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Effectiveness of Gefitinib as additional Radiosensitizer to Conventional Chemoradiation for Locally advanced non-metastatic Squamous Cell Carcinoma of Head and Neck. Prospective interventional Randomized Controlled Study

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Abstract

Approximately 90% of head and neck squamous cell carcinoma (HNSCC) overexpress epidermal growth factor receptor (EGFR). EGFR plays a role in predicting and modulating the response of HNSCC patients to radiation. Cetuximab is established as potent radiosensitizer. However data regarding use of tyrosine kinase inhibitors like gefitinib is limited. Aim of this study is to establish the radiosensitizer efficacy of daily gefitinib with concurrent chemoradiotherapy in patients with locally advanced non metastatic HNSCC (LAHNSCC). Between July, 2008 to October, 2011, 104 patients with LAHNSCC were randomized into two arms; in Arm A (experimental arm), patients received gefitinib (250 mg orally daily along with cisplatin based chemoradiation) and Arm B (control arm), patients received concurrent cisplatin based chemoradiation with Cisplatin dose of 100mg/m^2 intravenous infusion given on Days 1 and 22 with conventional fractionated radiation of 60-66 Gray. Response assessments were done using RECIST and adverse events by NCI-CTCAE version 3. The median follow-up time was 26 months (range 2-35 months). There was statistical difference in overall response between the two arms (p value 0.041) in favour of gefitinib arm (n=48) with overall response (ORR=CR+PR) of 91.6 % versus 69.5% in conventional cisplatin chemoradiation (n=46). Disease Free Survival favored the Gefitinib arm with Log Rank p value of 0.008. Gefitinib arm resulted in more grade 2 and 3 dermatitis, mucositis and diarrheal events. Adding Gefitinib to conventional chemoradiation in treatment of LAHNSCC improves ORR and DFS, with an increase in incidence of manageable toxicity.

Keywords: Chemoradiation, Gefitinib, Radiosensitizer.

1. Introduction

Locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC) have high risk of local recurrence and distant metastasis. Approximately 90% of HNSCC overexpress epidermal growth factor receptor (EGFR). Preclinical studies revealed EGFR as a predictor of radiation response of Head-neck cancer and have identified EGFR and its downstream signaling molecules as appealing targets for therapeutic intervention. Bonner showed that adding Cetuximab, an anti-EGFR antibody, to radiation yielded improved locoregional (LR) control and overall survival (Bonner *et al.* 2006). While role of cetuximab is established, data regarding use of Tyrosine kinase inhibitor (TKI) is limited. The aim of the study is to establish whether there is any benefit of adding Gefitinib to conventional chemoradiation.

2. Materials and Method

From July, 2008 to October, 2011, we enrolled patients with locally advanced, chemotherapy and radiation naïve non-metastatic squamous cell carcinoma of head and neck region (SCCHN) into this single

institution, interventional, open label, parallel, prospective, randomized controlled study that comprised of two cohorts: Arm A patients receiving additional gefitinib along with cisplatin based chemoradiation (experimental arm) and Arm B patients receiving concurrent cisplatin based chemoradiation (control arm). It was a simple randomization procedure by lottery in 1:1 allocation. The method of allocation concealment was sequentially numbered, sealed, opaque envelopes.

Patients with histologically proven stage III or IV (A and B) SCCHN, with no metastatic evidence on radiological or laboratory investigations; ECOG performance status 0–1; at least 40 years of age; normal bone marrow, hepatic, and renal functions; no prior invasive malignancy; no prior systemic therapy for SCCHN and no prior radiation therapy to head and neck region were eligible for inclusion in the study.

Patients were excluded from study if suffering with co-morbid conditions like uncontrolled diabetes, myocardial infarction or cerebrovascular accident in preceding one year, chronic obstructive lung disease or asthma that might require aborting the intervention; with nasopharyngeal cancer, as the incidence of cancer of this anatomic subsite is very low in the patient population attending this tertiary oncology centre; and with oral cavity cancers which were primarily treated with surgery followed by adjuvant radiation.

This clinical research protocol and the described study was conducted in compliance with the Helsinki protocol, Good Clinical Practices standards and associated local body ethical committee regulations.

The pretreatment work-up evaluation included history and physical examination including detailed ENT examination with biopsy, panendoscopy, hematology and biochemistry profile, dental evaluation, nutrition status evaluation, chest x-ray and contrast enhanced computed tomography of the head and neck.

2.1 Concurrent Chemotherapy and Targeted therapy

Concurrent cisplatin (CDDP, cis-diethylamine dichloroplatinum) chemotherapy was administered at 100 mg/m^2 intravenously, (IV) repeated every 21 days during RT for patients in both the treatment cohorts on days 1 and 22. Routine hydration with 1000 mL normal saline given before chemotherapy over 2 hours and 1000 mL of normal saline given over 2 hours after chemotherapy . CDDP was administered in 250 mL of normal saline with mannitol 12.5 g IV over 30 minutes immediately after cisplatin. Standard antiemetic prophylaxis consisted of 16 mg of ondansetron and 16 mg of dexamethasone given as intravenous bolus as pre-medication 30 minutes prior to chemotherapy. Cisplatin was given on Saturdays. Anti-emetic prophylaxis was continued with ondansetron and domperidone or metoclopramide orally two to three days after each cycle of cisplatin. Patients in arm A started taking gefitinib orally starting on day 1 of radiation, seven days a week till the end of chemoradiotherapy at 250 mg daily and 4 hours prior to daily radiation dose.

2.2 Radiation

Radiation was given with 1.25 MeV (average energy) photons using Cobalt 60 according to standard fields, including the primary tumour and involved lymph nodes. We prescribed a minimum tumour dose of 60-66 Gy (two Gy per fraction, five fractions per week) depending on tumour size, with larger tumours receiving the larger dose. Thus, patients who had a primary tumour and lymph nodes with a diameter of 4 cm or less, or both, were given 60 Gray (Gy) while others received 66 Gy. Patients were assigned five fractions per week, given one fraction daily from Monday to Friday. Patients were immobilized in a supine treatment position in a custom-made head-and-neck thermoplastic mask manufactured in the mould room. All patients underwent simulation, using conventional or contrast enhanced computed tomogram (CECT) scan planning, with 3 mm cut sections. The radiation field encompasses the gross disease (primary tumor and/or nodal disease) with a 2 cm margin. Two lateral parallel opposed fields were mostly used to treat the primary tumor and/or upper neck with a matched anterior field, as needed for the supraclavicular region. Field reductions at approximately 40 to 44 Gy were suggested to exclude the spinal cord from the large photon fields. After a total dose of 44 Gy, only the primary tumor and clinically or radiographically involved nodes were treated with a margin of 1 cm.

2.3 Response assessment

The response assessments in the patients were evaluated 8 weeks after completion of treatment by the head

and neck surgeon and radiation oncologist using the RECIST criteria. All patients underwent CECT Scan of head and neck along with detailed ENT examination with a directed biopsy performed in patients with clinical and /or radiological suspicion of persistent primary and/or nodal disease. Wherever feasible, patients with residual disease were sent for salvage surgery for removal of primary and/or nodal disease. The patients with no evidence of residual primary and nodal disease were followed up every 3 months till the end of study to assess the toxicity and the disease free survival rates.

The primary end point of the study was assessing the response rates by RECIST criteria (complete response [CR], partial response [PR], and overall response rate [ORR= CR+PR]). The secondary endpoints of the study were disease-free survival comparison (DFS, defined as locoregional recurrence or distant metastasis due to the cancer), acute toxicity (during chemoradiotherapy, weekly toxicity assessment was carried out using the NCI Common Toxicity Criteria Adverse Events version 3; acute toxicity assessment continued for an additional 8 weeks from the last date of chemoradiotherapy).

2.4 Statistical analysis

For calculation of sample size GPower statistical software was used and for other statistical analysis SPSS version 17 was used. With review of literature it was estimated that the complete response (CR) rate using cisplatin based chemoradiation for LASCCHN was 40%. For study to be statistically significant, gefitinib containing arm must show at least 20% increased CR over conventional chemoradiation arm. Thus the absolute effect was 60%. The power of the test was kept at 80%. Assuming attrition rate of 10% after review of previous hospital records, additional 8 patients would be recruited for the study. Randomization procedure was planned with 1:1 allocation. So the minimum sample size of study was 80, with 40 patients in each arm.

With Continuous data was summarized as Mean ± SE and categorical variables as frequencies. Chi Square and Fisher's tests for comparison of categorical data of demographic, stage profiles, treatment response and toxicity profiles and for continuous variables independent t test was used for comparison. Disease free survival was compared using Kaplan Meier analysis with log rank test. Subset analysis of tumour response was planned for anatomical subsites and stage of disease presentation. All tests were 2 tailed with p value less than 0.05 taken to be significant. Data are presented as 3-year actuarial values.

3. Results

Between July, 2008 and October 2011, 120 patients with LASCCHN were initially enrolled for inclusion in the study. 16 patients were left out of study after failing the eligibility criteria. The remaining 104 patients were randomized for study. The accruals of all patients were completed within the stipulated 6 months after initiation of study. 48 patients in arm A and 46 patients in arm B were analyzed.

The distribution of patients and tumour characteristics were similar in the two groups with baseline profiles (table 1). The average age in arm A (n=48) receiving concurrent chemoradiation with cisplatin and gefitinib was 56.6 ± 0.76 years (range 44 - 68 years), while for patients in arm B (n=46) receiving cisplatin and concurrent chemoradiation, the average age was 55.1 ± 1.00 years (range 42-68 years). Radiation was completed in within a median time of 52 days (range: 45 to 56 days).

The response assessment was done at 8 weeks post-treatment using RECIST. The overall response rates (ORR=CR+PR) were statistically significant (91.6 %) in gefitinib containing arm against 69.5% for conventional chemoradiation (Chi-square p value ~ 0.041). (table 2). The response analysis according to anatomical subsites and stages showed no significant differences between the arms. The Disease Free Survival (DFS) using Kaplan Meier analysis favored the Gefitinib arm with Log Rank (Mantel-Cox) 7.001, df 1 and p value of 0.008 (significant) (table 3A and B). The median disease free survival was 23 months for gefitinib and concurrent chemoradiation versus 17 months for only chemoradiotherapy arm. The patients in Arm B, receiving additional gefitinib had higher incidence of dermatitis (overall 80% vs 66.67% in Arm A, p value 0.025) and diarrhea (overall 80% vs 57.14% in Arm A, p value 0.010) (table 4). No patient in either of the treatment arms had Grade 4 toxicity graded according to Common Terminology Criteria for Adverse Events version 3.

4. Discussion:

Over one third of all cancers in India occur in the head and neck. Nearly 60% of patients of head and neck cancer present with locally advanced but non metastatic disease. Squamous-cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and Radiotherapy (*Overgaard et al. 1986).*

Traditional treatment with surgery and/ or radiation produces a 5-year survival rate of 40% or less. Historically, disease recurrence has been seen to be predominantly locoregional, whereas distant failure rate is 20% to 30%. Chemotherapy has been successfully employed in different clinical settings and role of chemotherapy in the curative management of advanced locoregional head and neck squamous cell carcinoma has been established. A rationale for combining chemotherapy and radiotherapy concomitantly in the treatment of locally advanced head and neck cancers exists. Chemotherapy can sensitize tumors to radiotherapy by inhibiting tumor repopulation, preferentially killing hypoxic cells, inhibiting the repair of sublethal radiation damage, sterilizing micrometastatic disease outside of the radiation fields and decreasing the tumor mass, which leads to improved blood supply and reoxygenation. Fractionated radiotherapy, in turn, may sensitize tumors to chemotherapy by inhibiting the repair of drug-induced damage and by decreasing the size of the tumor mass, leading to improved blood supply and enhanced drug delivery. Chemotherapy can be used in the setting of either (1) prior to locoregional therapy (neoadjuvant), (2) concurrent with definitive radiation therapy, or (3) after locoregional therapy with or without concomitant radiation therapy (adjuvant). In 1987, the Radiation Therapy Oncology Group (RTOG) first reported results from a phase II trial testing radiation and concurrent high-dose cisplatin (100 mg/m^2 given every 3 weeks during radiation therapy). They showed a complete response rate of 71% and a 4-year survival of 34% in a cohort of 124 patients. Concurrent chemoradiotherapy has become the standard nonsurgical treatment for locoregional advanced head and neck cancer. A lot of clinical trials have been undergone to establish the optimal chemotherapeutics for use concurrently with radiation to treat head and neck cancer. Results of cooperative group randomized trials in the United States favored use of cisplatin at a dose of 100 mg/m^2 every 3 weeks during conventional fractionation radiation. A survival advantage was demonstrated with the use of the above regimen over radiotherapy alone in unresectable disease and nasopharyngeal cancer (Al-Sarraf *et al*. 1998; Adelstein *et al.* 2003). Concurrent chemoradiotherapy with cisplatin in laryngeal cancer resulted in a higher rate of organ preservation. Finally, the combination of cisplatin and radiation therapy was superior to radiation therapy alone after a potentially curative surgical resection. A number of combination chemotherapy regimens, predominantly Cisplatin/fluorouracil (5-FU), have also been studied along with radiation and they produced superior results over radiation alone in randomized trials (Argiris 2002).

In the update of Meta-analysis of chemotherapy in head and neck cancer (MACH-NC), twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 ($p<0.0001$) with an absolute benefit of 4.5% at 5 years for chemotherapy, and a significant interaction ($p<0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio (of death) was 0.81 ($p<0.0001$) and the absolute benefit of 6.5% at 5 years. There was a decreasing effect of chemotherapy with age ($p=0.003$, test for trend). The MACH-NC confirmed the benefit of concomitant chemotherapy and was greater than the benefit of induction chemotherapy (Pignon *et al* 2009). However, sensitizing effects are not tumour specific and affect adjacent normal tissues within the radiation field. Concurrent chemoradiotherapy trials have consistently reported an increased incidence of acute grade 3 and 4 toxic effects, with mucositis and dermatitis being the most prominent. This rise creates concern about chronic toxic effects, including consequential late effects, which evolve from persistent severe acute toxic effects. Interestingly, multiple studies have confirmed that, compared with radiation alone, the long-term side effects of concurrent chemoradiotherapy, such as on swallowing function or speech, are not increased (Bernier *et al*. 2004; Cooper *et al.* 2004; Bachaud *et al*. 1996).

Epidermal growth factor receptor (EGFR) is overexpressed in several epithelial malignancies, including head and neck squamous cell carcinoma (HNSCC). EGFR overexpression occurs in up to 90% of tumors with overexpression of EGFR ligands such as transforming growth factor alpha. EGFR plays a critical role in HNSCC growth, invasion, metastasis and angiogenesis. EGFR inhibition through anti-EGFR antibody therapy or small-molecule inhibitors of EGFR may act in a synergistic fashion with radiotherapy through inhibition of cellular proliferation, tumor angiogenesis and DNA repair. The introduction of targeted agents against the epidermal growth factor receptor (EGFR) pathway has improved survival in locally advanced squamous cell head and neck cancer (LAHNC) though as monotherapy they have yielded only modest clinical outcomes.

Potential mechanisms for lack of response to EGFR inhibition in HNSCC include constitutive activation of signaling pathways independent of EGFR, as well as genetic aberrations causing dysregulation of the cell cycle. EGFR-directed therapy may be optimized by identifying and selecting those HNSCC patients most likely to benefit from EGFR inhibition. Resistance to EGFR inhibition may be circumvented by combination therapy employing EGFR inhibitors together with other treatment modalities (Kalyankrishna & Grandis 2006).

Bonner *et al*. reported the results of the first major randomized trial in head and neck cancer that directly compared radiotherapy alone with radiotherapy and concurrent biologic-targeted therapy in the definitive treatment of patients with locally advanced or unresectable head and neck cancers (Bonner *et al*. 2006). In this trial, 424 patients with stage III or IV oropharynx, larynx or hypopharynx cancer were randomized to either radiotherapy alone (either 2 Gy daily to 70 Gy, 1.2 Gy twice daily to 72-76.8 Gy, or accelerated fractionation with concomitant boost to 72 Gy as per RTOG 90-03) or to the same radiotherapy plus cetuximab, an anti-EGFR antibody. Local control at 3 years favored combined modality therapy (47 vs 34%; $p < 0.01$); 3-year overall survival was superior with cetuximab and radiotherapy (55 vs 45%; $p = 0.05$). The rate of distant metastases was similar in both groups. Toxicities were similar in both groups except that acneiform rash and infusion reactions were more common in the combined modality group.

Gefitinib is an anilinoquinazoline with antineoplastic activity which inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis. Gefitinib has been shown to inhibit repair of RT-induced DNA double-strand breaks (Shintani *et al* 2003). EGFR expression levels in head and neck cancer (HNC) cell lines correlated with increased RT resistance (Akimoto *et al*. 1999) and gefitinib enhanced radiosensitivity in HNC cells. In xenograft tumor models, gefitinib in combination with RT resulted in synergistic growth inhibition (Ochs *et al.* 2004).

Gefitinib applied before RT and before and/or during CDDP/fluorouracil improved the cytotoxic effect in HNC cell lines (Magne *et al.* 2002). Thus, combining gefitinib with RT or chemoradiotherapy showed cooperative effects in preclinical studies and warranted clinical investigation in patients with LAHNC (Ciardiello *et al*. 2000 and Sirotnak *et al*. 2000).

Changhu Chen et al. in a "Phase I Trial of Gefitinib in Combination With Radiation or Chemoradiation for Patients With Locally Advanced Squamous Cell Head and Neck Cancer", showed that Gefitinib (250 or 500 mg daily) was well tolerated with concomitant boost RT or concurrent chemoradiotherapy with weekly CDDP. Protracted administration of gefitinib for up to 2 years at 250 mg daily was also tolerated well (Chen et al. 2007)

Our study has also proved the effectiveness of Gefitinib as radiosensitizer; as with addition of it, DFS is significantly improved. There are certain limitations of this study. First, study population is very small with smaller number of patients in each subgroups. But this study, though being first of its kind, has shown some light regarding improved response and it should be validated with further studies accruing larger number of patients and more preferably in multicentric trials among different populations. Secondly, as most head-neck cancer recurs within two years, we kept study period within three years with median follow up of 26 months. So, what we achieved with improved DFS in study arm, might change over longer follow-up when calculating cancer free survival and overall survival. Third and most important one is that, this being a non-funding study and availability of EGFR-expression testing being very restricted in eastern part of India, patients could not be randomized based on this profile. So, the benefit what we have achieved from this study, is from a heterogeneous group of population, comprising both EGFR-positive and EGFR-negative patients. Larger study randomized with EGFR expression profile is needed to comment on whether Gefitinib can be used in EGFR-negative patients too or it is should be used only in EGFR-positive population with exact degree of response and benefit in this cohort.
Like previous study result, this study also shows that addition of Gefitinib increases the incidence of dermatitis and diarrhea. Lastly this is to declare that our study was a small study, to validate the results, large randomized study is necessary.

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TABLE 1A. BASELINE COMARISON BETWEEN PATIENTS INCLUDED IN BOTH THE COHORTS

BASELINE PROFILES		GROUP [no(%)]		P value
		CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	CONCURRENT CISPLATIN with RT (n=46)	
SEX	male	42 (87.5)	40 (87)	0.937
	female	6 (12.5)	6 (13)	
AGE (in years, Mean ± SE) [median]		56.6 ± 0.76 [57.0]	55.1 ± 1.00 [56]	0.206
ECOG PERFORMANCE STATUS	ECOG 0	26 (54.2)	28 (60.9)	0.511
	ECOG 1	22 (45.8)	18 (39.1)	
HEMOGLOBIN	≥ 10gm%	27 (56.3)	33 (71.7)	0.118
	< 10 gm%	21 (43.8)	13 (28.3)	
CREATININE CLEARANCE	50-60 ml/min	19 (39.6)	15 (32.6)	0.219
	61-70 ml/min	18 (37.5)	25 (54.3)	
	71-80 ml/min	11 (22.9)	6 (13.1)	

TABLE 1B. BASELINE COMPARISON BETWEEN PATIENTS INCLUDED IN BOTH THE COHORTS

Primary site	AJCC Stage	GROUP [no(%)]		P value
		CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	CONCURRENT CISPLATIN with RT (n=46)	
OROPHARYNX	III	3 (33.3)	5 (35.7)	
	IVA	3 (33.3)	6 (42.9)	0.805
	IVB	3 (33.3)	3 (21.4)	
LARYNX	III	6 (35.3)	1 (5.9)	
	IVA	8 (47.1)	12 (70.6)	0.105
	IVB	3 (17.6)	4 (23.5)	
HYPOHARYNX	III	9 (40.9)	8 (53.3)	
	IVA	7 (31.8)	2 (13.3)	0.435
	IVB	6 (27.3)	5 (33.3)	

Table 2 A. OVERALL RESPONSE COMPARISON BETWEEN GROUPS

RESPONSE	GROUP [No,(%)]		P value
	CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	CONCURRENT CISPLATIN with RT (n=46)	
CR	34 (70.8)	22 (47.8)	0.041*
PR	10 (20.8)	10 (21.7)	
SD	2 (4.2)	9 (19.6)	
PD	2 (4.2)	5 (10.9)	

CR-Complete response; PR – Partial response; SD – Stable disease; PD – Progressive disease. Assessment by RECIST criteria.

FIGURE 1. Bar diagram showing the response rates among patients in the study

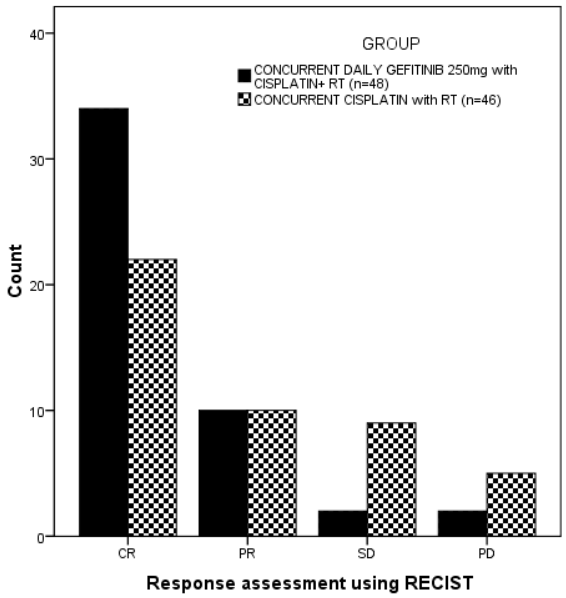

Table 2 B. PRIMARY SITE and STAGE SPECIFIC RESPONSE COMPARISON BETWEEN GROUPS

Parameters		RESPONSE	GROUP (no,%)		
			CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	CONCURRENT CISPLATIN with RT (n=46)	P value
STAGE	AJCC Stage III	CR	17 (94.4)	11 (78.6)	0.178
		PR	1 (5.6)	3 (21.4)	
		SD	0	0	
	AJCC Stage IVA	CR	13 (72.2)	9 (45.0)	0.099
		PR	4 (22.2)	3 (15.0)	
		SD	1 (5.6)	7 (35.0)	
		PD	0	1 (5.0)	
	AJCC Stage IVB	CR	4 (33.3)	2 (16.7)	0.620
		PR	5 (41.7)	4 (33.3)	
		SD	1 (8.3)	2 (16.7)	
		PD	2 (16.70	4 (33.3)	
PRIMARY SITE	*OROPHARYNX*	CR	6 (66.7)	3 (21.4)	0.176
		PR	1 (11.1)	4 (28.6)	
		SD	2 (22.2)	6 (42.9)	
		PD	0	1 (7.1)	
	LARYNX	CR	11 (64.7)	11 (64.7)	0.112
		PR	6 (35.3)	2 (11.8)	
		SD	0	2 (11.8)	
		PD	0	2 (11.8)	
	HYPOPHARYNX	CR	17 (77.3)	8 (53.3)	0.366
		PR	3 (13.6)	4 (26.7)	
		SD	0	1 (6.7)	
		PD	2 (9.1)	2 (13.3)	

CR-Complete response; PR – Partial response; SD – Stable disease; PD – Progressive disease. Assessment by RECIST criteria.

Table 3A. Means for Survival Time

Group	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	24.215	1.940	20.413	28.017
CONCURRENT CISPLATIN with RT (n=46)	15.924	2.591	10.847	21.002
Overall	20.969	1.649	17.737	24.201

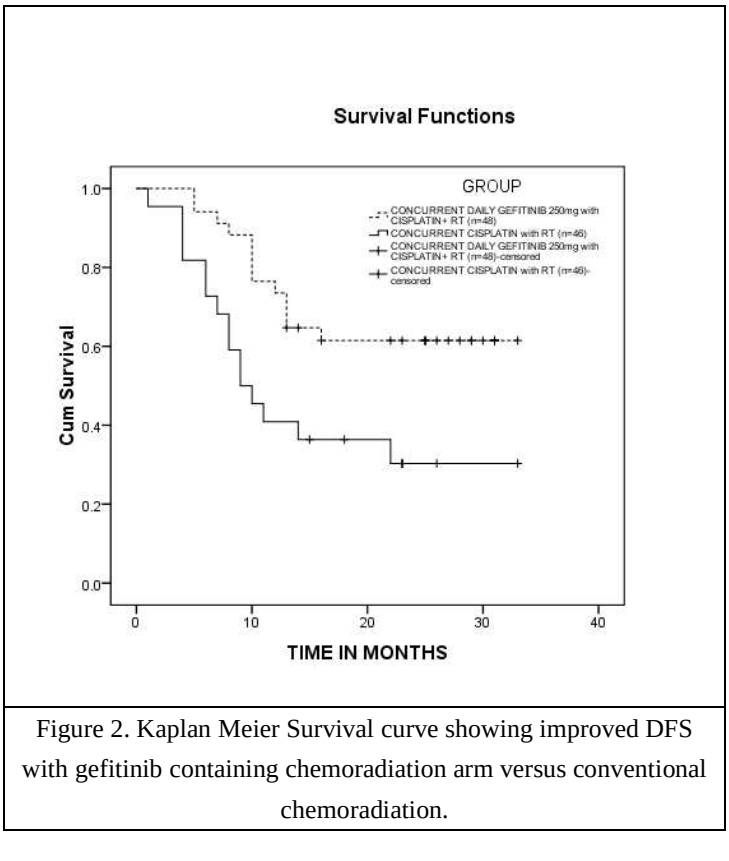

Figure 2. Kaplan Meier Survival curve showing improved DFS with gefitinib containing chemoradiation arm versus conventional chemoradiation.

Table 3B. DISEASE FREE SURVIVAL comparison between two treatment arms			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	7.001	1	0.008

Table 4. TOXICITY PROFILE COMPARISON (CTCAE version 3)

ADVERSE EVENTS			GROUP [no(%)]		P value
			CONCURRENT CISPLATIN and DAILY GEFITINIB 250mg with RT (n=48)	CONCURRENT CISPLATIN with RT (n=46)	
Dermatitis	GRADE	1	11 (22.9)	35 (76.1)	
	GRADE	2	25 (52.1)	7 (15.2)	0.000
	GRADE	3	12 (25)	4 (8.7)	
Mucositis	GRADE	1	17 (35.4)	32 (69.6)	
	GRADE	2	30 (62.5)	10 (32.6)	0.000
	GRADE	3	1 (2.1)	4 (8.7)	
Diarrhea	GRADE	0	14 (29.2)	25 (54.3)	
	GRADE	1	5 (10.4)	15 (32.6)	0.000
	GRADE	2	21 (43.8)	6 (13.0)	
	GRADE	3	8 (16.7)	0