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Recurrence and Metastasis in Cutaneous Squamous Cell Carcinoma: Clinicopathological Predictors From a 15-Year Single-Center Experience

Ferhat Bozkurt,[1] Ramal Hajiyev,[2] Cemal Alper Kemaloğlu,[3] İrfan Özyazgan,[1] Kemal Deniz[4]

[1]Department of Plastic, Reconstructive and Aesthetic Surgery, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Department of Plastic, Reconstructive and Aesthetic Surgery, A Plus Hospital, İstanbul, Türkiye
[3]Department of Plastic, Reconstructive and Aesthetic Surgery, Memorial Ankara Hospital, Ankara, Türkiye
[4]Department of Pathology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

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Address for correspondence:
Ferhat Bozkurt.
Department of Plastic, Reconstructive and Aesthetic Surgery, Erciyes University Faculty of Medicine, Kayseri, Türkiye
Phone: +90 352 207 66 66
E-mail:
ferhatbozkurt@erciyes.edu.tr

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ABSTRACT

Objective: Cutaneous squamous cell carcinoma (cSCC) is one of the most common non-melanoma skin cancers and carries a clinically significant risk of recurrence and metastasis. Identifying reliable prognostic factors is essential for improving risk stratification. This study evaluated the clinicopathological predictors of recurrence and metastasis in primary cSCC lesions treated at a large tertiary center over a 15-year period.

Materials and Methods: Demographic, clinical, and pathological data were collected for 428 surgically treated primary cSCC lesions between 2008 and 2022. The variables included tumor size, histological differentiation, histological subtype, anatomical site, and surgical margin status. Clinical outcomes were defined as local recurrence and nodal or distant metastasis. Associations between variables and outcomes were evaluated using appropriate univariate statistical tests. Univariable and multivariable binary logistic regression analyses were performed to identify independent predictors of local recurrence.

Results: The mean age was 71.5 years. During follow-up, local recurrence occurred in 4.5% of cases, nodal metastasis in 4.7%, and distant metastasis in 1.9%. Larger tumors had higher recurrence (10.2%) and metastasis rates (15.4%), particularly lesions exceeding 3 cm. Poor differentiation was associated with nodal metastasis (10.1%). Positive surgical margins were associated with both recurrence and metastasis (p=0.022). In the multivariable binary analysis, increasing tumor size and positive surgical margins were identified as independent predictors of local recurrence.

Conclusion: Tumor size, histological differentiation, anatomical site, histological subtype, and surgical margin status are critical prognostic factors in cSCC. Drawing on a large single-center cohort from Türkiye, our findings highlight the importance of margin control and vigilant follow-up in high-risk patients.

Keywords: Cutaneous squamous cell carcinoma, neoplasm metastasis, prognostic factors, recurrence, surgical margins.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common keratinocyte malignancy and represents an increasing global health burden. Its incidence continues to rise because of population aging and cumulative ultraviolet (UV) exposure. Although cSCC-specific mortality is lower than that of many other solid tumors, its high prevalence contributes substantially to cancer-related deaths and healthcare costs worldwide.[1,2] Meta-analyses have reported nodal metastasis in 3–5% of cases and disease-specific mortality of approximately 1–2%.[3]

The development of cSCC is multifactorial. Chronic UV exposure, advanced age, male sex, and immunosuppression—especially in transplant recipients or patients with hematologic malignancies—are well-established risk factors. Other contributing factors include prior radiotherapy or phototherapy, chronic scars, arsenic exposure, oncogenic human papillomavirus infection, and rare genetic disorders such as xeroderma pigmentosum and albinism. Lesions arising on the lip and ear are particularly aggressive and have a higher metastatic potential.[4–6] At the molecular level, cSCC carries one of the highest mutational burdens among solid tumors, primarily driven by UV-induced DNA damage.[7,8]

Clinically, prognosis is influenced by a combination of tumor- and host-related factors. Larger tumor size, poor differentiation, perineural or lymphovascular invasion, and high-risk anatomical sites are consistently associated with adverse outcomes.[3–6] Several staging systems have been proposed for risk stratification, including the AJCC 8th edition, the Brigham and Women's Hospital (BWH) classification, and the National Comprehensive Cancer Network (NCCN) guidelines, which integrate these features to guide clinical management.[9–11] The role of sentinel lymph node biopsy (SLNB) in clinically node-negative patients remains uncertain, and regional data on cSCC outcomes remain limited.[12–14]

Given the influence of environmental and demographic factors on tumor behavior, regional evidence is essential for refining prognostic assessment. Therefore, this study aimed to identify the clinicopathological predictors of recurrence and metastasis in a large single-center cohort of surgically treated primary cSCC cases over a 15-year period.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective cohort study was approved by the Erciyes University Health Sciences Research Ethics Committee (Approval Number: 2024/187, Date: 09.10.2024) and was conducted in accordance with the Declaration of Helsinki.

KEY MESSAGES

- Tumor size, histological grade, anatomical site, and surgical margin status are important predictors of outcomes in cSCC.
- Large, poorly differentiated tumors located in high-risk anatomical sites are associated with an increased risk of recurrence and metastasis.
- High-risk cSCC lesions require close follow-up and more aggressive clinical management.

We reviewed all patients who presented to the Department of Plastic, Reconstructive, and Aesthetic Surgery at Erciyes University Faculty of Medicine with histopathologically confirmed primary cutaneous squamous cell carcinoma (cSCC) between January 2008 and December 2022. Patients were eligible if they had a histopathological diagnosis of primary cSCC, underwent surgical treatment in our department, had complete clinicopathological and follow-up data, and were followed postoperatively for at least 18 months. Patients with non-SCC skin cancers, those treated primarily at another institution, those with incomplete medical records, and those with follow-up shorter than 18 months were excluded from the study. For the statistical analysis, the unit of analysis was the individual tumor lesion. In patients with multiple lesions, each lesion was evaluated separately. The mean follow-up duration was 3.3 years (range: 2–10 years). Follow-up data were obtained from routine outpatient visits and electronic medical records.

Data Collection

Demographic, clinical, and pathological data were obtained from the hospital's electronic medical records. The collected information included age, sex, anatomical site of the lesion, tumor size (maximum diameter in centimeters), histopathological grade (well, moderately, or poorly differentiated), histological subtype (classic, clear cell, spindle cell, de novo, or other rare variants), and surgical margin status (clear or positive, either lateral or deep). Clinical outcomes, including local recurrence, nodal metastasis, and distant metastasis, were also recorded. Anatomical sites were grouped into three major regions (head and neck, trunk, and extremities) for subgroup analysis. They were also categorized as high risk (lip, ear, temple, periorbital region, scalp, nose, periauricular region, and medial canthus) or low risk (cheek, forehead, trunk, extremities, and other body sites) according to established risk classifications. Recurrence was defined as the reappearance of a tumor at the same anatomical site after complete excision, regardless of the time interval.

Tumors were managed according to contemporary guideline principles, including the AJCC 8th edition staging system and NCCN recommendations. Surgical margins were determined based on tumor size, anatomical location, and high-risk features. In general, low-risk tumors were excised with clinically determined margins of approximately 4–6 mm, whereas wider margins were preferred for lesions with high-risk features. Wider margins were preferred for tumors larger than 2 cm, poorly differentiated lesions, lesions with perineural invasion, or tumors located on the lip and auricle. Routine preoperative imaging was not performed in clinically node-negative patients; ultrasonography, CT, or MRI was obtained when nodal involvement or deep invasion was suspected. Lymphadenopathy was considered suspicious when enlarged, firm, palpable, or progressively increasing lymph nodes were detected on clinical examination and was further evaluated with ultrasonography or cross-sectional imaging when indicated. Sentinel lymph node biopsy was not routinely performed. Patients with clinically positive lymph nodes underwent therapeutic lymph node dissection according to the involved anatomical basin. High-risk cases were discussed by a multidisciplinary tumor board including plastic surgery, otolaryngology, and medical oncology teams, and adjuvant treatment decisions were made accordingly.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for all variables. Continuous variables were expressed as mean±standard deviation (SD) or median (range) after normality was assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages.

Associations between categorical variables and outcomes, including local recurrence, nodal metastasis, and distant metastasis, were evaluated using the chi-square (χ^2) test or Fisher's exact test, as appropriate. For ordered categorical variables, including tumor size categories, linear-by-linear association testing was used to assess trends.

To identify independent predictors of local recurrence, a binary logistic regression model was constructed. The dependent variable was local recurrence (yes/no). The independent variables included age (continuous), tumor size (continuous), surgical margin status (positive vs. negative), and perineural invasion (present vs. absent).

Initially, univariable binary logistic regression analyses were performed to evaluate crude associations between variables and recurrence; the results are reported as crude odds ratios (cORs) with 95% confidence intervals (CIs). Variables with $p<0.10$ in the univariable analysis were subsequently entered into a multivariable binary logistic regression model using the enter method; the results are reported as adjusted odds ratios (aORs) with 95% CIs. Model assumptions were assessed, and no evidence of multicollinearity was observed. Because of the limited number of distant metastatic events, multivariable analysis for distant metastasis was not performed to avoid model overfitting.

A p-value of <0.05 was considered statistically significant. Analyses were performed using cases with complete data.

RESULTS

Between 2008 and 2022, 1,500 patients with non-melanoma skin cancer were evaluated. Among 1,612 lesions, 428 primary cutaneous squamous cell carcinoma (cSCC) lesions were identified and included in the analysis.

Multiple lesions were observed in 79 patients. Of the 428 cSCC lesions, 310 occurred in men and 118 in women. The mean age at diagnosis was 71.5±11.7 years (median, 72; range, 38–101 years).

The demographic and clinicopathological characteristics are summarized in Table 1.

Tumor Characteristics

The face was the most common individual anatomical subsite (57.2%), followed by the scalp (10.5%), lip (3.3%), and auricle (1.2%). High-risk anatomical sites accounted for 49.5% of all cases.

When anatomical locations were regrouped into three major regions, 358 lesions (83.6%) were located in the head and neck, 67 (15.7%) in the extremities, and 3 (0.7%) on the trunk. This difference reflects that the face represents a single anatomical subsite, whereas the head and neck category includes multiple anatomical regions, such as the scalp, lips, auricles, periorbital areas, and other head and neck subsites.

Nodal metastasis occurred more frequently in high-risk locations than in low-risk locations (7.1% vs. 2.3%, p=0.018).

Histopathology

Histological grading showed that 40.2% of lesions were well differentiated, 44.2% were moderately differentiated, and 15.7% were poorly differentiated (Fig. 1).

Poor differentiation was significantly associated with recurrence (8.7% vs. 3.2%, p=0.042) and nodal metastasis (10.1% vs. 2.5%, p=0.008).

Classic squamous cell carcinoma was the predominant subtype (92.1%), whereas 7.9% of lesions represented variant histologies, including clear-cell, spindle-cell, de novo, and other rare forms.

Table 1. Demographic and clinicopathological characteristics of cSCC lesions (n=428)

Variable	n (%)
Age, years	
<70	230 (53.7)
≥70	198 (46.3)
Sex	
Male	310 (72.4)
Female	118 (27.6)
Tumor size	
<2 cm	267 (62.4)
≥2 cm	161 (37.6)
Location	
Low-risk sites	216 (50.5)
High-risk sites	212 (49.5)
Differentiation	
Well differentiated	172 (40.2)
Moderately differentiated	189 (44.2)
Poorly differentiated	67 (15.7)
Histological subtype	
Classic SCC	394 (92.1)
Variant subtypes	34 (7.9)
Surgical margin status	
Negative	402 (93.9)
Positive	26 (6.1)
Recurrence	19 (4.5)
Nodal metastasis	20 (4.7)
Distant metastasis	8 (1.9)

cSCC: Cutaneous squamous cell carcinoma.

Variant subtypes showed higher recurrence rates than classic SCC (9.8% vs. 3.8%, p=0.041), although subgroup numbers were limited.

Recurrence and Metastasis

During follow-up, local recurrence occurred in 19 cases (4.5%), nodal metastasis in 20 (4.7%), and distant metastasis in 8 (1.9%).

Recurrence was significantly more common in tumors >2 cm (7.9% vs. 2.1%, p=0.003).

Nodal metastasis was most frequent in lip (11.9%) and extremity lesions (13.3%). Distant metastasis developed mainly in extremity (20%) and scalp tumors (3.1%).

When analyzed by major anatomical region, nodal metastasis occurred in 17 head and neck lesions (4.7%) and 3 extremity lesions (4.5%), whereas no nodal metastases were observed in trunk lesions. Distant metastasis occurred in 4 head and neck lesions (1.1%) and 4 extremity lesions (6.0%), whereas no distant metastases were observed in trunk lesions.

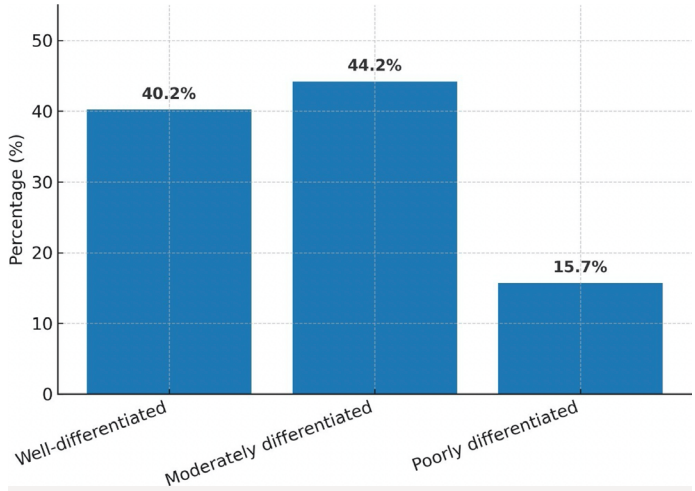

Figure 1. Distribution of histological differentiation.

Binary logistic regression analysis was performed to identify predictors of local recurrence. In the univariable binary logistic regression analysis, larger tumor size was significantly associated with recurrence (cOR, 1.56; 95% CI, 1.22–2.00; p<0.001), and positive surgical margin status was also significantly associated with recurrence (cOR, 5.17; 95% CI, 1.57–17.02; p=0.007). Age was not significantly associated with recurrence (cOR, 1.01; 95% CI, 0.97–1.05; p=0.711). Perineural invasion was associated with increased odds of recurrence, but this association did not reach statistical significance (cOR, 4.48; 95% CI, 0.50–40.34; p=0.181).

In the multivariable binary logistic regression model including age, tumor size, perineural invasion, and surgical margin status, tumor size remained independently associated with recurrence (aOR, 1.51; 95% CI, 1.17–1.95; p=0.002), and positive surgical margin status also remained independently associated with recurrence (aOR, 3.80; 95% CI, 1.05–13.67; p=0.041). Age (aOR, 1.00; 95% CI, 0.96–1.04; p=0.924) and perineural invasion (aOR, 3.69; 95% CI, 0.38–35.78; p=0.261) were not independently associated with recurrence (Table 2).

These findings are consistent with the observed dose–response relationship between tumor size and recurrence.

Tumor Size and Outcomes

Tumor size showed a strong dose–response relationship with recurrence and metastasis rates. Lesions ≤2 cm had recurrence and metastasis rates of 2.1% and 1.8%, respectively. These

Table 2. Logistic regression analysis of predictors of local recurrence in cSCC

Variables	Crude OR (cOR) (95% CI)	p	Adjusted OR (aOR) (95% CI)	p
Age, years	1.01 (0.97–1.05)	0.711	1.00 (0.96–1.04)	0.924
Tumor size, cm	1.56 (1.22–2.00)	<0.001	1.51 (1.17–1.95)	0.002
Perineural invasion	4.48 (0.50–40.34)	0.181	3.69 (0.38–35.78)	0.261
Positive surgical margin	5.17 (1.57–17.02)	0.007	3.80 (1.05–13.67)	0.041

cOR: Crude odds ratio; aOR: adjusted odds ratio; CI: Confidence interval. The multivariable model included age, tumor size, perineural invasion, and surgical margin status.

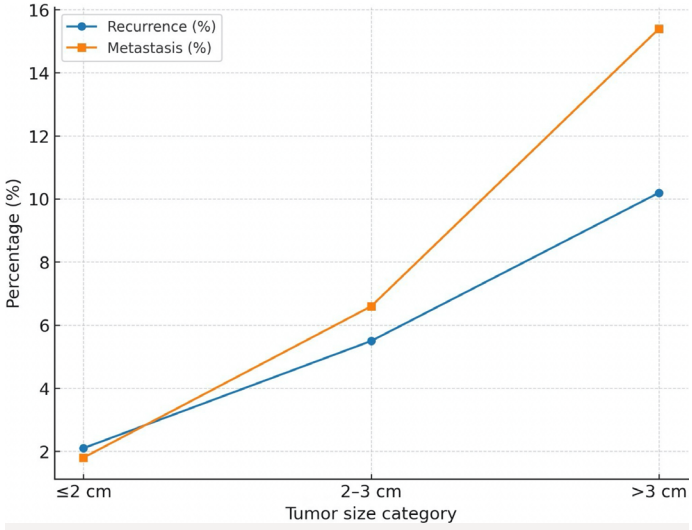

Figure 2. Association of tumor size with recurrence and metastasis.

rates increased to 5.5% and 6.6% for tumors measuring 2–3 cm and reached 10.2% and 15.4% for tumors >3 cm, respectively (p<0.001, linear-by-linear trend; Fig. 2).

Surgical Margins

Positive surgical margins were identified in 26 cases (6.1%). Among these cases, local recurrence occurred in 11.5%, nodal metastasis in 7.6%, and distant metastasis in 7.6%.

Margin positivity was significantly associated with recurrence and metastasis (p=0.022), although the subgroup size was small.

DISCUSSION

Cutaneous squamous cell carcinoma (cSCC) is one of the most common non-melanoma skin cancers worldwide; however, identifying reliable clinical predictors of outcomes remains challenging. Several large-scale studies and meta-analyses have attempted to clarify these prognostic parameters. Thompson et al.[3] analyzed more than 17,000 patients and found that tumor size >2 cm, poor differentiation, and high-risk anatomical location were strongly associated with recurrence and metastasis. More recent multicenter evaluations of staging systems, such as the AJCC and BWH classifications, have confirmed the prognostic value of these parameters.[10,11,15,16] Similarly, Brantsch et al.[17] demonstrated in a prospective cohort that tumor thickness and grade independently predicted nodal spread and disease-specific death. Furthermore, the 2023 European consensus guideline emphasized complete excision and rigorous margin control in all high-risk cSCCs.[15]

Despite the abundance of data from Western populations, regional evidence from Mediterranean and continental climates remains scarce. Variations in skin phototypes, environmental UV exposure, and occupational habits may influence tumor behavior and recurrence risk. Our study contributes to this gap by providing one of the largest single-center analyses from our region, including 428 surgically treated primary cSCC cases over a 15-year period.

In our cohort, local recurrence, nodal metastasis, and distant metastasis occurred in 4.5%, 4.7%, and 1.9% of cases, respectively—rates comparable to those reported internationally.[3,15] The strength of this study lies not only in its sample size but also in its detailed pathological documentation, particularly regarding margin status and histological subtypes, which are often underreported in similar retrospective cohorts.

Tumor size, differentiation, anatomical site, variant histology, and margin status emerged as the most relevant prognostic parameters. In the present study, multivariable binary analysis identified tumor size and positive surgical margins as independent predictors of local recurrence. Increasing tumor size was associated with a higher risk of recurrence, demonstrating a dose–response relationship. These findings are consistent with previous reports emphasizing the prognostic importance of tumor diameter and adequacy of excision in cutaneous SCC. Larger tumors may demonstrate more aggressive biological behavior and subclinical extension, increasing the risk of recurrence. Similarly, positive surgical margins remain one of the most important modifiable risk factors for local failure. A stepwise increase in recurrence and metastasis risk was observed with increasing tumor size, reinforcing the prognostic role of size previously highlighted in meta-analyses.[3,16] Poor differentiation also

independently correlated with adverse outcomes, supporting earlier observations that histological grade reflects tumor aggressiveness.[17] Moreover, variant histological subtypes, such as clear-cell and spindle-cell carcinoma, were associated with increased recurrence, adding valuable information to the limited data available on these rare variants.

Anatomical site analysis confirmed that tumors in high-risk regions, especially the lip and auricle, had a higher rate of nodal metastasis, consistent with previous evidence suggesting early lymphatic dissemination due to minimal subcutaneous tissue and rich vascularity.[15,16] Surgical margin status was another clinically meaningful prognostic variable; margin positivity correlated with recurrence and metastasis, aligning with current European guidelines emphasizing complete excision and, when necessary, re-excision or adjuvant therapy.[15]

This study's value also lies in its geographic and demographic relevance. Environmental UV exposure, occupational risks, and skin phototypes in our population differ from those in Western cohorts, and these factors likely contribute to the slightly higher proportion of high-risk anatomical sites observed in this study. Thus, our findings provide region-specific evidence that complements and broadens the global understanding of cSCC prognosis.

Despite its strengths, this study has limitations. Its retrospective design may introduce selection bias, and the tumor-based analytical approach may lead to intra-patient correlation in cases with multiple lesions. Although multivariable binary analyses were performed for local recurrence, the limited number of metastatic events restricted multivariable modeling for distant metastasis. In addition, detailed information on immunosuppression status, prior radiotherapy history, and chronic inflammatory conditions at the tumor site was not consistently available in the retrospective records and therefore could not be incorporated into the analysis. Detailed quantitative data on adjuvant radiotherapy administration were also not consistently available in the retrospective records and were therefore not analyzed separately. Furthermore, molecular data were unavailable; integrating biomarkers such as TP53 or NOTCH mutations could enhance risk stratification in future prospective studies.

CONCLUSION

Tumor size, histological differentiation, anatomical site, and margin status remain the most practical predictors of adverse outcomes in cutaneous squamous cell carcinoma. This 15-year, single-center study provides region-specific long-term data that fill an important gap in the literature and underline the value of margin control and close follow-up for high-risk lesions. Future prospective studies integrating molecular and immunologic biomarkers are needed to refine individualized prognostic models.

Ethics Committee Approval: Ethics committee approval was obtained from Erciyes University Health Sciences Research Ethics Committee (Approval Number: 2024/187, Date: 09.10.2024).

Informed Consent: Written informed consent was not required due to a retrospective nature of this study.

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