Pakistan Journal of Intensive Care Medicine
eISSN: 2708-2261; pISSN: 2958-4728
www.pjicm.com
DOI: https://doi.org/10.54112/pjicm.v5i01.78
Pak. J. Inten. Care Med., volume 2025: 78
Original Research Article

SAFETY AND EFFICACY OF CONCURRENT RADIOTHERAPY AND CETUXIMAB CHEMOTHERAPY VS RADIOTHERAPY ALONE FOR AGGRESSIVE SQUAMOUS CELL SKIN CANCER OF THE HEAD AND NECK

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(Received, 15th March 2025, Revised 10th April 2025, Accepted 26th April, Published 30th May 2025)

ABSTRACT

Background: *Aggressive squamous cell carcinoma (SCC) of the head and neck presents a therapeutic challenge due to its high recurrence and progression rates. While radiotherapy is a standard postoperative treatment, the addition of concurrent chemotherapy may enhance outcomes by improving locoregional control and overall survival. Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, has demonstrated efficacy in enhancing the therapeutic response in head and neck cancers.* ***Objective:*** *To compare the efficacy and safety of concurrent radiotherapy and cetuximab chemotherapy with radiotherapy alone in the treatment of aggressive squamous cell carcinoma of the head and neck.* ***Study Design:*** *Retrospective comparative study.* ***Setting:*** *Oncology Department, Nishtar Hospital, Multan, Pakistan.* ***Duration of Study:*** *February 2023 to February 2025.* ***Methods:*** *A total of 200 adult patients with histologically confirmed aggressive head and neck squamous cell carcinoma who underwent surgical resection were included through consecutive sampling. Patients were divided into two groups: Group A (n=100) received concurrent radiotherapy (average dose: 60 Gy in 2–2.25 Gy fractions) and cetuximab chemotherapy (400 mg/m² initial dose followed by 250 mg/m² weekly), and Group B (n=100) received radiotherapy alone. Key outcomes included local and metastatic recurrence rates, progression-free survival (PFS), overall survival (OS), and treatment-related adverse events. Statistical analysis was performed using chi-square and t-tests, with $p < 0.05$ considered statistically significant.* ***Results:*** *Local Non-Recurrence Rates: 1-year: 92% (Group A) vs. 94% (Group B); 2-year: 84% vs. 75%. Metastatic Non-Recurrence Rates: 1-year: 98% vs. 100%; 2-year: 94% vs. 89%. Progression-Free Survival: 1-year: 85% vs. 76%; 2-year: 73% vs. 55%. Overall Survival: 1-year: 99% (Group A) vs. 80% (Group B); 2-year: 79% vs. 74%. Adverse Events: Grade 3 dermatitis occurred in 15% of Group A and 30% of Group B patients.* ***Conclusion:*** *Concurrent radiotherapy with cetuximab chemotherapy demonstrated improved 2-year progression-free and overall survival in patients with aggressive head and neck squamous cell carcinoma compared to radiotherapy alone, with an acceptable safety profile. These findings support the use of combined modality treatment for better clinical outcomes.*

Keywords: Carcinoma, Chemotherapy, Radiotherapy, Squamous Cell Carcinoma

INTRODUCTION

Non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma, are common types of cancers with high incidence. About 20-30% of the skin cancers are squamous cell carcinomas, and their incidence is 4-8x higher in elderly (1). Although the remission rate of these cancers is excellent, some aggressive carcinomas pose a high risk of recurrence or metastasis. About 85% of the cancers metastasize in the lymphatic system, and despite aggressive treatment, the five-year survival rate is 14-40% (2). Surgical resection is the primary treatment for early stage CSCCs however, additional concomitant treatment with radiotherapy and chemotherapy is needed for locally advanced cancers. However, there is no standard treatment for high-risk CSCC.

The trend of using biologic therapy for CSCC is growing due to variability in expression of EGF receptor (3). One of these agents is Cetuximab, an antibody developed to target the EGF receptor to block intracellular signaling through RAS/MAP kinase pathway. Unlike other therapies, that only work when the receptor is mutated, cetuximab is effective on non-mutated receptor. It helps slow down the cell cycle which makes cancer cells sensitive to radiotherapy. Therefore, cetuximab has been reported to have improved survival rates and efficacy for squamous cell carcinomas including advanced cancers of head and neck (4, 5).

This study was conducted to compare the efficacy and safety of concurrent radiotherapy and chemotherapy with radiotherapy therapy for aggressive squamous cell skin cancer of head and neck.

METHODOLOGY

A retrospective analysis was conducted in the Oncology Department of Nishtar Hospital, Multan from February 2023 to February 2025. A total of 200 adult patients with aggressive head and neck skin cancer, confirmed by radiological examination and histology and underwent surgical resection were included in the study by consecutive sampling. Patients were also evaluated for metastasis and lymph node recurrence. The high-risk of cancer was assessed by location, perineural invasion, recurrence, poorly differentiated histology, positive surgical margins and lymphovascular involvement or invasion. Patients with initial signs of metastasis at the start of treatment or confirmation of non-cutaneous primary lesion through biopsy or pan-endoscopy were excluded. All patients agreed verbally to become a part of the study. The ethical review board approved the study.

Patients were divided into two groups; Group A included 100 patients who underwent concurrent treatment with radiotherapy and cetuximab chemotherapy and Group B included 100 patients who underwent radiotherapy alone. Both groups underwent CT simulation and radiotherapy according to physicians' discretion based on tumor

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location for 5-7 weeks. Radiotherapy was delivered by a linear accelerator of 6 MV x-ray beams or 6-9 MeV electron beams, targeting the tumor bed and surrounding lymph nodes identified by MRI or PET scan. The radiation beams were shaped and modulated by dynamic multi-leaf collimation as part of intensity modulated radiotherapy. The average dose of radiotherapy was 60 Gray (46-70 Gray), administered in 2-2.25 doses per session. In Group B, a 400 mg/m^2 initial dose of cetuximab was administered one week before the start of radiotherapy and then 250 mg/m^2 doses were administered weekly.

After completion of treatment, the outcome was noted by contrast enhanced MRI or CT of the head and neck. Patients were followed up after every 2-3 months for the first year and then after every 4-6 months in the next year. Those with a suspected recurrence based on symptoms or physical findings were further evaluated with imaging and biopsy. The primary outcome was disease-free survival rate, and secondary outcomes were overall survival rate, recurrence rate, and incidence of toxicities.

The outcomes of both groups were controlled for confounding variables, including age, sex, margin status, tumor size, tumor stage, location and laterality, recurrence, perineural & lymphatic invasion, Karnofsky performance score, histological grade, and Charlson comorbidity index. Continuous variables were calculated as mean ± SD or median (IQR), and categorical variables were calculated as frequency and percentage. Treatment outcomes between groups were compared by chi-squared test or t-tests. Secondary outcomes were assessed by cox proportional hazard models. The difference in long-term survival was visually plotted on Kaplan-Meier survival curves.

RESULTS

A total of 200 patients with subcutaneous squamous cell carcinoma were included in the study who either underwent concurrent radiotherapy and chemotherapy (Group A) or radiotherapy alone (Group B). The mean age in Group A was 75.4 ± 2.2 years and in Group B was 75.2 ± 2.3 years (p=0.86). majority of patients were males (88% vs 94%). 55% patients in Group A and 66% had a CCI of greater than 70 which indicated unfavorable prognosis. Most of the tumors was T1-2 (66% vs 80%) with no margins (65% vs 74%). The baseline demographic and tumor characteristics are shown in Table I. The surviving patients were followed up for a mean duration of 20 months. The 1-year local non-recurrence rate was 92% in Group A and 94% in Group B. The 2-year local non-recurrence rate was 84% and 75%, respectively. The 1-year and 2-year metastatic non-recurrence rate was 98% and 94% in concurrent treatment group and 100% and 89% in radiotherapy group. The Kaplan-Meier curves for local and metastatic recurrence were statistically insignificant and the Cox proportional hazards model also yield any significant predictors of recurrence or survival. The 1-year progression survival was 85% in Group A and 76% in Group B and 2-year survival was 73% vs 55%, respectively. The overall 1-year survival was 99% vs 80% and 2-year was 79% vs 74% for Group A and B, respectively.

A total of 15 (15%) in Group A and 30 (30%) in Group B experienced grade 3 adverse effects (treatment-related dermatitis). Only 2 patients (2%) in the chemotherapy group had grade 4 dysphagia while no grade 4 toxicity was noted in radiotherapy group. Treatment was paused in chemotherapy group in 20% patients and patients experienced an average weight loss of 3.5 kg. While in radiotherapy group, alopecia (12%) was the frequent long-term adverse effect with only 0.5 kg average weight loss.

Table 1: Adjusted Baseline Data of Patients

	Group A (n=100)	Group B (n=100)	P
Mean age	75.4 ± 2.2	75.2 ± 2.3	0.86
Gender			
Male	88 (88%)	94 (94%)	0.91
Female	12 (12%)	6 (6%)	
Karnofsky performance score			
≤ 70	45 (45%)	34 (34%)	0.88
>70	55 (55%)	66 (66%)	
Charlson comorbidity index			
1-3	8 (8%)	9 (9%)	0.97
4-6	34 (34%)	40 (40%)	
7-10	58 (58%)	51 (51%)	
Location of carcinoma			
Ear	38 (38%)	40 (40%)	1
Face, cheeks	20 (20%)	15 (15%)	
Forehead, temple	25 (25%)	33 (33%)	
Orbit, parotid, nose, neck	17 (17%)	12 (12%)	
Laterality			
Left	40 (40%)	40 (40%)	0.95
Midline	-	5 (5%)	
Right	60 (60%)	55 (55%)	
Tumor size			
T1-2	66 (66%)	80 (80%)	0.78
T3-4	44 (44%)	20 (20%)	
N stage			
0	50 (50%)	62 (62%)	0.79
1-2a/b	50 (50%)	38 (38%)	
Margins			
0	65 (65%)	74 (74%)	0.91
1	35 (35%)	26 (26%)	
Lymphovascular space invasion			
0	90 (90%)	94 (94%)	0.82
1	10 (10%)	6 (6%)	
Perineural invasion			
0	75 (75%)	70 (70%)	0.93
1	25 (25%)	30 (30%)	
Tumor grade			
1	3 (3%)	2 (2%)	0.89
2	20 (20%)	32 (32%)	
3	77 (77%)	66 (66%)	
Recurrence	55 (55%)	70 (70%)	0.74

Table 2: Acute Adverse Effects of Treatment of Study Groups

	Grading			
	1	2	3	4
Group A				
Nausea	2 (2%)	-	-	-
Vomiting	2 (2%)	-	-	-
Skin reaction to radiation	50 (50%)	31 (31%)	-	-
Skin reaction to chemotherapy	30 (30%)	25 (25%)	15 (15%)	-
Esophagitis	15 (15%)	7 (7%)	-	-
Mucositis	25 (25%)	17 (17%)	-	-
Dysphagia	15 (15%)	2 (2%)	-	2 (2%)
Dysgeusia	25 (25%)	-	-	-
Xerostomia	25 (25%)	-	-	-
Odynophagia	11 (11%)	-	-	-
Group B				

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Nausea	3 (3%)	-	-	-
Vomiting	-	-	-	-
Skin reaction to radiation	55 (55%)	32 (32%)	30 (30%)	-
Esophagitis	5 (5%)	-	-	-
Mucositis	8 (8%)	-	-	-
Dysphagia	8 (8%)	-	-	-
Dysgeusia	10 (10%)	-	-	-
Xerostomia	12 (12%)	-	-	-
Odynophagia	3 (3%)	-	-	-
Alopecia	12 (12%)	-	-	-

DISCUSSION

Cetuximab has been reported to be an excellent radiosensitizer for treatment of head and neck cancers, hence, we assessed its combined effect with radiotherapy in squamous cell carcinoma. The results revealed that the concurrent treatment was well-tolerated and had a higher survival rate and lower metastatic recurrence than radiotherapy treatment alone. Other studies have also reported similar results (3, 5, 6).

A previous retrospective study conducted on patients with unresectable cutaneous squamous cell cancer treated with radiotherapy and cetuximab combination therapy showed successful results in 67% of patients, progression-free survival of 91%, and an overall survival rate of 40% (7). The reduced survival rate may be due to the presence of 42% immunosuppressed patients.

In the present study, the 2-year local non-recurrence rate was 84% and 75%, respectively. The 1-year and 2-year metastatic non-recurrence rate was 98% and 94% in the concurrent treatment group and 100% and 89% in radiotherapy group. The Kaplan-Meier curves for local and metastatic recurrence were statistically insignificant and the Cox proportional hazards model also yielded no significant predictors of recurrence or survival. Chang et al reported a local recurrence rate of 16.7% and metastatic recurrence in 11.1% in a 20-month follow-up (8).

The 1-year progression survival was 85% in Group A and 76% in Group B, and the 2-year survival was 73% vs 55%, respectively. The overall 1-year survival was 99% vs 80% and the 2-year survival was 79% vs 74% for Groups A and B, respectively. A similar 1- year overall survival of 85.7% was reported by Yamauchi et al, however, the long-term survival was significantly lower than our study i.e. 47.6% (9). Rawat et al showed a 1-year and 2-year progression-free survival in concurrent cetuximab and radiotherapy of 85% vs 69%, which is similar to our study (10). Although, our study population was mostly elderly, with poor margins and KPS and had comorbidities and node involvement, the survival outcomes are promising.

The most common toxicity in our study was treatment-related dermatitis in both groups. However, the long-term adverse effects, like treatment breaks were significantly higher in the cetuximab group, where treatment was paused in 20% of patients, as compared to only 2% of patients in radiotherapy group. However, the overall treatment was well-tolerated in both groups. Skin conditions and mucositis and dysphagia are also frequently reported adverse outcomes in other studies (11-13).

Our study has some limitations. The research was single-centered with retrospective analysis of a small sample that enabled selection bias and failure to account for various clinical parameters. However, the promising results indicate more potential for better studies.

CONCLUSION

The concurrent treatment of radiotherapy and cetuximab chemotherapy is safe and effective in patients with aggressive squamous cell skin cancer of head and neck with better survival and recurrence as compared to radiotherapy alone.

DECLARATIONS

Data Availability Statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned. (IRBEC=??)

Consent for publication

Approved

Funding

Not applicable

CONFLICT OF INTEREST

The authors declared an absence of conflict of interest.

AUTHOR CONTRIBUTION

AALIA BASHIR (SR, Radiotherapy)

Conception of the study, development of research methodology, study design, critical revision of the manuscript, and final approval of the manuscript.

MUHAMMAD JUNAID HASSAN (SR, Radiotherapy)

Data entry, data analysis, and initial drafting of the article.
Assisted in manuscript drafting and reference management.
Contributed to statistical analysis and interpretation of data.
Study Design, Review of Literature.
Participated in patient data collection and clinical documentation.

FERWA NASIR (SR, Radiotherapy)

Conception of Study, Development of Research Methodology Design, Study Design.
Manuscript drafting.

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