International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Cetuximab in Locoregionally Advanced Head and Neck Cancer: A Real-World Case Series

Dr. Siddhesh Rajendra Tryambake[1], Dr. S. S. Nirni[2]

[1]MD, Resident Medical Oncology, Department of Medical Oncology, Omega Hospitals, Hyderabad, Telangana, India
Corresponding Author Email: *dr.srtryambake[at]gmail.com*

[2]M. D, DM, Senior Consultant and Head, Department of Medical Oncology, Omega Hospitals, Hyderabad, Telangana, India

Abstract: ***Background: Management of locoregionally advanced squamous cell carcinoma of the head and neck (LASCCHN) has evolved from primarily surgical approaches to radiotherapy (RT) - based regimens. Randomized trials have shown that adding cetuximab to RT or chemotherapy improves 5 - year overall survival (OS) in LASCCHN. However, real - world data remain limited. Methods: This retrospective study analyzed 20 patients with non - metastatic LASCCHN treated with cetuximab - based regimens at our institution between April 2015 and July 2023. Patients received cetuximab either concurrently with RT or with chemotherapy (CT). Outcomes assessed included OS, progression - free survival (PFS), overall response rate (ORR), disease control rate (DCR), and treatment - related toxicities. Results: The median age was 60 years (range 54–87); 80% were male. Half had an ECOG performance status of I, and half had II. Ten percent had multiple comorbidities. Cetuximab was used as 1st - line treatment in 70%, 2nd - line in 15%, 3rd - line in 5%, and 4th - line in 10% of patients. Eleven patients (55%) received cetuximab with RT, while the rest received it with CT. Median follow - up was 24 months. Median OS was 40 months (95% CI: 18–61.9), and median PFS was 4 months (95% CI: 0–12.7). Notably, OS was significantly higher in patients receiving cetuximab with RT (median OS 65 months; 95% CI: 27.8–102) compared to those receiving it with CT alone (median OS 21 months; 95% CI: 0–44.3; p = 0.04). ORR was 65%, and DCR was 75%. Grade ≥3 toxicities were observed in 30% of patients (fatigue), 15% (rash), 10% (hypersensitivity reactions), and 5% (combined rash and fatigue). No treatment - related mortality was reported. Conclusion: Cetuximab is well tolerated in Indian patients with LASCCHN and appears to provide a survival benefit, especially when used concurrently with radiotherapy. Further prospective studies are warranted to validate these real - world findings.***

Keywords: Cetuximab, head and neck cancer, radiotherapy, real - world data, squamous cell carcinoma

1. Introduction

The management of locoregionally advanced squamous - cell carcinoma of the head and neck (LAHNSCC), has progressively shifted from surgery as the primary treatment to radiotherapy as the main therapeutic approach. [1 - 6] In recent times, there have been more advantages observed with modified forms of radiotherapy, such as accelerated fractionation or hyper- fractionated radiotherapy. Additionally, combining radiotherapy with chemotherapy, known as chemoradiotherapy (CTRT), has been shown to be beneficial. The efficacy of CTRT is offset by the elevated and frequently insurmountable toxicity, especially in individuals with concurrent medical problems and reduced functioning status. [6, 12] The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptor tyrosine kinases, is abnormally activated in epithelial cancers, including head and neck cancer. [13, 14] The cells of almost all such neoplasms express high levels of EGFR, a feature associated with a poor clinical outcome. [13, 15 - 20] Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of radiation. [21, 22] Cetuximab, an IgG1 monoclonal antibody against the ligand binding domain of EGFR, enhances the cytotoxic effects of radiation in squamous - cell carcinoma. [23 - 27] In a preliminary study of radiotherapy plus cetuximab in patients with LAHNSCC, the regimen was well tolerated, and all the patients who could be assessed had a complete or partial regression. [28] Cetuximab as a single agent or combined with cisplatin was also associated with clinically significant rates of tumor regression in patients with platinum - refractory head and neck cancer. [29, 30] However, as on date the data from Indian patients is limited. To investigate the impact of including cetuximab in radiotherapy as the initial treatment and in subsequent treatments with other agents, we conducted a retrospective study. The study focused on patients with advanced head and neck cancer in a tertiary care cancer center in Southern India. Our aim was to share our own experience in managing such cases.

2. Methods

This retrospective analysis included patients who had non - metastatic, detectable squamous - cell carcinoma in the oral cavity (that was otherwise inoperable), oropharynx, hypopharynx, or larynx. The qualifying criteria also encompassed medical fitness for definitive radiation, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 - 2, and normal hematologic, hepatic, and renal function. The primary disease was evaluated with a thorough examination of the head and neck, which included pan - endoscopy. The primary tumors and affected lymph nodes were classified according on the staging classification of the American Joint Committee on Cancer (AJCC) 8th edition. [31] The patient underwent a computed tomographic (CT) scan of the head and neck, or a magnetic resonance imaging (MRI) scan of the head and neck, and either a chest radiograph or a whole - body PET - CT scan. Cetuximab treatment was given to patients in both sets of participants in the research. Patients were administered either cetuximab in combination with radiation therapy (RT) or other treatment regimens without RT. The evaluation of immediate harmful impacts was conducted up until the eighth week following the treatment.

Study Design
This is a single - center, retrospective audit wherein the data were collected in a retrospective manner including patient, disease, and treatment characteristics.

Selection Criteria
This is a single - center, retrospective audit wherein the data were collected in a retrospective manner including patient, disease, and treatment characteristics. The study included 20 patients diagnosed with LASCCHN, treated at our hospital and diagnosed between April 2015 to July 2023. Inclusion criteria included patients aged ≥18 years old, those with LAHNSCC, ECOG PS 0 - 2 and those with no contraindications to chemotherapy, cetuximab or RT. While, exclusion criteria included patients who were unable to tolerate chemotherapy for severe heart, lung, liver or kidney diseases, those with metastasis or recurrent disease, and those with other malignant tumors.

Objectives
The primary objective of the study was to evaluate effectiveness of cetuximab based RT and cetuximab based chemotherapy through overall survival (OS), progression - free survival (PFS), overall response rate (ORR), disease control rate (DCR) and safety through incidences of hematological and nonhematological toxicities in patients with LAHNSCC.

Study Methods
Staging was performed for all the patients with confirmed histopathological diagnosis based on TNM classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) 8th edition. All patients were administered cetuximab based RT or chemotherapy by the investigator in the given period of time. Cetuximab was first infused at 400 mg/m2 for 120 min and then at 250 mg/m2 per week for 60 min. Cetuximab was discontinued in the case of grade 3 or 4 hypersensitivity reactions. Combined chemotherapy was either methotrexate, paclitaxel plus carboplatin or SA paclitaxel. The informed consent was waived of in view of retrospective nature of the study.

Study Endpoints
In addition to the standard demographic information, the effectiveness of cetuximab - based chemotherapy was evaluated by analyzing the overall survival (OS), progression - free survival (PFS), overall response rate (ORR), and disease control rate (DCR) of the patients. PFS, or progression - free survival, was defined as the time interval between the initiation of cetuximab treatment and either the occurrence of disease progression or death from any cause, or the last follow - up date, whichever came first. The overall survival (OS) was determined by calculating the time from the date of diagnosis to the date of death due to any cause. The term ORR refers to individuals who achieved either complete response (CR) or partial response (PR) during the initial assessment. Disease control rate (DCR) is defined as the absence of disease progression and includes patients with CR, PR, and stable disease (SD). The retrospective evaluation of patient survival was conducted during the entire length of the trial. Furthermore, the evaluation of response was conducted by employing the institutional radiological assessment protocol every 8 weeks or by considering any symptoms or signs of clinical advancement according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.19. The data regarding complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were analyzed. The administration of cetuximab - based chemotherapy was maintained until the occurrence of disease progression or the development of intolerable adverse effects. The safety assessment involved evaluating the occurrence of hematological and nonhematological toxicities, using the Common Terminology Criteria for Adverse Events (v5.0).

Statistical Analysis
Data was descriptively analyzed using mean and standard deviation or median and interquartile range depending upon the normality of the data. Normality of the data was checked using the Shapiro–Wilk test while categorical variables were reported using frequency and percentage. ORR (CR + PR) and DCR (CR + PR + SD) were reported using frequency and percentage and their 95% Clopper–Pearson confidence interval (CI). Predictors of PFS, and OS were compared using Mantel– Haenszel log rank test and survival curves were generated using Kaplan–Meier method. The corresponding 6 - month and 2 - year survival rates were reported. Median follow - up was calculated using the reverse Kaplan–Meier method. Multivariate analysis was conducted using the cox proportional hazard regression. Proportional hazard assumption was tested using Schoenfeld's residual and did not violate in this data set. Data was analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, New York, United States) and R Studio version 1.2.1335.

3. Results

A total of 20 patients (median age of 60 years at the time of analysis (54 - 87) with LAHNSCC who received cetuximab concurrent with radiotherapy (RT) vs chemotherapy regimen (CT) were enrolled in this retrospective study.55% patients received cetuximab concurrently with RT while the rest received the same with other chemotherapy regimens. Median duration of follow up was 24 months. Majority were males (80%) with 10 % having multiple comorbidities and rest having single or no comorbidity. The ECOG PS score was I in 50% and II in 50% patients.70 % received Cetuximab in 1st line, 15 % in 2nd, 5% in 3rd and 10 % in 4th line [Table 2]. Median OS (mOS) was 40 months (95% CI: 18 - 61.9). (Fig 1) Median PFS (mPFS) was 4 months (95%CI: 0 - 12.7). (Fig 2). ORR was 65% and DCR was 75%. ORR and DCR in patients receiving RT was 81.8 % and 100 % respectively while in those receiving cetuximab with other form of chemotherapy was 44.44% each. Grade III and above toxicities were noted in 30 % patients showing fatigue, 15% with rash, 10% with hypersensitivity related reactions and 5% combined rash and fatigue. Patient characteristics are depicted in Table 1.

Table 1: Patient characteristics

Gender	
Male	16
Female	4
Age (Median)	60 years
PS (ECOG)	
I	50
II	50
Stage –	
LA	14
Residual	6
Subsite	
Tongue	4
OPX	6
Larynx	4
Hypopharynx	2
NPX	2
OC	1
MUO	1
Concurrent Therapy	
Paclitaxel plus carboplatin	2
Methotrexate	2
Paclitaxel	5
RT	11
Comorbidities –	
Nil/Single	18
Multiple	2

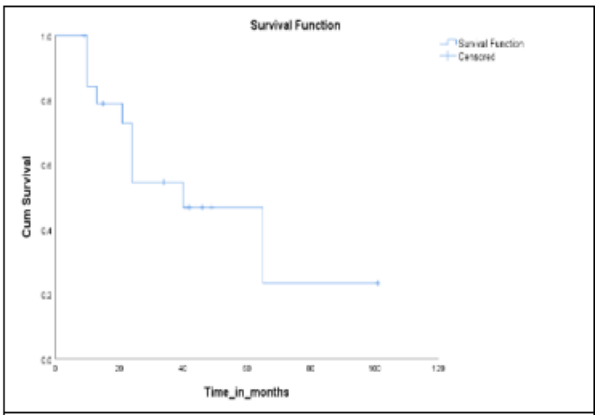

Figure 1: KM curve depicting OS [mOS for all the participants is 40.00 ± 11.188 (months). (95%CI, 18.07 - 61.92)]

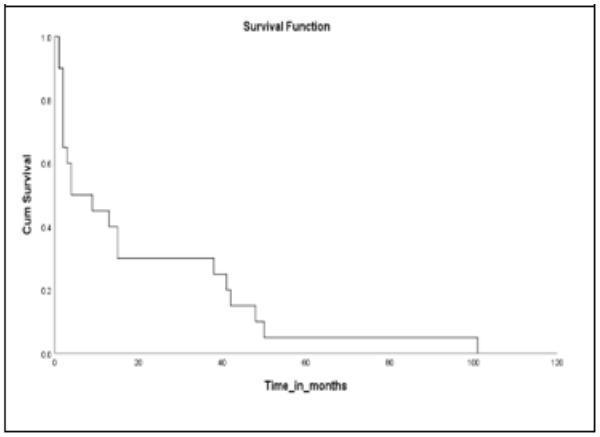

Figure 2: KM curve depicting PFS [mPFS for the participants is 4.00 ± 4.472 (months). (95%CI, 0 - 12.76)]

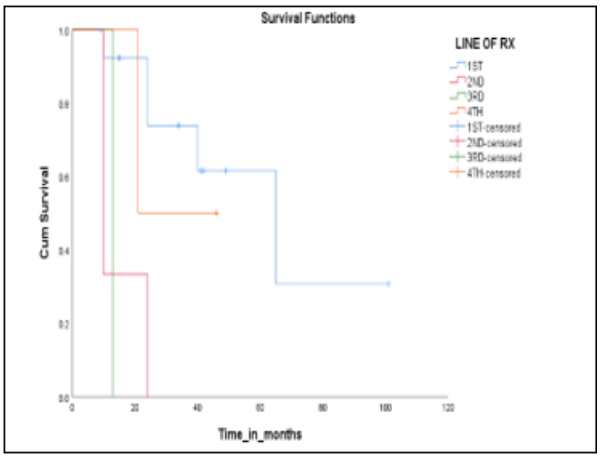

Figure 3: KM curve depicting effect of line of treatment on overall survival

The overall survival time based on 1st line RX is 65.00 ± 18.787 (months).
The overall survival time based on the 2nd line of RX is 10.00 (months).
The Overall survival time based on the 3rd line of RX is 13.00 (months).
The overall survival time based on the 4th line of RX is 40.00 ± 11.188 (months).
P - value is 0.012

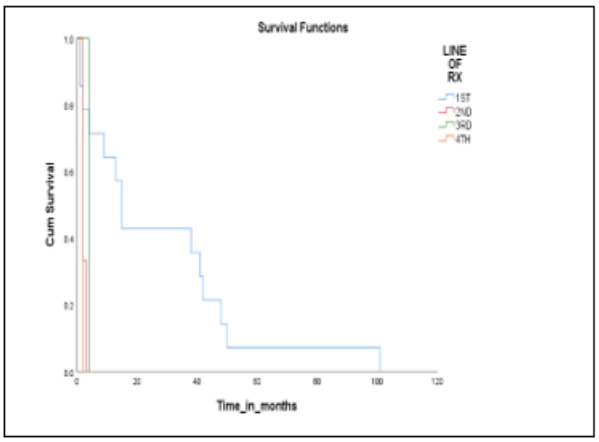

Figure 4: KM curve depicting effect of line of treatment on progression - free survival

The Progression - free survival time for 1st line of RX is 15.00 ± 1.852 (months).
The Progression - free survival time for 2nd line of RX is 2.00 (months).
The Progression - free survival time for the 3rd line of RX is 4.00 (months).
The Progression - free survival time for the 4th line of RX is 2.00 (months).
P - value is 0.037

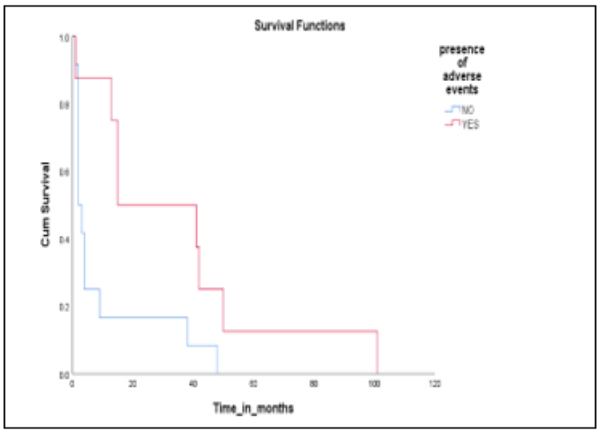

Figure 5: KM curve depicting effect of adverse events on PFS

The estimated progression - free survival for the participants witnessing the adverse event is 15.00 ± 13.199 (months). The estimated progression - free survival for the participants not witnessing the adverse events is 2.00 ± 0.577 (months). P - value = 0.022

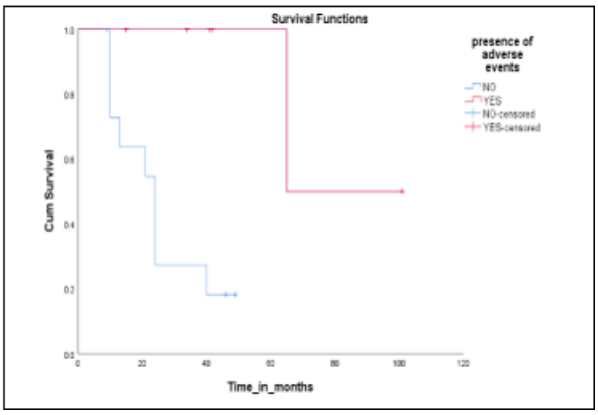

Figure 6: KM curve depicting effect of adverse events on OS. The estimated overall survival time for the participants witnessing the adverse event is 65.00 (months). The estimated overall survival for the participants not witnessing the adverse events is 24.00 ± 4.062 (months). P - value = 0.002

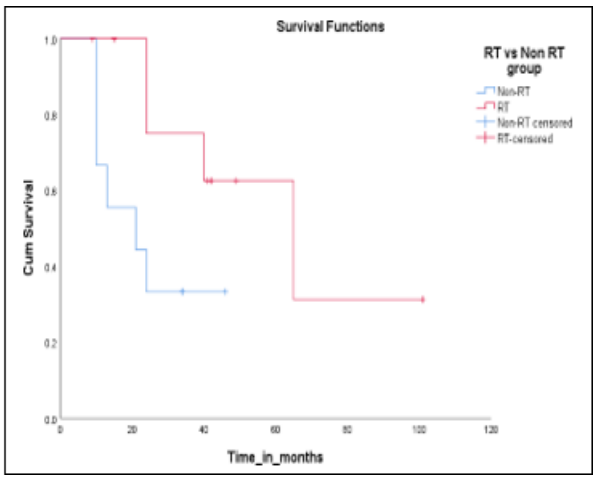

Figure 7: KM curve depicting effect of RT on mOS. OS w. r. t RT and no RT (65 (27.84 - 102.15) vs 21 (0 - 44.37)) (p=0.046)

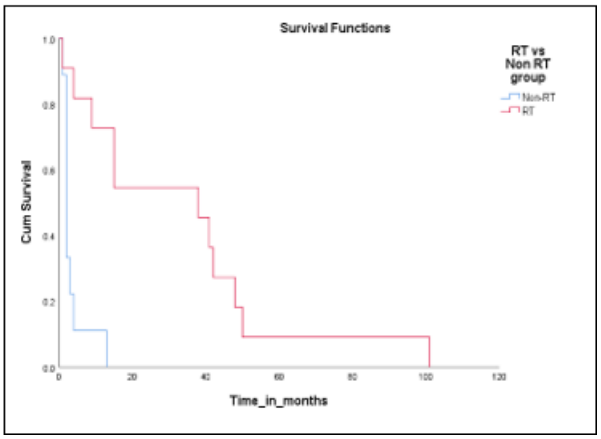

Figure 8: KM curve depicting effect of RT on mPFS. PFS w. r. t RT and no RT (38 (12.1 - 63.89) vs 2 (1.44 - 2.55)) (p=0.001)

Table 2: Line of treatment

Line of RX	Total N	N of Events	N Censored	Percent Censored
1st	14	5	9	64.3%
2nd	3	3	0	0.0%
3rd	1	1	0	0.0%
4th	2	1	1	50.0%
Overall	20	10	10	50.0%

Table 3: Presence or absence of adverse event on OS

Presence of AE	Total N	N of Events	N Censored	Percent Censored
No	12	12	0	0.0%
Yes	8	8	0	0.0%
Overall	20	200	0	0.0%

Prognostic Factors

Table 4: Presence or absence of adverse event on PFS

Presence of AE	Total N	N of Events	N Censored	Percent Censored
No	12	9	3	25.0%
Yes	8	1	7	87.5%
Overall	20	10	10	50.0%

The effects of the gender, comorbidities, PS, and stage was evaluated as far as clinical outcomes are concerned. There was no significant difference in the mOS seen with respect to the gender, PS, comorbidities. mOS was 65 months (27.84 - 102.15) in patients receiving cetuximab in first line with RT, compared to 21 months (0 - 44.37) in residual diseases where cetuximab was given alone or with other form of chemotherapy (p=0.048). There was no significant difference in the mPFS seen with respect to the gender, PS or comorbidities. The PFS as well as OS for 1st line of RX was greater with PFS being 15.00 ± 1.852 (months) (p=0.03) and the OS being 65.00 ± 18.787 (months) (p=0.01) [Fig 3 - 4]. mOS was 65 months (27.8 - 102) in patients with RT compared to 21 months (0 - 44.3) in patients with no RT (other agents) (p=0.04). mPFS w. r. t RT and no RT was 38 (12.1 - 63.89) vs 2 (1.44 - 2.55) (p=0.001). Estimated mPFS for the participants witnessing the adverse event (AE) is 15.00 ± 13.199 (months) vs 2.00 ± 0.577 (months) in those without adverse events (p=0.02). The estimated mOS for the participants witnessing the adverse event was 65.00 (months) vs 24.00 ± 4.062 (months), in those without AE. (p=0.002)

[Table 3 - 4] [Fig 5 - 6]. Thus, there was no significant difference in survival w. r. t, gender, comorbidities and PS, however, line of treatment, presence or absence of adverse effects and RT played an important role in defining the outcomes. ORR AND DCR in patients receiving RT was 81.8 % and 100 % respectively while in those receiving cetuximab with other form of chemotherapy was 44.44% each with a statistically significant difference in DCR seen with both the groups. (p = 0.0893 for ORR and p = 0.005 for DCR)

Toxicity Profile

There were no fatalities resulting from significant adverse responses during the course of treatment. Grade III and higher toxicities were observed in 27% of patients, with rash being reported in 12%, diarrhea in 15%, mucositis in 21%, exhaustion in 21%, and febrile neutropenia in 5%.

4. Discussion

The involvement of the epidermal growth factor receptor (EGFR) in the formation and advancement of head and neck squamous cell carcinoma (HNSCC) has been extensively researched [38]. EGFR is a transmembrane glycoprotein belonging to the tyrosine kinase growth factor receptor family. It has a role in controlling cell growth and proliferation [39]. Up to 90% of HNSCC cases exhibit an increased expression of this receptor, which has been linked to worse survival rates [39 - 41]. The increasing evidence prompted the assessment of medicines that target the EGFR pathway in this specific form of tumor. Cetuximab is currently the sole anti - EGFR medication that has been scientifically demonstrated to be efficacious in treating HNSCC [42, 43]. Cetuximab is a monoclonal antibody of the IgG1 subclass that binds to the extracellular domain of the EGFR with greater affinity than the natural ligands EGF and TGFα. This binding prevents the activation of the EGFR's intracellular domain and the following signal transduction pathway that relies on tyrosine kinase activity [44]. Cetuximab additionally induces the internalization of EGFR, leading to the removal of the receptor from the cell surface and thus inhibiting its interaction with the ligand [45]. Furthermore, being an IgG1 molecule, it induces antibody dependent cell cytotoxicity (ADCC) [46, 47]. Multiple preclinical studies have shown that cetuximab, an inhibitor of EGFR, enhances the effectiveness of radiotherapy (RT). This is achieved by reducing the number of cells in the S phase and increasing the number in the G1 phase, promoting apoptosis, reducing DNA repair capabilities, and exerting an antiangiogenic effect. In addition, cetuximab augmented the antitumor efficacy of various chemotherapeutic agents in mouse xenograft models [51]. CTRT or RT alone were the sole conservative therapy options available for patients with locally - advanced (LA) conditions, depending on their functional state and comorbidities. Cetuximab enhanced the range of options, but its application in clinical practice is now limited to patients who are unable to tolerate high doses of cisplatin or who have experienced significant residual toxicity after three cycles of cisplatin - based induction chemotherapy. It is typically used in combination with RT. For patients with recurrent/metastatic RMHNSCC, the treatment options were limited to either using a single drug or a combination of multiple chemotherapeutic drugs until the findings from the EXTREME study became available. Incorporating cetuximab into the initial chemotherapy regimen resulted in a substantial enhancement in disease management and OS compared to chemotherapy alone, establishing it as the new standard treatment for this group of patients [6]. The addition of cetuximab to radiotherapy has shown significant improvements in outcome, with a 10 - percentage point increase in absolute survival at three years. These results are comparable to the largest increases in effectiveness observed with chemoradiotherapy compared to radiotherapy alone. Additionally, the Kaplan - Meier curves for both locoregional control and survival consistently show a distinct separation, indicating that the benefits of adding cetuximab to radiotherapy continue for several years after treatment completion. Our study findings are consistent with the literature available and depicts real world experience with cetuximab based therapy in LAHNSCC. In our investigation, which involved patients with ECOG PS 0 - 2, the combination of radiation and cetuximab did not result in an excessive occurrence of severe side effects and its combination with RT lead to better outcomes as against the one with other chemotherapeutic agents. Cetuximab placed in first line of treatment showed better results. So also with significant differences in the clinical outcomes based on presence or absence of adverse events, the later may be used as a predictive indicator of response to the treatment which again is consistent with the literature available. Despite of the limited sample size and retrospective form of the study, we may still suggest that concurrent use of RT, line of treatment and presence of adverse effects to cetuximab based therapy leads to better outcomes.

5. Conclusion

Cetuximab is well tolerated in Indian set of patients with LAHNSCC and a greater OS is evident when cetuximab is given with RT in first line as compared to no RT in further lines of the treatment. Presence of adverse effects may be of predictive significance towards better clinical outcomes.

Conflict of Interest: None declared

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