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HEAD AND NECK

Clinicopathological characteristics, treatment and prognosis of oral adenocarcinoma: a population-based study

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Abstract

Objectives The aim of this study was to identify clinicopathologic features, treatment and prognosis of oral adenocarcinoma (OADC).

Study design Retrospective cohort analysis.

Setting National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program.

Methods Patients diagnosed with OADC between 2000 to 2018 were identified from the SEER database. Overall survival (OS) and disease-specific survival (DSS) were assessed using Kaplan–Meier analyses and Cox regression models.

Results There were 924 OADC and 37,500 oral squamous cell carcinoma (OSCC) patients identified. Patients with OADC were more significantly associated with younger age, female gender, well differentiation and early AJCC Clinical stage. The study revealed that patients with OADC had better 10-year OS and DSS than those with OSCC (OS: 69.3% vs 40.8%, $P<0.001$; DSS: 83.6% vs 53.3%, $P<0.001$). The survival advantage still persisted in multivariable analyses (OS: hazard ratio [HR] = 0.427, $P<0.001$; DSS: HR = 0.320, $P<0.001$). For OADC, multivariable analysis showed that advanced age, stage, and histologic grade were associated with worse OS and DSS, and surgery was associated with better OS and DSS.

Conclusions OADC has a significantly better prognosis than OSCC, with better differentiation, and more early stage. Surgery was the preferred treatment, for patients with lymph node metastasis, radiotherapy may afford a survival benefit.

Keywords Adenocarcinoma · Oral · Treatment · Prognosis · SEER

Introduction

Oral cancer is the 16th most common malignancy worldwide, with approximately 355,000 patients newly diagnosed annually and an increasing trend [1]. Despite important therapeutic advances in oral cancer in recent decades, no significant improvement in overall survival has been observed [2]. Therefore, oral cancer has become a serious worldwide public health problem [3].

Among the various types of oral cancer, adenocarcinoma is extremely rare compared to squamous cell carcinoma, the most common histological type, accounting for only about 2.0–5.9% [4–6]. Based on the mechanism that adenocarcinoma usually exhibits completely different biological and clinical outcomes compared to squamous cell carcinomas, previous knowledge of oral squamous cell carcinoma (OSCC) may not apply to oral adenocarcinoma (OADC) [7]. Therefore, the clinicopathological characteristics and survival of OADC needs to be further studied.

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In this study, large sample data were identified from the Surveillance, Epidemiology and End Results (SEER) database to describe the clinicopathological features, prognosis, and treatment modalities specific to OADC.

Materials and methods

Data source and study cohort

The data presented in our study were retrieved from the SEER database maintained by the National Cancer Institute. SEER, a public cancer database, represents approximately 48.0% of the US population. SEER*Stat Version 8.4.0.1 was used to obtain individual patient-level data.

Patients with OADC and OSCC diagnosed between 2000 and 2018 were retrospectively enrolled. The primary sites were defined by the following international classification of disease version 3 (ICD-O3): C000–C009, C020–023, C028–050, C058–069. The histological types of adenocarcinomas were defined using histology codes 8140, 8141, 8147, 8211, 8260, 8290, 8310, 8440, 8450, 8480, 8481, 8525, 8550 and 8574, and squamous cell carcinoma using codes 8070–8078. Patients diagnosed with non-primary tumors and those with no follow-up or vital status information were excluded.

Survival analysis

Overall survival (OS) and disease-specific survival (DSS) was defined as the time from initial diagnosis to death from any cause and the primary neoplasm, respectively. The Chi-squared test or Fisher exact test was used to compare clinical characteristics of patients with OADC/OSCC. The survival curves were depicted using the Kaplan–Meier method, and the log-rank test was used to compare differences. To identify potential independent risk factors of OS and DSS, univariate and multivariate survival analyses were conducted using the Cox proportional hazard model. The P value < 0.05 was considered statistically significant. All statistical analysis was conducted using SPSS (version 24.0; SPSS, Inc., Chicago, IL).

Results

Demographic and clinicopathologic characteristics

A total of 38,424 patients were enrolled into this study, of whom 924 patients were pathologically confirmed OADC and 37,500 were OSCC (Fig. 1). The baseline and clinicopathologic characteristics are shown in Table 1. The average age of the patients with OADC was 59.4 years. The male–female ratio was 0.56 for the incidence of OADC, and 65.8% presented with well/moderately differentiated. The palate was the most common location ($n = 419$; 45.3%), followed by the floor of mouth ($n = 163$; 17.6%) and cheek mucosa ($n = 138$; 14.9%).

When compared to patients with OSCC, OADC was more significantly associated with younger age, female gender, well differentiation, and early AJCC stage. As for treatment, more patients with OADC received surgery, but fewer received radiotherapy (RT).

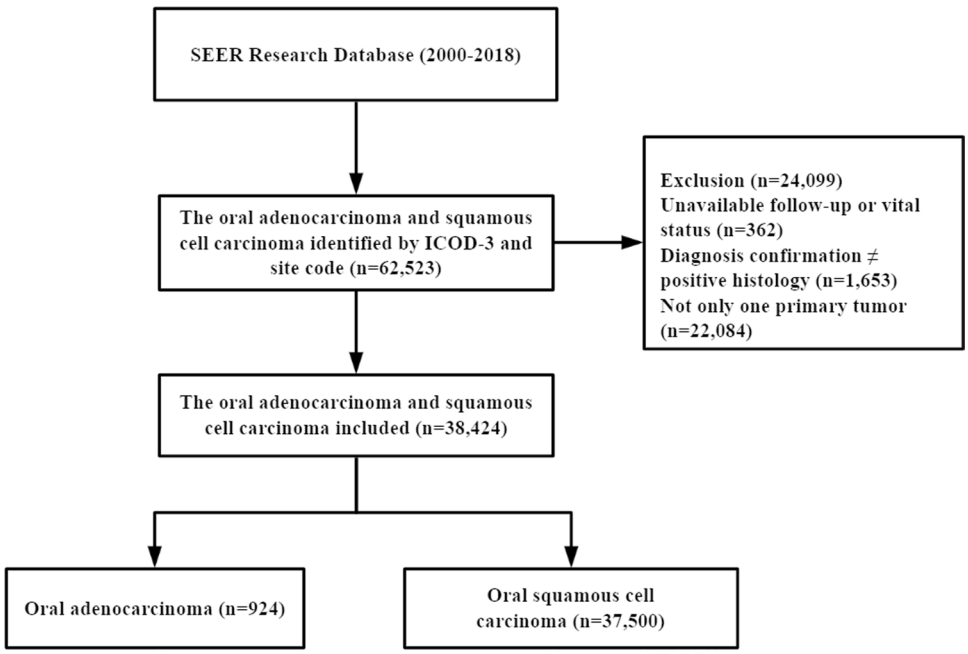

Fig. 1 Flow diagram of patient selection. SRC, signet ring cell carcinoma; non-SRC, non-signet ring cell carcinoma

Table 1 Baseline demographic and clinicopathologic characteristics of patients with OADC Compared to OSCC

	OADC (n = 924)	OSCC (n = 37,500)	*P* value
Age			
≤ 60	476	16,194	< 0.001
> 60	448	21,306	
Sex			
Male	330	23,284	< 0.001
Female	594	14,216	
Race			
White	686	31,632	< 0.001
Black	195	2365	
Other	43	2820	
Primary site			
Lip	107	6921	< 0.001
Oral tongue	39	16,237	
Gum	20	3329	
Floor of mouth	163	5899	
Palate	419	1118	
Cheek mucosa	138	2128	
Other sites	38	1868	
Clinical T-stage			
T1–T2	446	17,738	< 0.001
T3–T4	118	7528	
Unknown	360	12,234	
Clinical N-stage			
N0	576	19,097	< 0.001
N1–3	57	9058	
Unknown	291	9345	
Clinical M-stage			
M0	663	28,821	< 0.001
M1	20	552	
Unknown	241	8127	
AJCC clinical stage			
I + II	403	13,360	< 0.001
III + IV	154	11,833	
Unknown	367	12,307	
Histologic grade			
Well/moderately differentiated	608	26,063	< 0.001
Poorly/undifferentiated	62	5267	
Unknown	254	6170	
Surgery			
Local resection	277	7183	< 0.001
Radical resection	504	22,260	
No surgery	132	7760	
Unknown	11	297	
Radiotherapy			
Yes	166	10,352	< 0.001
No	758	27,148	
Year of diagnosis			
2000–2009	475	17,553	0.006
2010–2018	449	19,947	

T tumor, *N* node, *M* metastasis, *OADC* oral adenocarcinoma, *OSCC* oral squamous cell carcinoma

Survival

Compared with OSCC, patients with OADC exhibited significantly higher 2-, 5- and 10-year OS and DSS (OS: 90.2%, 81.5% and 69.3% vs 66.0%, 52.8% and 40.8%, $P < 0.001$; DSS: 91.6%, 87.1% and 83.6% vs 66.7%, 57.7% and 53.3%, $P < 0.001$) (Fig. 2a, b). Cox proportional regression modeling was used to adjust for known confounders. The results indicated that histological type was an independent prognostic factor for oral cancer, and OADC predicted better OS and DSS compared with OSCC (OS: hazard ratio [HR] = 0.427, 95% confidence interval [CI] = 0.344–0.529; DSS: HR = 0.320, 95% CI = 0.235–0.437) (Table 2).

To identify the prognostic factors of OADC, we conducted the univariate and multivariate analyses in the OADC patients (Table 3). The result of the univariate analysis showed that age, sex, primary site, T-stage, N-stage, M-stage, AJCC Clinical stage, histologic grade, surgery and RT were all associated with OS and DSS. Meanwhile, the multivariate analysis suggested that advanced age, stage, and histologic grade were associated with worse OS and DSS, and surgery was associated with better OS and DSS. As for RT, the multivariate analysis showed an interesting result that RT was associated with worse OS, whereas there was no significant difference in DSS.

The effect of treatment modalities for patients with OADC were further explored. Of the 924 patients with OADC enrolled, 15 patients were excluded due to unknown treatment information. In the remaining 909 patients, 619 (68.1%) received surgery alone, 162 (17.8%) received surgery + RT, and 128 (14.1%) received no treatment. The 10-year OS rates of patients with surgery alone, surgery + RT, and no treatment were 77.3%, 64.3% and 35.3%, respectively. Overall, surgery alone and surgery + RT resulted in significantly longer OS than no treatment ($P < 0.001$ and $P < 0.001$). Meanwhile, the surgery alone group showed significantly better survival than the surgery + RT groups ($P < 0.001$) (Fig. 3).

The effect of treatment modalities was further explored through subgroup analysis with stratification by stage. For patients with stage I–II tumors, both surgery alone and surgery + RT appeared to confer a benefit than no treatment in OS ($P < 0.001$ and $P < 0.001$), and the surgery alone group showed significantly better survival than the surgery + RT groups ($P = 0.036$) (Fig. 4a). For patients with stage III–IV tumors, although both surgery alone and surgery + RT appeared to confer a benefit than no treatment in OS ($P < 0.001$ and $P < 0.001$), no significant difference was found between the two groups ($P = 0.514$) (Fig. 4b).

Next, to determine the effect of RT, subgroup analysis were carried out based on primary sites, lymph node metastasis, and extent of the surgery (Supplementary

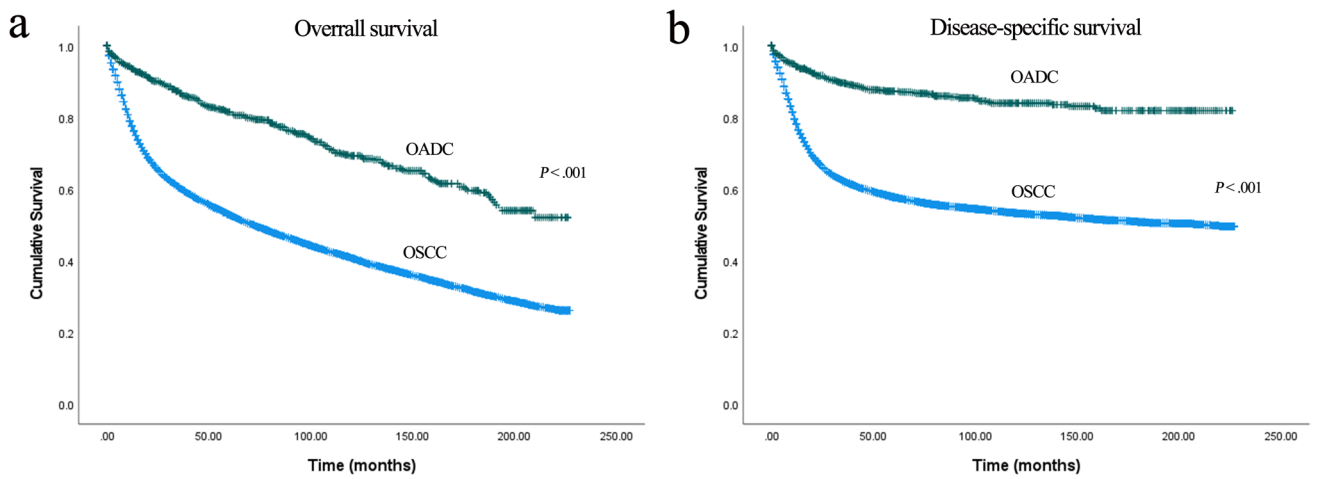

Fig. 2 **a** Overall survival of patients with OADC and OSCC. **b** Disease-specific survival of patients with OADC and OSCC. *OADC* oral adenocarcinoma, *OSCC* oral squamous cell carcinoma

Fig. 1). When divided by primary sites, the results revealed that RT was not able to significantly improve the prognosis regardless of the tumor primary sites (lip, $P=0.896$; tongue, $P=0.729$; mouth, $P=0.724$; palate, $P=0.491$; cheek mucosa, $P=0.130$). Similarly, for patients without lymph node metastases, the survival benefit of RT was not observed. However, for patients with lymph node metastases, the results revealed that RT significantly improved the prognosis. In addition, patients were divided by extent of the surgery, and it was revealed that RT did not improve the prognosis of patients undergoing local resection ($P=0.068$), but was associated with worse OS of patients undergoing radical resection ($P=0.005$).

Discussion

OADC is an extremely rare histological subtypes of oral cancer, resulting in the limited comprehension of the clinicopathological characteristics and prognosis. Previous understanding of OADC is mainly extrapolated from anecdotal case reports, and optimal treatment modalities remains controversial [8, 9]. Therefore, a study of a large population-based cohort from the SEER database is necessary to provide a more comprehensive and in-depth understanding. To our knowledge, this study is the first to investigate the clinicopathologic characteristics, prognosis and treatment modalities specific to OADC based on the SEER database.

According to our study, 924 patients with OADC were identified from the SEER database, representing only 2.4% of all oral cancer patients, similar to prior studies [4–6]. The average age of the patients with OADC patients was 59.4 years, which was significantly lower than that of patients with OSCC (63.6 years). Contrary to the known findings of male predilection for primary OSCC, our study showed that the male–female ratio was 0.56 for OADC, presenting a female predilection. Previous studies have suggested the difference may be due to more men smoking, a risk factor for OSCC [10–12]. In addition, we found that patients with OADC were more significantly associated with younger age, well differentiation, and early AJCC stage than those with OSCC. After adjusting for potential confounding factors, adenocarcinoma was identified as an independent positive prognostic factor. Similar phenomena were observed in pancreatic and esophageal cancers [13, 14], but reversed in cervical and rectal cancers [15, 16]. Thus, perhaps histology is not always a trustworthy prognostic risk factor, and location should also be considered.

Due to the significant characteristics diversity between OADC and OSCC, the prognostic factors specific to OADC were further analyzed. As with most known malignancies, advanced age was also identified as an independent negative prognostic factor for OADC, possibly due to more concomitant medical comorbidities [17, 18]. Meanwhile, we found advanced histologic grade and clinical stage were independent prognostic factors for OS and DSS. Of patients with valid information, majority presented with well/moderately differentiated (88.8%) and stage I–II (78.5%) tumor, which may account for the excellent survival of OADC. However, due to the potential impact of genetic predisposition and

Table 2 Univariate analysis and multivariate analysis for entire cohort

Characteristic	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age								
≤60	Reference	–	Reference	–	Reference	–	Reference	–
>60	2.044 (1.983–2.108)	<0.001	1.885 (1.807–1.965)	<0.001	1.842 (1.775–1.911)	<0.001	1.697 (1.614–1.783)	<0.001
Sex								
Male	Reference	–	–	–	Reference	–	Reference	–
Female	1.019 (0.989–1.049)	0.212	–	–	1.037 (1.000–1.076)	0.049	1.008 (0.960–1.059)	0.743
Race								
White	Reference	–	Reference	–	Reference	–	Reference	–
Black	1.664 (1.582–1.750)	<0.001	1.160 (1.082–1.242)	<0.001	1.900 (1.793–2.014)	<0.001	1.138 (1.052–1.232)	0.001
Other	0.925 (0.872–0.981)	0.009	0.878 (0.815–0.946)	<0.001	0.991 (0.926–1.061)	0.795	0.895 (0.822–0.975)	0.011
Primary site								
Lip	Reference	–	Reference	–	Reference	–	Reference	–
Oral tongue	1.756 (1.677–1.838)	<0.001	1.381 (1.275–1.496)	<0.001	4.838 (4.415–5.303)	<0.001	2.894 (2.491–3.361)	<0.001
Gum	2.382 (2.243–2.530)	<0.001	1.375 (1.249–1.513)	<0.001	6.551 (5.907–7.264)	<0.001	2.895 (2.460–3.408)	<0.001
Floot of mouth	2.737 (2.601–2.879)	<0.001	1.688 (1.546–1.842)	<0.001	7.904 (7.185–8.695)	<0.001	3.384 (2.897–3.954)	<0.001
Palate	2.171 (2.007–2.348)	<0.001	1.438 (1.270–1.628)	<0.001	6.050 (5.364–6.824)	<0.001	2.983 (2.475–3.596)	<0.001
Cheek mucosa	2.439 (2.280–2.610)	<0.001	1.665 (1.499–1.849)	<0.001	6.894 (6.183–7.688)	<0.001	3.546 (2.995–4.199)	<0.001
Other sites	2.814 (2.627–3.014)	<0.001	1.404 (1.261–1.563)	<0.001	8.135 (7.287–9.082)	<0.001	2.811 (2.367–3.338)	<0.001
Clinical T-stage								
T1–2	Reference	–	–	–	Reference	–	–	–
T3–4	3.085 (2.970–3.203)	<0.001	–	–	3.925 (3.751–4.107)	<0.001	–	–
Clinical N-stage								
N0	Reference	–	–	–	Reference	–	–	–
N1–3	2.948 (2.845–3.055)	<0.001	–	–	4.130 (3.953–4.316)	<0.001	–	–
Clinical M-stage								
M0	Reference	–	–	–	Reference	–	–	–
M1	5.180 (4.732–5.671)	<0.001	–	–	6.035 (5.481–6.644)	<0.001	–	–
AJCC clinical stage								
I+II	Reference	–	Reference	–	Reference	–	Reference	–
III+IV	3.267 (3.144–3.396)	<0.001	2.461 (2.340–2.589)	<0.001	5.110 (4.851–5.382)	<0.001	3.184 (2.982–3.399)	<0.001
Differentiated grade								
Well/moderately differentiated	Reference	–	Reference	–	Reference	–	Reference	–
Poorly/undifferentiated	1.669 (1.608–1.734)	<0.001	1.277 (1.218–1.338)	<0.001	1.893 (1.811–1.979)	<0.001	1.333 (1.263–1.408)	<0.001

Table 2 (continued)

Characteristic	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Surgery								
No	Reference	–	Reference	–	Reference	–	Reference	–
Yes	0.295 (0.286–0.304)	< 0.001	0.350 (0.331–0.370)	< 0.001	0.234 (0.226–0.243)	< 0.001	0.302 (0.282–0.323)	< 0.001
Radiation								
No	Reference	–	Reference		Reference	–	Reference	–
Yes	1.236 (1.198–1.276)	< 0.001	0.959 (0.911–1.010)	0.112	1.397 (1.346–1.450)	< 0.001	1.043 (0.979–1.111)	0.189
Histology								
OSCC	Reference	–	Reference	–	Reference	–	Reference	–
OADC	0.387 (0.340–0.439)	< 0.001	0.427 (0.344–0.529)	< 0.001	0.267 (0.220–0.325)	< 0.001	0.320 (0.235–0.437)	< 0.001
Year of diagnosis								
2000–2009	Reference	–	Reference	–	Reference	–	Reference	–
2010–2018	0.783 (0.759–0.807)	< 0.001	0.816 (0.783–0.850)	< 0.001	0.619 (0.597–0.642)	< 0.001	0.696 (0.663–0.731)	< 0.001

OADC, oral adenocarcinoma; OSCC, oral squamous cell carcinoma; T, tumor size; M, metastasis; N, node; HR, hazard ratio; CI, confidence interval;

environmental factors, patients with a history of cancer have an increased risk for developing metachronous carcinomas, which will seriously affect the long-term survival of patients [19, 20]. Therefore, when oral cancer is diagnosed, careful screening should be carried out for the possibility of hereditary nonpolyposis colorectal cancer, which can be manifested as oral cancer with multiple malignancies [21].

Total tumor excision is the mainstay of treatment for oral cancer at present, and RT is typically used for patients who cannot tolerate surgery or who have advanced tumors [22, 23]. However, no standardized protocol and guideline for the treatment of OADC are available at present because of the limited number of cases. In our analysis, we found that surgery was associated with improved OS and DSS, whereas the association with RT was not significant. Meanwhile, although both surgery alone and surgery + RT had all significantly improved survival, the long-term survival of patients treated with surgery alone were obviously better than patients treated with surgery + RT, perhaps due to long-term adverse effects of RT. This has previously been reported that lymph node metastasis is the key factors affecting whether adjuvant RT is necessary [24]. Therefore, subgroup analysis was carried out to further determine the effect of RT on survival in various subgroups of patients with OADC. Interestingly, we found that RT can significantly improve the survival of patients with lymph node metastasis, and similar phenomena can also be observed in patients with OSCC [25]. Another essential factor is, undoubtedly, the condition of the surgical margins [26]. For patients with positive margins, the preferred recommendation is re-resection. When re-resection is not feasible, patients with oral cancer may potentially benefit from adjuvant RT [27]. However, due to the relatively small sample size of advanced patients, the role of RT remains to be further established in the future. Nonetheless, there is no doubt that surgery is clearly the preferred treatment for well-tolerated patients.

The present study represents the first and largest study on OADC to date, but several limitations remain. First, selection bias could not be avoided considering the retrospective nature of the study. Second, detailed information regarding some important treatment information was not available in the SEER database, such as the chemotherapy and biotherapy. Third, as important prognostic factors for patients in the real-world, detailed information of multiple simultaneous/metachronous carcinomas is not available from the SEER database. Moreover, certain variables which may affect

Table 3 Univariate analysis and multivariate analysis for oral adenocarcinoma

Characteristic	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age								
≤60	Reference	–	–	–	Reference	–	–	–
>60	4.450 (3.312–5.980)	<0.001	4.624 (2.741–7.801)	<0.001	3.299 (2.182–4.988)	<0.001	2.124 (1.032–4.372)	0.041
Sex								
Male	Reference	–	–	–	Reference	–	–	–
Female	0.705 (0.546–0.910)	0.007	0.801 (0.508–1.264)	0.341	0.551 (0.373–0.812)	0.003	0.680 (0.331–1.399)	0.295
Race								
White	Reference	–	–	–	Reference	–	–	–
Black	1.163 (0.861–1.572)	0.325	–	–	1.042 (0.649–1.674)	0.865	–	–
Other	0.931 (0.506–1.712)	0.818	–	–	0.602 (0.190–1.906)	0.388	–	–
Primary site								
Lip	Reference	–	–	–	Reference	–	–	–
Oral tongue	5.253 (2.812–9.813)	<0.001	1.821 (0.615–5.392)	0.279	10.216 (3.874–26.942)	<0.001	0.225 (0.036–1.401)	0.110
Gum	4.035 (10,896–8.589)	<0.001	0.891 (0.224–3.538)	0.870	9.895 (3.515–27.856)	<0.001	0.361 (0.056–2.318)	0.283
Floor of mouth	2.232 (1.348–3.697)	0.002	1.000 (0.416–2.408)	0.999	4.627 (1.952–10.969)	<0.001	0.458 (0.115–1.818)	0.267
Palate	1.397 (0.872–2.237)	0.164	0.679 (0.312–1.478)	0.329	1.271 (0.524–3.078)	0.596	0.301 (0.077–1.171)	0.083
Cheek mucosa	1.018 (0.580–1.785)	0.951	0.476 (0.161–1.405)	0.179	0.774 (0.250–2.400)	0.657	0.277 (0.053–1.457)	0.130
Other sites	1.029 (0.471–2.247)	0.943	0.212 (0.054–0.836)	0.027	1.720 (0.485–6.098)	0.401	0.159 (0.023–1.090)	0.061
Clinical T-stage								
T1–2	Reference	–	–	–	Reference	–	–	–
T3–4	3.830 (2.625–5.587)	<0.001	–	–	9.481 (5.310–16.929)	<0.001	–	–
Clinical N-stage								
N0	Reference	–	–	–	Reference	–	–	–
N1/N2	6.002 (4.017–8.968)	<0.001	–	–	12.749 (7.523–21.606)	<0.001	–	–
Clinical M-stage								
M0	Reference	–	–	–	Reference	–	–	–
M1	9.772 (5.734–16.661)	<0.001	–	–	16.753 (8.999–31.188)	<0.001	–	–
AJCC clinical stage								
I + II	Reference	–	Reference	–	Reference	–	Reference	–
III + IV	4.547 (3.159–6.545)	<0.001	3.254 (2.019–5.245)	<0.001	16.647 (8.366–33.125)	<0.001	12.812 (5.108–32.136)	<0.001
Differentiated grade								
Well/moderately differentiated	Reference	–	Reference	–	Reference	–	Reference	–
Poorly/undifferentiated	3.883 (2.674–5.640)	<0.001	2.217 (1.256–3.916)	0.006	8.750 (5.368–14.263)	<0.001	2.289 (1.052–4.984)	0.037

Table 3 (continued)

Characteristic	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Surgery								
No	Reference	–	Reference	–	Reference	–	Reference	–
Yes	0.217 (0.165–0.287)	< 0.001	0.134 (0.069–0.258)	< 0.001	0.092 (0.062–0.136)	< 0.001	0.117 (0.047–0.292)	< 0.001
Radiation								
No	Reference	–	Reference	–	Reference	–	Reference	–
Yes	1.238 (0.903–1.699)	0.185	5.961 (2.142–16.591)	< 0.001	1.888 (1.238–2.880)	0.003	0.810 (0.0.346–1.898)	0.628
Year of diagnosis								
1998–2009	Reference	–	Reference	–	Reference	–	Reference	–
2010–2016	0.808 (0.589–1.109)	0.186	0.528 (0.327–0.851)	0.009	0.677 (0.443–1.034)	0.071	0.584 (0.292–1.167)	0.128

T, tumor size; M, metastasis; N, node; HR, hazard ratio; CI, confidence interval;

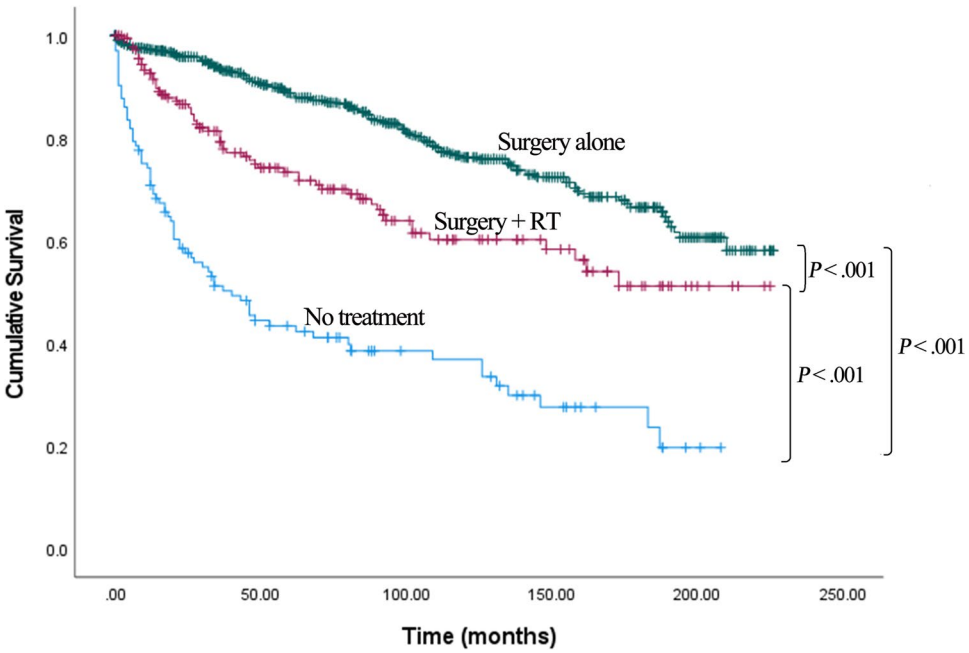

Fig. 3 Effect of treatment modalities on overall survival. RT = radiotherapy;

survival, including the surgical margins, comorbidities, perineural invasion, and immunohistochemical evaluation of p16 were also not accessible. Finally, since no patient received RT alone, the efficacy was not investigated. Despite these limitations, the findings of this study can still increase awareness with regard to this rare tumor, and provide clinical decisions for clinicians.

Conclusion

Our study demonstrated that OADC has a significantly better prognosis than OSCC, with better differentiation, and more early stage. For patients with OADC, advanced age, stage, and histologic grade were associated with worse OS and

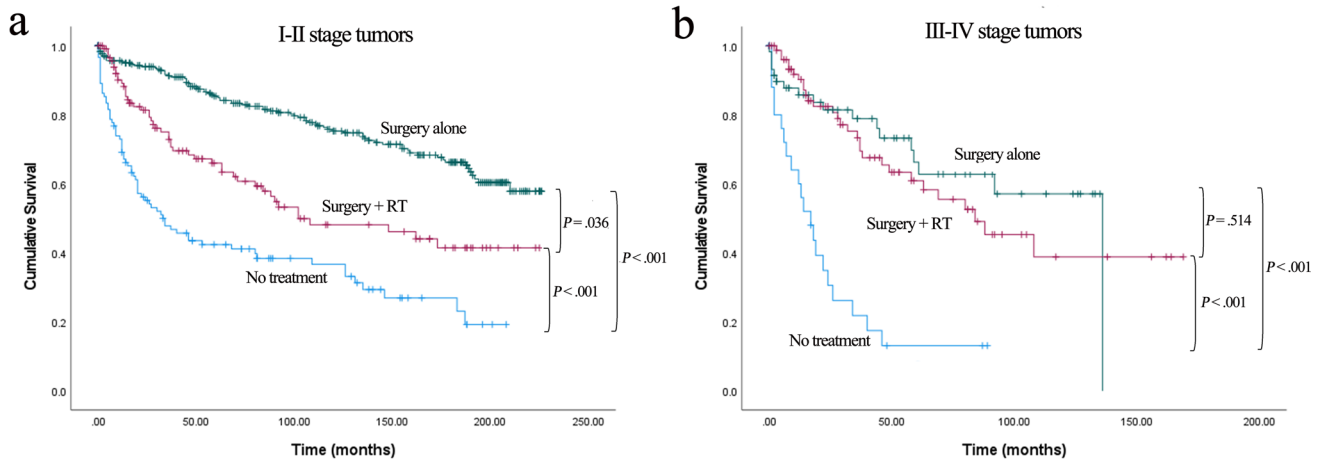

Fig. 4 **a** Effect of therapeutic modalities on overall survival for stage I–II tumors. **b** Effect of therapeutic modalities on overall survival for stage III–IV tumors. *RT* radiotherapy

DSS. Surgery was the preferred treatment, for patients with lymph node metastasis, RT may afford a survival benefit.

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Declarations

Conflict of interest All authors have declared no conflict of interest.

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