Article published online: 2025-08-26

Clinical Outcomes and Toxicity Profile of Cetuximab-Containing Regimen in Locoregionally Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma: A Single-Institution Retrospective Audit

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Ind J Med Paediatr Oncol 2025;46:489–496.

Abstract

Introduction Recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) remains one of the most prevalent and challenging malignancies worldwide. The combination of cetuximab and chemotherapy continues to be a preferred therapeutic option for these patients. However, despite extensive research aimed at optimizing this combination, the median overall survival (OS) remains limited to approximately 1 year. Long-term survival outcomes continue to be dismal, highlighting the urgent need for more effective treatment strategies and real-world data to guide clinical decision-making.

Objectives The aim of this study is to evaluate the differential effectiveness of cetuximab-containing treatment in locoregional recurrence versus distant metastasis and identify clinical factors associated with improved survival in patients with R/M SCCHN.

Materials and Methods This retrospective study included patients with histopathologically confirmed R/M SCCHN, staged according to the Union for International Cancer Control TNM classification and American Joint Committee on Cancer seventh edition. Eligible patients were ≥18 years old, had locoregional recurrence or distant metastasis, an ECOG (Eastern Cooperative Oncology Group) performance status of 0 to 2, and no contraindications to treatment. All patients received cetuximab-based treatment during the defined study period. Study endpoints included OS, progression-free survival (PFS), overall response rate (ORR), and disease control rate (DCR). Response was assessed using RECIST 1.1 criteria after at least three cycles or earlier if clinically indicated. Safety was evaluated based on CTCAE v5.0 criteria.

Results A total of 100 patients (median age: 56.5 years) with R/M SCCHN received cetuximab-based chemotherapy. In the overall population, the median OS was 19 months (95% confidence interval [CI]: 17.1–20.9), with 1- and 2-year OS rates of 77.9 and 33%, respectively. Median PFS was 3 months (95% CI: 2.7–3.3), with 3- and

Keywords
- advanced SCCHN
- cetuximab-based treatment
- distant metastasis
- recurrent disease
- survival outcomes
- toxicity profile

article published online
August 26, 2025

DOI https://doi.org/10.1055/s-0045-1811268.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

6-month PFS rates of 34.7 and 12.6%, respectively, and tumor responses indicated meaningful disease control (ORR: 37%; DCR: 55%). Patients with locoregional recurrence had significantly longer OS than those with distant metastasis (23 vs. 17 months, $p = 0.01$). Treatment was well-tolerated.

Conclusion Cetuximab-based therapy is more effective in achieving disease control and survival in patients with SCCHN who have locoregional recurrence, compared with those with distant metastases.

Introduction

Squamous cell carcinoma of head and neck (SCCHN) is one of the most common cancers worldwide, with more than 900,000 new cases and over 400,000 deaths annually.[1,2] According to the recent GLOBOCAN 2022 estimates, the incidence of SCCHN in India has risen notably, with approximately 239,000 new cases reported annually.[2] This surge has established SCCHN as the most common cancer among men and the fourth most prevalent cancer among women, underlining its growing public health impact and the urgent need for intervention.[2] Although a rigorous combination of surgery, radiation therapy, and platinum-based chemotherapy is used for curative treatment, the rate of recurrence is 20 to 30% in early-stage SCCHN and up to 50% in locally advanced SCCHN.[3–7]

Currently, the treatment options for recurrent or metastatic SCCHN (R/M SCCHN) are still limited, and the survival outcomes remain poor.[8,9] The addition of cetuximab to systemic chemotherapy resulted in a substantial enhancement of treatment results in two randomized clinical trials.[10,11] The EXTREME trial demonstrated that the addition of cetuximab to platinum and fluorouracil (FU) resulted in a 20% reduction in the risk of death, a 36% reduction in the risk of disease progression, and a 16% improvement in the response rate. The TPExtreme trial found that the combination of cetuximab, docetaxel, and cisplatin yielded comparable overall survival (OS) and progression-free survival (PFS) outcomes to the EXTREME regimen. Additionally, this combination led to an objective response rate (ORR) of 57%. Therefore, the combination of cetuximab and chemotherapy remains a preferred therapeutic option for R/M SCCHN.

Nevertheless, despite extensive study into finding the most effective combination of cetuximab and chemotherapy, the median survival rate for patients with R/M SCCHN treated with cetuximab-based chemotherapy remains at approximately 1 year, with long-term survival outcomes remaining extremely poor. Therefore, it is crucial to assess prognostic factors for the effectiveness of cetuximab treatment. Two previous extensive retrospective studies have found various prognostic variables, with distant metastasis being recognized as a critical factor associated with unfavorable survival in SCCHN.[12,13] It is still unclear whether distant metastasis continues to be an important prognostic factor for R/M SCCHN when treated with a regimen that includes cetuximab.

Materials and Methods

Study Design

This is a single-center (single institute), retrospective audit of patients with R/M SCCHN. The data were obtained retrospectively using electronic medical records, which included information on patient demographics, disease features, and treatment details.

Patients

The study comprised 100 patients who were diagnosed with R/M SCCHN at Omega Hospitals in Hyderabad, Telangana, India, from January 2013 to May 2023. The inclusion criteria comprised individuals who were at least 18 years old, had recurrent and metastatic head and neck squamous cell carcinomas, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and had no contraindications to treatment. Individuals with intolerance to chemotherapy, including those with left ventricular ejection fraction $<50\%$, Child–Pugh class B or C liver dysfunction, serum total bilirubin >2 mg/dL, creatinine clearance <30 mL/min (as per the Cockcroft–Gault formula), or concurrent malignancies were excluded from the study.

Objectives

Our study aimed to investigate the disparity in the effectiveness of cetuximab-containing treatment between locoregional recurrence and distant metastasis in patients with R/M SCCHN at our institution. Additionally, the study aimed to determine the clinical characteristics that are associated with improved survival outcomes.

Expected Outcomes

The primary outcome of this study was to assess the OS in patients with R/M SCCHN treated with cetuximab-containing regimens. Secondary outcomes include evaluation of PFS, ORRs, and disease control rate (DCR) of the patients, and safety, including the treatment-related toxicities and adverse events.

Study Methods

All patients with a confirmed histopathological diagnosis underwent staging according to the TNM classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC seventh edition). The investigator delivered cetuximab-based treatment to all patients within the specified time period. Cetuximab was initially administered intravenously at a dose of 400 mg/m^2 over a period of 120 minutes. Subsequently, it was given at a weekly dose of 250 mg/m^2 with infusion durations of 60 minutes. Concurrent chemotherapy regimens included combinations of paclitaxel and carboplatin, single agent (SA) paclitaxel, gemcitabine, methotrexate, nab-paclitaxel, and other regimens. This study did not involve any interventions or collection of identifiable personal data and was based on retrospective analysis of anonymized clinical records. Ethical approval for the study was obtained from the Ethics Committee of Omega Hospital, Hyderabad via letter dated 04.05.2024.

Study Endpoints

Besides the regular demographic data, the efficacy of cetuximab plus chemotherapy combination therapy was assessed by OS, PFS, ORR, and DCR of the patients. PFS was defined as the time duration between the start of the combination therapy and the date of progression or death due to any cause, or the last follow-up date, whichever was earlier. The OS was calculated from the date of start of the combination therapy to the date of death due to any cause. ORR was defined as patients who had complete response (CR) or partial response (PR) on initial assessment. DCR was defined as absence of progression and included patients with CR, PR, and stable disease (SD). Patient's survival was evaluated retrospectively throughout the study duration.

In addition, response assessment was performed by using the institutional radiological evaluation protocol after minimum completion of three cycles or after any symptoms/signs of clinical progression as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[14] and CR, PR, SD, and progressive disease (PD) data were evaluated. Cetuximab plus chemotherapy was continued until disease progression or unacceptable toxicities. Safety assessments were performed by assessing the severity of adverse events, using the Common Terminology Criteria for Adverse Events v.5.0.[15]

Statistical Analysis

Data were 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 the Mantel–Haenszel log rank test and survival curves were generated using the 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 residual and did not violate in this dataset. Data were analyzed using IBM SPSS version 25.0 (IBM Corp., Armonk, New York, United States) and R Studio version 1.2.1335. $p < 0.05$ was considered as statistically significant.

Results

Demographics and Clinical Characteristics of the Overall Population

A total of 100 patients (median age of 56.5 years at the time of analysis [interquartile range: 29–84]) with R/M SCCHN treated with cetuximab-based chemotherapy were evaluated. Majority of the patients were male (85%) with 13% having multiple comorbidities and the rest having single or none. Fifty-two percent of patients had metastatic disease, while 48% had recurrent disease, 25% of the patients had tongue cancer as the major site, followed by 24% with cancer in the buccal mucosa, 15% with cancer in the hypopharynx, 10% with cancer in the larynx, and a few additional less prevalent subsites in the oral cavity, nasopharynx, and oropharynx. The ECOG PS score was 1 in 56% of patients and 2 in 44% of patients. Median follow-up was 33.5 months (10–39).

The combined chemotherapy regimens consisted of concurrent administration of paclitaxel and carboplatin in 35% of cases, SA paclitaxel alone in 30% of cases, methotrexate in 15% of cases, nab-paclitaxel combined with carboplatin in 7% of cases, and as an SA in 3% of cases. Additional less frequent treatment protocols consisted of carboplatin combined with 5 FU, cisplatin combined with nab-paclitaxel and 5 FU, cisplatin combined with irinotecan, and gemcitabine combined with cisplatin. Patient and clinical characteristics are summarized in ►**Table 1**.

Treatment Outcomes

Among the patients with R/M SCCHN who had received cetuximab-based chemotherapy, the median OS was 19 months (95% CI: 17.1–20.9), 1-year OS was 77.9%, while 2-year OS was 33%. The median PFS was 3 months (95% CI: 2.7–3.3) and 3-month PFS rate was 34.7%, while 6-month PFS rate was 12.6%. ►**Figs. 1** and **2** illustrate the survival curves for the median OS and PFS among overall population. Tumor responses to cetuximab-based treatment regimen revealed that 37 out of 100 (37%) patients had achieved a PR, 18% exhibited SD, while 45% patients experienced PD as their initial response to the combination therapy. This resulted into an ORR of 37% and a DCR of 55%.

Toxicity Profile

None of the patients in the overall population experienced severe adverse reactions that resulted in death during the treatment period. However, grade 3 or higher toxicities were reported in 10% of patients presenting with rash, 5% with diarrhea, 8% with mucositis, 7% with fatigue, and 5% exhibiting febrile neutropenia (►**Table 2**).

Table 1 Demographic and clinical characteristics of the overall population

Parameters	$n = 100$
Age, y (median [IQR])	56.5 [29–84]
Sex, *n* (%)	
Male	85 (85.0)
Female	15 (15.0)
Comorbidities, *n* (%)	
No comorbidity	57 (57.0)
Single comorbidity	30 (30.0)
Multiple comorbidities	13 (13.0)
Performance status, *n* (%)	
ECOG = 1	56 (56.0)
ECOG = 2	44 (44.0)
Stage of cancer, *n* (%)	
Recurrent	48 (48.0)
Metastatic	52 (52.0)
Tumor site distribution, *n* (%)	
Tongue	25 (25.0)
Buccal mucosa	24 (24.0)
Hypopharynx	15 (15.0)
Larynx	10 (10.0)
Retromolar trigone	6 (6.0)
Alveolus	5 (5.0)
Palate	3 (3.0)
Parotid	3 (3.0)
Others[a]	9 (9.0)
Concurrent chemotherapy regimen, *n* (%)	
Paclitaxel plus carboplatin	35 (35.0)
SA Paclitaxel	30 (30.0)
Methotrexate	15 (15.0)
Nab-paclitaxel plus carboplatin	7 (7.0)
SA Nab-paclitaxel	3 (3.0)
Others[b]	10 (10.0)
Line of chemotherapy, *n* (%)	
First line	2 (2.0)
Second line	69 (69.0)
Third line	22 (22.0)
Fourth line	7 (7.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SA, single agent.
[a]Includes tumor sites such as the external auditory canal, lower lip, gingivobuccal sulcus, base of the tongue, nodal metastasis of unknown origin, and floor of the mouth.
[b]Includes concomitant chemotherapy, including carboplatin combined with 5-fluorouracil (FU), cisplatin combined with nab-paclitaxel and 5-FU, cisplatin combined with irinotecan, gemcitabine combined with cisplatin, SA docetaxel, SA cisplatin, and docetaxel plus cisplatin plus 5-FU.

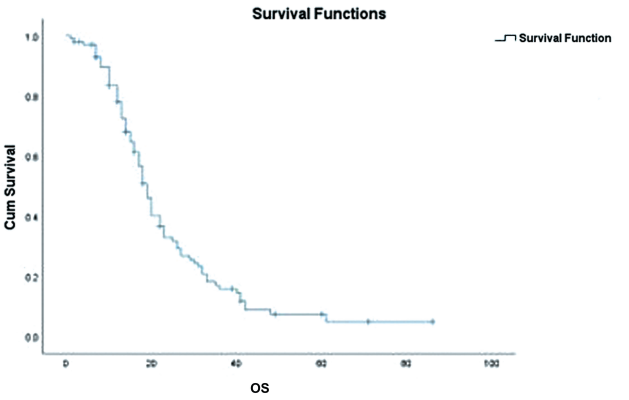

Fig. 1 Kaplan–Meier estimates of overall survival for patients with recurrent/metastatic squamous cell carcinoma of head and neck.

Independent Prognostic Factors

Cox regression analyses were performed on clinical and treatment characteristics to evaluate independent prognostic factors for survival outcomes. The variables analyzed for OS and PFS were gender, stage of the disease, ECOG PS, line of treatment, and comorbidities.

In the overall population with R/M SCCHN, gender-based differences in survival outcomes were observed with females experiencing prolonged OS compared with males (median: 31 vs. 18 months, $p = 0.06$). Further, a statistically significant improvement in the OS was observed among patients with ECOG PS 1 compared with patients with ECOG PS 2 (median: 22 vs. 15 months, $p = 0.031$) and also in the patients with recurrent disease compared with metastatic stage (median: 23 vs. 17 months, $p = 0.01$).

OS was nearly identical between patients receiving cetuximab-based therapy in earlier (first/second) versus later (third or beyond) lines of treatment (median: 19 vs. 18 months, $p = 0.8$). However, significantly notable difference in OS was observed between the patients with no or a single comorbidity, and those with multiple comorbidities (median: 20 vs. 14 months, $p = 0.007$).

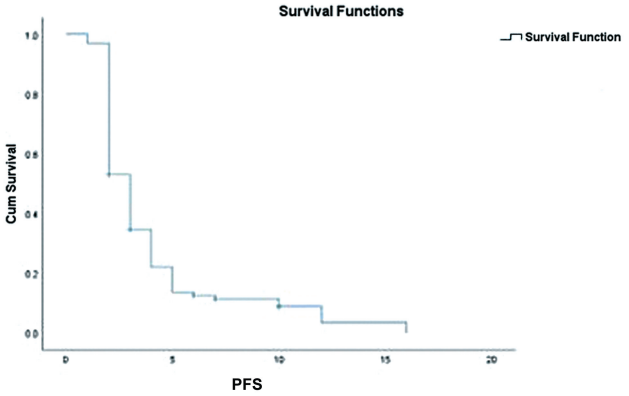

Fig. 2 Kaplan–Meier estimates of progression-free survival for patients with recurrent/metastatic squamous cell carcinoma of head and neck.

Table 2 Reported adverse events in the overall population[a]

Adverse event	Description as per CTCAE v.5.0	CTCAE v.5.0 grading			*n* (%)
		Grade 3 definition	Grade 4 definition	Grade 5 definition	
Rash	A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self- care ADL[b]	–	–	10 (10)
Diarrhea	A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL[b]	Life-threatening consequences; urgent intervention indicated	Death	5 (5)
Mucositis	A disorder characterized by ulceration or inflammation of the oral mucosa	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death	8 (8)
Febrile neutropenia	A disorder characterized by an ANC <1,000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour	ANC <1,000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour	Life-threatening consequences; urgent intervention indicated	Death	5 (5)
Fatigue	A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities	Fatigue is not relieved by rest, limiting self-care ADL[b]	–	–	7 (7)

Abbreviations: ADL, activities of daily living; ANC, absolute neutrophil count; BSA, body surface area; CTCAE, common technology criteria for adverse events.

Note: A single dash (-) indicates a grade is not available. Not all grades are appropriate for all adverse events (AEs). Therefore, some AEs are listed with fewer than five options for grade selection.

[a]Grade 3 or higher adverse events were recorded and reported as part of the analysis.

[b]Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. A semi-colon (;) indicates "or" within the description of the grade.

Patients with ECOG PS 1 reported a median PFS of 4 months, while it was 2 months for the patients with ECOG PS 2 ($p < 0.001$). PFS was comparable among patients with recurrent and metastatic disease (median: 3 months, $p = 0.49$). PFS showed minimal differences across treatment lines (3 vs. 2 months, $p = 0.13$) and comorbidity status (3 months for both groups, $p = 0.97$).

Patients with recurrent disease showed better response rates, with an ORR of 43.8% and DCR of 60.5% in recurrent setting, compared with an ORR of 30.8% and a DCR of 50% in those with metastatic disease. Although not statistically significant, locally recurrent cases exhibited a more favorable trend toward the response rates than metastatic ones. The absolute difference in ORR between the two groups was 13.0% ($p = 0.1808$), and the difference in DCR was 10.5% ($p = 0.2941$).

Overall, no significant differences in survival were observed concerning age or line of treatment. However, key factors such as stage at the initiation of cetuximab-based chemotherapy, presence or absence of multiple comorbidities, and ECOG PS played an important role in influencing the outcomes (►**Figs. 3** and **4**).

Discussion

The study aimed to assess the effectiveness of a cetuximab-containing treatment in the entire cohort of patients with R/M SCCHN, as well as in the subgroups of patients with only locoregional recurrence or distant metastasis. In this study, it was observed that the locoregional recurrence group had a notably longer OS compared with the distant metastasis group. Nevertheless, there was no significant difference in the PFS between the two groups. The subsequent observation diverges from the existing literature. Furthermore, an improvement in DCR was observed in the group of patients with locoregional recurrence who were treated with a regimen incorporating cetuximab. These data provide evidence that the cetuximab-containing

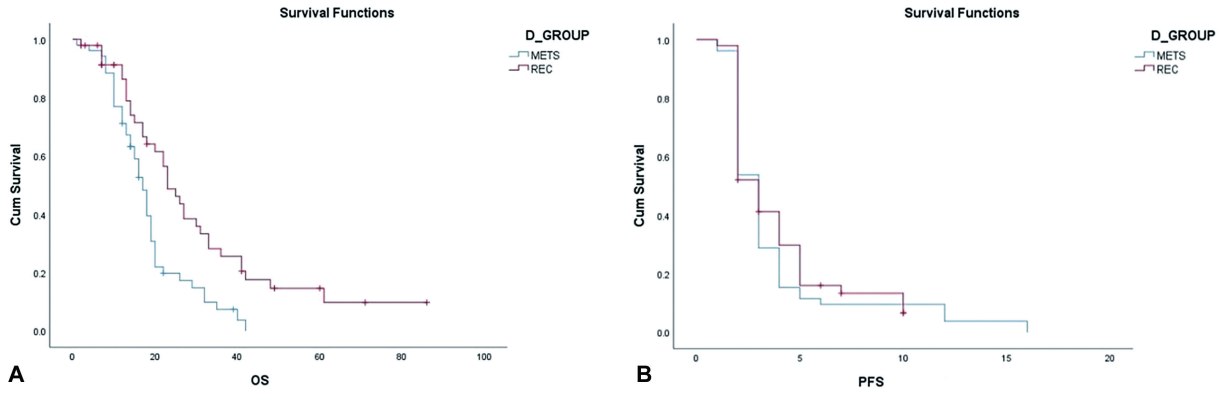

Fig. 3 (**A**) Kaplan–Meier estimates comparing overall survival in patients with recurrent and metastatic squamous cell carcinoma of head and neck. (**B**) Kaplan–Meier estimates comparing progression-free survival in patients with recurrent and metastatic squamous cell carcinoma of head and neck.

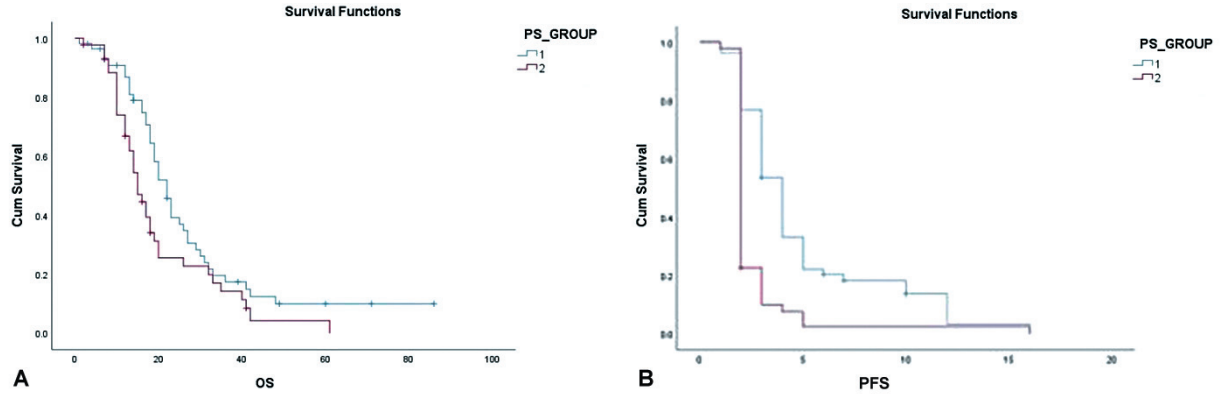

Fig. 4 (**A**) Kaplan–Meier estimates comparing overall survival in patients with Eastern Cooperative Oncology Group performance status scores 1 and 2. (**B**) Kaplan–Meier estimates comparing progression-free survival in patients with Eastern Cooperative Oncology Group performance status scores 1 and 2.

regimen is the preferred treatment for locoregionally recurrent SCCHN.

Within our group of participants, the median OS was 19 months, and the median PFS was 3 months. The median OS for patients with locoregional recurrent disease was 23 months (18.2–27.8), while it was 17 months (14.8–19.1) for patients in the metastatic stage ($p = 0.01$). Nevertheless, the median PFS was the same for both recurrent and metastatic diseases, specifically 3 months ($p = 0.49$). Patients experiencing a relapse of their illness demonstrated higher rates of positive response, with an ORR of 43.8% and a DCR of 60.5% in the context of relapse. In contrast, patients with metastatic disease had lower response rates, with an ORR of 30.8% and a DCR of 50%.

The survival outcomes seen in this trial were near-consistent with the findings reported in the EXTREME study (median OS: 10.1 months, median PFS: 5.6 months) and the KEYNOTE-048 study (median OS: 10.7 months, median PFS: 5.1 months).[11,16] The enhanced OS in the locoregionally recurrent group could be attributed to the fact that approximately 15% of the patients had undergone salvage surgery or treated with immunotherapy later in the course of their treatment. The disparity in the PFS may be related to the observation that substantial proportion of patients had lower PS, resulting in suboptimal adherence and increased rates of treatment abandonment. As previously stated, the ECOG PS score was 1 in 56% of patients, and 2 in 44% of patients. The median OS was 22 months (range: 19.06–24.93) in patients with PS 1, while it was 15 months (range: 12.35–17.64) in patients with PS 2. This difference was statistically significant ($p = 0.031$). The median PFS was 4 months (range: 3.42–4.57) in patients with PS 1, compared with 2 months (range: 1.83–2.16) in PS 2 ($p < 0.001$).

The survival outcome of the entire group in this study was as well consistent with the results of the single-arm observational ENCORE study (median OS: 10.2 months, median PFS: 6.5 months) and another randomized, open-label, phase III CHANGE-2 study (median OS: 11.1 months, median PFS: 5.5 months).[17,18] The therapeutic efficacy of cetuximab-based chemotherapy in both the locoregional and distant metastatic groups was not assessed in both the KEYNOTE-048 and ENCORE studies. In a rigorous investigation, the effect of the arm containing cetuximab had a greater influence on OS in the locoregional recurrence group (OS: hazard ratio [HR]: 0.65, 95% CI: 0.49–0.87) compared with the distant metastatic group (OS: HR: 0.99, 95% CI: 0.72–1.38).[19] The CHANGE-2 trial found that treatment with

cetuximab had similar OS advantages in the group of patients with locoregional recurrence (HR: 0.6, 95% CI: 0.4–0.9). However, there were no significant OS benefits observed in the group of patients with distant metastasis (HR: 0.7, 95% CI: 0.3–1.7) or in the group with both locoregional recurrence and distant metastasis (HR: 0.9, 95% CI: 0.5–1.8).[20] The JROSG 12–2 trial, which observed patients over time, found a noticeable increase in the likelihood of death in patients with lung and bone metastases (lung: HR: 2.12, $p = 0.12$; bone: HR: 2.29, $p = 0.11$).[21]

A key strength of our real-world study lies in its reflection of routine clinical practice, providing insights into the comparative outcomes of locoregional versus distant metastatic SCCHN when treated with cetuximab-containing regimens. However, this study has some limitations. First, this study was conducted at a single center and is observational in nature, which may restrict the capacity to apply the findings to other populations with varying demographics or characteristics. The small sample size poses a major challenge, making it difficult to draw definitive conclusions about the site of disease and its relationship with the benefit of cetuximab. This limitation impacts the generalizability and statistical robustness of the findings to larger or more diverse populations. Another possible limitation was the exclusion of various medicines combined with cetuximab as prognostic variables for further statistical analysis owing to the complexity of the treatment regimens. Due to the small sample size of the study cohort, stratifying the benefit of cetuximab by disease site was not feasible, limiting the ability to draw definitive conclusions in this regard. The impact of immunotherapy also could not be assessed in our cohort due to limited availability and uptake during the study period. Future studies with larger sample sizes and a more comprehensive evaluation of treatment modalities will be helpful to explore these aspects in greater detail. Further research should explore the underlying biological mechanisms and treatment-related factors contributing to the observed differences in outcomes between locoregional and distant recurrences, which remain a gray area in current understanding.

Conclusion

Our real-world study with a limited sample size indicates that SCCHN with locoregional recurrence is associated with better disease control and survival outcomes compared with distant metastatic SCCHN when treated with cetuximab-containing regimen. The ECOG PS and presence or absence of multiple comorbidities play an important role in defining the outcomes.

Patient Consent

Patient consent is not required due to the retrospective nature of the study.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

The authors gratefully acknowledge the support provided by the institution where the work was conducted. No additional contributions, technical assistance, or external funding were involved in the development of this manuscript.

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