Cerrahpaşa Med J 2026; 50: 1-8 ORIGINAL ARTICLE

Cetuximab-Related Skin Toxicity as a Prognostic Marker in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Retrospective Analysis of the EXTREME Regimen

Mehmet Cem Fidan, Shamkhal Safarov, Hamza Abbasov, Vali Aliyev, Emir Çerme, Özkan Alan, Nebi Serkan Demirci

Division of Medical Oncology, Department of Internal Medicine, İstanbul University - Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye

Cite this article as: Fidan MC, Safarov S, Abbasov H, et al. Cetuximab-related skin toxicity as a prognostic marker in recurrent or metastatic head and neck squamous cell carcinoma: a retrospective analysis of the EXTREME regimen. *Cerrahpaşa Med J*. 2026, 50, 0093, doi: 10.5152/cjm.2026.26093.

What is already known on this topic?

- *Prior clinical studies have documented a survival benefit linked to the development of cetuximab-associated dermatological toxicity in patients with colorectal cancer and head and neck squamous cell carcinoma (HNSCC) receiving cetuximab-containing therapies.*
- *Despite the EXTREME regimen (platinum + 5-FU + cetuximab) representing the established standard first-line treatment for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), validated pharmacodynamic markers capable of predicting individual cetuximab benefit have yet to be identified.*
- *Patient functional status, as assessed by the Eastern Cooperative Oncology Group (ECOG) scale, is a well-established determinant of prognosis in R/M HNSCC.*

Abstract

Objective: Cetuximab-induced skin toxicity has been proposed as a predictive biomarker of treatment efficacy in cetuximab-based regimens. However, its prognostic significance in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with the EXTREME regimen remains limited. This study investigated the impact of cetuximab-related skin toxicity on progression-free survival (PFS) and overall survival (OS) in R/M HNSCC.

Methods: This single-center, retrospective cohort study included 79 patients with histopathologically confirmed unresectable locally advanced or metastatic HNSCC who received first-line platinum-based chemotherapy with 5-fluorouracil (5-FU) and cetuximab (EXTREME regimen) between June 2014 and July 2024. Patients were stratified by the presence or absence of cetuximab-related skin toxicity. Toxicities were graded per National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE v5.0. Survival analyses were performed using the Kaplan–Meier method and Cox proportional hazards regression.

Results: Median age was 63 years (range 34-87), and 75.9% were male. Cetuximab-related skin toxicity was observed in 27 patients (34.2%), and was the most frequent toxicity type, followed by diarrhea (17.0%) and hypomagnesemia (13.2%). Patients with skin toxicity had significantly longer OS (14.1 vs. 10.1 months; HR: 0.545; 95% CI: 0.325-0.916; $P = .022$). No significant difference was observed in PFS (6.3 vs. 5.2 months; HR: 0.91; 95% CI: 0.57-1.47; $P = .715$). On multivariate analysis, skin toxicity was independently associated with improved OS (HR: 0.545; 95% CI: 0.325-0.916; $P = .022$). Eastern Cooperative Oncology Group (ECOG) ≥2 was an independent adverse prognostic factor for both PFS (HR: 3.084; 95% CI: 1.578-6.028; $P < .001$) and OS (HR: 6.419; 95% CI: 3.140-13.121; $P < .001$).

Conclusion: Cetuximab-induced skin toxicity was independently associated with improved OS in R/M HNSCC patients treated with the EXTREME regimen, suggesting its potential role as a pharmacodynamic biomarker of cetuximab efficacy. Prospective studies incorporating molecular biomarkers are warranted.

Keywords: Cetuximab, EXTREME regimen, head and neck squamous cell carcinoma, overall survival, prognostic biomarker, skin toxicity

Introduction

Global cancer surveillance data published in 2020 (GLOBOCAN) rank head and neck squamous cell carcinomas among the 10 most prevalent malignancies worldwide, with considerable associated mortality.[1] Despite definitive treatments for local or locally advanced stages, a significant proportion of patients develop recurrences that are unresponsive to local treatments or lead to distant metastases.[2,3] Unresectable or metastatic head and neck squamous cell carcinomas (HNSCC) have poor prognoses, high morbidity, and low survival rates.

Received: June 26, 2026 **Revision Requested:** July 12, 2026 **Last Revision Received:** July 16, 2026 **Accepted:** July 27, 2026 **Publication Date:** September 8, 2026
Corresponding author: Mehmet Cem Fidan, Division of Medical Oncology, Department of Internal Medicine, İstanbul University - Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye **e-mail:** mcemfidan@gmail.com
DOI: 10.5152/cjm.2026.26093

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

What does this study add on this topic?

- *Using real-world clinical data, this study provides evidence that the occurrence of cetuximab-induced cutaneous toxicity independently predicts a meaningful overall survival advantage in patients with R/M HNSCC receiving the EXTREME regimen.*
- *The absence of a significant skin toxicity–progression-free survival association suggests that the prognostic signal operates through pathways not exclusively attributable to direct anti-tumor cytostatic effects.*
- *Taken together, these results reinforce the rationale for considering cetuximab-induced skin rash as a practical, readily observable pharmacodynamic marker to stratify patients according to likelihood of benefit from the EXTREME regimen.*

As a transmembrane tyrosine kinase receptor, Epidermal Growth Factor Receptor (EGFR) activates multiple downstream signaling cascades upon ligand-induced autophosphorylation, ultimately promoting malignant behaviors including uncontrolled cell division, resistance to programmed cell death, local invasion, and tumor-associated angiogenesis.[4] High EGFR expression levels are frequently detected in HNSCC and have been consistently linked to inferior clinical outcomes.[5,6]

Cetuximab, a human-murine chimeric immunoglobulin G1 (IgG1) monoclonal antibody, exerts its anti-tumor effect by targeting the extracellular domain of EGFR and blocking natural ligand interaction.[7] The landmark Phase 3 EXTREME trial established the clinical benefit of incorporating cetuximab into platinum-based chemotherapy backbones, demonstrating statistically significant improvements in both progression-free survival (PFS) and overall survival (OS) among recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) patients. This pivotal evidence positioned the platinum-5FU-cetuximab combination as the preferred first-line systemic approach in unresectable or metastatic disease.[8]

Dermatological toxicity, manifesting predominantly as an acneiform eruption, represents the most frequently encountered adverse effect associated with cetuximab and affects the majority of treated patients.[8] Multiple prior investigations have demonstrated a survival advantage among patients who develop cetuximab-related cutaneous toxicity, spanning both colorectal cancer and HNSCC coh orts.[9-15] These observations lend support to the concept that skin rash occurrence may serve as an early, clinically accessible surrogate of cetuximab pharmacodynamic activity.

This study aimed to investigate the impact of cetuximab-induced skin toxicity on PFS and OS in patients with R/M HNSCC.

Methods

Study Design

The authors conducted a single-institution retrospective cohort analysis. Eligible patients carried a histopathologically verified diagnosis of unresectable locally advanced or distantly metastatic HNSCC and had received first-line platinum-based chemotherapy combined with 5-fluorouracil (5-FU) and cetuximab (EXTREME regimen) between June 2014 and July 2024 were included in the study. Patients with nasopharyngeal carcinoma and salivary gland malignancies were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the İstanbul University Cerrahpaşa Clinical Research Ethics Committee (Approval No.: E-83045809-604.01-1094461; Date: September 18, 2024). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

Patient Population

A total of 79 patients were included in this study. Clinicopathological data were obtained from patient files and hospital electronic health records. Demographic and clinical variables of the patients were recorded as follows: age, gender, smoking and alcohol use history, primary tumor localization, disease presentation at diagnosis (locoregional or metastatic), Eastern Cooperative Oncology Group (ECOG) performance status, and disease status before first-line systemic treatment (unresectable locoregional recurrence or distant metastasis). The inclusion criteria were as follows: histopathologically confirmed diagnosis of HNSCC, radiological evidence of metastatic or unresectable locally advanced disease, and administration of at least 1 cycle of the EXTREME regimen. Exclusion criteria included insufficient clinical documentation, inadequate radiological data for treatment response, and diagnosis of nasopharyngeal carcinoma or salivary gland malignancy.

Treatment Protocol

All patients received the EXTREME regimen as the first-line systemic treatment. The administration of cetuximab maintenance therapy was recorded. Second- and third-line treatment regimens were also documented.

Toxicity Assessment

All treatment-emergent adverse events were prospectively recorded and retrospectively graded according to the NCI-CTCAE (version 5.0) grading system. Cetuximab-associated toxicities were categorized into 5 distinct types: cutaneous reactions, hypomagnesemia, mucositis, diarrhea, and infusion-related reactions. Chemotherapy-related and cetuximab-specific toxicity profiles were assessed independently. Toxicity requiring dose modification (dose reduction or discontinuation) and permanent treatment discontinuation, as well as the distribution of drugs causing these toxicities, were also recorded. Patients were divided into 2 groups based on whether they developed cetuximab-related skin toxicity (no toxicity/toxicity present) for comparative analysis.

Efficacy Results

The co-primary endpoints of interest were PFS and OS. Progression-free survival was calculated from the date of EXTREME regimen initiation to the date of radiologically or clinically confirmed disease progression or death due to any cause; patients event-free at last contact were censored. Overall survival was measured from treatment start to the date of death from any cause, with living patients censored at the date of last follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM SPSS Corp.; Armonk, NY, USA). Categorical variables were compared between groups using the chi-square or Fisher's exact test. Survival analyses were performed using the Kaplan–Meier method, and the log-rank test was used to compare the PFS and OS curves between groups. Univariate analyses were performed using the Cox proportional regression model to determine the prognostic factors for PFS and OS. Variables found to be significant at $P < .20$ in the univariate analysis were included in the multivariate model. Hazard ratios (HR) were calculated for each variable along with 95% CIs. A *P*-value of less than .05 was considered statistically significant

This study used Paperpal (Cactus Communications) to improve language and edit grammar during the preparation of the manuscript. However, all content of the study has been reviewed and edited by the author(s) following the use of AI/LLM tools.

Results

Baseline Characteristics of Patients

A total of 79 patients were included in this study. The median age of the patients was 63 years (34-87), and 60 (75.9%) were men. Fifty-two (65.8%) patients had a history of smoking, 17 (21.5%) had never smoked, and smoking status was unavailable for 10 patients. Of the 66 patients for whom alcohol use status could be assessed, 16 (24.2%) were alcohol users. The most common primary tumor localization was laryngeal cancer (n = 38, 48.1%), followed by oral cavity cancer (n = 22, 27.8%) and unknown primary cancer (n = 8, 10.1%). Most patients had an ECOG performance score of 0-1 (n = 68, 86.1%). At the time of diagnosis, 62 patients (78.5%) presented with locoregional disease and 17 (21.5%) with metastatic disease (Table 1).

At the start of first-line systemic treatment, 25 patients (31.6%) had unresectable locoregional recurrence, and 49 patients (62.0%) had distant metastases. Among the distant metastatic locations, the lung was the most frequently affected organ (n = 34, 43.0%), followed by extraregional lymph nodes (n = 20, 25.3%) and bone (n = 15, 19.0%). A total of 54 patients (68.4%) received carboplatin + 5-fluorouracil + cetuximab, and 25 patients (31.6%) received cisplatin + 5-fluorouracil + cetuximab. Seventeen patients (21.5%) received maintenance cetuximab therapy (Table 2).

Second-line treatment was not administered in 37 patients (46.8%), most commonly due to disease progression or death (n = 34, 43.0%). Among patients who received second-line treatment, the most frequently used regimens were docetaxel (n = 17, 21.5%), paclitaxel (n = 7, 8.9%), nivolumab (n = 7, 8.9%), and gemcitabine (n = 4, 5.1). Third-line treatment was not administered to 59 patients (74.7%). Among those who received third-line therapy, gemcitabine (n = 7, 8.9%), nivolumab (n = 3, 3.8%), and docetaxel (n = 2, 2.5%) were the most commonly used agents (Supplementary Table 1).

When patients were divided into 2 groups based on the presence of cetuximab-related skin toxicity, no statistically significant differences were found between patients who developed toxicity and those who did not in terms of age (*P* 0.152), sex ($P = .784$), smoking ($P = .296$), alcohol use ($P = .782$), presentation at diagnosis ($P = .296$), and ECOG performance score ($P = .059$) (Table 3).

Survival Outcomes

Progression-free survival and overall survival were analyzed using the Kaplan–Meier method according to the presence of cetuximab-induced skin toxicity. Median PFS was 5.2 months (95% CI: 3.2-7.2) in patients without skin toxicity and 6.3 months (95% CI: 5.8-6.8) in patients who developed skin toxicity, with no statistically significant difference between the 2 groups (HR: 0.91, 95% CI: 0.57-1.47; $P = .715$) (Figure 1).

In the overall survival analysis, the median OS was 10.1 months (95% CI: 8.2-12.0) in patients without cetuximab-related skin toxicity and 14.1 months (95% CI: 10.5-17.6) in those who developed skin toxicity. Patients with cetuximab-related skin toxicity

Table 1. Demographic and Clinical Characteristics of Patients

Age, years (median, min-max.)	63 years (34-87)			
		—	n	%
Sex	Female	—	19	24.1
	Male	—	60	75.9
Smoking status	Never smoker	—	17	21.5
	Ever smoker	—	52	65.8
	Not available	—	10	12.7
Alcohol use	No	—	50	63.3
	Yes	—	16	20.3
	Not available	—	13	16.5
Primary tumor site	Oral cavity	—	22	27.8
	Lip	—	3	3.8
	Buccal mucosa	—	5	6.3
	Gingiva/Alveolar ridge	—	2	2.5
	Oral tongue	—	8	10.1
	Floor of the mouth	—	4	5.1
	Oropharynx	—	3	3.8
	Hypopharynx	—	1	1.3
	Larynx	—	38	4.,1
	Nasal cavity and paranasal sinuses	—	6	7.6
	External auditory canal	—	1	1.3
	Unknown primary	—	8	10.1
ECOG	0-1	—	68	86.1
	≥2	—	11	13.9
Presentation of diagnosis	Locoregional	—	62	78.5
	Metastatic	—	17	21.5

ECOG, Eastern Cooperative Oncology Group.

Table 2. Clinical and Treatment Characteristics

		n	%
Initial Treatment	Surgery alone	10	12.7
	Surgery + adjuvant chemotherapy	25	31.6
	Surgery + adjuvant chemoradiotherapy	13	16.5
	Induction chemotherapy + chemoradiotherapy + surgery	1	1.3
	Chemotherapy + radiotherapy	4	5.1
	Radiotherapy alone	4	5.1
	Systemic chemotherapy	22	27.8
Disease status at the time of first-line systemic treatment	Locoregional recurrence (unresectable)	25	31.7
	Distant metastasis	49	62.0
	Locoregional recurrence + distant metastasis	5	6.3
Sites of distant metastasis	Non-regional lymph node metastasis	20	25.3
	Lung	34	43.0
	Bone	15	19.0
	Liver	4	5.1
	Cranial	2	2.5
	Adrenal gland	1	1.3
	Other	4	5.1
First-line systemic treatment regimens	Carboplatin + 5-fluorouracil + cetuximab	54	68.4
	Cisplatin + 5-fluorouracil + cetuximab	25	31.6
Cetuximab maintenance therapy	No	62	78.5
	Yes	17	21.5

Table 3. Baseline Characteristics of Patients According to Cetuximab-Related Skin Toxicity

		Cetuximab-Related Skin Toxicity				
		No		Yes		
		n	%	n	%	*P*
Age, years	<65	30	57.7	20	74.1	.152
	≥65	22	42.3	7	25.9	
Sex	Female	13	68.4	6	31.6	.784
	Male	39	65.0	21	35.0	
Smoking status	Never smoker	11	64.7	6	35.3	.296
	Ever smoker	31	59.6	21	40.4	
Alcohol use	No	28	56.0	22	44.0	.782
	Yes	9	56.3	7	43.8	
Primary tumor site	Oral cavity	16	72.7	6	27.3	—
	Oropharynx	3	100.0	0	0.0	—
	Hypopharynx	0	0.0	1	100.0	—
	Larynx	24	63.2	14	36.8	—
	Nasal cavity and paranasal sinuses	2	33.3	4	66.7	—
	Unknown primary	6	75.0	2	25.0	—
	External auditory canal	1	100.0	0	0.0	—
Presentation of diagnosis	Locoregional	39	62.9	23	37.1	.296
	Metastatic	13	76.5	4	23.5	
ECOG	0-1	42	61.8	26	38.2	.059
	≥2	10	90.9	1	9.1	

Primary tumor site was not statistically tested owing to sparse cell counts across multiple categories.
ECOG, Eastern Cooperative Oncology Group.

demonstrated significantly longer OS (HR: 0.55, 95% CI: 0.33-0.92; $P = .022$) (Figure 2).

When factors associated with PFS and OS were evaluated using Cox regression analyses, an ECOG performance score of ≥2 was identified as a significant predictor of both progression and death. For PFS, ECOG ≥2 was associated with an approximately 3-fold increased risk of progression on univariate analysis (HR: 3.020, 95% CI: 1.547-5.893; $P = .001$), which was confirmed as an independent prognostic factor on multivariate analysis (HR: 3.084, 95% CI: 1.578-6.028; $P < .001$). The impact of ECOG ≥2 on OS was even more pronounced, remaining an independent prognostic factor in both univariate (HR: 5.498, 95% CI: 2.758-10.959; $P < .001$) and multivariate analyses (HR: 6.419, 95% CI: 3.140-13.121; $P < .001$). Additionally, cetuximab-related skin toxicity was associated with a significantly reduced risk of death in both univariate (HR: 0.577, 95% CI: 0.347-0.962; $P = .035$) and multivariate analyses (HR: 0.545, 95% CI: 0.325-0.916; $P = .022$) (Tables 4 and 5).

Treatment-Related Toxicities and Dose Modifications

Chemotherapy-related toxicity was observed in 47 patients (59.5% of the total). Dose modification was required in 23 patients (29.1%), with platinum being the most frequently modified agent (n = 16, 55.2%), followed by 5-fluorouracil (n = 11, 37.9%) and cetuximab (n = 2, 6.9%). Chemotherapy dose discontinuation occurred in 40 (50.6%) patients. The most common reasons for dose modification or discontinuation were neutropenia (n = 23, 42.6%), infection (n = 15, 27.8%), and acute kidney injury (n = 5, 9.3%).

Cetuximab-related skin toxicity was observed in 27 patients (34.2%). Among the 53 reported cetuximab-related toxicity events, skin toxicity was the most frequently observed type, accounting for 27 events (50.9%), followed by diarrhea (17.0%) and hypomagnesemia (13.2%). (Table 6).

Discussion

The primary finding of this retrospective analysis is that the development of cetuximab-related cutaneous toxicity was independently associated with a significant improvement in overall survival among R/M HNSCC patients managed with the EXTREME regimen, whereas no comparable benefit was identified for progression-free survival.

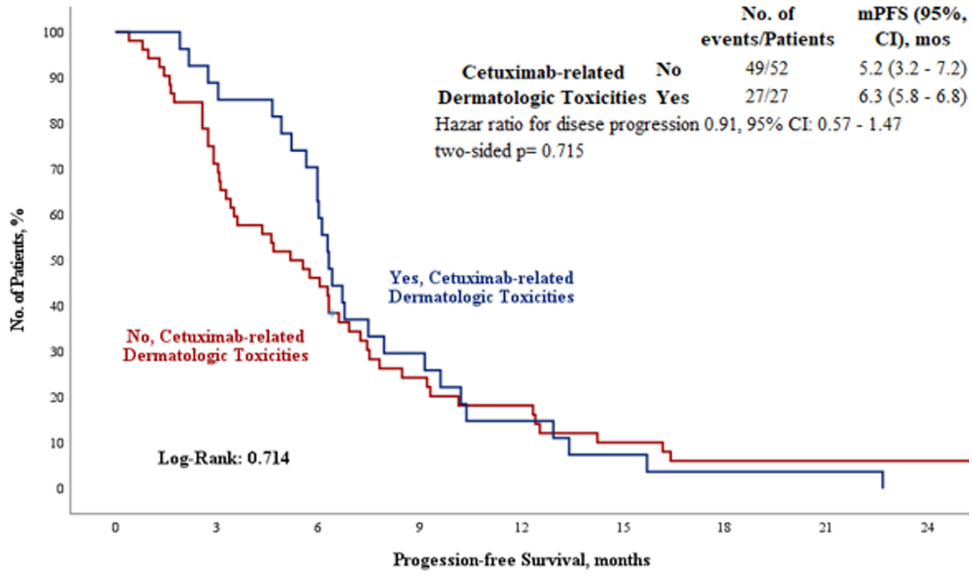

Figure 1. Kaplan–Meier curves illustrating progression-free survival (PFS) according to the presence or absence of cetuximab-induced skin toxicity in patients with recurrent or metastatic head and neck squamous cell carcinoma treated with the EXTREME regimen. The difference between groups was not statistically significant (HR: 0.91, 95% CI: 0.57-1.47; *P* = .715).

A pooled analysis synthesizing evidence from 13 clinical studies across multiple tumor entities reported that emergence of cetuximab-induced cutaneous toxicity conferred significantly superior PFS and OS relative to patients without such toxicity.[16] The OS data align with and extend the conclusions drawn from that meta-analytic work.

In a randomized phase 3 trial evaluating the addition of cetuximab to radiotherapy in patients with locally advanced HNSCC, the results of a 5-year survival analysis and the relationship between cetuximab-induced skin toxicity and survival were reported. Patients who developed skin toxicity had significantly longer survival times. This finding indicates a consistent relationship between skin toxicity and survival, despite the use of different treatment modalities. Similarly, a longer overall survival was reported in patients who received cetuximab concomitantly with radiotherapy and developed skin toxicity, particularly in p16-negative patients.[11]

In a retrospective study of patients with R/M HNSCC, cetuximab-induced skin toxicity was an independent predictor of OS.[17] The fact that the median OS and PFS values obtained in the study were consistent with those of this study supports the notion that the EXTREME regimen has a consistent efficacy profile in real-world data in this disease group.

In a subgroup analysis of the randomized, phase 3 FIRE-3 study in patients with colorectal cancer, OS was significantly longer in patients who developed cetuximab-induced skin toxicity, and when evaluated together with early tumor shrinkage, both parameters were shown to have independent prognostic value in terms of OS.[18] In this study, skin toxicity did not affect PFS. Although a direct comparison between tumors with

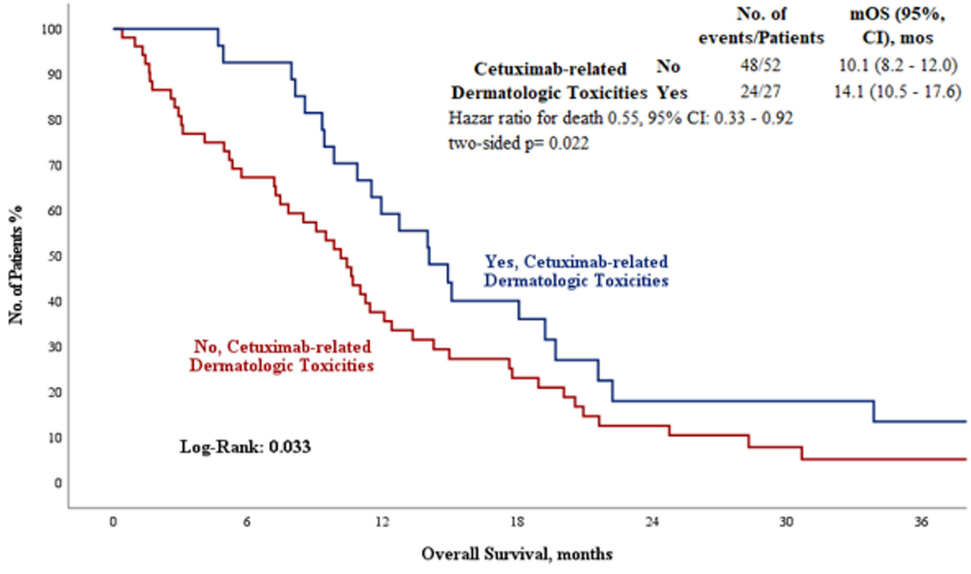

Figure 2. Kaplan–Meier curves illustrating overall survival (OS) according to the presence or absence of cetuximab-induced skin toxicity in patients with recurrent or metastatic head and neck squamous cell carcinoma treated with the EXTREME regimen. Patients who developed skin toxicity demonstrated significantly longer OS compared to those who did not (HR: 0.545, 95% CI: 0.325-0.916; *P* = .022).

Table 4. Univariate and Multivariate Cox Regression Analyses of Factors Associated with Progression-Free Survival

	Univariate			Multivariate		
	HR	**95%**	***P***	**HR**	**95%**	***P***
Age (<65 vs. ≥65)	1.154	0.742-1.843	0.549	—	—	—
Sex (female vs. male)	1.188	0.698-2.020	0.526	—	—	—
Smoking status (never vs. ever)	1.005	0.578-1.749	0.985	—	—	—
Alcohol use (no vs. yes)	0.795	0.447-1.412	0.433	—	—	—
Presentation of diagnosis (locoregional vs. metastatic)	1.076	0.617-1.877	0.795	—	—	—
ECOG (0-1 vs. ≥2)	3.020	1.547-5.893	***0.001***	3.084	1.578-6.028	***<.001***
Chemotherapy-related toxicity	1.183	0.740-1.892	0.482	—	—	—
Chemotherapy dose modification	0.949	0.580-1.554	0.836	—	—	—
Chemotherapy dose discontinuation	1.447	0.912-2.297	***0.117***	—	—	—
Cetuximab-related skin toxicities (no vs.yes)	0.915	0.570-1.471	0.715	—	—	—

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
Bold p values indicate statistically significant results ($p < 0.05$).

2 different biologics such as HNSCC and colorectal cancer is difficult, in line with the results of this subgroup analysis of the FIRE-3 study, it has been shown that skin toxicity can affect OS independently of PFS.

The ECOG performance status emerged as a robust and independent determinant of both PFS and OS in the cohort, consistent with the established literature. An analysis of a large multicenter registry encompassing over 1400 HNSCC patients similarly identified ECOG ≥2 as an independent adverse prognostic indicator for OS, alongside heavy alcohol consumption.[19] In this dataset, alcohol use reached statistical significance as a negative OS predictor on univariate analysis, yet this association did not persist after adjusting for competing variables in the multivariable model.

The disease stage at diagnosis (locoregional vs. metastatic) had no significant effect on survival outcomes. This finding differs somewhat from the existing literature,[19,20] which may be due to the relatively small sample size and limitations of the single-center retrospective design.

When the toxicity profile was evaluated in thisstudy, the most frequent reasons for dose reduction were chemotherapy-related toxicities (especially neutropenia). Among cetuximab-related toxicities, cutaneous side effects were the most prominent, followed by diarrhea and hypomagnesemia. This distribution is consistent with the literature and comparable to the toxicity rates reported in the original EXTREME study.[8]

The incidence of cetuximab-related skin toxicity in the cohort (34.2%) was lower than the 50-80% range reported in the pivotal

Table 5. Univariate and Multivariate Cox Regression Analyses of Factors Associated with Overall Survival

	Univariate			Multivariate		
	HR	**95%**	***P***	**HR**	**95%**	***P***
Age (<65 vs. ≥65)	1.097	0.675-1.783	.709	—	—	—
Sex (female vs. male)	1.019	0.590-1.760	.946	—	—	—
Smoking status (never vs. ever)	0.792	0.453-1.385	.413	—	—	—
Alcohol use (no vs. yes)	0.645	0.346-1.203	***.168***	—	—	—
Presentation of diagnosis (locoregional vs. metastatic)	0.805	0.444-1.462	.477	—	—	—
ECOG (0-1 vs. ≥2)	5.498	2.758-10.959	***<.001***	6.419	3.140-13.121	***<.001***
Chemotherapy-related toxicity	0.995	0.614-1.614	.985	—	—	—
Chemotherapy dose modification	0.680	0.397-1.163	***.159***	—	—	—
Chemotherapy dose discontinuation	1.266	0.790-2.029	.328	—	—	—
Cetuximab-related Skin Toxicities (no vs.yes)	0.577	0.347-0.962	***.035***	0.545	0.325-0.916	***.022***

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
Bold p values indicate statistically significant results ($p < 0.05$).

Table 6. Treatment-Related Toxicities and Dose Modifications

		n	%*
Chemotherapy-related toxicity	No	32	40.5
	Yes	47	59.5
Chemotherapy dose modification	No	56	70.9
	Yes	23	29.1
Chemotherapy dose discontinuation	No	39	49.4
	Yes	40	50.6
Drug requiring dose modification	Total	29	100.0
	5-Florouracil	11	37.9
	Platin	16	55.2
	Cetuximab	2	6.9
Reason for dose modification or discontinuation	Total	54	100.0
	Neutropenia	23	42.6
	Thrombocytopenia	2	3.7
	Anemia	2	3.7
	Acute kidney injury	5	9.3
	Infection	15	27.8
	Nausea/vomiting	3	5.6
	Diarrhea	1	1.9
	Mucositis	1	1.9
	Performance status deterioration	2	3.7
Cetuximab-related toxicity	No	42	53.2
	Yes	37	46.8
	Total	53	100.0
Type of cetuximab-related toxicity	Skin toxicities	27	50.9
	Hypomagnesemia	7	13.2
	Mucositis	7	13.2
	Diarrhea	9	17.0
	Infusion reaction	3	5.7

*Percentages are per patient (denominator = 79) for the no/yes rows (chemotherapy-related toxicity, dose modification, dose discontinuation, cetuximab-related toxicity), and per event for the three "Total"-headed subgroups: drug requiring dose modification (n = 29), reason for dose modification/discontinuation (n = 54), and type of cetuximab-related toxicity (n = 53). Skin toxicity occurred in 27 patients (34.2%).

EXTREME trial and in most prospective real-world series. This difference most likely reflects the retrospective nature of the data collection, in which low-grade or transient dermatologic reactions may have been under-documented in routine clinical records, together with differences in the systematic assessment and grading of cutaneous toxicity between prospective trials and retrospective cohorts. In addition, prophylactic skin-directed measures such as topical corticosteroids or systemic doxycycline, which can reduce the incidence and severity of cetuximab-induced dermatologic reactions, may have been used in some patients but were not systematically recorded and therefore could not be quantified. Consistent with incomplete capture of milder events, any cetuximab-related toxicity was documented in 46.8% of patients. These factors should be considered when interpreting the observed toxicity rate.

The retrospective design, relatively small sample size, and missing data on some variables are among the main limitations of the study. While previous studies have shown that more severe skin toxicity is associated with longer survival times,[11,21] CTCAE grade-level information could not be reliably retrieved for all patients owing to the retrospective design; therefore, skin toxicity was analyzed as a binary variable, and a grade-based survival analysis could not be performed. In addition, the timing of skin toxicity onset relative to the induction versus maintenance phases could not be determined. Furthermore, sufficient data on HPV status, a very important biomarker and a significant factor affecting survival times, especially in patients with oropharyngeal cancer, cannot be obtained. Finally, the fact that almost half of the study consisted of patients with laryngeal cancer limits its generalizability to all head and neck subgroups.

In conclusion, this study provides real-world data supporting the association between cetuximab-induced cutaneous toxicity and better overall survival in patients with HNSCC treated with the EXTREME regimen. Skin toxicity should be considered not only as a side effect to be managed, but also as a potential pharmacodynamic biomarker of clinical efficacy. Larger prospective studies supported by molecular biomarkers are needed to comprehensively elucidate this relationship.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: This study used Paperpal to improve language and grammar during the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the İstanbul University-Cerrahpaşa Clinical Research Ethics Committee (Approval No.: E-83045809-604.01-1094461; Date: September 18, 2024).

Informed Consent: Informed consent was waived due to the retrospective design of this study.

Peer-review: Externally peer-reviewed.

Acknowledgments: Mehmet Cem Fidan was given full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions: Concept – M.C.F., N.S.D.; Design – M.C.F., N.S.D.; Supervision – N.S.D., Ö.A.; Resources – Ö.A., N.S.D.; Materials – S.S., H.A.; Data Collection and/or Processing – S.S., H.A.; Analysis and/or Interpretation – M.C.F., V.A.; Literature Search – M.C.F., E.Ç.; Writing – M.C.F., S.S.; Critical Review – N.S.D., Ö.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study has received no financial support.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. [CrossRef]
2. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. In: *Mayo Clin Proc*. Elsevier Ltd; Amsterdam. 2008;83(4):489-501. [CrossRef]
3. Seiwert TY, Cohen EEW. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer*. 2005;92(8):1341-1348. [CrossRef]
4. Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. *Nat Rev Mol Cell Biol*. 2006;7(7):505-516. [CrossRef]
5. Temam S, Kawaguchi H, El-Naggar AK, et al. Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. *J Clin Oncol*. 2007;25(16):2164-2170. [CrossRef]
6. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol*. 2006;24(25):4170-4176. [CrossRef]
7. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res*. 1995;1(11):1311-1318.
8. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116-1127. [CrossRef]
9. Stintzing S, Kapaun C, Laubender RP, et al. Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the German AIO CRC Study Group. *Int J Cancer*. 2013;132(1):236-245. [CrossRef]
10. Orditura M, De Vita F, Galizia G, et al. Correlation between efficacy and skin rash occurrence following treatment with the epidermal growth factor receptor inhibitor cetuximab: a single institution retrospective analysis. *Oncol Rep*. 2009;21(4):1023-1028. [CrossRef]
11. Bar-Ad V, Zhang QE, Harari PM, et al. Correlation between the severity of cetuximab-induced skin rash and clinical outcome for head and neck cancer patients: the RTOG experience. In: *Int J Radiat Oncol Biol Phys*. Elsevier Inc.; Amsterdam. 2016;95(5):1346-1354. [CrossRef]
12. Uozumi S, Enokida T, Suzuki S, et al. Predictive value of cetuximab-induced skin toxicity in recurrent or metastatic squamous cell carcinoma of the head and neck. *Front Oncol*. 2018;8:616. [CrossRef]
13. Racca P, Fanchini L, Caliendo V, et al. Efficacy and skin toxicity management with cetuximab in metastatic colorectal cancer: Outcomes from an oncologic/dermatologic cooperation. *Clin Colorectal Cancer*. 2008;7(1):48-54. [CrossRef]
14. Jatoi A, Green EM, Rowland KM, Sargent DJ, Alberts SR. Clinical predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. *Oncology*. 2009;77(2):120-123. [CrossRef]
15. Göksu SS, Tatlı AM, Geredeli Ç, et al. Cetuximab-induced rash is associated with overall survival in patients with recurrent/metastatic squamous cell carcinoma of head and neck. *Cancer Chemother Pharmacol*. 2021;88(5):805-812. [CrossRef]
16. Abdel-Rahman O, Fouad M. Correlation of cetuximab-induced skin rash and outcomes of solid tumor patients treated with cetuximab: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. Elsevier Ireland Ltd.; Ireland. 2015;93(2):127-135. [CrossRef]
17. Pontes F, Garcia AR, Domingues I, et al. Survival predictors and outcomes of patients with recurrent and/or metastatic head and neck cancer treated with chemotherapy plus cetuximab as first-line therapy: a real-world retrospective study. *Cancer Treat Res Commun*. 2021;27:100375. [CrossRef]
18. Holch JW, Held S, Stintzing S, et al. Relation of cetuximab-induced skin toxicity and early tumor shrinkage in metastatic colorectal cancer patients: results of the randomized phase 3 trial FIRE-3 (AIO KRK0306). *Ann Oncol*. 2020;31(1):72-78. [CrossRef]
19. Yang MH, Chen TH, Wang HM, et al. Prognostic factors and risk-stratification model of recurrent or metastatic head and neck squamous cell carcinoma treated with cetuximab containing regimen. *BMC Cancer*. 2024;24(1):1227. [CrossRef]
20. Chen TH, Pan YY, Lee TL, et al. Treatment outcomes of cetuximab-containing regimen in locoregional recurrent and distant metastatic head and neck squamous cell carcinoma. *BMC Cancer*. 2022;22(1):1336. [CrossRef]
21. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus Cetuximab for Locoregionally Advanced Head and Neck Cancer: 5-Year Survival Data from a Phase 3 Randomised Trial, and Relation between Cetuximab-Induced Rash and Survival. 2010;11(1):21-28. doi: 10.1016/S1470-2045(09)70311-0 [CrossRef]

Supplementary Table 1. Second- and Third-Line Treatment Regimens

	Second Line		Third Line	
	n	%	n	%
Not administered	37	46,8	59	74,7
Disease progression or death	34	43,0	58	73,4
Ongoing prior-line treatment	3	3,8	1	1,3
Paclitaxel	7	8,9	2	2,5
Docetaxel	17	21,5	2	2,5
Nivolumab	7	8,9	3	3,8
Gemcitabine	4	5,1	7	8,9
Carboplatin + Paclitaxel	3	3,8	1	1,3
Platinum re-challenge	2	2,5	0	0,0
Capecitabine	1	1,3	1	1,3
Temozolomide	1	1,3	0	0,0
Methotrexate (MTX)	0	0,0	2	2,5
Vinorelbine	0	0,0	1	1,3
Paclitaxel + Cetuximab	0	0,0	1	1,3