



Prognostic implications of skin invasion in locally advanced oral cavity squamous cell carcinoma

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Background: Locoregionally advanced oral cavity squamous cell carcinoma (OCSCC) has a poor prognosis, with 5-year overall survival rates around 50%. Understanding how specific tumor factors, including skin invasion, affect oncologic outcomes is crucial to counsel patients regarding prognosis and treatment options. Several studies have investigated skin invasion in combination with other adverse features in OCSCC. A recent study investigating the prognostic impact of various T4a qualifying criteria reported that tumor invading the mandible, maxilla, maxillary sinus, and/or skin invasion had a significantly worse 5-year disease specific survival and overall survival. This data was significant, but outcome measures did not specifically study the impact of skin prognosis as an independent risk factor. [1] There are two other studies that have studied skin invasion as an independent outcome, but the study populations only included patients with squamous cell carcinoma (SCC) of the buccal mucosa and do not include the six other subsites of the oral cavity. In both studies, skin invasion predicted a significantly worse 5-year locoregional control rate and overall survival rate. [2, 3] However, there is no definitive evidence to confirm or refute this suspicion.

Objectives: To evaluate the prognostic effect of pathologic skin invasion on 2 and 5 year disease-free and overall survival in patients treated with primary surgery for locally advanced OCSCC.

Methods: A retrospective case-control study was performed comparing previously untreated patients with pT4a OCSCC with and without skin invasion treated at a tertiary care center between January 2004 and April 2019. Patients > 18 years of age with pT4a OCSCC treated with primary surgery were eligible for inclusion. Pathologic re-review of all tumor specimens was completed to ensure accurate assessment of skin invasion by the primary tumor.

Table 1: Survival at 2 and 5 years

	Control	Skin invasion	P-value
Overall Survival			
2 years, % alive	53.3 (38.6 – 68)	30.8 (12.4 – 49)	P = 0.018
5 years, % alive	42.2 (26.9 – 57.5)	16.4 (0 – 34.4)	P = 0.010
Disease Free Survival			
2 years, % alive	47.7 (33.4 – 62)	23.7 (26.3 – 56.5)	P = 0.037
5 years, % alive	41.4 (26.3 – 56.5)	15.8 (0 – 33)	P = 0.024

Data are given are percentages (95% CI)

Discussion: Skin invasion through direct extension has been previously characterized as a form of dermal metastases. Numerous studies have shown that skin metastases from lymphatic or hematogenous spread indicate poor prognoses in patients with OCSCC [4]. However, an initial presentation with direct extension of disease into the skin has rarely been evaluated. While the median survival for patients with skin invasion may be better than those with distant metastases, our results indicate that skin invasion portends an abysmal prognostic outcome and may be considered an independent factor for outcome prediction [5, 6]. Currently, the main form of management for these patients is primary surgery, which frequently requires extensive reconstruction due to the disease status and has been shown to somewhat improve median survival [6]. Due to the poor overall prognosis, other forms of management such as neoadjuvant radiotherapy or primary chemoradiation may be considered during shared-decision making to optimize patient quality of life.

Conclusions: Histopathologic skin invasion in OCSCC is associated with dismal prognosis and significantly lower OS in patients who underwent primary surgical treatment, with median survival around 10 months. Future directions include direct comparison of quality-of-life outcomes for primary surgery versus palliative surgery and other forms of therapy for patients with T4a OCSCC with skin invasion.

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2. Fang, F.M., et al., Combined-modality therapy for squamous carcinoma of the buccal mucosa: treatment results and prognostic factors. Head Neck, 1997, 19(6): p. 506-12.
3. Lin, C.S., et al., Squamous cell carcinoma of the buccal mucosa: an aggressive cancer requiring multimodality treatment. Head Neck, 2006, 28(2): p. 150-7.
4. Yoskovitch A., et al., Skin metastases in squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg, 2001, 124(3): p. 248-52.
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6. Stavrianos S.D., et al., Head and neck skin involvement by non-cutaneous head and neck cancers: free flap reconstruction. Eur J Surg Oncol, 2000, 26(6): p. 594-8.

Results: A total of 172 patients met inclusion and exclusion criteria. After pathologic re-review, 25 patients were identified to have pathologic skin invasion and 50 patients without pathologic skin invasion were selected as a matched control group. There were no significant differences in matched covariates between cases and controls. Median age for the overall cohort was 63 years (IQR: 56-70). Both groups were predominately male: 68% of the control and skin invasion groups. OS was significantly lower for patients with skin invasion compared to controls at 2-years (30.8% vs 53.3%, p=0.018) and 5-years (16.4% vs 42.2%, p=0.01). DFS was also significantly lower for patients with skin invasion compared to controls at 2-years (23.7% vs 47.7, p=0.037) and 5-years (15.8% vs 41.4%, p=0.024). Table 1 shows the full set of survival data. Median survival time was more than one year greater for patients in the control group (21 months, 0 – 66) compared to the skin invasion group (9.5 months, 3.9 – 9.8). Figure 1 and figure 2 show the Kaplan-Meier curves for OS and DFS.

Figure 1: Kaplan-Meier overall survival curves

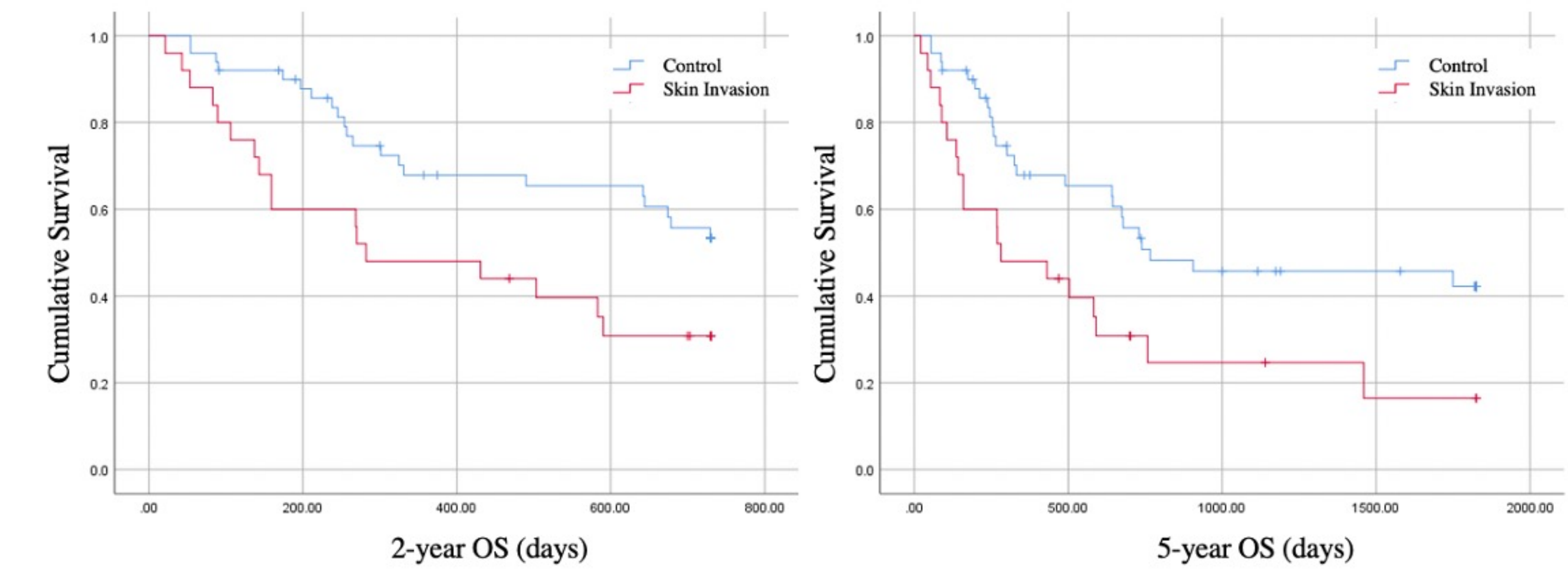


Figure 2: Kaplan-Meier disease free survival curves

