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BRIEF REPORT

Architectural dysplasia in surgical margins and the risk of local relapse in oral cancer

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Abstract

Background: A major challenge in the clinical management of oral cavity squamous cell carcinoma is local relapse. Even when surgical margins are tumor-free, local relapses occur frequently, and relapse prediction by histology remains suboptimal. In leukoplakia, an oral potentially malignant disorder, the presence of architectural dysplasia is a critical risk factor for malignant transformation. This study aimed to investigate whether the presence of architectural dysplasia in oral cavity squamous cell carcinoma surgical margins is a risk factor for local relapse.

Methods: Hematoxylin and eosin-stained slides of resection margins from a consecutive cohort of surgically treated patients diagnosed with stage I–IV oral cavity squamous cell carcinoma between 2008 and 2014 were assessed for the presence of architectural dysplasia ($N = 311$). Five-year local relapse-free survival rates of oral cavity squamous cell carcinoma with architectural dysplasia were compared to those of oral cavity squamous cell carcinoma without architectural dysplasia.

Results: In total, 92 of 311 (29.6%) of oral cavity squamous cell carcinoma displayed architectural dysplasia in the margins. The presence of architectural dysplasia was associated with higher patient age, female sex, less pack years, lower cT-stage, and a cohesive tumor growth pattern. In oral cavity squamous cell carcinomas with architectural dysplasia, postoperative (chemo)radiotherapy was less often indicated compared with oral cavity squamous cell carcinoma without architectural dysplasia (19.5% vs. 36.1%, $p = 0.009$). Five-year local relapse-free survival was significantly lower in oral cavity squamous cell carcinoma with architectural dysplasia than in oral cavity squamous cell carcinoma without architectural dysplasia (83.1% vs. 94.9%, $p = 0.017$).

Conclusions: Oral cavity squamous cell carcinoma arising in the background of architectural dysplasia displays relatively favorable clinical and histopathological characteristics. Nonetheless, the presence of architectural dysplasia in oral cavity squamous cell carcinoma surgical margins is associated with a higher risk of local relapse, indicating its clinical relevance.

KEYWORDS
architectural dysplasia, local relapse, oral cavity squamous cell carcinoma, surgical margins

1 | INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is the most prevailing form of head and neck cancer.[1] OCSCC is preferably treated surgically, with postoperative (chemo)radiotherapy on indication. Yet, even with these intensive treatment protocols, 5-year survival is only 65%.[1] The major clinical challenge is local relapse. Despite histopathological clear (>5 mm) resection margins, local recurrence still appears in 10%–20%.[2] Furthermore, second primary tumors (SPTs) may arise, originating >2 cm from or >3 years after the index tumor. Local recurrences and SPTs do not only emerge from tumor cells that stayed behind, but also from precancerous changes of genetically altered cells surrounding the original tumor, indicated as "fields".[3,4] These fields might be visible to the naked eye as leukoplakia or erythroplakia, but generally do not manifest macroscopically. Yet, they can be identified microscopically as classic epithelial dysplasia, categorized by the World Health Organization (WHO) as either mild, moderate or severe.[5]

In 2022, the WHO incorporated architectural changes without pronounced cytonuclear atypia, that in themselves diagnose dysplasia. Recently, it was demonstrated that this architectural pattern of dysplasia, termed "architectural dysplasia (AD)" (or differentiated dysplasia) is a strong predictor of malignant progression in oral leukoplakia.[6] AD is characterized by squamous epithelium with broad elongated anastomosing rete ridges, displaying hyperkeratosis and parakeratosis. The keratinocytes show intercellular edema with marked desmosomes. Cytonuclear changes are subtle, with cells having small nuclei in the basal layer and showing an abrupt suprabasal transition with enlarged nuclei in abundant eosinophilic cytoplasm, indicative for abnormal premature keratinization.[6]

We questioned whether the presence of AD in the surgical margins of OCSCC might form a risk factor for local relapses in the oral cavity.

2 | MATERIALS AND METHODS

2.1 | Study design and inclusion criteria

We investigated a consecutive cohort of surgically treated OCSCC patients who were diagnosed with stage I–IV OCSCC between 2008 and 2014 at Amsterdam UMC. Tumors were restaged according to TNM-8. OCSCCs of the external lip (ICD-10 codes: C00.0-C00.2 and C00.6-C00.9) were excluded, all other subsites were included (C00.3-C00.5, C02.0-C02.3, C02.8-C05.0, and C06.0-C06.9). Furthermore, unconventional squamous cell carcinomas such as verrucous carcinomas and papillary carcinomas were excluded, resulting in a cohort of 329 OCSCCs. Hematoxylin and eosin-stained slides from 311 of 329 could be retrieved that contained all resection margins, as well as tumor, stroma, and squamous epithelium to assess the presence of dysplasia. Patient characteristics and survival outcomes were obtained from the patient files. Comorbidity was classified through the Adult Comorbidity Evaluation-27.[7]

2.2 | Histopathologic evaluation

Histopathological features were scored by dedicated head and neck pathologists (LP and EB) according to the WHO Classification of Head and Neck Tumours. The definition of AD was used as stated above.

2.3 | Clinical endpoints

Clinical endpoints were 5-year overall survival (OS) and 5-year local relapse-free survival (LRS). Five-year OS was defined as the time from histologically confirmed OCSCC diagnosis until death from any cause. Five-year LRS was defined as the time from histologically confirmed OCSCC diagnosis until histologically confirmed local relapse, with

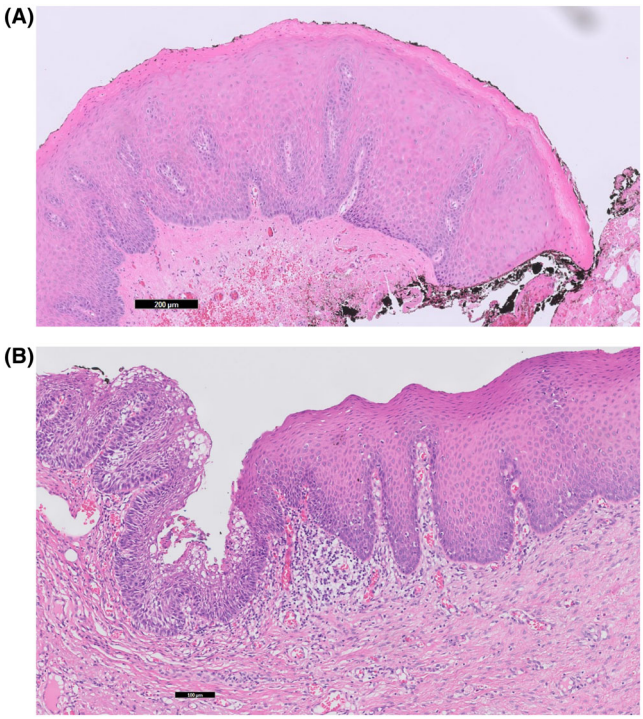

FIGURE 1 (A) Example of architectural dysplasia in the surgical margins of OCSCC. (B) Example of severe classic epithelial dysplasia (left) adjacent to architectural dysplasia (right) in the surgical margins of OCSCC.

TABLE 1a Demographic and clinical characteristics of OCSCC with and without AD in the surgical margins.

	Architectural dysplasia						
	No ($N = 219$)			Yes ($N = 92$)			
	Mean (SD)	*N*	%	Mean (SD)	*N*	%	*p* value
Age at diagnosis	62 (12)			65 (12)			**0.048**[a]
Sex							
Male		128	58.4%		40	43.5%	**0.016**[b]
Female		91	41.6%		52	56.5%	
Comorbidity (ACE-27)							
None		90	41.1%		38	41.3%	0.983[b]
Mild		75	34.2%		31	33.7%	
Moderate		40	18.3%		18	19.6%	
Severe		14	6.4%		5	5.4%	
Pack years (smoking)	27 (25)			21 (25)			**0.013**[a]
Unit years (alcohol)	116 (138)			109 (194)			0.294[a]
Tumor location							
Mobile tongue		97	44.3%		51	55.4%	**0.022**[c]
Floor of mouth		81	37.0%		19	20.7%	
Vestibule of mouth		21	9.6%		12	13.0%	
Hard palate		0	0.0%		2	2.2%	
Cheek mucosa		13	5.9%		6	6.5%	
Retromolar trigone		7	3.2%		2	2.2%	
cT-stage (TNM-8)							
T1		94	42.9%		57	62.0%	**0.018**[b]
T2		83	37.9%		26	28.3%	
T3		16	7.3%		3	3.3%	
T4a		26	11.9%		6	6.5%	
T4b		0	0.0%		0	0.0%	
cN-stage (TNM-8)							
N0		173	79.0%		83	90.2%	0.236[c]
N1		23	10.5%		6	6.5%	
N2a		1	0.5%		0	0.0%	
N2b		14	6.4%		2	2.2%	
N2c		5	2.3%		0	0.0%	
N3a		0	0.0%		0	0.0%	
N3b		3	1.4%		1	1.1%	
Treatment received							
Surgery		140	63.9%		74	80.4%	**0.009**[b]
Surgery + RT		49	22.4%		14	15.2%	
Surgery + CRT		30	13.7%		4	4.3%	

Note: Pack year = 20 cigarettes a day during 1 year. Unit year = one alcoholic unit a day during 1 year.
All significant *p*-values are in bold.
Abbreviations: ACE-27, adult comorbidity evaluation-27; CRT, chemoradiotherapy; RT, radiotherapy.
[a]Mann–Whitney *U* test.
[b]Pearson chi-square.
[c]Fisher's exact test.

local relapse comprising local recurrences (recurrent tumor <2 cm and <3 years of diagnosis of the index tumor) and SPTs in the oral cavity (tumor >2 cm from the index tumor or >3 years after diagnosis of the index tumor). Residual disease (tumor detected <6 months after treatment completion) was considered a consequence of inadequate treatment and not included in 5-year LRS.

TABLE 1b Histopathological characteristics of OCSCC with and without AD.

	Architectural dysplasia						
	No ($N = 219$)			Yes ($N = 92$)			
	Mean (SD)	*N*	%	Mean (SD)	*N*	%	*p* value
Tumor diameter (cm)	2.02 (1.30)			1.80 (1.20)			0.142[a]
Tumor depth of invasion (cm)	0.92 (0.97)			0.68 (0.51)			0.133[a]
Preexistent leukoplakia							
Absent		167	76.3%		59	64.1%	0.177[b]
Present		47	21.5%		26	28.3%	
Unknown		5	2.3%		7	7.6%	
Classic epithelial dysplasia in resection margins							
None		103	47.0%		43	46.7%	0.927[b]
Mild		16	7.3%		8	8.7%	
Moderate		16	7.3%		8	8.7%	
Severe		35	16.0%		13	14.1%	
Unknown		49	22.4%		20	21.7%	
Tumor pattern of invasion							
Cohesive		85	38.8%		42	45.7%	**0.041**[b]
Noncohesive		101	46.1%		28	30.4%	
Unknown		33	15.1%		22	23.9%	
Lymphovascular invasion							
No		180	82.2%		76	82.6%	0.421[b]
Yes		18	8.2%		5	5.4%	
Unknown		21	9.6%		11	12.0%	
Perineural invasion							
No		154	70.3%		71	77.2%	0.120[b]
Yes		45	20.5%		12	13.0%	
Unknown		20	9.1%		9	9.8%	
Peritumoral immune infiltrate							
Little to none		52	23.7%		23	25.0%	0.768[b]
Moderate to severe		165	75.3%		67	72.8%	
Unknown		2	0.9%		2	2.2%	
Stromal desmoplasia							
Little to none		96	43.8%		58	63.0%	**0.001**[b]
Moderate to severe		121	55.3%		32	34.8%	
Unknown		2	0.9%		2	2.2%	
Differentiation grade							
Well differentiated		30	13.7%		15	16.3%	0.336[b]
Moderately differentiated		123	56.2%		47	51.1%	
Poorly differentiated		40	18.3%		10	10.9%	
Unknown		26	11.9%		20	21.7%	
pT-stage (TNM-8)							
T1		87	39.7%		46	50.0%	0.302[b]
T2		66	30.1%		26	28.3%	
T3		35	16.0%		10	10.9%	
T4a		30	13.7%		9	9.8%	
T4b		0	0.0%		0	0.0%	
Tx (unknown)		1	0.5%		1	1.1%	

(Continues)

TABLE 1b (Continued)

	Architectural dysplasia						
	No ($N = 219$)			Yes ($N = 92$)			
	Mean (SD)	N	%	Mean (SD)	N	%	p value
pN-stage (TNM-8)							
N0		121	55.3%		56	60.9%	0.101[c]
N1		27	12.3%		5	5.4%	
N2a		10	4.6%		4	4.3%	
N2b		4	1.8%		4	4.3%	
N2c		2	0.9%		1	1.1%	
N3a		0	0.0%		0	0.0%	
N3b		32	14.6%		6	6.5%	
n.a. (no neck dissection)		22	10.0%		16	17.4%	
Nx (unknown)		1	0.5%		0	0.0%	
Extranodal extension							
No		154	70.3%		66	71.7%	0.120[b]
Yes		42	19.2%		10	10.9%	
n.a. (no neck dissection)		22	10.0%		16	17.4%	
Unknown		1	0.5%		0	0.0%	
Surgical margins							
Clear (>5 mm)		154	70.3%		69	75.0%	0.585[b]
Close (1–5 mm)		44	20.1%		14	15.2%	
Involved (<1 mm)		15	6.8%		7	7.6%	
Unknown (not assessable)		6	2.7%		2	2.2%	

Note: All significant *p*-values are in bold.
[a]Mann–Whitney *U* test.
[b]Pearson chi-square.
[c]Fisher's exact test.

3 | RESULTS

3.1 | Characteristics of OCSCC with and without AD

A total of 92 of 311 (29.6%) OCSCCs contained AD in the surgical margins (Figure 1A). Demographic and clinical characteristics of OCSCCs with and without AD are displayed in Table 1a. To summarize, patients with AD were older, more frequently female, and had smoked less pack years. OCSCC with AD were more often located in the mobile tong and had a lower cT-stage. OCSCCs were never treated with preoperative chemotherapy and/or radiotherapy.

Histopathological features of OCSCCs with and without AD are displayed in Table 1b. Summarized, OCSCCs with AD more frequently exhibited a cohesive growth pattern with little to no desmoplastic stromal reaction. Twenty-nine OCSCCs with AD also displayed classic epithelial dysplasia (Figure 1B).

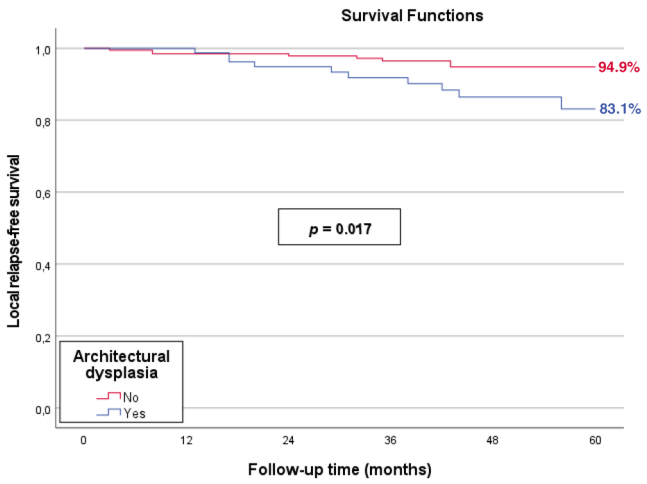

FIGURE 2 Local relapse-free survival of OCSCC with AD (blue line, 5-year local relapse-free survival 83.1%) and OCSCC without AD (red line, 5-year local relapse-free survival 94.9%). Log-rank analysis showed a significant difference in 5-year local relapse-free survival between OCSCC with and without AD ($p = 0.017$).

3.2 | Local relapse in OCSCCs with and without AD

The median follow-up time was 43 months. Within a follow-up period of 5 years, 10 of 92 (10.9%) OCSCCs with AD developed a local relapse, against 8 of 219 (3.7%) OCSCCs without AD ($p = 0.013$). Five-year LRS was 83.1% for OCSCCs with AD compared with 94.9% for OCSCCs without AD in the surgical margins ($p = 0.017$, Figure 2).

Of note, 5-year LRS was 87.0% for OCSCC with any form of dysplasia ($N = 116$) versus 94.2% for OCSCC without any form of dysplasia ($N = 146$, $p = 0.096$).

4 | DISCUSSION

AD was found in the surgical margins of almost one-third of OCSCCs, making it a common feature to be identified upon histopathological examination. OCSCCs with AD displayed specific clinical features, such as female sex and less pack years of smoking. Interestingly, these characteristics resemble the subgroup of copy number alteration-silent HNSCC.[8–10] Furthermore, the presence of AD was associated with favorable histopathologic features, such as a tendency toward a smaller tumor diameter and depth of invasion, a cohesive growth pattern, and a little to no stromal desmoplasia. These findings might implicate that OCSCCs arising in the context of AD are biologically distinct from OCSCCs without AD.

Our data demonstrate that despite the more favorable clinicohistopathological characteristics, OCSCCs with AD have a higher rate of local relapses compared with OCSCCs without AD. Of note, only 19.5% of OCSCCs with AD received postoperative (chemo)radiotherapy as per protocol compared with 36.1% of OCSCCs without AD, likely because of these specific favorable histopathologic features. We intended to perform multivariate analyses to correct for these associations and other potential confounder(s). However, the number of events was too low to carry out such analyses. Accordingly, larger studies are warranted to verify that AD is an independent risk factor for local relapse in OCSCC. Once established, AD should become a mandatory element in the histopathologic evaluation of OCSCC resection specimen. It would be valuable to investigate whether OCSCC with AD might benefit from increased surveillance, surgical re-resection, or adjuvant treatment to prevent local relapses.

AUTHOR CONTRIBUTIONS

Irene H. Nauta, Laura A. N. Peferoen, Ruud H. Brakenhoff, C. René Leemans, and Elisabeth Bloemena performed study concept and design; Irene H. Nauta, Laura A. N. Peferoen, Ruud H. Brakenhoff, C. René Leemans, and Elisabeth Bloemena performed development of methodology and writing, review and revision of the paper; Irene H. Nauta, Laura A. N. Peferoen, Ruud H. Brakenhoff, C. René Leemans, and Elisabeth Bloemena provided acquisition, analysis and interpretation of data, and statistical analysis. All authors read and approved the final paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jop.13570.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in agreement with the Declaration of Helsinki and the medical ethical guidelines in the Code of Conduct for Proper Secondary Use of Human Tissue of the Dutch Federation of Biomedical Scientific Societies. This retrospective study was approved by the Institutional Review Board on 2-9-2021 with number 2021-0511.

PATIENT CONSENT STATEMENT

The Institutional Review Board of VUmc approved the use of the material for this study as a non-WMO protocol.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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