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RESEARCH ARTICLE
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A RANDOMIZED PROSPECTIVE COMPARATIVE STUDY TO ASSESS THE EFFICACY OF CONCURRENT CHEMORADIATION WITH ERLOTINIB VERSUS CISPLATIN IN LOCALLY ADVANCED HEAD AND NECK CANCER PATIENTS

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INTRODUCTION

Cancer, responsible for nearly 10 million deaths in 2020, equating to one in six deaths globally, has about one-third deaths attributed to factors like tobacco use, high BMI, alcohol, low diet quality, and physical inactivity.

- ***World Health Organisation (2022)*** *[1]*

Non-communicable diseases (NCDs) are responsible for the major proportion of mortality worldwide with cancer projected to be the leading cause of death and the single critical barrier to increasing life expectancy globally. (1)

Head and neck cancer (HNC), ranking as the seventh most common cancer globally, encompasses a diverse array of tumours affecting the upper aero digestive tract. Head and neck squamous cell carcinoma (HNSCC) is a group of malignancies originating from the squamous cells lining the tissues of the head and neck region, including the oral cavity, hypo pharynx, nasopharynx, oropharynx, lip, nasal cavity, paranasal sinuses, and salivary glands .

HNSCC is a major global health concern, displaying variable incidence and mortality rates across different geographic areas and demographic characteristics.. (2)

1.1 EPIDEMIOLOGY

The latest GLOBOCAN estimates (2020) suggest than HNSCCs account for approximately 890,000 new cases; which is roughly equal to 4.5% of all cancer diagnoses around the world; and 450,000 deaths per year i.e., approximately 4.6% of global cancer deaths. The incidence includes approximately 380,000 cases of cancer of the lip and oral cavity, 185,000 of the larynx, 133,000 of the nasopharynx, 98,000 of the oropharynx, 84,000 of the hypo-pharynx, and 54,000 of the salivary glands. (2)

Globally, the incidence of HNSCC is more common in men and older adults. The male-to-female ratio is approximately 2:1, and is common in those over 50 years of age. The highest incidence is observed in South and Southeast Asia (where chewing of areca nut is prevalent), followed by Central and Eastern Europe, and South America. Among these, India records the highest incidence, where consumption of tobacco (with/ without areca nut) accounts for up to 80% of all HNSCC cases. (2)

Problem statement in India: The number of cases of cancer, in India, is on the rise. It has been estimated that by 2040, there would be 2.1 million new cases of cancer in India, a 57.5% rise from 2020. (5) Head and neck cancer (HNC) makes up 30% of all cancer cases in India; they rank 2nd overall and are the most common cancer among men. (1,6) In India, 1 in 107 women and 1 in 33 men are at a risk for developing HNC. A significant increase in the incidence of HNC was reported in the Indian population-based cancer registries (PBCRs) of Aurangabad, Chennai, Delhi, and Bhopal for males, and Nagpur for females. (5)
As per **Bagal S et al (2023)**, the incidence rate of cancer (all sites included), in India was 103.7 per 1,00,000 population among males and 102.4 per 1,00,000 population among females. The age standardised incidence rate (ASIR) of HNC, in India, was reported to be 25.9 per 1,00,000 population among males and 8.0 per 1,00,000 population among females.

The highest incidence of HNC was reported in males in the northeastern region of India (31.7 per 100,000 population) followed by northern and central India. With regards to age group, those aged 60 and above reported higher ASIR for both males (114.9 per 1,00,000) and females (36.9 per 1,00,000). The leading sites of cancer, as per **Bagal S et al (2023)** were the mouth, tongue, larynx, hypo-pharynx and tonsil in the central, eastern, northern, southern and western regions PBCRs while hypo pharynx was the leading site in the northeastern region followed by mouth, larynx tongue and tonsil. (5)AIMS AND

Aims
The aim of the study is to assess the loco regional response, efficacy and toxicity of chemo radiotherapy concurrent with erlotinib and cisplatin in locally advanced head and neck cancer.

2.1Primary objective
1. To analyses the efficacy of conventional chemo radiotherapy along erlotinib and cisplatin in locally advanced head and neck cancer in both arm.
2. To compare loco-regional response in both arm.

2.2Secondary objective
•To evaluate acute toxicity

REVIEW OF LITERATURE
Cancer
3.1Definition of cancer
Cancer refers to any one of a large number of diseases characterised by the development of abnormal cells that divide y and have the ability to infiltrate and destroy normal body tissue.Cancer often has the ability to spread throughout your body .The latter process is called metastasising and is major cause of death from cancer .

3.2**RISK FACTORS**
1. **Tobacco and Alcohol Consumption:**
Argiris A et al (2008) discussed that 75% cases of all SCCHN were associated with tobacco and alcohol consumption and had a multiplicative effect. Increased risk has also been observed among people who had never smoked but consumed substantial amounts of alcohol. (7) Smokeless tobacco

and betel quid chewing are associated with increased risk of oral cavity cancers. (4,7) They added that fruit and vegetable consumption has been known to be associated with a reduced risk of SCCHN. (7) **Chow (2020)** in their study discussed similarly that heavy use of alcohol and tobacco was associated with HNC. However, a declining trend has been reported globally, partly due to decreased consumption of tobacco nowadays. (8) **Barsouk A et al (2023)** discussed that the use of tobacco, in developed nations, had declined overall but increased among their women. But in developing nations, it continues to rise because the progress in economy has increased the household disposable income. (2) They further added that the risk of cancer was 5-25 times higher in cigarette smokers as compared to non-smokers. Regular chewing of tobacco was associated with a 1.7 and 3.0 odds ratio for HNSCC and oral cancer respectively. Exposure to second hand smoke during childhood was associated with a 1.28 odds ratio for HNSCC, adjusted for smoking, drinking, and HPV status. (2) They discussed that the amount and frequency of alcohol consumption was associated with the increasing risk of HNSCC, and higher risks were observed among those who consumed spirits, such as vodka or whiskey, as compared to those who consuming wine or beer. Also, both alcohol and tobacco contributed to a multiplicative effect. (2)

The **National Cancer Institute (NCI), USA (2021)** stated that alcohol and tobacco use (which includes both second hand smoke and smokeless tobacco) are associated with cancers of oral cavity, hypo pharynx and voice box. The risk is greater in those who consume both alcohol, as well as, tobacco compared to those who use either alone. (4)

The **Centers for Disease Control and Prevention (CDC) (2023)** similarly reported that all tobacco products are linked to head and neck cancer (except for salivary gland cancers). Also, any type of alcohol (beer, wine, liquor) increases the risk of cancers of the mouth, throat, and voice box. (9)

Kulkarni MR (2013) discussed that tobacco is smoked in the form of cigarettes, bidis, cigars/ chutta/cheroot, dhumti in the region of Goa; water pipes/hookah in the north Indian region; in the form of reverse chutta smoking in the coastal regions of Andhra Pradesh and Orissa; hookli in Gujarat and chillum in the northeastern parts of India. They added that an estimated 57% men and 11% women in India, between 15 and 49 years of age used some form of tobacco. (6) A recent study by **Chauhan R et al (2022)** among 500 biopsy proven HNCs showed a high prevalence of tobacco use among HNC patients in the state of Bihar in India. (10)

2. Areca nut (Betel Quid):

Barsouk A et al (2023) discussed that chewing of areca nut was associated with more than half the cases of head and neck carcinomas in South and Southeast Asia and Polynesia. Areca nut being an affordable and accessible stimulant and suppressant of appetite makes its usage prevalent especially among the underprivileged and rural population. Often, it is prepared by adding tobacco, thus increasing the risk up to 8 times for HNCs. (2) **Argiris A et al (2008)** similarly discussed that areca nut chewing was associated with increased risk of oral cavity cancers. (7)

3. Human Papilloma Virus:

HPV as a risk factor has been reported by **CDC (2023)** in 70% of cancers in the oropharynx (tonsils, soft palate, base of the tongue). (9) As per **Argiris A et al (2008),** HPV type 16 and type 18 have been identified as a causal factor for SCCHN. HPV genomic DNA has been observed in about 25% of SCCHN cases. The association between HPV and SCCHN has been reported to be the strongest for cancers of the tonsil, intermediate for the rest of oropharyngeal cancers, and the weakest for larynx and oral cavity. HPV-associated SCCHN has been frequently observed in individuals who are not smokers, drinkers, or immunosuppressed. Some sexual practices have also been reported to be risk factors for oropharyngeal cancers due to their high risk of HPV transmission. The carcinogenic effect of HPV16 and HPV18 is mediated through E6 and E7 viral oncoprotein, which cause inactivation of the tumour-suppressor proteins, P53 and PRb, respectively. They further discussed that HPV-positivity is associated with better prognosis and such tumours have better responsiveness to radiation and chemotherapy. (7) This was also discussed by **Chow (2020)** in their study, who further added

that HPV-positive cases were generally more fit and had fewer comorbidities as compared to HPV-negative cases, who were often physiologically compromised due to the chronic use of alcohol and tobacco. **Chow (2020)** further discussed that though cases of tobacco and alcohol consumption-associated HNC are declining, there has been observed a rise in the number of HPV-associated cancers. This could be attributed to increased awareness and enhanced diagnostic evaluation for HPV. (8) Similar findings were discussed by **Barsouk A et al (2023)** as well. (2)

Occupational exposure: As per National Cancer Institute (NCI) USA (2021), occupational exposure among certain factory workers is associated with HNC. Wood dust is reported to be a risk factor for nasopharyngeal cancer. Industrial exposure to asbestos and synthetic fibres, those working in construction, textile, ceramic, metal, logging and food industries are all at risk of development of voice box cancer. Nickel dust, wood dust and formaldehyde are associated with cancers of nasal cavity and paranasal sinuses.(4) This has also been reported by CDC (2023). (9) Occupational factors as a risk have also been discussed by Argiris A et al (2008). (7)

4. **Radiation exposure:**

Individuals who have been exposed to radiation either for cancer or any non-cancerous lesion are at risk for development of salivary gland cancer, as per the National Cancer Institute (NCI) USA (2021) and CDC (2023). (4,9)

5. **Epstein-Barr virus (EBV) infection:**

The **National Cancer Institute (NCI) USA (2021), CDC (2023)** and **Barsouk A et al (2023)** state that EBV infection is a risk factor for development of nasopharyngeal and salivary gland cancer. (2,4,9)

6. **Ancestry:** Asian, particularly, Chinese ancestry, has been known to be a risk factor for nasopharyngeal cancer, as stated by **National Cancer Institute (NCI) USA (2021).** (4)

7. **Underlying genetic disorder:**Fanconi anaemia, can increase the risk of development of precancerous lesions and cancers in early life, as discussed by **National Cancer Institute (NCI) USA (2021).** (4)

Certain genetic variations in the enzymes that metabolise alcohol and tobacco have been connected to a higher risk of SCCHN, as per **Argiris A et al (2008).** (7) They further discussed that those with cancer susceptibility syndromes, such as Li-Fraumeni syndrome, Fanconi's anaemia, hereditary non-polyposis colorectal cancer and ataxia telangiectasia are also at risk for development of HNC. (7)

Opium Barsouk A et al (2023) discussed that opium use was associated with a higher risk of laryngeal cancer. Opium is considered carcinogenic to humans when smoked or consumed in various forms; which include raw, dross, or sap opium. (2)

9. **Other risk factors:**

Other risk factors as discussed by **Barsouk A et al (2023)** include poor oral hygiene, any chronic inflammation or infection of the oral cavity (for e.g.chronic periodontitis) or poor nutrition. Also, frequent consumption of preserved meats may increase the risk of nasopharyngeal carcinoma. (2)

3.3**PATHOGENESIS**

The development of SCCHN is controlled by a multitude of genetic processes that result in the activation of porto-oncogenes, the inactivation of tumour-suppressor genes, or both, as discussed by **Argiris A et al (2008).** (7)

Treatment resistance and carcinogenesis are influenced by stromal and immune/inflammatory cells. 90% of SCCHN and premalignant lesions have reactivated telomerase, which is important in telomere maintenance and immortalisation (thus safeguarding the acquired genetic alterations). 9p21 deletion is a relatively prevalent genetic abnormality, accounting for 70–80% of cases of SCCHN. Early events in the carcinogenesis could be due to p16 inactivation, which may occur due to point mutations, promoter hyper methylation, homozygous deletion or loss of 3p. In 50% cases, loss of 17p heterozygosity and TP53 point mutations may be seen. These TP53 mutations have been also shown

to be associated with decreased survival after surgical treatment. An aggressive tumour behaviour is correlated with 11q13 amplification and cyclin D1 overexpression.

Argiris A et al (2008) further discussed that a key component of SCCHN biology is the EGFR (Epidermal Growth Factor Receptor) - a member of the ErbB growth factor receptor tyrosine kinase family. Ligand binding (eg, epidermal growth factor) leads to the homo - dimerisation or heterodimerisation of EGFR with other ErbB family members. As a result, a series of chemical events take place that lead to the activation of receptor-linked tyrosine kinase and numerous other pathways that control proliferation, apoptosis, metastatic potential, and angiogenesis. Cross-talk with other receptors, such as G-protein-coupled, platelet-derived growth factor, insulin-like growth factor, and hormone receptors, can also activate EGFR. 90% or more of SCCHN patients exhibit EGFR protein expression. Patients with SCCHN who over-express EGFR have poor outcomes. Targeting of this receptor has been effectively utilised for therapeutic purposes. (7)

Angiogenesis in cancer is regulated by various proangiogenic and antiangiogenic factors- of which the vascular endothelial growth factor (VEGF) and its receptors play an important role and have prognostic significance as well. Anti angiogenesis therapeutic strategies are under study for treatment of SCCHN. Various mechanisms for immune evasion have also been proposed. These include escape from immune recognition and elimination, activity of immunosuppressive cells, impaired activity of T-lymphocyte cells, cytokine mediated local and systemic effects. Reduced concentrations of CD3+,CD4+,and CD8+ T cells in peripheral blood have been observed in SCCHN cases, which might persist even several years after curative treatment

3.4 SYMPTOMS

The NCI and CDC have described the symptoms of head and neck cancers as follows: (4,9)

In the mouth –

white/ red sore on the gums, tongue or lining of the mouth that doesn't heal.

- Swelling in the jaw.
- Pain or unusual bleeding in the mouth.
- Any lump/ thickening.
- Any problems with denture.

In the pharynx –

- Trouble while breathing or speaking.
- Any lump/ thickening.
- Trouble while chewing or swallowing food.
- A feeling of something caught in the throat.
- Pain in the throat that won't go away.
- Pain or ringing in the ears or trouble hearing.
- **In the larynx –**
- Pain during swallowing.
- Ear pain.
- Hoarseness of voice.

In the sinuses and nasal cavity –

- Blocked sinuses that don't clear.
- Sinus infections that do not respond to treatment with antibiotics.
- Bleeding through the nose.
- Headaches.
- Pain and swelling around the eyes.
- Pain in the upper teeth.
- Problems with dentures.
- **In the salivary glands –**
- Swelling under the chin/ around the jawbone.

- Numbness/ paralysis of muscles of the face.
- Pain in the face/ chin/ neck that doesn't go away.

3.5. DIAGNOSIS

After a thorough history and physical examination, radiologic imaging should be performed ideally, before large biopsy specimens are obtained. This will avoid possible biopsy-induced anatomical distortion or false positive results induced by biopsy on positron emission tomography (PET).
Fine-needle aspiration (FNA) biopsy is considered to be highly sensitive, specific, and accurate for the histological diagnosis of tumours initially. In case cervical node biopsy is required, complete nodal resection is preferred so as to prevent extra capsular metastatic spread and tumour spillage, which requires more radical treatment. (8)

3.6 STAGING

The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) system use the TNM (tumour, node, metastasis) staging for the classification of HNC and determining its therapy.

The cancers of the head and neck can be classified as early, locally advanced or metastatic (recurrent) for the purpose of treatment. (1) The management includes surgery, radiation therapy, chemotherapy , targeted therapy, immunotherapy, or a combination of treatments depending on the primary site, stage of the tumour, age, performance status and pre-existing comorbidities of the patient. (1,4)The present study is aimed to assess the efficacy of concurrent chemoradiation with erlotinib versus cisplatin in locally advanced head and neck cancer patient. We shall discuss the drugs in detail below.

3.7 CISPLATIN

Cisplatin is an antineoplastic agent. Though highly toxic, Cisplatin is one of the most profoundly utilised chemotherapeutic agents for haematological and solid tumour malignancies. It came into use during the 1970s. It can be used for induction and neoadjuvant therapy either as a single-agent or combination therapy. (11)

3.7.1Mechanism of action:

Cisplatin acts via non-cell cycle-specific cytotoxicity. This is achieved by covalent binding of platinum to guanine and adenine (purine bases) leading to intra-strand and inter-strand cross-linking which further leads to subsequent strand breaks. While DNA repair mechanisms are underway, the cells undergo apoptotic or non-apoptotic cell death due to remnant damaged DNA, RNA, and proteins. Chemotherapy using Cisplatin is particularly effective at targeting rapidly dividing cells, as in rapidly growing malignant tumours. (11).Primary excreted occurs in the urine, while approximately 10% is excreted in the bile.The initial half-life of Cisplatin is approximately 20 to 30 minutes, and the terminal half-life is of 24 hours. (11)

Administration: Cisplatin can be administered both intravenously and as an intra-arterial agent. Cisplatin can be used as mono-therapy or as part of a multi-drug regimen. The patient must achieve and maintain adequate hydration and urinary output before and 24 hours after administration. Anti-emetic agents can be used for prevention of nausea and vomiting prophylactically. (11)

Renal Dose Adjustments: (11)

- Creatinine clearance between 10 and 50: decrease dose by 25%
- Creatinine clearance below 10: decrease dose by 50%
- Haemodialysis: Decrease the dose by 50% with no supplement; administer after dialysis-on-dialysis days with no supplement
- Peritoneal dialysis: Decrease the dose by 50% with no supplement

- **Adverse effects:** (11)
- Extravasation – In case of any suspected extravasation, infusion must be stopped immediately and any obvious fluid aspirated, and the extremity should be elevated as well. Sodium thio- sulphate, the antidote, should be administered.
- Secondary malignancy - Leukaemia which is the most common secondary malignancy following treatment with cisplatin, typically occurs years after completion of the treatment.
- Tumour lysis syndrome- may manifest as hyperuricemia, hyperkalaemia, alteration in hemodynamic and azotaemia.

Common Side Effects: (11)
- Mild nausea
- Vomiting
- Diarrhoea
- Temporary hair loss
- Loss in the ability to taste food
- Hiccups
- Dry mouth
- Dark urine
- Decreased sweating
- Dry skin
- Dehydration
- **Contraindications:** (11)

Severe hypersensitivity to cisplatin or platinum compounds.
- Pregnancy
- Lactation

Monitoring: (11)
- Haematological - Complete blood count (CBC) before initiation of treatment and before initiation of each subsequent treatment course.
- Renal function - Serum creatinine, BUN (blood urea nitrogen), creatinine clearance, and electrolytes (Na, K, Ca, Mg) before treatment administration.
- Hearing and vestibular - Audiometric testing should be ordered in paediatric patients to determine baseline and before each administration. The testing should continue for several years after discontinuation of therapy.
- Infusion – Assessment of infusion site before, during, and after administration to assess for infection and extravasation.
- Monitoring for neuropathy, ocular changes, and signs of systemic infection.
- **Toxicity:** (11)
- Gastrointestinal toxicity - Nausea and vomiting are dose-related; and can be severe leading to metabolic derangements. It may persist for up to 1 week after administration. Prophylactic treatment with antiemetic agents is highly recommended.
- Myelosuppression – This may lead to morbidity and mortality associated with infection. Frequent monitoring for signs of infection through CBC must be done. Haematological toxicity may require total treatment interruption, or dose modification if treatment is to continue.
- Neurotoxicity - Peripheral neuropathy is the most common manifestation of dose-related neurotoxicity. It may progress even after discontinuation and might be irreversible in some cases. Dosage alteration may be-required in case of neuropathy, but high-grade peripheral neuropathy may require discontinuation of treatment.
- Nephrotoxicity - Severe renal toxicity, including acute renal failure, may occur; and may be dose-related. Maintaining adequate hydration prior to and during treatment plays a significant role in

preventing renal toxicity. Close monitoring of the glomerular filtration rate (GFR) is necessary and dose adjustment may be required.

- Ocular toxicity/retinopathy – Can manifest in any form from colour discrimination to cortical blindness. Improvement is usually seen after discontinuation of cisplatin and total recovery may be possible in some cases.
- Ototoxicity – Assessment of the patient for symptoms such as decreased ability to follow conversations, high-frequency hearing loss and ringing in the ears. Deafness has been reported but is not common effect.
- Gonadotoxicity - Impairment of spermatogenesis and dose-dependent ovarian failure may be seen

3.8 ERLOTINIB

The EGFR (Epidermal Growth Factor Receptor) belongs to the ErbB family of cell membrane receptors that have known to be involved in cancer. These receptors are important mediators of cell growth, cell differentiation and survival. EGFR over-expression is known to be involved in growth and-progression of tumour, cell proliferation, inhibition of apoptosis, angiogenesis and metastasis. The ErbB family consists of four closely related members: ErbB-2/Neu/HER2, ErbB-3/HER3 and ErbB-4/HER4. (12,13)

The EGFR is also known as ErbB-1/ HER1. It is a 170-kDa transmembrane glycoprotein and consists of an extracellular, hydrophobic and intracellular domain. The extracellular domain binds to specific ligands; the hydrophobic domain helps in interaction between the receptors within the cell membrane; and the intracellular domain consists of the tyrosine kinase (TK) enzymatic activity. The EGF-like growth factors bind and may lead to activation of one or more ErbB family receptors. On binding to the extracellular domain, EGFR experiences homodimerization or heterodimerization. This leads to TK domain activation causing auto phosphorylation of critical tyrosine residues on the cytoplasmic terminal. These residues act as sites for attachment of various-cellular-docking proteins; and thus activate a diversity of downstream signalling cascades which affect gene transcription. These pathways are:

- Ras/Raf mitogen-activated protein kinase,
- Phosphoinositide-3 kinase (PI3K)/Akt, and
- Jak2/STAT3 pathways

Activation of these pathways leads to the initiation of a cascade of a complex that regulates cell proliferation, angiogenesis, apoptosis, invasion and metastasis. The over-expression of EGFR has been demonstrated in 95-100% head and neck cancers. The blockade of EGFR signalling in cancer cells can inhibit the entire cascade of the complex mentioned above. It may also cause potentiation of anti tumour activity of cytotoxic drugs and of radiotherapy. (12)

Two EGFR-targeted pharmacologic approaches have brought about clinical activity among the cancer patients include: (12)

- monoclonal antibodies (mAbs), such as cetuximab and panitumumab, that act against the extracellular domain of EGFR and block binding to ligand and activation of receptors; and small-molecule inhibitors of EGFR tyrosine kinase, such as gefitinib and erlotinib, that prevent auto phosphorylation of EGFR and downstream signalling.

Erlotinib is an oral low-molecular weight quinazoline based agent.

Mechanism of action: (12,15)

It causes selective and reversible inhibition of TK activity of EGFR and competes with adenosine triphosphate for binding to the TK domain of the receptor. Erlotinib interacts both with the wild-type and mutation EGFR.

Administration: (12,15)

Erlotinib is available in the form of oral tablets in 25 mg, 100 mg, and 150 mg. It is recommended to take erlotinib on an empty stomach, as its bioavailability increases when taken with food. Concomitant use of proton pump inhibitors (PPIs) must be avoided as higher pH alters the

concentration of erlotinib. They should be taken several hours before erlotinib administration. When using with potent CYP3A4 inhibitors, the dose of erlotinib should be reduced to avoid adverse interactions. The dose must be increased when combining the drug with CYP3A4 inducers. (15)
It is 60% absorbed after oral administration. Once absorbed, 93% of it is protein bound. Metabolisation of erlotinib occurs through the cytochrome P450 system primarily by CYP3A4. With a half-life of 36 hours, this drug is mainly excreted in faeces. The maximal tolerated dose was 150 mg/daily on a protracted daily schedule. (12)

Adverse effects: (12,15)

General:

- Fatigue
- **Gastrointestinal:**
- Diarrhoea
- Anorexia
- Weight loss

Dermatologic

- Rash
- Pruritus
- Acne
- Dermatitis acneiform
- Xerosis
- Paronychia

Diarrhoea and skin rash are the most notable and dose-limiting toxic effects. (17)

Serious Adverse Effects: (12,15)

- Acute renal failure and renal insufficiency.
- GI perforations, including fatalities.
- Hepatotoxicity and hepatorenal syndrome, including fatalities.
- Cardiac arrhythmias in patients taking erlotinib with gemcitabine.
- INR elevations in patients taking erlotinib and Warfarin concomitantly.
- Exfoliative skin disorders.
- Corneal perforation.

Monitoring: (12,15)

It is recommended to discontinue erlotinib in case of an increase in total bilirubin levels (up to three times higher than the patient's baseline) or in case of an increase in transaminase levels (up to five times higher than the patient's baseline).

Toxicity: (12,15)

Patients can tolerate a weekly dosing of total 1600 mg without toxicity. In case of an overdose, symptomatic treatment, is recommended along with discontinuation of the medication.

3.9 ERLOTINIB IN HEAD AND NECK CANCERS

Treatment of HNC patients has been evolving continually. Treatment of patients has moved from definitive RT to chemo radiotherapy in the last decade among patients with unresectable tumours. (14)

Erlotinib has shown anti tumour effect as a single-agent therapy in advanced head and neck cancer patients who were heavily pretreated, as discussed by **Bareschino MA et al (2007)** (12)

EGFR as a treatment strategy for head and neck squamous cell cancer (HNSCC), is supported by several lines of evidence. EGFR over-expression is seen in 80–100% of HNSCCs, supporting the target's possible therapeutic utility. Additionally, when compared to control normal mucosa, higher amounts of EGFR and TGF-alpha messenger RNA were found in tumours and in histologically normal mucosa from patients with HNSCC. (12,14).

Mehta VK (2012) in their review discussed that though no striking benefits have been observed in studies combining erlotinib and radiotherapy, there are modest improvements reported with this

approach. Undoubtedly, adverse events for either approach do not seem to be aggravated, and toxicities are manageable. (14)

Rao K et al (2013) in their phase II study among 21 patients presenting with locally advanced (T3-4) lesions treated with a combination of radiation with intra-arterial (IA) cisplatin and erlotinib for seven weeks reported that this treatment combination suggested improved survival outcomes in the patients along with reduced distant metastatic rates. The overall survival was found to be 63 %, and the relapse/persistent disease rate was observed to be 36.8%. 15.2% of major adverse events were thought to be associated with erlotinib. They further proposed that maintenance therapy with anti-EGFR agent could prove to be beneficial. (18)

Herchenhorn D et al (2010) evaluated the safety and therapeutic efficacy of erlotinib in combination with radiotherapy and cisplatin for locally advanced HNSCC among 31 patients with histologically proven AJCC Stage III/IV, M0, oropharynx, larynx or hypo-pharynx SCC. They observed that 74% of the patients showed complete response. The 3-year progression-free and overall survival rates were 61% and 72%, respectively, with a median follow-up of 37 months. An unexpected observation was a 51% incidence of severe in-field dermatitis of grades 3 and 4. Other common nonhematologic toxicities observed by them included diarrhoea, xerostomia, stomatitis, nausea/vomiting, and acneiform rash. They stated that this combination appeared to be safe and had a promising approach. (19)

Hayes DN et al (2010) in their multi-centre phase II randomized trial of combination of radiotherapy and cisplatin with or without erlotinib among patients of locally advanced SCCHN reported that 14 patients on erlotinib reported side effects as compared to 16 patients on cisplatin alone. Nausea, vomiting and dehydration were among the most common adverse effects they concluded that Erlotinib did not increase the rate of any serious adverse events associated with cisplatin and radiotherapy in SCCHN. (20)

Kim ES et al (2006) evaluated the addition of erlotinib to cisplatin–docetaxel doublet. They reported complete response in three patients, partial response in eighteen, disease stabilisation in eight patients, overall response rate of 66% and disease control rate of 91%. The most common grade 1-2 toxicities were nausea, diarrhoea and skin rash. They concluded that this combination had a very encouraging early activity in advanced SCCHN and was well tolerated by the patients. (21)

Martins RG et al (2013) in their randomized phase II trial among 204 patients with histologically confirmed Stage III, IVA or IVB SCC of head and neck divided patients into two groups with one receiving cisplatin-radiotherapy and the other receiving same treatment along with erlotinib. No difference between both groups was reported in terms of toxicities (p-value>0.20). with the exception of more rash among patients receiving erlotinib (p-value<0.001). For both groups grade 3 or higher GI toxicity—which mostly consisted of mucositis, nausea, and vomiting—was the most frequent category of adverse events. When evaluated by central review, complete response rate (CRR) in those receiving erlotinib was 52% compared to 40% in the other group (p-value=0.08). Also, there was no difference in progression free survival (PFS) with a median follow-up period of 26 months (p-value=0.71), between both groups. No statistical difference between the two groups was observed in overall survival or loco regional control. Another finding reported was better CRR (p-value=0.008) and superior PFS (p-value=0.03) among patients who developed a rash following the treatment. **Martins RG et al (2013)** concluded that though erlotinib did not increase cisplatin and radiotherapy toxicity in the patients, it failed to significantly increase the PFS or CRR. (22)

Soulieres D et al (2004) in their multi-centre phase II study of erlotinib, reported that even among patients with recurrent or metastatic SCCHN, disease stabilisation was achieved and maintained in 38.3% patients for a median duration of 16.1 weeks. Median progression free survival was of 9.6 weeks and median overall survival was of 6 months. Significant difference was observed in overall survival (p-value=.045) which was in favour of the patients who developed skin rashes (at least grade 2) vs those who didn't. Rash and diarrhoea were the most common drug related toxicities. (23)

Similarly, **Siu LL et al (2007)** in their Phase I/II trial of erlotinib and cisplatin, reported one complete and eight partial responses among patients with recurrent or metastatic SCCHN. Disease stabilisation

was reported to be achieved in 49% patients. Median progression-free survival was 3.3 months and median overall survival was 7.9 months. The combination of erlotinib and cisplatin was found to be well-tolerated with minimal toxicity. Better survival outcome was observed in patients who developed a higher grade of skin rash. They concluded that this drug combination of cisplatin and erlotinib had a favourable toxicity profile, as well as, anti-tumour activity when compared to standard combination chemotherapy regimens in SCCHN. (24)

Soulieres D et al (2004) in another study among thirty-one patients with recurrent/ metastatic HNSCC treated with a combination of erlotinib and cisplatin reported complete response in one patient and partial response in seven patients. They further added that the anti-tumour activity of the combination treatment with cisplatin and erlotinib was comparable to the standard cisplatin-based combination chemotherapy but had a more favourable toxicity profile. (25)

Le x et al (2022) discussed that the combination of erlotinib and platinum-taxane chemotherapy is generally well-tolerated but does not induce higher major pathological rates, progression free survival rates or overall survival rates or benefits. However, those patients who received this combination and achieved major pathologic response had excellent clinical outcomes. (26)

Cossyleon R et al (2024) conducted a study to assess the quality of life of 21 patients with locally advanced head and neck cancer who had enrolled between May 2006 and May 2010, pre- and post-treatment with cisplatin (intra-arterial) along with concurrent radiation and erlotinib. Most common side effects observed in our patients while taking erlotinib for 7 weeks were grade 1–2 skin rash, diarrhoea, and nausea. One of the most common side effects observed Xerostomia , regardless of the type of radiotherapy received. These patients required fluids while eating or complained about having food stuck in their mouth along with a perception of “dry mouth”. The 1-, 3-, and 5-year overall survival rates regardless of comorbidities, were 83%, 67%, and 55%, respectively. (27) Materials & Methods

4.1 MATERIAL AND METHODS

This is two arm comparative prospective type study conducted at government cancer hospital in department of radiation oncology, M.G.M medical college Indore after getting approval from ethics committee of medical college. Total 60 patient registered in government cancer hospital with locally advanced stage 3 & 4 head and neck cancer .

- The personal details of the patients like name, age, gender, address, contact number and the significant data were recorded.
- The detailed case history of the patient was recorded for the further treatment and the investigations as per needed.
- The study population comprised of 60 patients of clinically and histo-pathologically diagnosed head and neck cancer of stage 3 or stage 4
- The study population was divided as

❖ Group A = 30 cases – received conventional radiation therapy with CISPLATIN 40 mg/m2

❖ Group B = 30 cases - received conventional radiation therapy with tablet ERLOTINIB 150 mg daily throughout RT

4.2 WORK UP OF PATIENTS:

❖ A detailed case history was taken and a full clinical examination was carried out for subjects in the study group. Biopsy was taken from the affected region for clinical histopathological examination.After confirmed histopathology report the patients was enrolled in the study.According to TNM and AJCC guidelines and criteria clinical diagnosis and staging done.

❖ Evaluation of patients was done weekly and monthly for the treatment responses and complications recurrence of disease and distant metastasis.

- The all patient was kept on 6 monthly follow up to evaluate the probability of any local recurrence as well as any distant metastasis in this duration.

SCREENING

- History
- Signs and symptoms
- Personal history
- Previous treatment history

4.4 PRE-TREATMENT EVALUATIONS

Complete physical and clinical examinations and ENT check up with KPS evaluation.

4.5 LABORATORY STUDIES:

- Hemogram
- Blood urea and sugar
- Serum creatinine
- Liver function test
- Imaging:
- X-ray chest
  X-ray mandible
  X-ray ST neck
  X-ray PNS
  USG abdomen pelvis

4.6. INCLUSION AND EXCLUSION CRITERIA

4.6.1 INCLUSION CRITERIA

- Patients of both sex
- Patients of age preferred>18 and <65years
- Patients with KPS (karnofsky performance status) 50 or more.
- Biopsy proven patients with locally advanced squamous cell carcinoma of head and neck stage 3 and 4.

4.6.2 EXCLUSION CRITERIA

- Patients refuse to give consent.
- Patients who have received radiotherapy before.
- Patients having major comorbidities who are not fit for receiving RT.i.e. CAD, DM, renal disease, auto immune disease bronchial asthma and collagen vascular disease.
- patients who are having a life expectancy less than 6 months

4.7 PROCEDURE AND PLAN

Patient counselled and informed about treatment plan, about radiation therapy. Informed Consent was signed by patient and thumb impression by illiterate patient in presence of witness. Total 60 patients were randomized and divided in two arm Group A & B.

4.7.2 METHOD OF DELIVERING CHEMOTHERAPY

After the blood report ,each patient in arm A ,on the day chemotherapy was PRE-medicated with injection dexamethasone 8 mg IV ondansetron ,injection ranitidine 50mg IV and injection ondansetron 8mg IV with normal saline 100 mL over 30 minutes.After the injection cisplatin at a dose of 40mg/m2 was given in normal saline 500 mL over 2 hours slow infusion followed by which mannitol was given at a dose of 20% 200 mL over 1 hour followed by hydration with injection KCL 1 ampoule and injection MGSO4 in normal saline 500 mL over 1 hour .Injection filgrastim 300mcg was given subcutaneously on day 2 of chemotherapy.

Erlotinib was started orally 1week before radiation and continued daily until the last day of radiation therapy.A dose of 150 mg PO OD was started and was advised to patient that the tablet should not be chewed or swallowed. Patient we're closely monitored for pulmonary symptoms including cough ,dyspnea and fever . Patient who developed skin rash were administered topical antibiotic such as clindamycin gel or erythromycin cream/gel. Patient ere advised to avoid Seville oranges ,star fruit ,pomelos ,grapefruit while on erlotinib therapy.
Following chemotherapy all patients were counselled to maintain adequate hydration , protein calorie intake and oral hygiene during the entire treatment.

4.7.3METHOD OF RADIOTHERAPY PLANNING

After clinical examination and symptomatic assessment and on the basis of diagnosis ,tumour extension anatomically and lymphatic drainage, patient was simulated by placing the radio opaque marker on the basis of clinical maximum extension of the tumour .The arms were adducted and pulled caudally with neck extended.The superior and inferior radio opaque simulation marker were placed on the possible anatomical extension of the tumour and the posterior border was marked at the spinous process.Any gross lymph node ,if present, was also included the field.Depending on the TNM staging and location of the tumour ,the decision to use whether to use unilateral or bilateral filed was made, and lung and thyroid shielding done wherever required.The requirement for the tissue compensator and /or bite block was decided on an individual basis. After demarcating all the boundaries, steel spool wire is used to get and X-ray of desired field . After confirmation, the field was then tattooed with the indelible dye, isocentre was marked , and separation was taken for calculation of the treatment time which was done by the physicist.

4.7.4METHOD OF RADIOTHERAPY DELIVERING

After calculation of the treatment time the patient was taken to the tele-cobalt theratron 780C cobalt-60 machine with SSD set at 80 cm. The patient was then asked to lie on the treatment couch in the same position as the planning couch. Field was then set on the gantry head and isocentre were then matched with the laser beams. If necessary, shielding trays and lead blocks were employed, according to individual planning, to protect the organs at risk. Then, RT was administered to each arm .

GROUP A PATIENTS RECEIVED

- External beam radiotherapy with Theratron 780-C machine 80 cm SSD.
- All patient were planned to give 66 gy/33#//2gy/# from Monday to Friday with concurrent CISPLATIN 40 mg /m2. In 2nd phase of treatment cord off done in posterior neck if clinically indicated.
- Build up and mouth gag used where required.

GROUP B PATIENTS RECEIVED

- External beam radiotherapy with Theratron 780-c machine 80cm SSD.
- All patient were planned to give 66 gy/33#//2gy/# from Monday to Friday with concurrent erlotinib 150 mg. In 2nd phase of treatment cord off done in posterior neck if clinically indicated.
- Build-up and mouth gag were used where needed.

Treatment gap allowed only in case of severe mucositis and skin reaction to allow healing of normal tissue. During therapy patient examined after every fraction of RT for remarking of field borders and for the examination of mucositis and skin reactions. Also examined weekly as a routine for mucosal reaction, skin reaction and haematological toxicity, dysphagia, nausea and vomiting and renal toxicity. Oral and dental hygiene instruction and medication given. Dental evaluation done. Both arms were compared using chi square test to check balance in term of disease and patient related characters like sex, age, tumour site, performance status. Tumour regression response don as per

RECIST criteria, mucositis and dermatitis as per RTOG guidelines and analysis was done using descriptive statistics by use of the available charts. Toxicity grade also compared between both arms by use of chi square and Fishers exact test. After the end of radiotherapy follow up was done on day 0, monthly and 6 months.

4.8 EVALUATION

- Done weekly along radiation therapy- for acute complications.
- Done Monthly after radiation therapy- for late complications, distant metastasis DFS (disease free survival) local control
- At least 6 months follow up

For mucositis and skin reactions grading done as per RTOG/EORTC (radiation therapy oncology group/ European Organisation for Research and Treatment of Cancer). Haematological toxicities (on the basis of blood haemoglobin level), was assessed as per WHO toxicity criteria in all patients weekly up to 6 weeks.Dysphagia, Xerostomia, and pain also assessed. Pain assessment done accordingly Wong-baker pain rating scales.In case of local recurrence clinical examination done and FNAC/BIOPSY done for confirmation. For distant metastasis ultrasound, X-rays done.

OBSERVATION TABLES

5.1AGE WISE DISTRIBUTION CASES

Age	Frequency	Percent
<40	3	5
41-50	32	53.3
51-60	19	31.7
>60		
Total	60	100

5.2GENDER WISE DISTRIBUTION OF CASES

Gender	Frequency	Percent	Valid percent
Male	41	68.3	68.3
Female	19	31.7	31.7
Total	60	100	100

5.3STAGING WISE DISTRIBUTION OF CASES

Staging	Frequency	Percent	Valid percent
2	17	28.3	28.3
3	36	60	60
4	7	11.7	11.7

5.4TABLE SHOWING DYSPHAGIA IN TWO GROUP

Dysphagia	Frequency	Percent	Valid percent
Yes	40	66.7	66.7
No	20	33.3	33.3

5.5TABLE SHOWING SKIN TOXICITY

Skin toxicity	Frequency	Percent	Valid percent
Grade 1	7	11.7	11.7
Grade 2	30	50	50
Grade3	23	38.3	38.3

5.6TABLE SHOWING GASTROINTESTINAL TOXICITY

Grade	Frequency	Percent	Valid percent
1	21	35.0	35.0
2	31	51.7	51.7
3	8	13.3	13.3

5.7TABLE SHOWING HAEMATOLOGICAL TOXICITY

Grade	Frequency	Percent	Valid percent
1	32	53.3	53.3
2	16	26.7	26.7
3	12	20	20

5.8 TABLE SHOWING CNS COMPLICATION m

	Frequency	Percent	Cumulative percent
Yes	1	1.7	1.7
No	59	98.3	98.3

5.9TABLE SHOWING RENAL COMPLICATION

	Frequency	Percent	Cumulative percent
Yes	27	45	45
No	33	55	100

5.10TABLE SHOWING TREATMENT GAP IN TWO GROUPS

Group	Frequency	Percent	Cumulative percent
Arm A	37	61.7	61.7
Arm B	23	38.3	100

5.11TABLE SHOWING LOCAL RECURRENCE

	Frequency	Percent	Valid percent
YES	21	35	35
NO	39	65	65

5.12DISTANT METASTASIS

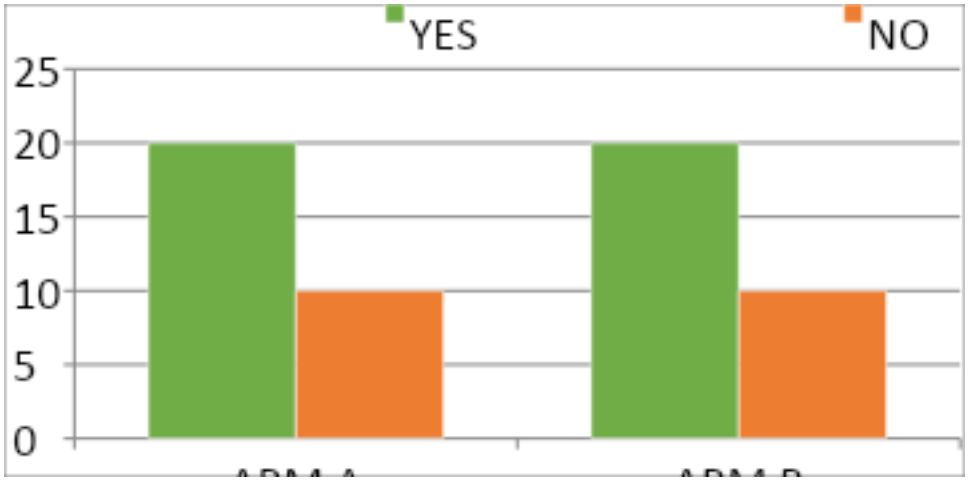
Group	Frequency	Percent	Cumulative percent
Arm A	10	16.7	16.7
ARM B	50	83.3	83.3

5.13TABLE SHOWING DIFFERENT RESPONSES

RESPONSE	Frequency	Percent	Valid percent
PR	14	23.3	23.3
PD	16	26.7	26.7
SD	30	50	50

GRAPH SHOWING DISTRIBUTION OF CASES ON BASIS OF DYSPHAGIA

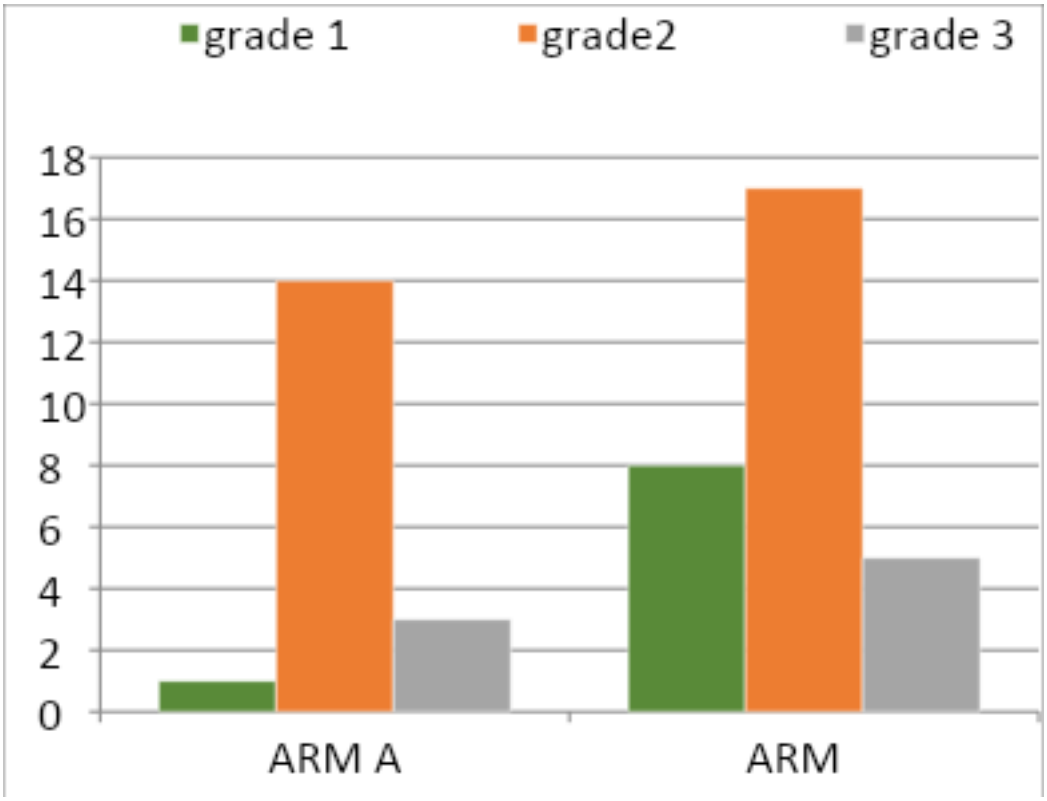
DYSPHAGIA	ARM A	ARM B	P value
Yes	20	20	1
No	10	10	



Skin toxicity	ARM A	ARM B	P value
Grade 1	2	5	0.481
Grade 2	16	14	
Grade 3	12	11	

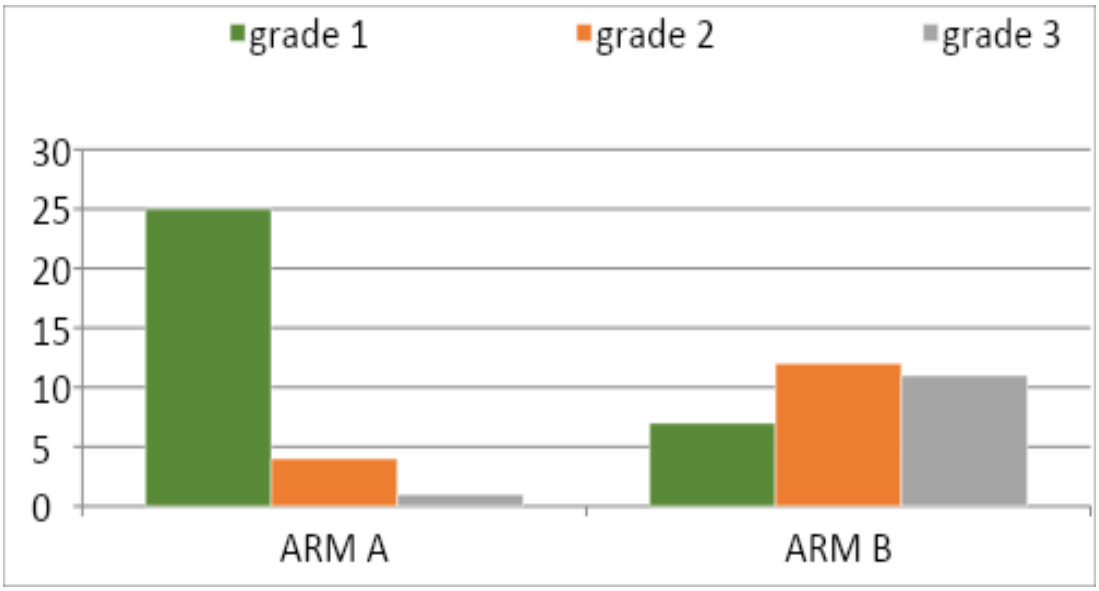
GRAPH SHOWING DISTRIBUTION OF CASES ON THE BASIS OF GASTROINTESTINAL TOXICITY

GI TOXICITY	ARM A	ARM B	P VALUE
Grade 1	13	8	0.371
Grade 2	14	17	
Grade 3	3	5	



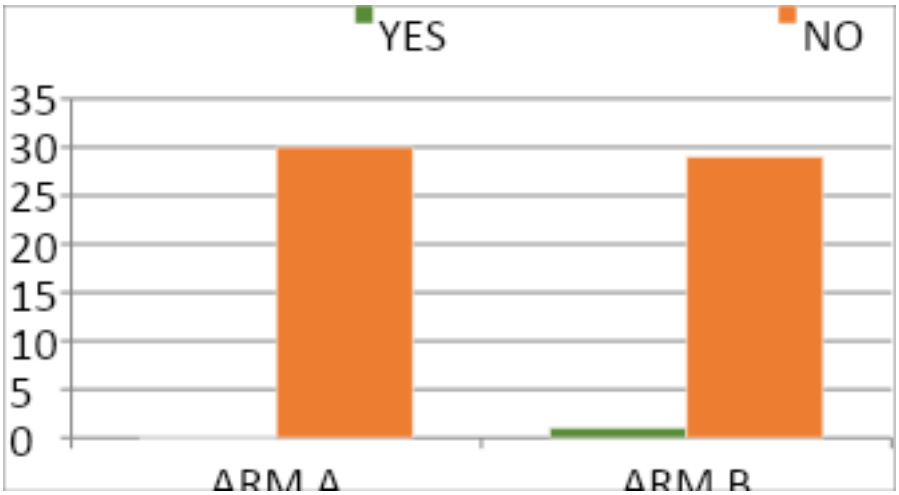
GRAPH SHOWING DISTRIBUTION OF CASES ON THE BASIS OF HAEMATOLOGICAL TOXICITY

HAEMATOLOGICAL TOXICITY	ARM A	ARM B	P VALUE
Grade 1	25	7	0.0
Grade 2	4	12	
Grade 3	1	11	



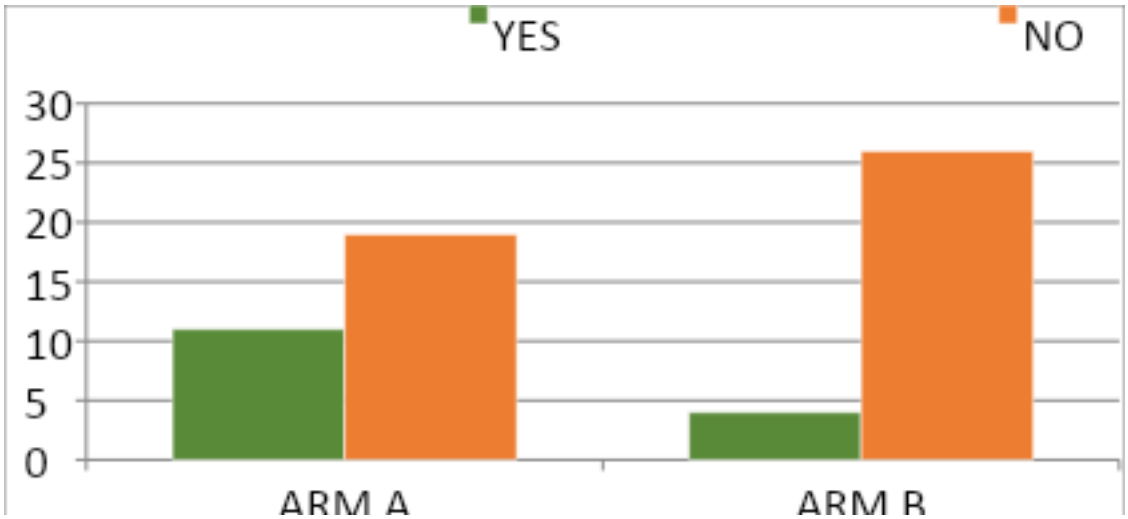
DISTRIBUTION OF CASES ON BASIS CNS COMPLICATION

CNS COMPLICATIONS	ARM A	ARM B	P VALUE
Yes	0	1	0.313
No	30	29	



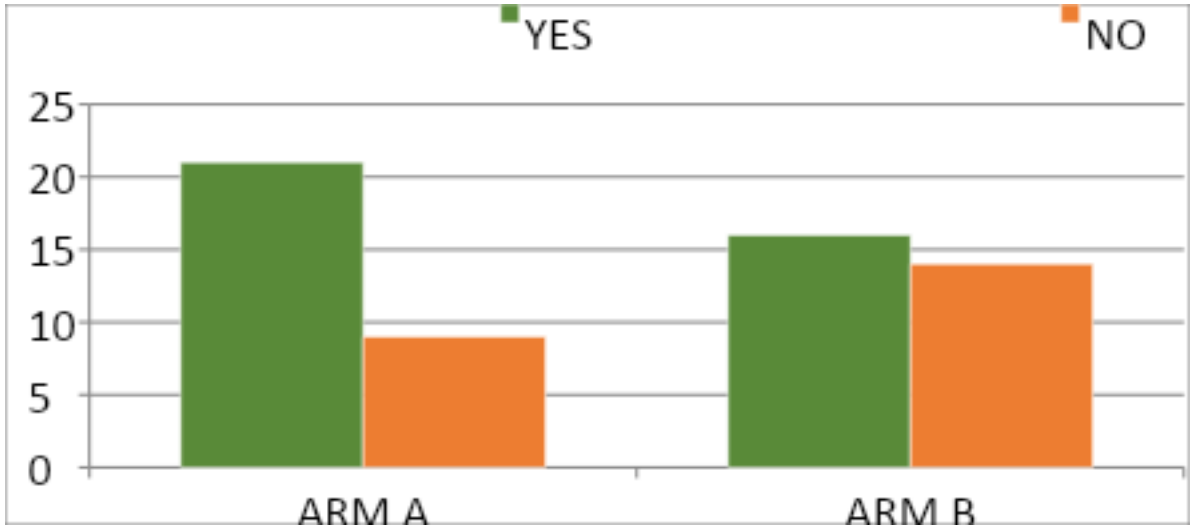
GRAPH SHOWING DISTRIBUTION OF CASES ON THE BASIS OF RENAL COMPLICATION

RENAL COMPLICATION	ARM A	ARM B	P value
Yes	27	0	<0.0001
No	3	30	



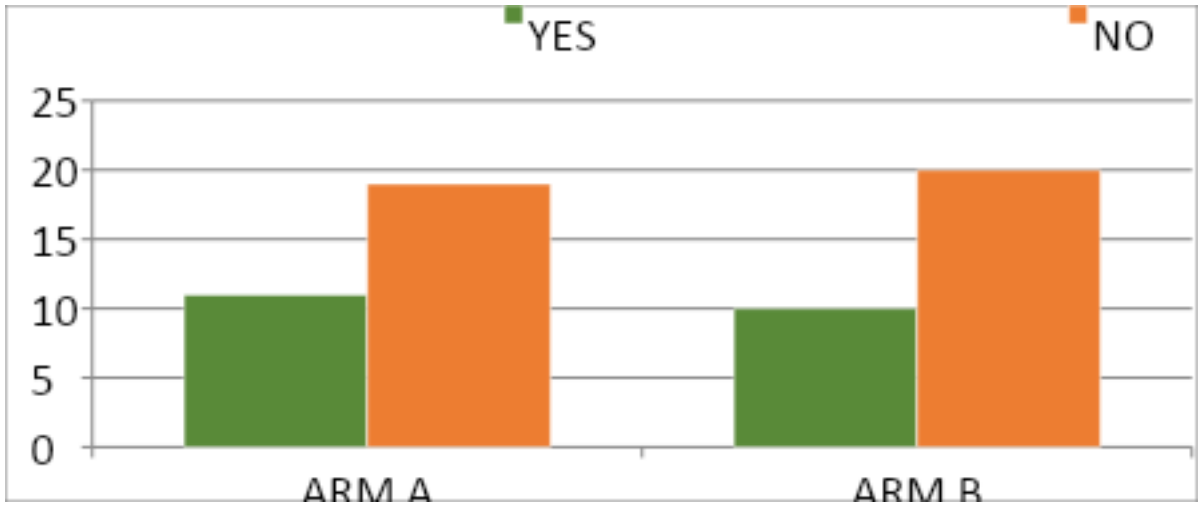
GRAPH SHOWING DISTRIBUTION OF CASES ON BASIS OF TREATMENT GAP

Treatment gap	Arm A	Arm B	P VALUE
Yes	21	16	0.184
No	9	14	



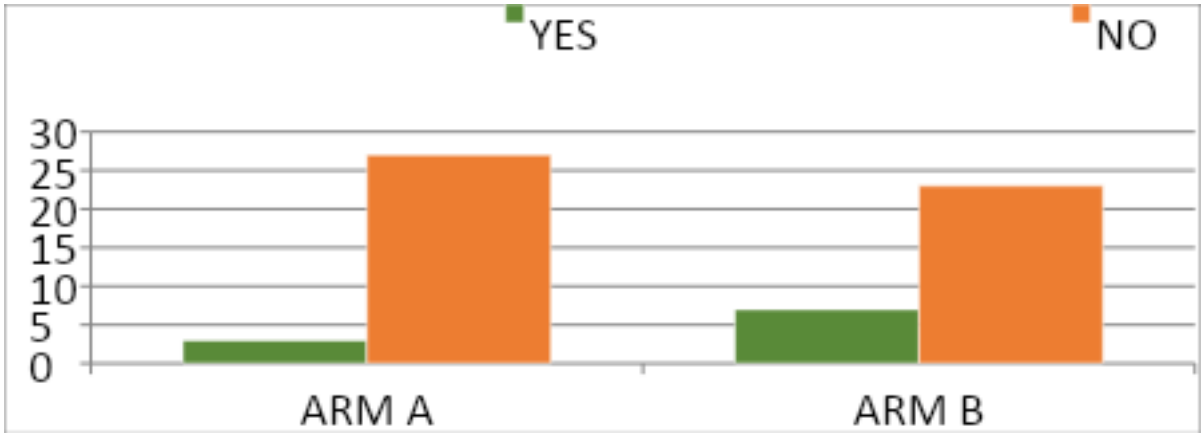
GRAPH SHOWING DISTRIBUTION OF CASES ON THE BASIS OF LOCAL RECURRENCE

Local recurrence	Arm A	ARM B	P VALUE
YES	11	10	0.787
NO	19	20	



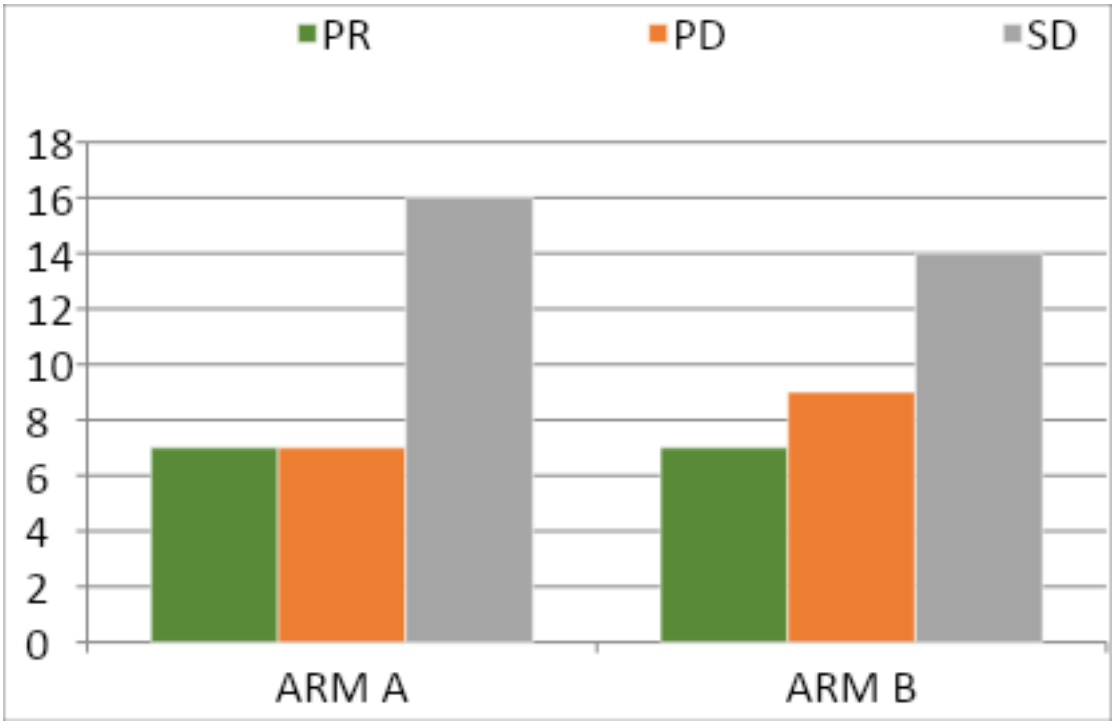
GRAPH SHOWING DISTRIBUTION OF CASES ON BASIS OF DISTANT METASTASIS

Distant metastasis	Arm A	Arm B	P VALUE
YES	3	7	0.166
NO	27	23	



GRAPH SHOWING DISTRIBUTION OF CASES ON BASIS OF RESPONSE

Response	Arm A	ARM B	P VALUE
CR	0	1	0.826
PR	7	7	
PD	7	9	
SD	16	14	



RESULTS

PATIENT CHARACTERISTIC

Following table shows baseline patient characteristics of total 60 patient on the basis of number of adverse events. Approximately two third of the patient were from stage III disease and only 3 required tracheostomy because of airway obstruction .

TOXICITY EVALUATION

Tablet Erlotinib was proceeded with no significant dose limited toxicity allowing full dose administration 150 mg to 29 patient ,only 1 patient required dose de escalation due to acneifrom rash probably because of interaction between erlotinib cutaneous side effects and RT.
Last cycle of chemotherapy was suspended in 11 patient with cisplatin arm due to increased creatinine clearance and low performance status.

EFFICACY EVALUATION

Of all the patients treated with erlotinib 150 mg ,7 patient had progressive disease status ,9 had pathological response and 14 had stable disease .
Of all the patients treated with cisplatin 40mg/m2, 7had progressive disease ,7 had pathological response and 16 had stable disease .

SURGERY AND FOLLOW UP

1 patient underwent elective surgery for the cause of residual disease after4 weeks of treatment During treatment patient were assessed weekly ,after treatment monthly follow up 3months and then 6 monthly follow up.

DISCUSSION

Cisplatin based chemoradiation is considered the care for locally advanced head and neck squamous cell carcinoma . In the present study which is comparative type of study, patients with locally advanced head and neck cancers stage 3 & 4 given treatment with concurrent cisplatin 40mg/m2 in arm A and erlotinib 150 mg in arm B ,with patient receiving conventional radiation dose of 66Gy/33#//2gy/# from Monday to Friday .In present study most of the patients belongs to 41-45 year of age group which is approximately 53.3% . Mostly patients belongs to stage III group which 60%.
In study group out of 30 patients patients 16 had stable disease and 1patient had complete response,7 patient had pathological disease,7 had progressive disease . Dysphagia was present in 20 patient in study group .In present study patient of locally advanced head and neck cancer presented with large fungating nodal mass had a good response of in study arm . In study arm complete response was 1 ,pathological disease was 7 , progressive disease was 7 and stable disease 16 which was non significant on comparison with experimental arm. It has further been studied that the study arm patients showed greater rate of renal complication on comparing with experimental arm which was statistically non significant. At the end of treatment and first month follow up, it was observed that 7 (23.3%) had partial response,7(23.3%)has progressive disease and 16(53.3%) had stable disease and 1 had complete response.
In experimental arm 7 (23.3%) had partial response, 9(30 %) had progressive disease and 14(46.7%) had stable disease .The responses were comparable as there was statistically non significant.
Skin toxicity grade 3 in study group was 40% and in control group 36.7% which is statistically non significant. Haematological toxicity in study group grade 3 was 1in arm A and in ARM B 7, grade 2 was 4% and 14% respectively in arm A and Arm B, grade 1 was25% and 9% respectively in arm A and arm B and this difference statistically not significant .
During follow-up after 6-month local recurrence occur in arm A 11 patients and 10 in arm B.,which was statistically non significant.
There were 3 cases of development of secondary in ARM A and 7 arm B.

CONCLUSION

There is no doubt that cisplatin offers major potential advantages to patients with node positive status , but erlotinib can be offered in renal impairment patient and for patient who cannot tolerate toxic chemotherapy.

8.SUMMARY

comparative prospective randomised study was undertaken clinically to evaluate the role of conventional radiotherapy concurrent with cisplatin versus concurrent erlotinib in locally advanced head and neck cancer of stage 3 and 4 disease. All subjects histologically confirmed and previously untreated patients were randomly distributed in to study and control groups.

Patient in study group treated with conventional radiotherapy of 66Gy/33#//2gy/# with concurrent cisplatin40mg/m2 from Monday to Friday and in control group patients treated with conventional radiotherapy with. 66Gy/33#//2gy/# with concurrent erlotinib 150mg from Monday to Friday. Response assessment done according to recist criteria and toxicity assessment done by RTOG guidelines.

There is no doubt that cisplatin offers major potential advantages to patients with node positive status , but erlotinib can be offered in renal impairment patient and for patient who cannot tolerate toxic chemotherapy.

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