainties and variations, using similar principles as for the PTV. This lead, in analogy with the PTV, to the concept of PRV". As with the OAR itself, margins in the PRV will be affected by the serial or parallel attributes of the adjacent tissues.
- Remaining volume at risk (RVR): The RVR is operationally defined by the difference between the volume enclosed by the external contour of the patient and that of the CTVs and OARs on the slices that have been imaged. Definition of an RVR and its inclusion in the treatment plan (at least in the form of dose constraints) is essential in IMRT. Without such limits, the optimization software could craft excellent dose distributions for the CTV and OAR but cause toxic irradiation levels in otherwise uncontoured tissues.
- Treated volume (TV): The TV is the volume of tissue enclosed within a specific isodose envelope, with the absorbed dose specified by the radiation oncology team as appropriate to achieve tumor eradication or palliation, within the bounds of acceptable complications". The TV is what is physically deliverable given limitations of beam collimation and homogeneity and, more importantly, the risks of treatment-associated morbidity acceptable to the oncologist and the patient.

- DOSIMETRIC QUALITY ASSURANCE: -
  - In our institution, Intensity Modulated Radiotherapy {IMRT} is delivered with multi-leaf collimation (MLC), using the step and shoot technique. Because of the complexity, a dedicated quality assurance (QA) protocol is followed in our institution.
- DOSE FRACTIONATION:
  - 70Gy/35fractions/7weeks

Patients were treated daily from Monday to Friday, 5 days a week. The Biological Equivalent Dose (BED) for the tumor and the normal tissues for IMRT is 84 Gy10 and 116.7 Gy3 for tumor control and late reacting normal tissue complications respectively. (Annexure-XIV) 5-7 Beams and 7-9 beamlets per beam will be placed at different angles and different weightages to give an adequate dose to the CTV while maintaining dose constraints to the OAR's as per prescription. As per institutional protocol biweekly, digitally reconstructed radiographs (DRR) to be taken and bony points are to be matched on DRR.

- DOSE PRESCRIPTION (Annexure XI):
    - Gross Tumor Volume (GTV): GTV70=70 Gy
    - Clinical Target Volume (CTV):
        - A generous CTV should be delineated due to the lack of anatomical barriers to submucosal tumor spread, extending to include the maxillary gingival-buccal sulcus superiorly, the mandibular gingival-buccal sulcus and submandibular gland inferiorly, immediately lateral to the labial commissure anteriorly, and the retromolar trigone posteriorly.
        - CTV70= GTV70 + 1cm=70 Gy
        - CTV60= CTV70 + 1cm=60 Gy
        - Elective Nodal Irradiation was not considered due to very low incidence of regional nodal involvement in T1N0M0 Buccal Mucosa Cancer.**[**41**]**
    - Planning Target Volume (PTV):
        - PTV70=CTV70 + 5 mm=70 Gy
        - PTV60= CTV60 +5mm= 60 Gy
    - Critical Structure Dose Constraints:
        - Parotid Gland: V30< 45%
        - Spinal Cord: 0.03cc<45Gy
        - Brain Stem: Maximum < 54 Gy
        - Lens: 10Gy

- Retina: 45Gy
- Optic Chiasma: Maximum <54 GY
- Optic Nerve: Maximum <54Gy
- Oral cavity: Mean< 40Gy
- Mandible, Temporo-mandibular joint -Maximum < 70Gy.
- Lips – mean dose < 20Gy

Treatment will be implemented in the following manner (Linear Accelerator, Artiste "Siemens"):

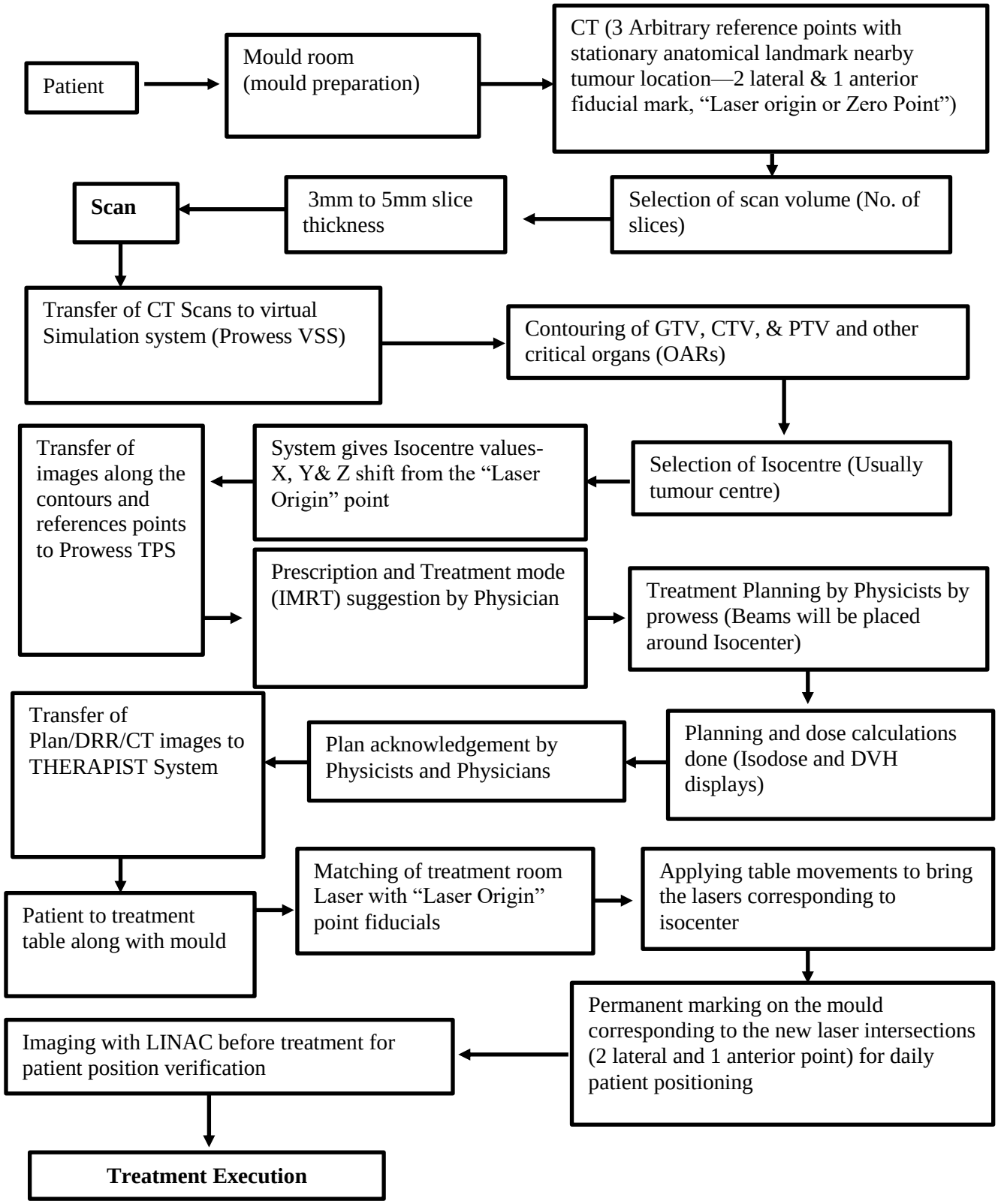


Fig 1: Patient Immobilisation with Thermoplastic Cast in Mould Room

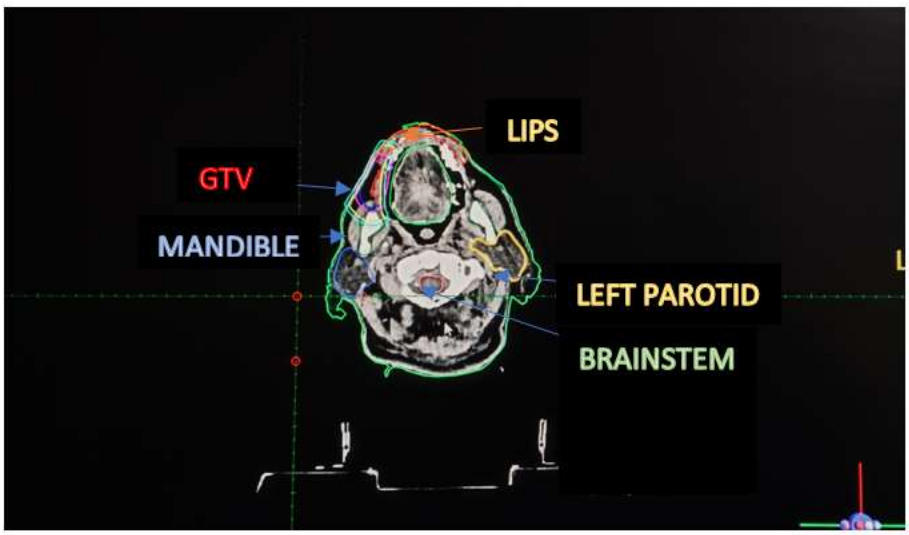


Fig 2: Contouring of the Target Volumes and Organs at Risk

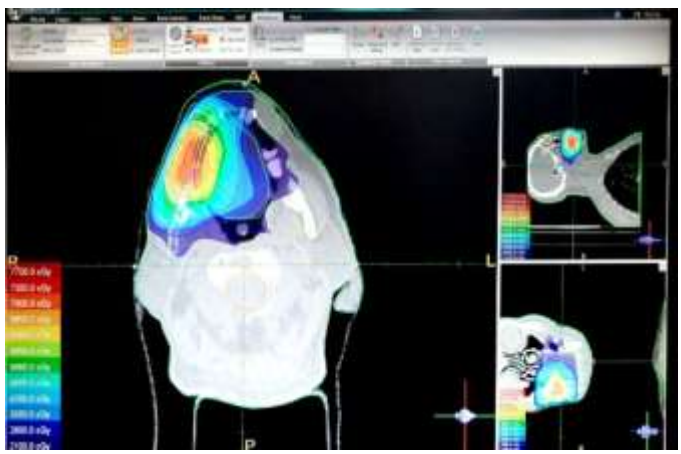


Fig 3: Dose Colour wash of an IMRT planning in Buccal Mucosa Cancer using Prowess Planning System

Fig 4: Patient Positioning and Treatment

ARM B: 'HDR ISBT'

RADIOTHERAPY TECHNIQUE

1. Under general anesthesia, the target area was defined by the palpation of the tumor bed.
2. A hallow thin walled stainless-steel Trocar with a needle was inserted through the ipsilateral cheek into the target. The tip of trocar was brought through to outside of cheek along the mucosa. Each Trocar with a needle was placed approximately 1cm apart and parallel to each other in single or double planes.
3. Hollow after loading plastic (nylon) catheter was introduced through stylet. After removal of the trocar, these catheters were secured with plastic buttons at the cheek skin surface and numbered. The patient received broad-spectrum antibiotics and steroids during and after the implant procedure.
4. All the patients underwent CT simulation for 3D brachytherapy planning the next day. Patients went for a CT scan of the involved region with a slice thickness of 3 mm. Images were then, transferred to Oncentra Planning Software System. The target definition and dose calculation were performed using the Oncentra Planning Software System.
5. The Clinical Target Volume (CTV) was defined as the circumferential area of connecting the peripheral catheters encompassing the target plus 5mm margins and was limited to tumor weight in the cranio-caudal direction. In brachytherapy, typically no additional margin is required to ensure that the CTV receives the planned dose and therefore, unlike external beam irradiation, CTV and PTV (Planning Target Volume) are considered equivalent.
6. Organ at risk (particularly Mandible) was delineated. Modification of PTV was allowed to exclude a critical organ (particularly Mandible).

7. To define the source position and calculate the dwell times, 3D planning was performed by 3D reconstruction of target and surrounding structures.
8. The plan was optimized to deliver the prescription dose (so-called Minimum Peripheral Dose) to cover a minimum of 95% of PTV. Those to the Mandible was kept as low as possible to minimize the risk of Osteoradionecrosis.
9. Irradiation was performed by connecting the catheters to after loading device (Micro-selectron HDR, Nucletron).
10. This device uses an Iridium-192 stepping source, which is moved to different positions separated by 2.5mm sequentially in all catheters where it stops for different dwell times.
11. A custom acrylic radiation stent (density 1.19 g/cm 3) was constructed prior to treatment in prosthodontics to conform to the patient's lower jaw and attach to his teeth for fixation. The left central section of the stent was extended laterally to minimize dose to the tongue and mandible.
12. Treatments were delivered by HDR ISBT using nylon plastic tubes after loaded with 192 Iridium with source strength in the range of 0.05cGy/m2.

Dosimetric Quality Assurance

In our institution, dedicated quality assurance (QA) protocol – 'AERB SAFETY CODE' has been instituted for HDR brachytherapy.

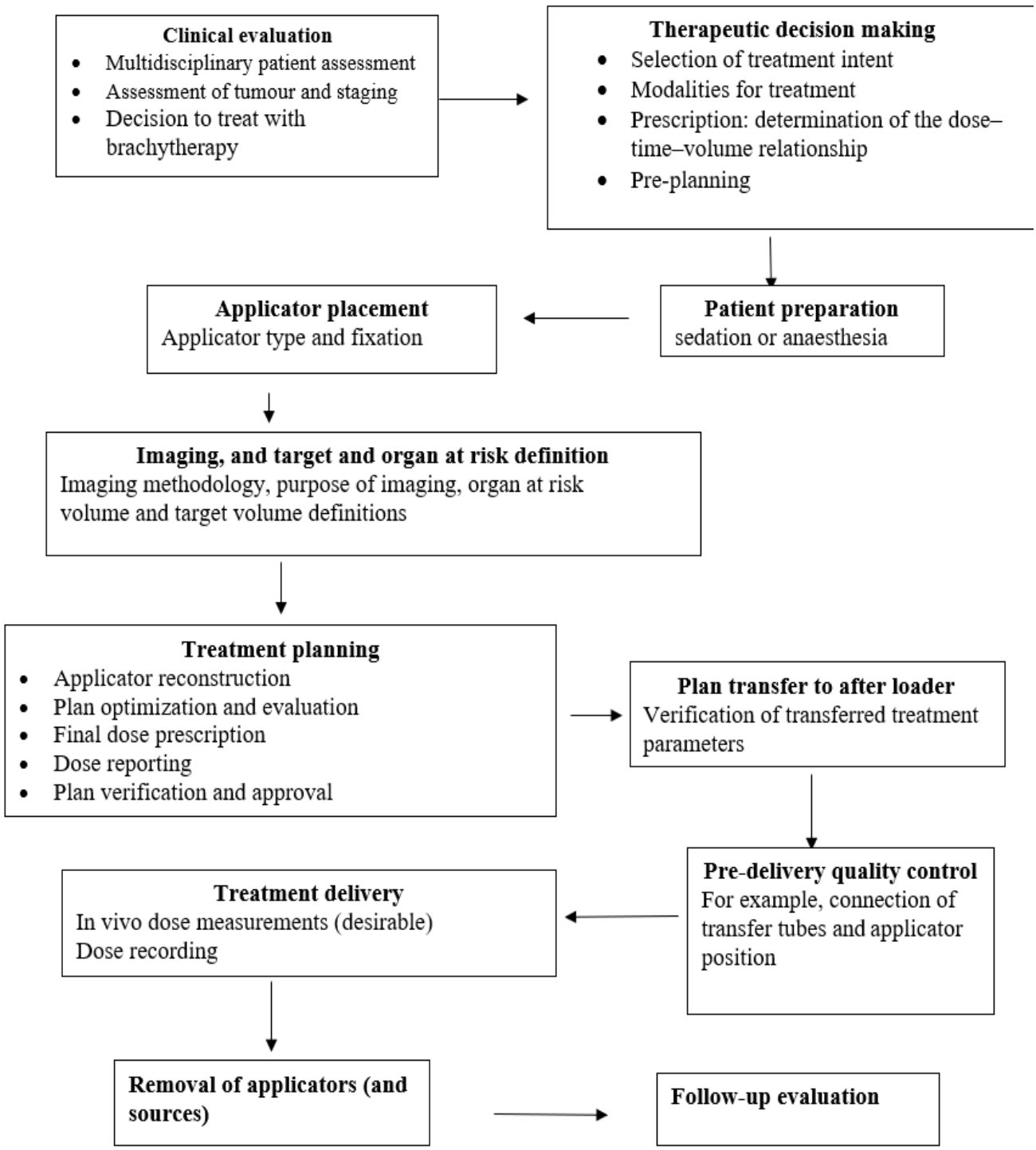
Dose Fractionation (Annexure XII)

- 48 Gy/12fractions/6days.**[**42**]**
- 4 Gy/ fraction delivered twice daily with a minimum interval of 6 hrs.
- The Biological Equivalent Dose **[**BED**]** for the tumor and normal tissues for HDR ISBT is 67.2Gy10 and 112.0Gy3 for tumor control and late reacting normal tissue complication respectively. (Annexure-XIV)

Planning Evaluation Considerations

- Low-dose region: A region, within the CTV, where the dose is less than 90% of the prescribed dose,
- High-dose region: A region, within the CTV that is encompassed by the isodose corresponding to 150% of the mean central dose (MCD) around the sources in any plane parallel to the central plane where a high-dose region is suspected.
- The dose homogeneity index (DHI): the ratio of minimum target dose (MTD) to the mean central dose (MCD).
    - Minimum target dose (MTD) is the dose selected and specified by the radiation oncologist as adequate to treat the PTV.
    - Mean central dose (MCD) is defined as the arithmetic mean of the local minimum doses between sources in the central plane (or in the central planes if there is more than one).
- Treated volume is the tissue volume that, in the actual implant, receives at least a dose selected and specified by the radiation oncologist as appropriate to achieve the purpose of the treatment
- Reporting for interstitial brachytherapy was done as per ICRU 58 with description of the clinical conditions, including GTV and CTV; description of the technique; source specification, including RAKR and TRAK; complete description of time-dose pattern; treatment prescription; mean central dose (MCD); minimum target dose; homogeneity index; and volumes and their dimensions, including PTV, treated volume, high-dose regions, low-dose regions, reference volume, irradiated volume and organs at risk.
- Standardized Organ at Risk (OAR) dose-volume constraints in H&N brachytherapy is lacking. We tried to keep the dose in bone, nerves, vessels and other dose-limiting organs as low as possible provided that the CTV coverage is adequate (i.e., D90 is at least 90% of the prescribed dose).

3-D BRACHYTHERAPY PROCEDURE FLOW CHART



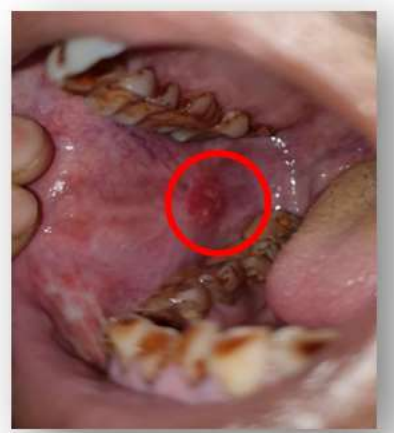


Fig 5: A case of 45yr old having 1.5 X 1.5 cm ulcer-infiltrative growth in the right buccal mucosa

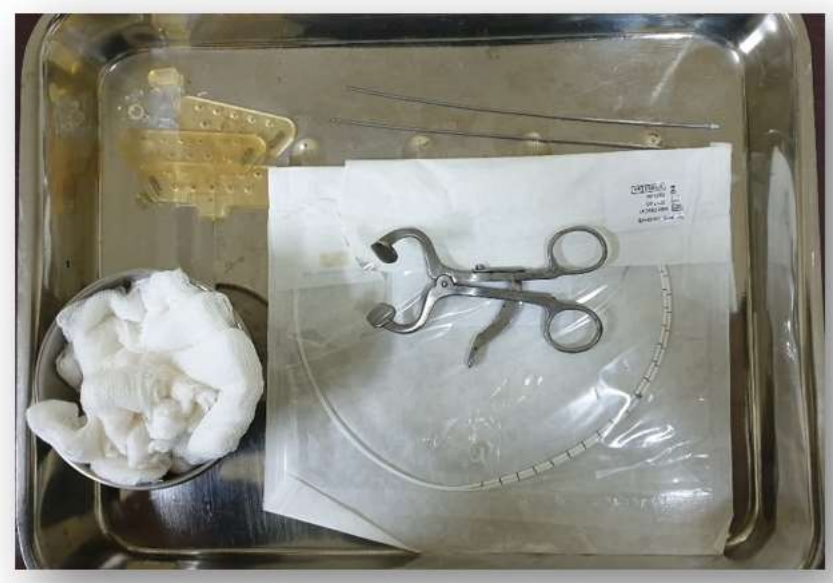


Fig 6: Instruments to be used during the Procedure

Fig 7: Insertion of Catheters

Fig 8: Numbering of Catheters

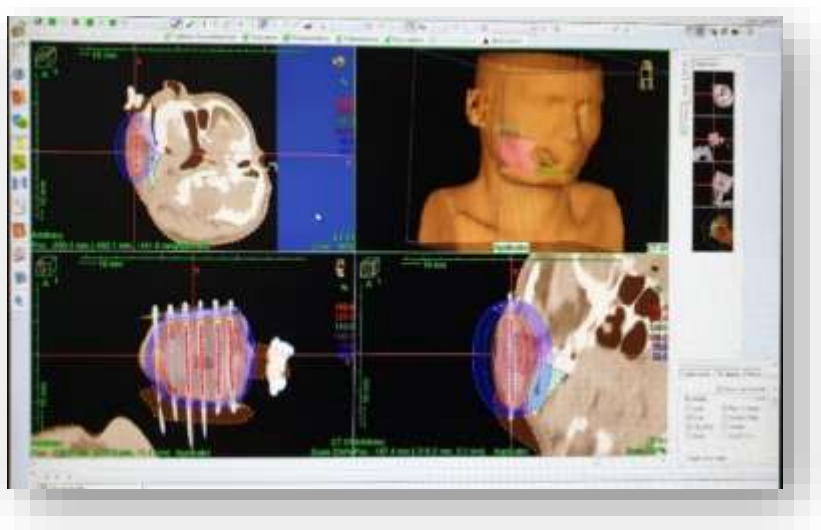


Fig 9: Buccal Mucosa Interstitial Brachytherapy: Dose Coverage and Colour Wash

Fig 10: Nucletron Corporation's Microselectron HDR Afterloader system

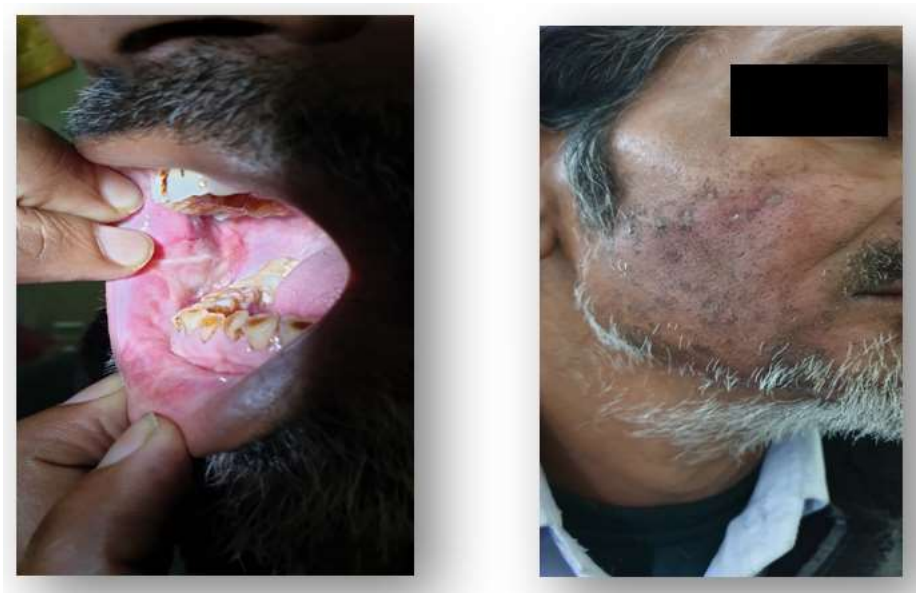


Fig 11: Complete Response after 1 Month Post Treatment: Grade 1 Mucositis and Grade 1 Skin Reactions

Patients Monitoring

Patients were monitored regularly during radiotherapy, every week for complications, secondary infections, and nutritional intake, and were managed promptly. Toxicities during treatment and after completion of treatment were recorded as per RTOG criteria (Annexure-III, IV).

Follow Up Schedule

- All the patients were kept on regular assessment after treatment.
- Initially every week for 4-6 weeks for assessing the acute radiation toxicity.
- Monthly follow up for 6 months to assess the clinical response.
- On each follow up we did a thorough physical examination to see the response, toxicity, and disease status and follow up CT Scan was done at the end of 6 months.
- Patients were evaluated for the residual / recurrence for the primary tumor and regional adenopathy.
- Patients with the residual disease were sent for salvage surgery
- The study clearance and regular evaluation were reviewed every quarterly by the Scientific and Hospital Ethics Committee.

Statistical Methods

Statistical analysis was performed using SPSS, Version 14. Patients and tumor-related characteristics were observed and analyzed using Chi-Square Test.

Informed Consent Form (Annexure XVI)

All the participants were provided written bilingual consent for participation in the study. The ICF is given in Annexure B. One was retained by the patient, one by the institution and one by the researcher. All possible side effects of radiotherapy were explained.

Ethical Clearance (Annexure XV)

The protocol was submitted to IERB and after getting the approval, the study was conducted.

Adverse Reactions

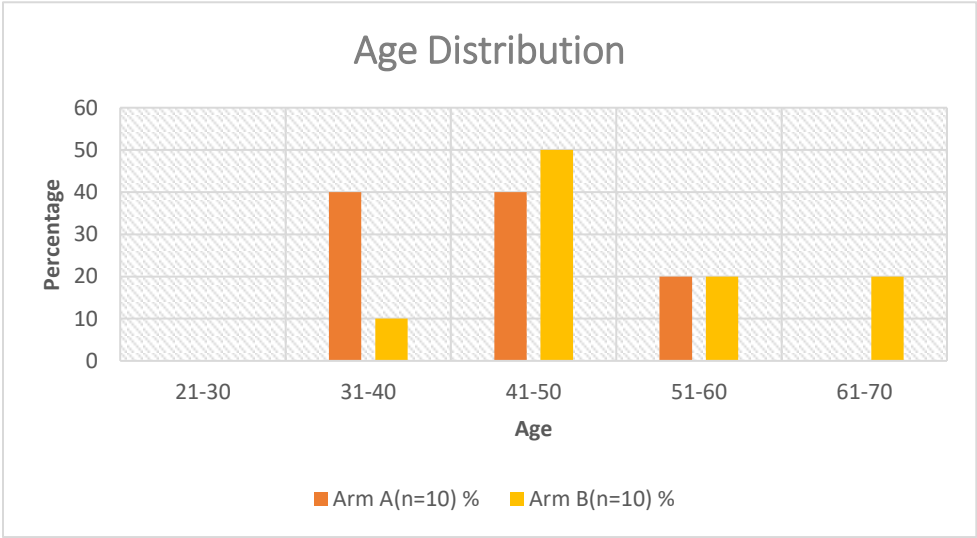
Patients reporting any adverse reactions (other than reported) was recorded and reported. They were provided treatment by the PI in the department.

Observations

Under this study, 20 patients were enrolled and grouped on the basis of two arms by Computer Randomization Method (CRM).

Age (in years)	Arm A(n=10)		Arm B(n=10)	
	No. of Patients		No. of Patients	%
21-30	0	0	0	
31-40	4	40	1	10
41-50	4	40	5	50
51-60	2	20	2	20
61-70	0	0	2	20
Total	10	100	10	100

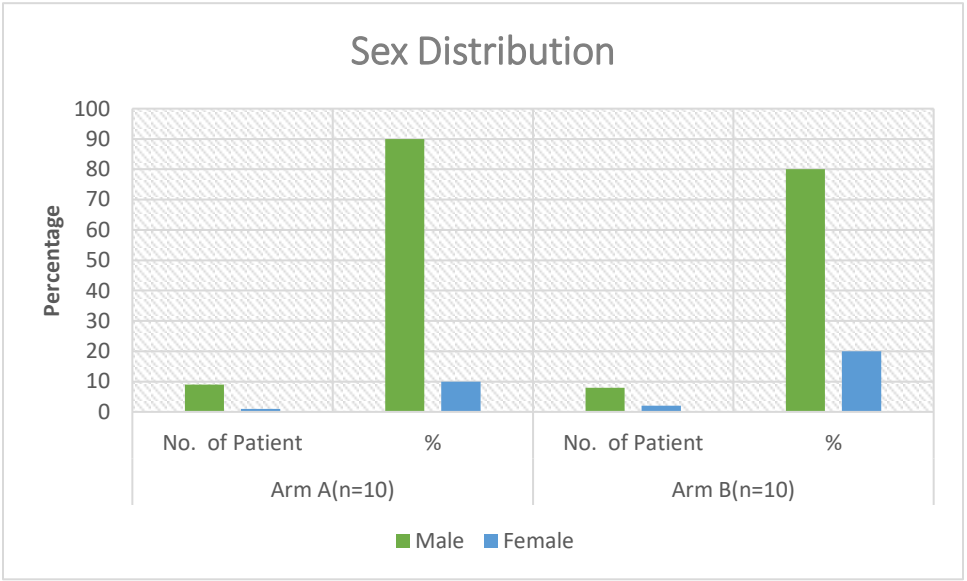
Table 1: Age Distribution



From the above data under Age Distribution, it was observed that most of the patients in both arms were between 41-50 years.

Sex	Arm A(n=10)		Arm B(n=10)	
	No. of Patient	**%**	**No. of Patient**	**%**
Male	9	90	8	80
Female	1	10	2	20
Total	10	100	10	100

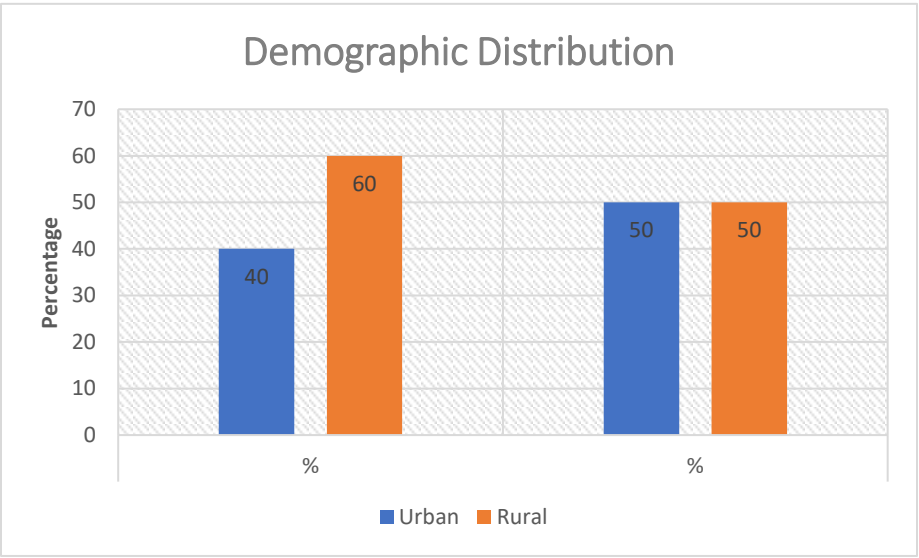
Table 2: Sex Distribution



Under the study of Sex Distribution, it was observed that all the patients in both arms were male except one female patient in arm A and two female patients in arm B.

Demographic distribution	Arm A (n=10)		Arm B (n=10)	
	No. of Patients	%	No. of Patients	%
Urban	4	40	5	50
Rural	6	60	5	50
Total	10	100	10	100

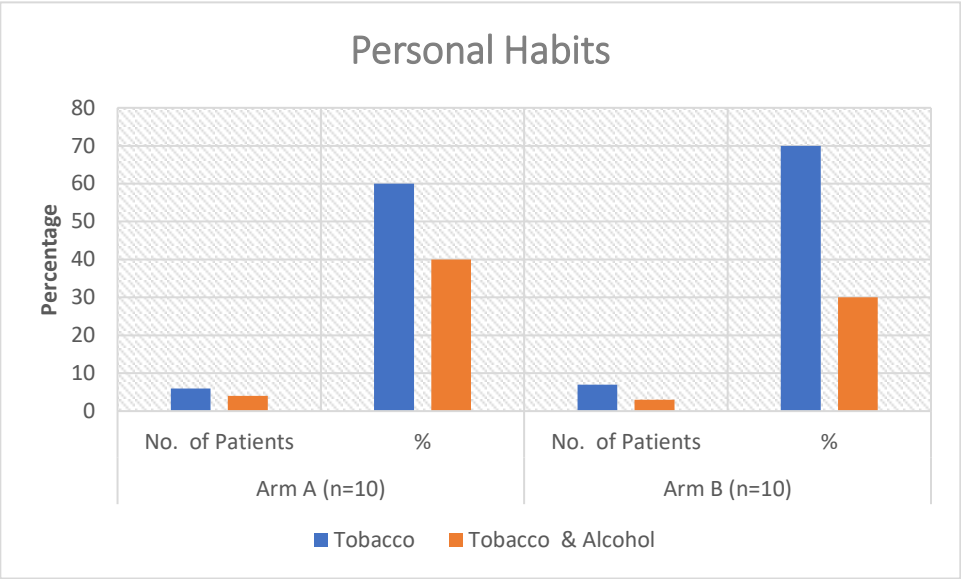
Table 3: Demographic Distribution



From the Demographic Distribution data, it was observed that 40% of patients were urban and 60% were rural in arm A while 50% of patients were urban and 50% were rural in arm B.

Personal Habits	Arm A (n=10)		Arm B (n=10)	
	No. of Patients	%	No. of Patients	%
Tobacco	6	60	7	70
Tobacco & Alcohol	4	40	3	30

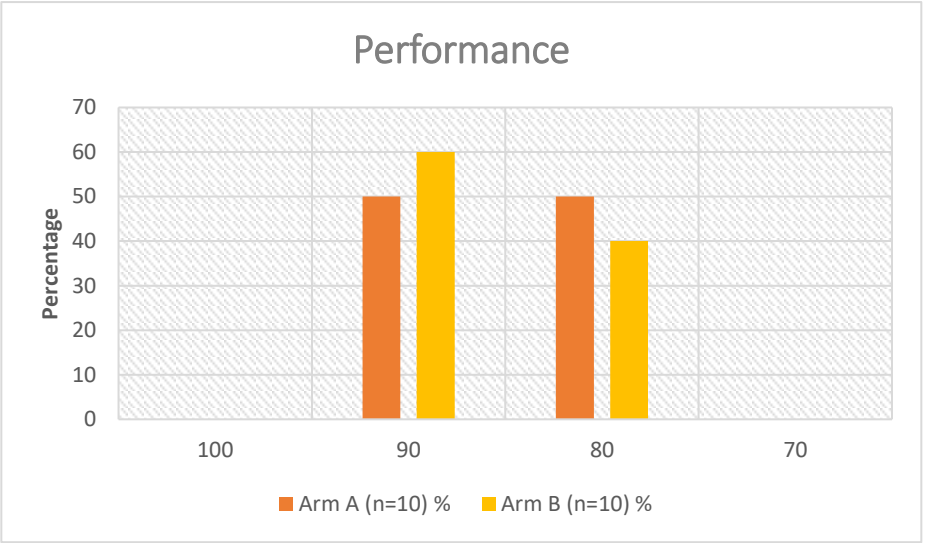
Table 4: Personal Habits



As shown data under Personal Habits, 65% of patients had a history of only tobacco in the form of ghutka or cigarette smoking and 35% of patients had a history of both tobacco and alcohol consumption. Treatment given to the patients did not depend on personal habits.

KPS	Arm A (n=10)		Arm B (n=10)	
	No. of Patients	%	No. of Patients	%
100	0	0	0	0
90	5	50	6	60
80	5	50	4	40
70	0	0	0	0
Total	10	100	10	100

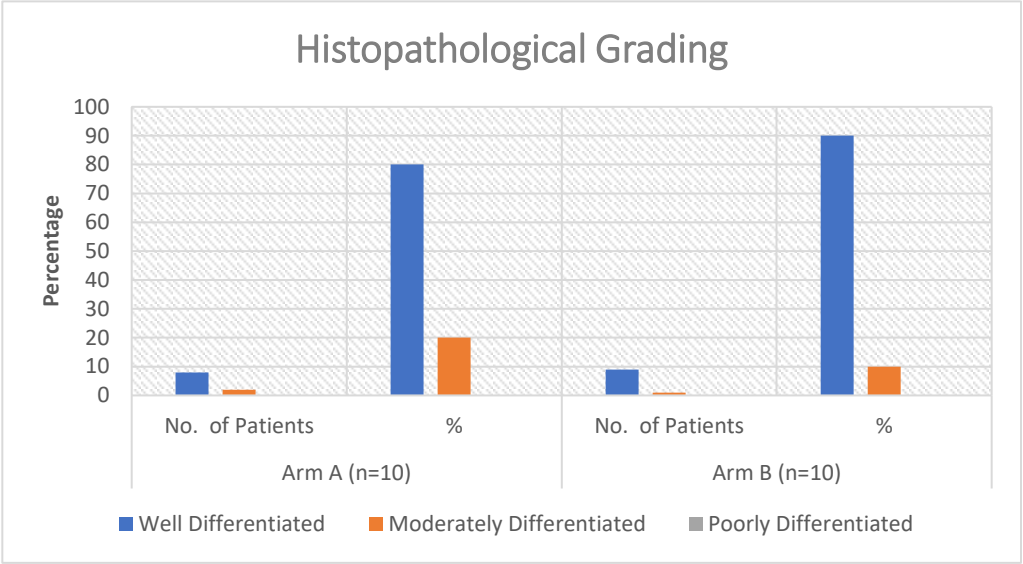
Table 5: Performance Status



From the data, as shown under Performance Status, it was observed that 50% of patients had KPS value 90 and 50% had KPS value 80 in arm A while 60% of patients had KPS value 90 and 40% of patients had KPS value 80 in arm B.

Grading	Arm A (n=10)		Arm B (n=10)	
	No. of Patients	%	No. of Patients	%
Well Differentiated	8	80	9	90
Moderately Differentiated	2	20	1	10
Poorly Differentiated	0	0	0	0
Total	10	100	10	100

Table 6: Histopathological Grading



Data under Histopathological Grading, it was observed that 80% of patients had histopathology of Well-Differentiated grade of squamous cell carcinoma, 20% had Moderately Differentiated, 0% had poorly Differentiated in arm A while 90% patients had Well Differentiated, 10% had Moderately Differentiated and 0% had Poorly Differentiated in arm B.

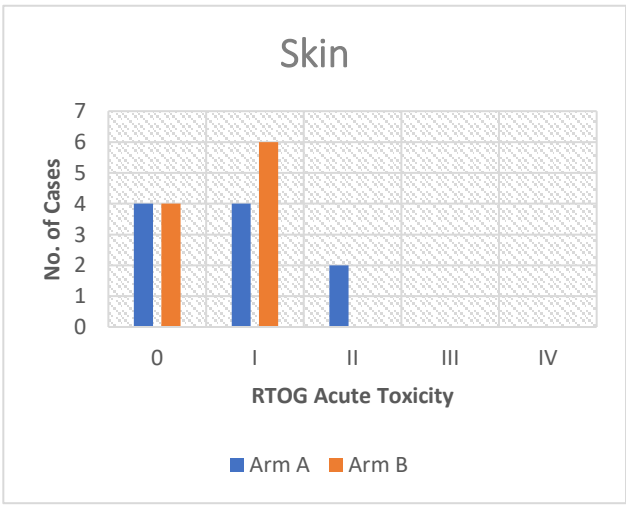
Organ Tissue	RTOG Grading	No. of Patients	
		Arm A	Arm B
Skin	0	0	0
	I	6(60%)	8(80%)
	II	4(40%)	2(20%)
	III	0	0
	IV	0	0
Mucous Membrane	0	0	0
	I	6(60%)	7(70%)
	II	4(40%)	3(30%)
	III	0	0
	IV	0	0
Pharynx/ Oesophagus	0	10(100%)	10(100%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0
Salivary Gland	0	5(50%)	10(100%)
	I	3(30%)	0
	II	2(20%)	0
	III	0	0
	IV	0	0

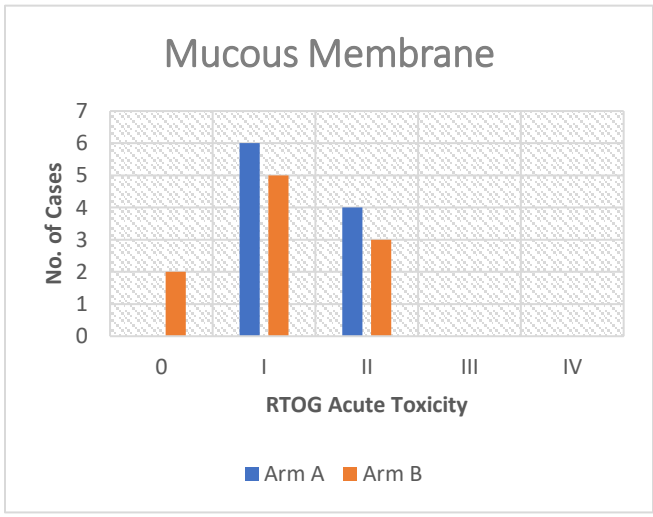
Table 7: Acute Radiation Toxicity Immediately after completing RT

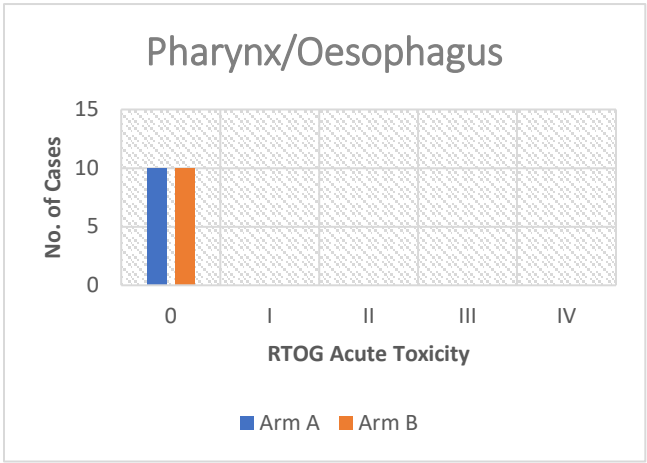
At the completion of treatment, 60% of patients had Grade I skin reactions, 40% had Grade II skin reactions, 60% had Grade I mucosal reactions, 40% had Grade II mucosal reactions, no pharyngeal reactions, 30% had Grade I and 20% had Grade II salivary gland reactions in Arm A. While 80% had Grade I, 20 % had Grade II skin reactions, 70% had Grade I mucosal reactions, 30% had Grade II mucosal reactions and no pharyngeal or salivary gland reactions in Arm B.

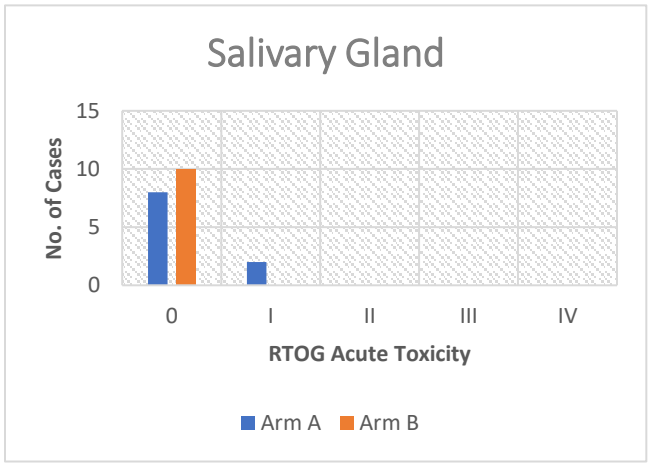
Organ Tissue	RTOG Grading	No. of Patients	
		Arm A	Arm B
Skin	0	4(40%)	4(40%)
	I	4(40%)	6(60%)
	II	2(20%)	0
	III	0	0
	IV	0	0
Mucous Membrane	0	0	2(20%)
	I	6(60%)	5(50%)
	II	4(40%)	3(30%)
	III	0	0
	IV	0	0
Pharynx/ Esophagus	0	10(100%)	10(100%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0
Salivary Gland	0	8(80%)	10(100%)
	I	2(20%)	0
	II	0	0
	III	0	0
	IV	0	0

Table 8: Acute Radiation Toxicity at end of 1st Month Post RT





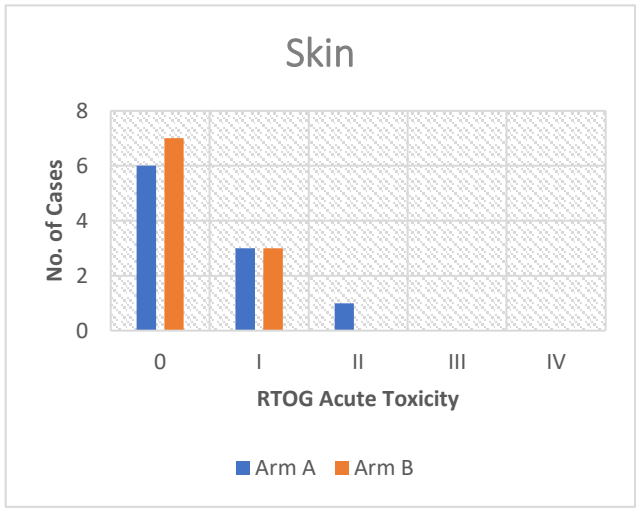


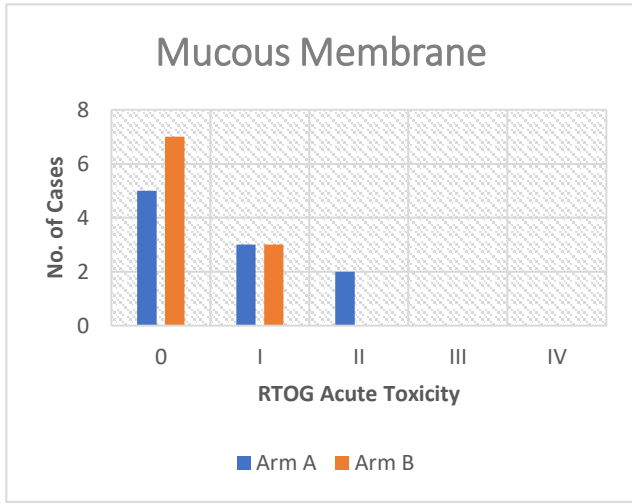


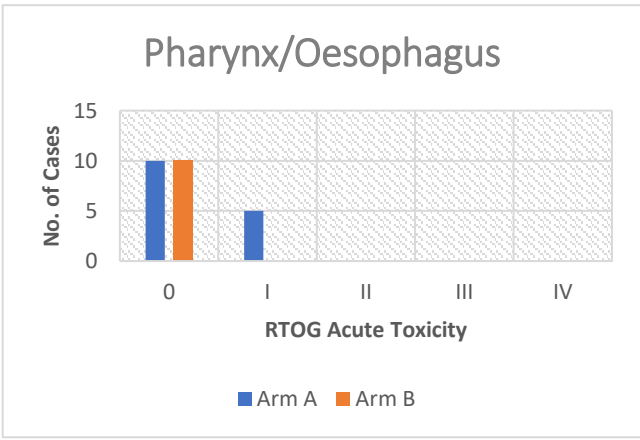
After 1st month of completion of treatment, 40% of patients had Grade I skin reactions, 20% had Grade II skin reactions, 60% had Grade I mucosal reactions, 40% had Grade II mucosal reactions, no pharyngeal reactions and 20% had Grade I salivary gland reactions in Arm A. While 60% had Grade I skin reactions, 50% had Grade I mucosal reactions, 30% had Grade II mucosal reactions and no pharyngeal or salivary gland reactions in Arm B.

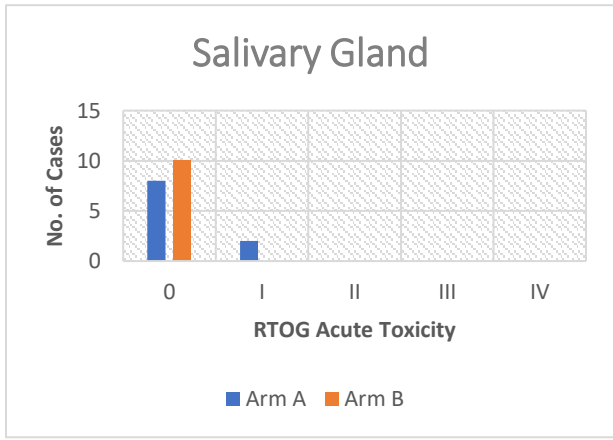
Organ Tissue	RTOG Grading	No. of Patients	
		Arm A	Arm B
Skin	0	6(60%)	7(70%)
	I	3(30%)	3(30%)
	II	1(10%)	0
	III	0	0
	IV	0	0
Mucous Membrane	0	5(50%)	7(70%)
	I	3(30%)	3(30%)
	II	2(20%)	0
	III	0	0
	IV	0	0
Pharynx/ Esophagus	0	10(100%)	10(100%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0
Salivary Gland	0	8(80%)	10(100%)
	I	2(20%)	0
	II	0	0
	III	0	0
	IV	0	0

Table 9: Acute Radiation Toxicity at end of 2nd Month Post RT





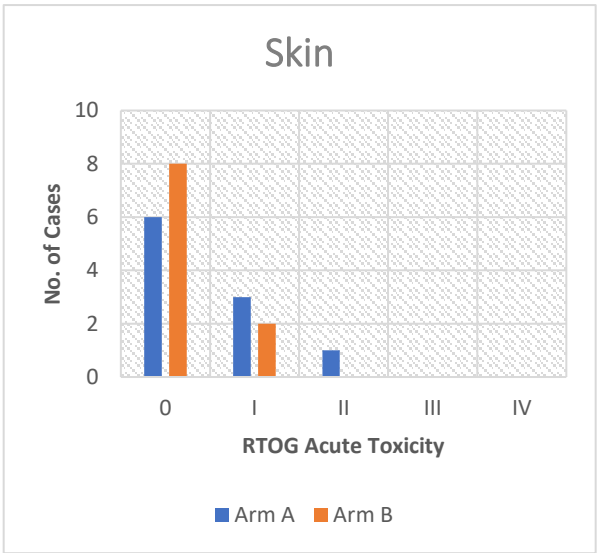


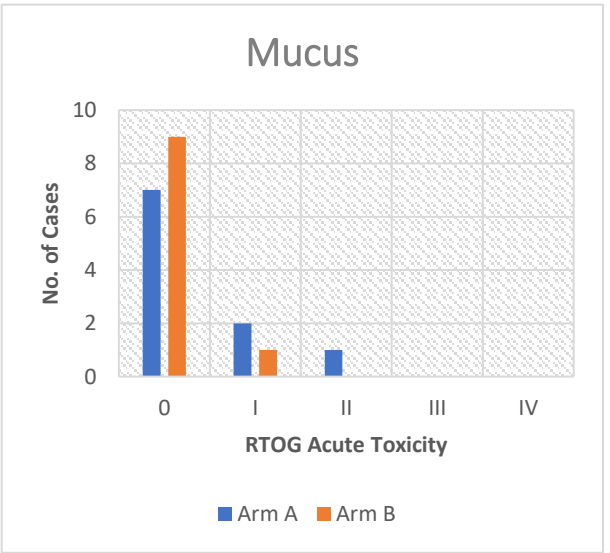


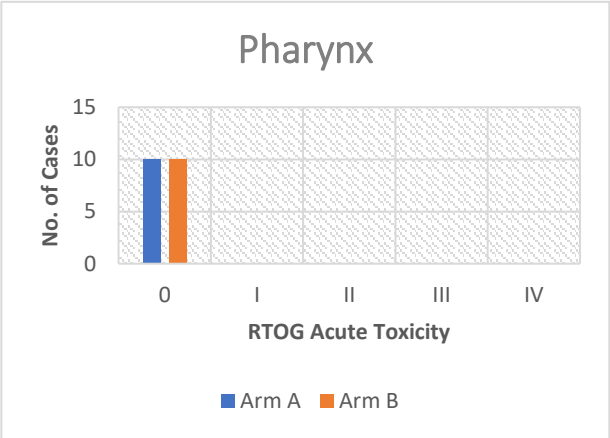
After 2nd month of completion of treatment, 30% of patients had Grade I skin reactions, 10% had Grade II skin reactions, 30% had Grade I mucosal reactions, 20% had Grade II mucosal reactions, no pharyngeal reactions and 20% had Grade I salivary gland reactions in Arm A. While 30% had Grade I skin reactions, 30% had Grade I mucosal reactions, and no pharyngeal or salivary gland reactions in Arm B.

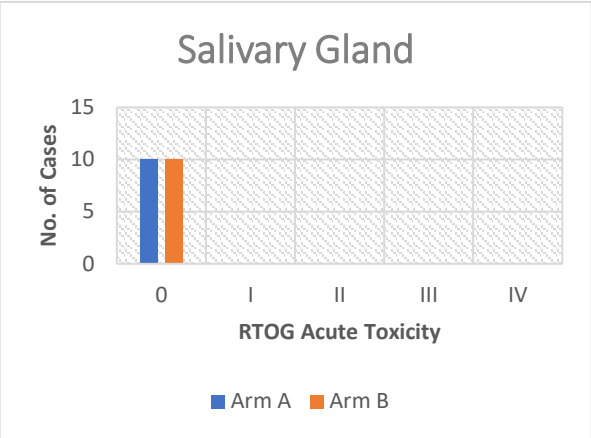
Organ Tissue	RTOG Grading	No. of Patients	
		Arm A	Arm B
Skin	0	6(60%)	8(80%)
	I	3(30%)	2(20%)
	II	1(10%)	0
	III	0	0
	IV	0	0
Mucus Membrane	0	7(70%)	9(90%)
	I	2(20%)	1(10%)
	II	1(10%)	0
	III	0	0
	IV	0	0
Pharynx/ Esophagus	0	10(100%)	10(100%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0
Salivary Gland	0	10(100%)	10(100%
	I	0	0
	II	0	0
	III	0	0
	IV	0	0

Table 10: Acute Radiation Toxicity at end of 3rd Month Post RT





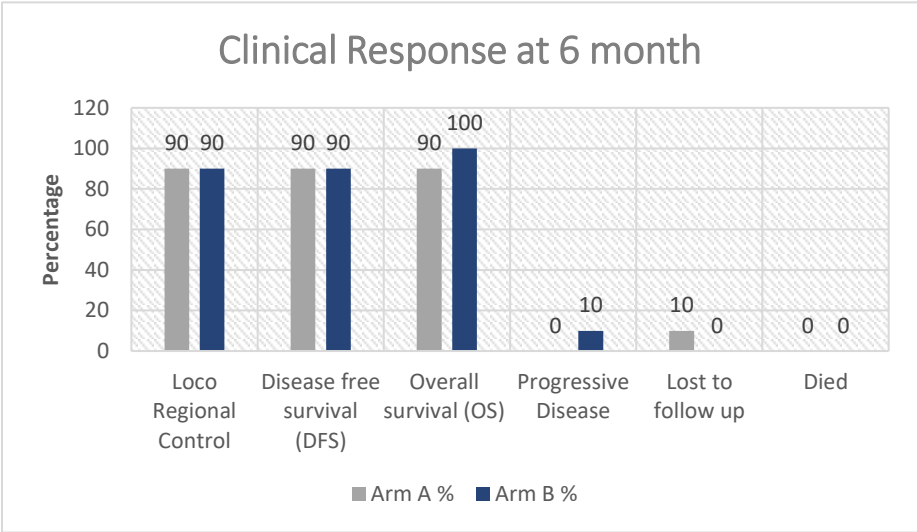




After 3rd month of completion of treatment, 30% of patients had Grade I skin reactions, 10% had Grade II skin reactions, 20% had Grade I mucosal reactions, 10% had Grade II mucosal reactions, no pharyngeal and salivary reactions in Arm A. While 20% had Grade I skin reactions, 10% had Grade I mucosal reactions, and no pharyngeal or salivary gland reactions in Arm B.

Treatment Response	Arm A		Arm B	
	No. of Patients	%	No. of Patients	%
Loco Regional Control	9	90	9	90
Disease free survival (DFS)	9	90	9	90
Overall survival (OS)	9	90	10	100
Progressive Disease	0	0	1	10
Lost to follow up	1	10	0	0
Died	0	0	0	0

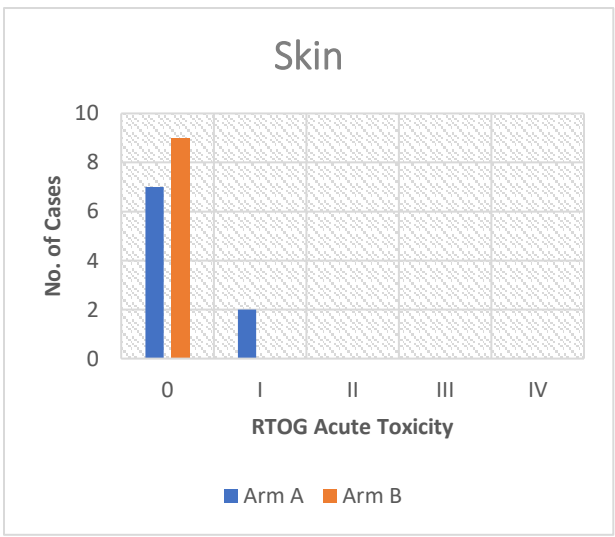
Table 11: Clinical Response at the end of 6 months Post RT

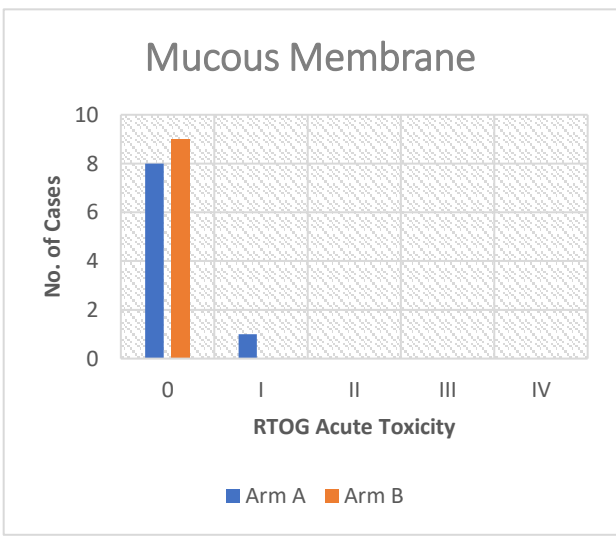


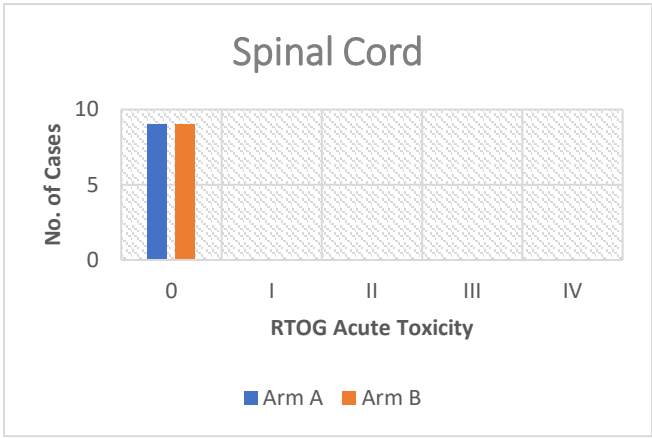
At last, follow up, various clinical responses were assessed. The local regional control was 90% in arm A and 90% in arm B (p= 0. 9126; significant level < 0. 05) which was statistically not significant. The disease-free survival (DFS) was 90% in both the arms. Overall survival was 90% in arm A and 100% in arm B (p= 0. 9426; significant level < 0. 05). Statistically, a significant difference was not observed. There was one patient in arm A who was lost to follow up during the study period after 5th-month post-treatment. In arm B, there was one patient who had a suspected residual disease on clinical examination who was further evaluated by imaging studies and confirmed by HPE and thereafter managed according to our departmental protocol.

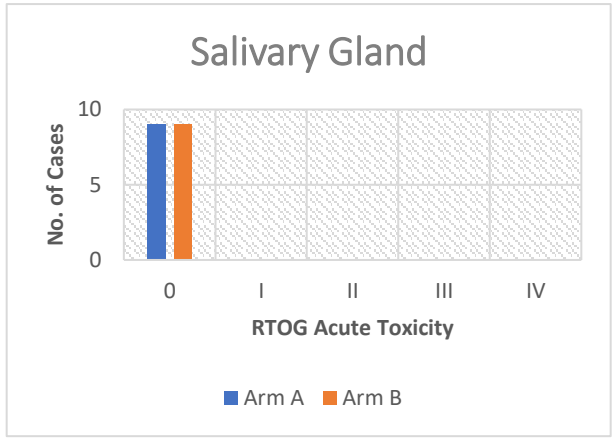
Organ Tissue	RTOG Grading	No. of Patients	
		Arm A	Arm B
Skin	0	7(70%)	9(90%)
	I	2(20%)	0
	II	0	0
	III	0	0
	IV	0	0
Mucous Membrane	0	8(80%)	9(90%)
	I	1(10%)	0
	II	0	0
	III	0	0
	IV	0	0
Spinal Cord	0	9(100%)	9(90%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0
Salivary Gland	0	9(90%)	9(90%)
	I	0	0
	II	0	0
	III	0	0
	IV	0	0

Table 12: Late Radiation Morbidity at end of 6 months









Among late toxicities observed, in arm A, 20% had Grade 1 skin reactions, 10% had Grade 1 mucositis and no pharyngeal and salivary toxicities. While in Arm B there were no Late toxicities observed during the study period.

Discussion

Head and Neck squamous cell carcinoma is the sixth commonest cancer in the world.**[**1**]** Head and neck is one of the commonest sites for squamous cell carcinoma in our country accounting for 23% of all cancers in males and 6% in females.**[**2**]** Cancers of the oral cavity constitute about 30% of all head and neck malignancies.**[**8**]** As per the hospital-based cancer registry of Kamala Nehru Memorial Hospital, Regional Cancer Centre, Allahabad, the hospital-based incidence of total head and neck cancer patients constitute 1301 cases of all cancer patients reported from 2016-2017. Among them 36.27 % are exclusively buccal mucosa cancers, accounting for 472 cases of all age groups including both the sexes. The ratio of male: female is 3:1.10 In 2017, total no. of cases of buccal mucosa cancers were 467 out of which 351 were males and 116 were females whereas, in 2018, total no. of cases of buccal mucosa cancers were 423 out of which 317 were males and 106 were females.**[**10**]** The registry shows a strong male predominance. The evaluation presented in this study has been based on the treatment data of 20 patients comprising of stage I (T1N0M0) of buccal mucosa cancers of both the sexes.

In the present study, only 3 patients were female out of 20 patients which shows that incidence among males is much higher than females. The male preponderance in our study was similar to that reported in many

other studies and was largely attributed to the increasing use of tobacco chewing, smoking, and alcohol (Llewellyn et al. 2001).**[**43**]** Our study confirmed the fact that a significantly higher proportion of males were addicted to tobacco and alcohol use than females.

The mean age in the present study group was 48.1 years. Majority of patients were in the age group of 41-50 years (9/20; 45 %). This is in agreement with many other Indian series that the peak age frequency of occurrence of oral cavity cancers in India is around 5th decade of life (SS Rahman et al., 2014).**[**44**]**

Demographically out of 20 patients, the urban population in arm A and arm B was 40% and 50% respectively and rural population in arm A and arm B was 60% and 50% respectively. 13(65%) patients have a history of both tobacco chewing and smoking, whereas 7(35%) patients are chronic smokers. There were 13(65%) non-smokers in our study.

Considering the histological grading of buccal mucosa squamous cell carcinomas, we found that well-differentiated SQCC accounted for 85 % cases and moderate differentiated SQCC accounted for 15% of cases. There were no cases accounting for poorly differentiated in our study. The low number of poorly differentiated cancers were found in other epidemiological studies also (Padma et al., 2017).**[**45**]**

In our study, all the patients of arm A received external beam radiation through Intensity Modulated Radiation Therapy with dose to PTV being prescribed 70 Gy /35 fractions/5 weeks. Radiation was given from Monday to Friday. Similarly, all the patients of arm B received Radical HDR Brachytherapy with the dose prescribed at 48 Gy/12 fraction/4 Gy twice daily 6hrs apart. Patients were assessed for nutritional status, acute reactions according to RTOG criteria including skin reactions, salivary gland toxicity, mucosal reactions during radiation weekly and were treated symptomatically.

At the end of completion of treatment, 60% of patients had Grade I skin reactions, 40% had Grade II skin reactions, 60% had Grade I mucosal reactions, 40% had Grade II mucosal reactions, no pharyngeal reactions, 30% had Grade I and 20% had Grade II salivary gland reactions in Arm A. While 80% had Grade I, 20 % had Grade II skin reactions, 70% had Grade I mucosal reactions, 30% had Grade II mucosal reactions and no pharyngeal or salivary gland reactions in Arm B. The difference observed was not statistically significant (p= 0. 9726; significant level< 0. 05). At the 1st month of completion of treatment, 40% of patients had Grade I skin reactions, 20% had Grade II skin reactions, 60% had Grade I mucosal reactions, 40% had Grade II mucosal reactions, no pharyngeal reactions and 20% had Grade I salivary gland reactions in IMRT arm. Whereas 60% had Grade I skin reactions, 50% had Grade I mucosal reactions, 30% had Grade

II mucosal reactions and no pharyngeal or salivary gland reactions in HDR-BRT arm. The difference observed was not statistically significant. At the 2nd month of completion of treatment, 30% of patients had Grade I skin reactions, 10% had Grade II skin reactions, 30% had Grade I mucosal reactions, 20% had Grade II mucosal reactions, no pharyngeal reactions and 20% had Grade I salivary gland reactions in IMRT arm. While in HDR-BRT arm, 30% had Grade I skin reactions, 30% had Grade I mucosal reactions and no pharyngeal or salivary gland reactions. The difference observed was not statistically significant. At 3rd month of completion of treatment, 30% of patients had Grade I skin reactions, 10% had Grade II skin reactions, 20% had Grade I mucosal reactions, 10% had Grade II mucosal reactions, no pharyngeal and salivary reactions in Arm A. While 20% had Grade I skin reactions, 10% had Grade I mucosal reactions, and no pharyngeal or salivary gland reactions in Arm B. The difference observed was not statistically significant. The patient compliance was appreciable and the toxicities were treated symptomatically and the general condition of all the patients was satisfactory. This is in agreement with other studies (Parthasarathy Vedasoundaram et al., 2008-2013.**[**38**]**

At 6th month follow up, a direct clinical examination and CT Scan Face and Neck were done and overall Loco-Regional Control found to be 90% in both arms. In arm A, one patient (10%) was lost to follow up after 5 months of completion of treatment. In arm B one patient was detected with a residual disease which was evaluated with the relevant investigation including imaging studies and once confirmed by histopathological examination by biopsy, the patient was referred to the surgical oncology department for salvage surgery. He had good salvage surgery and had no further events during the follow-up period. Similarly, disease-free survival was 90% in both the arms. Overall survival in arm A vs arm B was 90% and 100% respectively (p= 0. 9426; significant level< 0. 05). Progressive disease was seen in 10% of patients in arm B only. Statistically, our data was found not significant.

Late Radiation toxicities were assessed clinically and radiologically at 6 months and results had been recorded. 2 patients in arm A had grade I skin reactions while none of the patients in arm B had any skin reactions. 1 patient in arm A had grade I mucosal reactions while none of the patients in arm B had any mucosal reactions. No spinal cord or salivary gland late toxicities were seen in either of the arms at 6 months follow up. The results showed no statistical significance in our study (p= 0. 9526; significant level <0. 05).

With the invention of newer technologies and highly conformal dose delivery, modern radiotherapy has set a high standard for the management of oral cavity cancers. The ability to preserve normal anatomy and provide better cosmetic and functional outcomes have made radiotherapy an effective alternative to surgery,

which has been the gold standard for the management of early and locally advanced oral cavity cancers(Matsui et al. 2007).**[**46**]** Three-Dimensional Conformal radiotherapy (3D CRT) and Intensity Modulated Radiotherapy (IMRT) have made possible higher dose delivery with curative intent to the tumor, with acceptably lower doses to normal organs and critical structures around the tumor (Studer et al. 2007).**[**47**]** However, higher costs and complexity in planning and treatment delivery have precluded their widespread adoption, especially in third world nations, where cost-effectiveness and ease of implementation are the need of the hour (Nijdam et al. 2008).**[**48**]** Brachytherapy has proven itself indispensable in the management of specific cancers like cancer cervix and oral cavity cancers over the decades, as a primary modality or as a boost. Its lower cost and simplicity, coupled with its ability to provide high localized dose with rapid dose fall-off has made it an excellent tool to provide conformal therapy in these cancers, with minimal side effects compared to EBRT. A study by Sresty et al. (2010)**[**49**]** showed that interstitial brachytherapy conferred more dose heterogeneity to target volume when compared with IMRT and lesser dose to critical structures. Also, the planning time was much less in most cases. It concluded that interstitial brachytherapy was an ideal option for high dose delivery exclusively to the primary tumor volume, while limiting the risk of osteoradionecrosis, evading the occurrence of xerostomia as well as trismus also.

Our evaluation indicates that there are quite a number of positive developments in the treatment of early-stage buccal mucosa cancers but there is still much to evolve. Variables such as patient factors which includes performance status, comorbidities, tumor biology, radiation dose, method of delivery, expertise level and institutional experience influence the treatment outcome. Multicentric trials, especially in Indian setup, is required to develop definitive guidelines for cost-effective treatment with good results, acceptable compliance, and decreased toxicities.

The study has been compromised by a smaller number of patients and short duration. Patients reporting to our institution are generally having the locally advanced disease due to lack of awareness. A long-term study including a greater number of patients will be required to define the results and outcomes statistically significant.

Conclusion

Successful management of early stage of squamous cell carcinoma of buccal mucosa must address two treatment goals which are conflicting sometimes. The first goal, of course, would be disease eradication, and the second is organ function preservation and cosmetic. Surgery with or without adjuvant radiotherapy has been the standard of treatment for buccal mucosal cancers. A number of early buccal mucosal cases being reported to the Radiation Oncology department is rather small. Management of patients with head and neck cancer continues to be a challenging and evolving field filled with numerous and complex issues that necessitates a multidisciplinary approach. Such a team approach will help attain the optimal treatment strategy for patients with head and neck cancer. Brachytherapy has been shown to be an integral part of organ preservation and improvement in the quality of life, with the best functional, emotional, and cosmetic outcome. In addition, brachytherapy provides an avenue to achieve high therapeutic radiation doses for patients with recurrent or persistent head and neck cancers with prior RT. Good brachytherapy technique and meticulous planning are essential to ensure adequate dose coverage of the tumor and better treatment outcomes.

Our conclusion, taken up in this thesis could be enumerated as follows:

At 6 months follow up locoregional control was 90 % in both the arms (p=0. 9126, significant level 0. 05), Overall survival in arm A vs arm B was 90% and 100% respectively. Statistically, a significant difference was not observed.

Acute toxicities particularly skin, mucosal reactions, and salivary gland reaction were more in arm A receiving IMRT compared to arm B receiving HDR-Brachytherapy. Results were statistically not significant.

Few patients in arm A presented with skin and mucosal reactions have a late complication of radiation as per RTOG criteria but none in HDR-BT group. Results were statistically not significant.

Results in our study at 6 months were found statistically not significant, therefore LRS, DFS, OS did not depend on treatment modality.

In our experience, interstitial HDR brachytherapy seems to be a feasible and safe technique in early stage buccal mucosa with acceptable minimal toxicities. Our study was conducted in a short period of time with a smaller number of patients with limited follow up for evaluation of responses. A study involving a greater number of patients with longer period of duration would be required to come to any definitive conclusion.

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