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Original Article

Survival and risk factors of adenosquamous carcinoma in the oral and maxillofacial region: a population-based study

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Abstract: Background: The features and prognosis of adenosquamous carcinoma (ASC) in oral and maxillofacial region have not thoroughly investigated, the purpose of this study is to describe clinicopathologic characteristics, treatment, and prognostic factors of this disease. Methods: The data of 276 patients diagnosed with ASC in oral and maxillofacial region between 1975 and 2016 were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The prognostic factors influencing overall survival (OS) and disease-specific survival (DSS) were identified by the Kaplan-Meier analysis and Cox regression analysis. The nomograms for OS and DSS were constructed to predict the prognosis of these patients. Results: Of 276 included patients, 62.7% were male and 37.3% were female, with an average age at diagnosis of 63.5 years. The most common primary site is oral cavity (170/276), followed by salivary gland (106/276). The 3-, and 5-year OS of patients with ASC in oral and maxillofacial region were 49.0% and 38.9%, while the 3-, and 5-year DSS were 67.7%, and 60.4%, respectively. Patients who underwent surgery had longer OS (mOS: 58 m vs. 8 m) and DSS (mDSS: 193 m vs. 18 m) than those who did not. Age, AJCC-T/N/M category as well as surgery were independently associated with OS. Advanced T stage, distant metastases, and surgery were independent factors for DSS. The prognostic nomograms for OS and DSS were constructed, and the C-indexes were 0.71 (95% CI 0.66-0.76) and 0.76 (95% CI 0.67-0.85), respectively. Conclusion: Surgery was the favorable prognostic factor for both OS and DSS among patients with ASC in oral and maxillofacial region.

Keywords: Adenosquamous carcinoma, oral and maxillofacial region, SEER database, survival, nomogram

Introduction

Adenosquamous carcinoma (ASC) has been classified as a distinct entity due to its aggressive nature, poor prognosis, and the specific morphological features [1]. ASC patients often had poor prognosis, which is related with aggressive behavior, local invasiveness, and distant metastasis early in the disease course, and high recurrence rates after treatment [2]. Due to its aggressive nature, the optimal treatment is surgery, but it remains questionable whether radiotherapy or chemotherapy could improve the survival [3, 4].

ASC in oral and maxillofacial region is a rare and aggressive malignant epithelial malignancy, and previous studies on the clinicopathological characteristics and prognosis of this disease were typically based on case reports or single-center case series [5-9], which limited the reliability or accuracy of our knowledge on ASC in oral and maxillofacial region. In 2017, Lee et al. conducted a population-based study using the data of 235 patients with ASC in head and neck region from SEER database, which was the largest study to date to determine the correlates of survival for this disease [10]. However, no larger investigation has focused on ASC in oral and maxillofacial region until now. In an effort to comprehensively summarize the clinicopathological characteristics and prognosis of patients with ASC in oral and maxillofacial region in a large cohort, a descriptive, retrospective, and comprehensive analysis was carried out using the data from the SEER database between 1975 and 2016. The purpose of this study included: 1) describe the demographics

and clinicopathological characteristics of all patients diagnosed with ASC in oral and maxillofacial region, 2) estimate the influence of each characteristics on the survival, and 3) establish the prognostic nomogram to predict the survival of patients with ASC in oral and maxillofacial region.

Materials and methods

Patients

The database "SEER 18 Regs Custom Data with additional treatment fields, Nov 2018 Sub (1975-2016)" were used to searched for all patients diagnosed with ASC in oral and maxillofacial region. Inclusion criteria were as follows: pathological diagnosis was ASC using ICD-0-3 (topography codes of "8560:3"), diagnosis year were from 1975 to 2016, primary site was limited to the oral and maxillofacial region. SEER*STAT 8.3.6 was used to isolate the information of all patients, including race, sex, age at diagnosis, primary tumor site, tumor differentiation grade, SEER historic stage, the 7th AJCC-TNM stage, T/N/M category, the use of surgery, radiation and chemotherapy, and survival status. The primary tumor sites included tongue, gum, tonsil, salivary gland, gingiva, the floor of month, palate, etc. The survival was defined as the interval from initial diagnosis to the last follow-up or to death due to all causes (overall survival, OS), or to death caused by this disease (disease-specific survival, DSS).

Statistical analyses

The demographics and clinicopathological characteristics of patients diagnosed with ASC in oral and maxillofacial region were present as means ± standard deviations for continuous data, and counts with percentages for categorical data, respectively. The effect of each characteristic on OS or DSS were assessed using Kaplan-Meier curve and log-rank test. The factors associated with OS or DSS were analyzed using univariate COX proportional hazards regression analysis, while multivariate COX proportional hazards regression analysis was used to identify independent prognostic factors after including factors significantly associated with OS or DSS in univariate Cox analysis. All survival analyses were carried out using MedCalc software (Mariakerke, Belgium), and the prognostic nomogram was established using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) with R packages "foreign", "rms", "Hmisc", "lattice", "survival", "formula", and "ggplot2". Harrell's concordance index (C-index) was used to assessed the discrimination of established prognostic nomograms. A two-tailed *P* value less than 0.05 was regarded as statistically significant.

Results

Demographics and clinicopathological characteristics

In total, 276 patients diagnosed with ASC in oral and maxillofacial region were identified between 1975 and 2016 from SEER database (**Table 1**). The average age was 63.5 years (13 to 91 years) for the entire cohort, and the incidence of this disease peaked at age of 50 to 80. The white population accounted for 84.0% (231/276) of the entire cohort. 173 of the cases were men, and 103 were women. The oral cavity (170/276) was the most affected primary site including the tongue (59/170), gum (50/170), and tonsil (33/170), followed by the salivary gland (106/276) including parotid gland (91/106), submandibular gland (10/106), major salivary gland (5/106).

Regarding pathological grade, 201 cases have definite pathological information. Most cases were grade III/IV (poorly differentiated/undifferanted: 145/201). The percentages of patients with lymph node metastasis and distant metastasis were 49.6% (62/125) and 7.9% (20/126), respectively. TNM information was available for 111 patients, and most patients were diagnosed with TNM stage IV (63/111). A total of 259 patients had information on SEER historic stage, with 88 cases categorized into regional stage, 118 with localized stage, and 53 with distant stage.

Survival analysis

In entire cohort, the median OS and DSS were 34 months (95%CI 24-47) and 179 months (95% CI 80-193). The 1-, 3-, and 5-year OS rates were 70.2%, 49.0% and 38.9%, while the 1-, 3-, 5-year DSS rates were 81.4%, 67.7% and 60.4% (**Figure 1A**, **1B**). The survival was significantly associated with tumor stage that OS and DSS became shorter as tumor stage (AJCC TNM stage or SEER historic stage) (**Figure 2**).

Table 1. Clinicopathological characteristics

Characteristics	Total (N, %)
Age (Year)	63.5±14.3
<40	13 (4.7%)
40-49	23 (8.3%)
50-59	62 (22.5%)
60-69	78 (28.3%)
70-79	65 (23.6%)
>=80	35 (12.6%)
Gender	
Female	103 (37.3%)
Male	173 (62.7%)
Ethnicity	
White	231 (84.0%)
Black	30 (10.9%)
Other (American Indian/AK Native, Asian/Pacific Islander)	14 (5.1%)
Unknown	1
Pathological Differentiation	
Well/Moderately	56 (27.9%)
Poorly/Undifferentiated	145 (72.1%)
Unknown	75
SEER historic stage classification	
Localized	88 (34.0%)
Regional	118 (45.6%)
Distant	53 (20.4%)
Unstaged	17
Primary Site	
Oral Cavity	170 (61.6%)
Salivary Gland	106 (38.4%)
Tumor Size	
T1	28 (26.2%)
T2	32 (29.9%)
T3	19 (17.8%)
T4	29 (27.1%)
Unknown	168
Lymph Node Metastases	
N0	63 (50.4%)
N1	21 (16.8%)
N2	41 (32.8%)
Unknown	151
Distant Metastases	
M0	116 (92.1%)
M1	10 (7.9%)
Unknown	150
TNM stage	
I	18 (16.2%)
II	16 (14.4%)
III	14 (12.6%)
IV	63 (56.8%)
Unknown	165

The Kaplan-Meier curve and log-rank test showed that age, T/N/M category were significantly correlated with OS (**Figure 3**, P<0.01 for all), whereas gender (P=0.39), race (P=0.58), tumor differentiation grade (P=0.83), and primary site (P=0.86) were not significantly associated with OS. Similarly, T/M category were significantly correlated with DSS (**Figure 3**, P<0.01 for both), whereas age (P=0.72), gender (P=0.27), race (P=0.87), primary site (P=0.92), N category (P=0.24), as well as tumor differentiation grade (P=0.72) were not significantly associated with DSS.

Treatment

Surgical resection was the primary treatment modality among all patients with ASC in oral and maxillofacial region in the entire cohort. Surgery was performed in 206 (75.7%) patients (**Table 1**), and 119 patients received surgery plus radiotherapy. A total of 62 patients underwent chemotherapy. Patients who underwent surgery had much longer OS (mOS: 58 m vs. 8 m) and DSS (mDSS: 193 m vs. 18 m) than those who did not (**Figure 4A**, **4D**).No significant differences in OS and DSS regarding radiotherapy (P=0.16, P=0.67, respectively). Patients receiving chemotherapy had shorter mDSS (P=0.03), but not mOS (P=0.43) than who did not. In addition, patients receiving surgery plus radiotherapy did not have significantly longer OS (P= 0.27, **Figure 4B**) or DSS (P= 0.23, **Figure 4E**) than those undergoing surgery alone.

Surgery	
Yes	206 (75.7%)
No	66 (24.3%)
Unknown	4
Radiotherapy	
Yes	160 (58.0%)
No	116 (42.0%)
Chemotherapy	
Yes	62 (22.5%)
No	214 (77.5%)

Similarly, patients receiving the combination of surgery with chemotherapy also did not have significantly longer OS (P=0.15, **Figure 4C**) or DSS (P=0.10, **Figure 4F**), when compared with those who underwent surgery alone.

Cox regression analysis

The prognostic indicators for OS and DSS were identified using the Cox regression analysis (**Tables 2**, **3**). Age, SEER historic stage, TNM stage, T/N/M category, as well as surgery were significantly correlated with OS in univariate Cox analysis. Multivariate Cox regression analysis demonstrated that older age, advanced T stage, metastases (lymph node and distant), as well as the use of surgery were independent prognostic factors for OS (**Table 2**).

As for DSS, the univariate Cox regression analysis revealed that SEER historic stage, TNM stage, T/M category, surgery and chemotherapy were significantly correlated with DSS (**Table 3**). Advanced T stage, distant metastases, and the use of surgery were identified as independent prognostic factors in multivariate Cox analysis.

Establishment of the prognostic nomograms

The prognostic nomograms were established using the independent prognostic factors from multivariate Cox regression analysis, further to predict the OS and DSS of patients with ASC in oral and maxillofacial region. The nomogram for OS demonstrated that T stage and M stage contributed the most, followed by age and the use of surgery. The concordance index for OS prediction was 0.71 (95% CI 0.66-0.76) (**Figure 5A**). The nomogram for DSS showed that T stage contributed the most, followed by the M category. The concordance index for DSS prediction was 0.76 (95% CI 0.67-0.85) (**Figure 5B**).

Discussion

Due to the low incidence of ASC in oral and maxillofacial region, the knowledge concerning this disease was mainly from previous case reports or single-institution case series, which are less comprehensive. The present population-based study included the largest sample regarding ASC in oral and maxillofacial region based on the SEER database. First, we described the clinicopathological characteristics of ASC in oral and maxillofacial region and determine the characteristics influencing patients' survival, including OS and DSS. We also established the prognostic nomogram models to predict OS and DSS. This study is particularly significant for the clinical management and future research of this rare carcinoma.

Due to its rarity, there were still no adequate data describing the clinicopathological characteristics of patients with ASC in oral and maxillofacial region. In current investigation, the sex incidence distribution showed a higher number of men than women, with a ratio of 1.98:1. This disease can develop at any age, but the average age was 63 years, and the incidence peaked between the ages of 50 to 80. Although there have been no enough investigations reported on this disease, several studies have reported the clinicopathological characteristic and survival of patients with ASC in head and neck region. However, most previous research was based on single-center experiences, and due to small sample sizes, these studies were often not sufficiently powered to evaluate the influence of demographic parameters on survival [10-13]. In the current study, the survival analysis among 276 patients with ASC in oral and maxillofacial region revealed that significant differences in OS could be related to age. Age was also the independent prognosis indicator for OS with patients under the mean age of 63 years having more favorable OS than those over 63 years old. In addition, sex and race had no influence on OS or DSS among these patients.

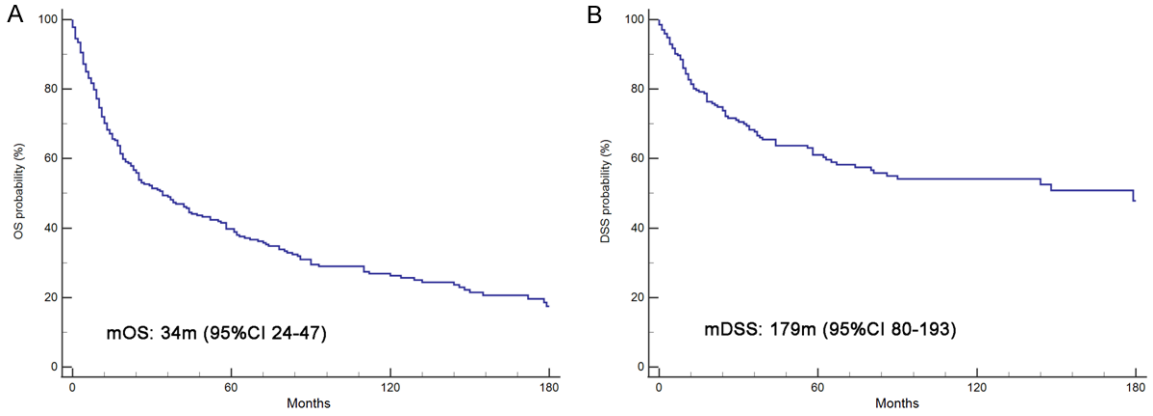

Figure 1. Kaplan-Meier estimate for OS (A) and DSS (B) in the entire cohort (n=276).

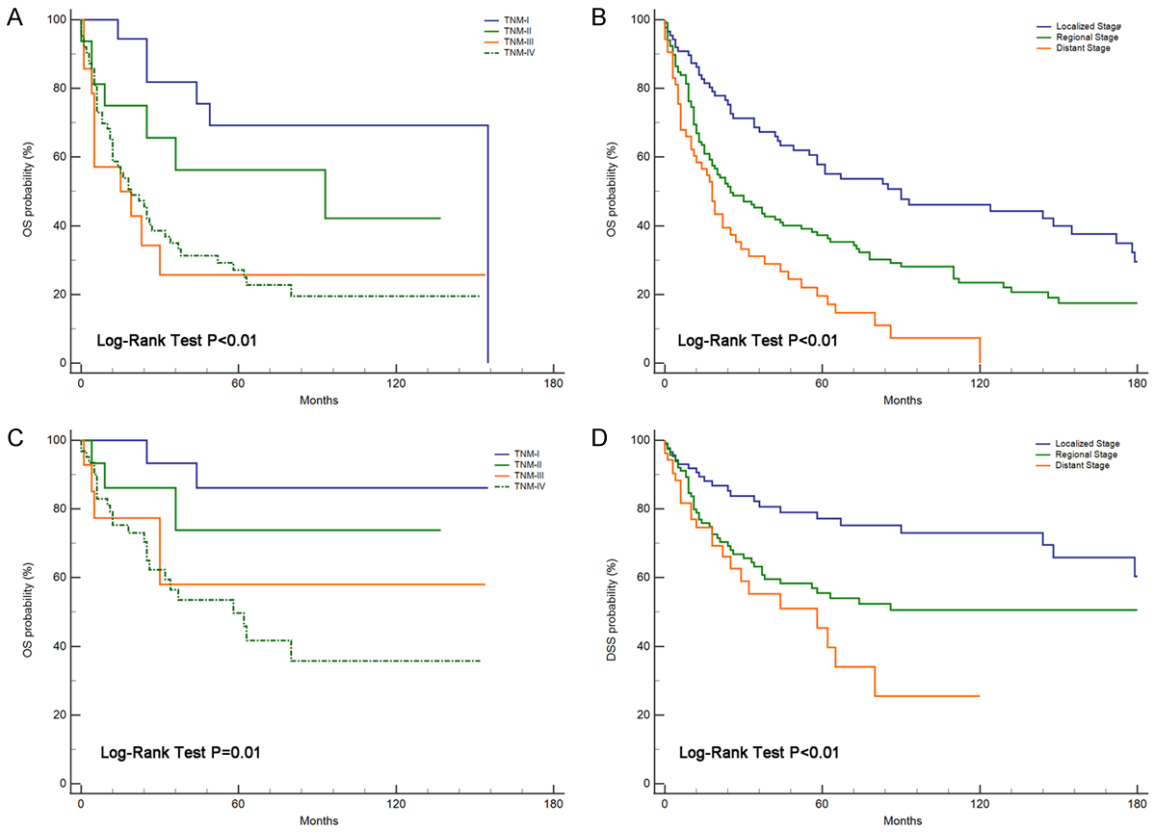

Figure 2. OS and DSS for patients with ASC in oral and maxillofacial region stratified by tumor stage. (A) OS stratified by AJCC-TNM stage, (B) OS stratified by SEER historic stage, (C) DSS stratified by AJCC-TNM stage, (D) OS stratified by SEER historic stage.

Previous studies reported the squamous cell carcinoma of ASC displayed higher proliferative ability including local invasiveness and distant metastasis [2]. Thus, ASC showed a more aggressive disease course than adenocarcinoma. Squamous carcinoma is the main pathological type of oral and maxillofacial region. An epidemiological analysis including 33,065 patients with oral squamous carcinoma revealed that almost half (49.4%) of these patients could survival 5 years [14]. Compared with oral squamous carcinoma, the survival is worse among

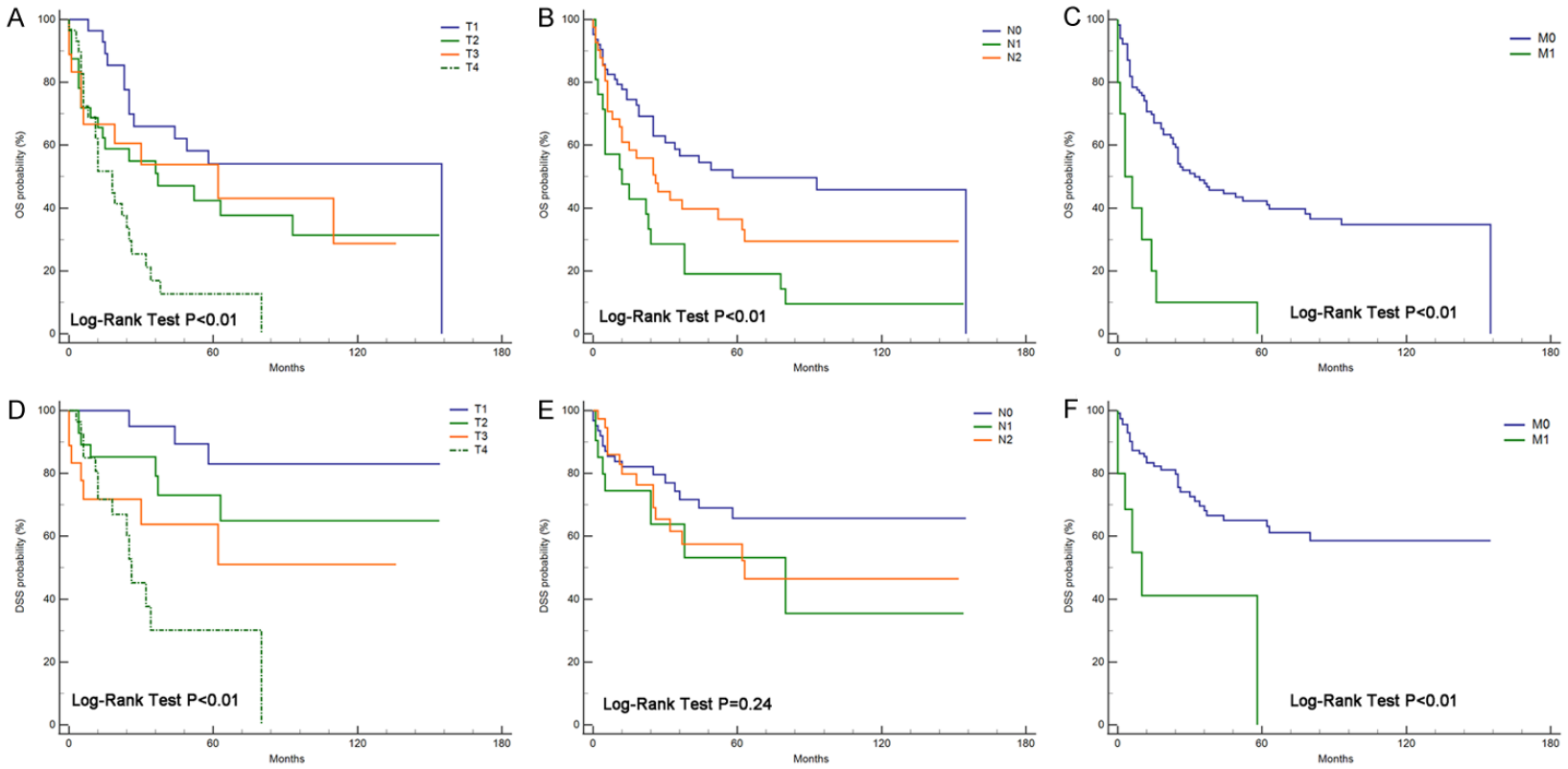

Figure 3. OS and DSS for patients with ASC in oral and maxillofacial region stratified by T/N/M category. A. OS and T stage; B. OS and N stage; C. OS and M stage; D. DSS and T stage; E. DSS and N stage; F. DSS and M stage.

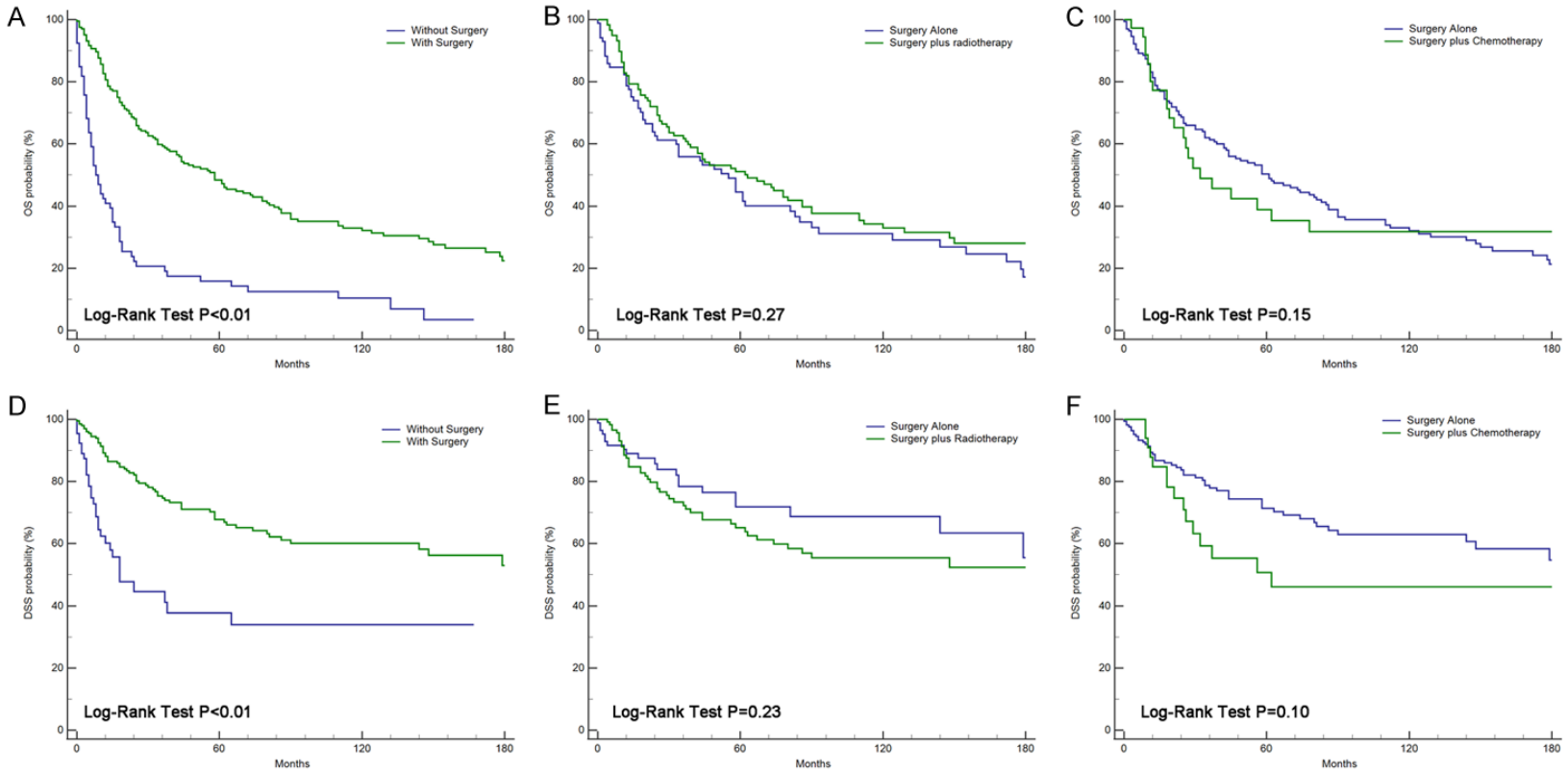

Figure 4. The association of different treatment regimens with survival of patients with ASC in oral and maxillofacial region. A. Surgery and OS; B. Combination of surgery with radiotherapy and OS; C. Combination of surgery with chemotherapy and OS; D. Surgery and DSS; E. Combination of surgery with radiotherapy and DSS; F. Combination of surgery with chemotherapy and DSS.

Table 2. Univariate and multivariate Cox proportional hazard analyses of the characteristics for OS

Factor	Category	Univariate		Multivariate	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age*	<64	Reference		Reference	
	>=64	1.66 (1.24-2.21)	<0.01	1.77 (1.32-2.37)	<0.01
Gender	Female	Reference			
	Male	1.13 (0.85-1.51)	0.39		
Race	White	Reference			
	Black	1.31 (0.86-1.98)	0.21		
	Other	0.87 (0.45-1.71)	0.69		
Pathological Differentiation	Well + Moderately	Reference			
	Poorly + Undifferentiated	1.01(0.70-1.44)	0.97		
Primary Site	Oral Cavity	Reference			
	Salivary Gland	0.97 (0.73-1.29)	0.83		
SEER historic stage classification	Localized	Reference			
	Regional	1.86 (1.31-2.64)	<0.01		
	Distant	3.13 (2.07-4.75)	<0.01		
TNM	I	Reference			
	II	1.96 (0.66-5.84)	0.23		
	III	4.32 (1.57-11.9)	<0.01		
	IV	4.09 (1.75-9.60)	<0.01		
Tumor	T1+T2/ T3+T4	Reference			
		2.07 (1.28-3.36)	<0.01	1.89 (1.14-3.13)	0.01
Lymph Node Metastases	Yes/N0	1.97 (1.25-3.13)	<0.01	1.83 (1.14-2.94)	0.01
Distant Metastases	Yes/N0	4.59 (2.34-8.97)	<0.001	4.37 (2.02-9.48)	<0.01
Surgery	Yes/No	0.34 (0.25-0.46)	<0.001	0.38 (0.27-0.52)	<0.01
Radiotherapy	Yes/No	0.82 (0.62-1.08)	0.16		
Chemotherapy	Yes/No	1.14 (0.82-1.59)	0.44		

*The average age at diagnosis of 276 included patients was 63.5 years, 64-year-old was set as a cut-off point.

patients with ASC in oral and maxillofacial region. Overall, the 5-year OS rates were only 38.9% in the present cohort. As for other pathological type, previous studies using the data from the National Cancer Database reported 2-year survival rates of small cell carcinoma in oral cavity was only 44.5% [15], which is less than patients with ASC in the present cohort (55.9%). Likewise, several studies based on SEER database also demonstrated that small cell carcinoma and neuroendocrine carcinoma in the head and neck region had worse prognosis, with the 5-year survival rate of 27%, 26.2%, respectively [16, 17]. Conversely, acinic cell carcinoma had in oral and maxillofacial region has a favorable prognosis. Patel NR, et al. reported the 5-, 10-year survival rate of 97.2%, 93.8%, respectively [18]. Due to the nature of these retrospective studies, the difference in prognosis between ASC and other pathological type in oral and maxillofacial region requires to be investigated in the future.

Previous studies revealed that pathological grade was used as an important prognostic reference for tumors in the head and neck region [19-22]. Our study did not indicate a significant association between pathological differentiation and survival, although 75 patients were missing pathological information. As for the primary site, the most affected site was the oral cavity, followed by salivary gland. Survival analysis stratified by primary site showed no significant association related to anatomic location. This finding demonstrates the patients with ASC in oral and maxillofacial region may have similar prognosis. AJCC-TNM staging plays an essential role in tumor treatment planning and prognosis evaluation. Among 108 patients with information on T stage, 48 had an advanced T stage (T3/T4). ASC located in oral and maxillofacial region exhibited a propensity for metastases, with 62/125 and 10/126 patients with lymph node metastases and distant metastases, respectively. Consequently, more than half

Table 3. Univariate and multivariate Cox proportional hazard analyses of the characteristics for DSS

Factor	Category	Univariate		Multivariate	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age*	<64	Reference			
	>=64	1.08 (0.72-1.61)	0.72		
Gender	Female	Reference			
	Male	1.27 (0.83-1.93)	0.27		
Race	White	Reference			
	Black	1.27 (0.69-2.32)	0.45		
	Other	1.19 (0.52-2.74)	0.18		
Pathological Differentiation	Well + Moderately	Reference			
	Poorly + Undifferentiated	0.89 (0.53-1.49)	0.65		
Primary Site	Oral Cavity	Reference			
	Salivary Gland	0.98 (0.65-1.47)	0.92		
SEER historic stage classification	Localized	Reference			
	Regional	2.08 (1.25-3.47)	<0.01		
	Distant	3.13 (1.72-5.70)	<0.01		
TNM	I	Reference			
	II	2.45 (0.41-14.7)	0.33		
	III	5.02 (0.92-27.4)	0.06		
	IV	6.38 (1.51-26.9)	0.01		
Tumor	T1+T2/T3+T4	3.80 (1.78-8.08)	<0.01	4.15 (1.92-8.98)	<0.01
Lymph Node Metastases	Yes/N0	1.70 (0.91-3.18)	0.09		
Distant Metastases	Yes/N0	5.04 (2.10-12.1)	<0.01	4.19 (1.60-10.9)	<0.01
Surgery	Yes/No	0.36 (0.22-0.52)	<0.01	0.40 (0.25-0.64)	<0.01
Radiotherapy	Yes/No	1.08 (0.72-1.64)	0.65		
Chemotherapy	Yes/No	1.61 (1.04-2.49)	0.03	1.17 (0.74-1.87)	0.50

*The average age at diagnosis of 276 included patients was 63.5 years, 64-year-old was set as a cut-off point.

of patients (63/111) were diagnosed with AJCC-IV stage. The AJCC-TNM stage could predict the DSS and OS of these patients. Based on the prognostic nomogram for DSS or OS, both T stage and M stage contributed the most to survival. Similar to the AJCC-TNM stage, the SEER historic stage was used in the SEER database, which could also reflect the prognosis of cancer patients. In the present study, 259 patients had information on the SEER historic stage, which was much more than those with information on AJCC-TNM staging. Most patients presented with regional disease (118/259) or distant metastases (53/259) at diagnosis based on the SEER historic stage classification. Survival analysis showed that both OS and DSS shortened as tumor stage (TNM stage and SEER historic stage) increased. Thus, early examination and diagnosis are vital in improving the survival to decrease the development to an advanced tumor stage.

Several previous studies have demonstrated that surgery is the superior method for oral/maxillofacial cancer patients with a significant advantage of survival [23, 24]. As for patients with ASC in oral and maxillofacial region, surgery was also the primary treatment modality, almost 75.7% patients underwent surgery. Surgery significantly prolonged OS (mOS: 58 m vs. 8 m) and DSS (mDSS: 193 m vs. 18 m) based on the analysis of 279 patients in the present cohort. Survival analysis demonstrated that surgery was an independent favorable prognostic factor. Surgery could lower the risk of death by 62% for all causes and 60% of risk of death for ASC. Thus, surgery is also the recommended optimal treatment strategy. Radiotherapy and chemotherapy are alternative regimens for patients who cannot tolerate surgery, or serve as adjuvant treatments for patients undergoing surgery to decrease the recurrence risk [25]. In particular, radiotherapy is often used in the head and neck cancer [26-28]. In the present cohort, radiotherapy was administered to 160 (58.0%) patients. Radiotherapy, especially postoperative radiotherapy, can prolong survival, including DSS or

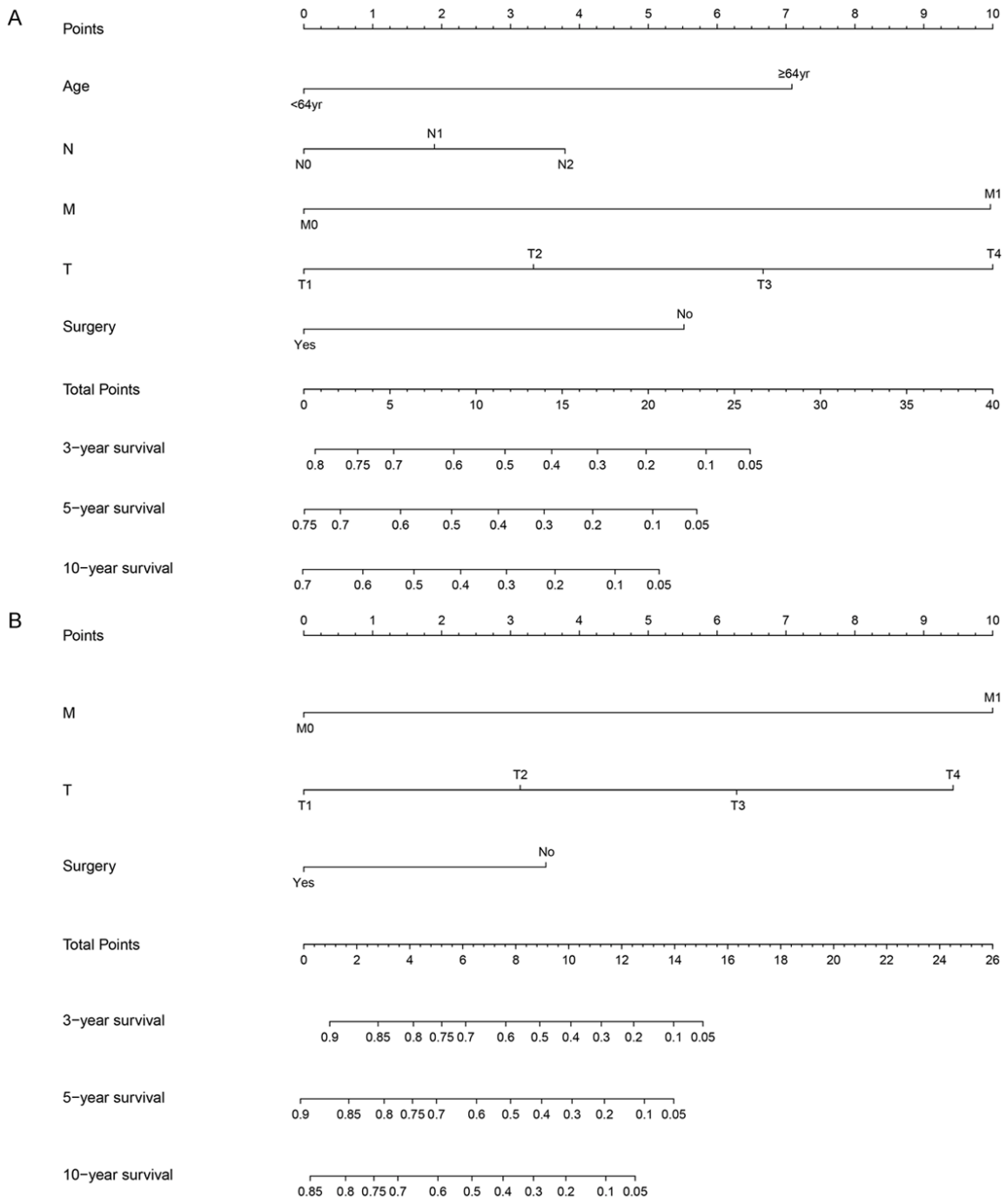

Figure 5. Established prognostic nomogram for predicting 3-, 5-, and 10-year survival (A: OS, B: DSS) among patients with ASC in oral and maxillofacial region.

OS, in several tumor types in the oral and maxillofacial region [29, 30]. However, no significant differences in survival could be observed among patients with ASC in oral and maxillofacial region who received radiotherapy or not. Postoperative radiotherapy also could not prolong DSS or OS compared with surgery alone. Similarly, chemotherapy or the combination of chemotherapy and surgery had no significant favorable effect on OS. Interestingly, these patients who received chemotherapy had a relatively shorter DSS. This may be due to patients receiving chemotherapy mostly had advanced-stage tumors. Thus, standard treat-

ment for patients with ASC in oral and maxillofacial region still needs to be confirmed due to the lack of larger-scale, prospective study.

Of course, the present study also had several limitations [16, 22, 31]. First, some crucial data could not be obtained from SEER database such as surgical type, surgical margins, chemotherapy type, recurrence, etc, thereby restricting survival analysis on several potential factors. Meanwhile, information on TNM stage, T/N/M category and pathological grade was missing in some patients. Second, we only constructed the prognostic nomograms to predict OS and DSS in these patients; therefore, the repeatability and reliability of the OS- and DSS-specific nomograms could not further be validated due to the lack of an independent cohort.

To our knowledge, the present study is the largest cohort using a population-based study and a long follow-up time to describe the clinicopathological characteristics and identify the prognostic indicators of patients with ASC in oral and maxillofacial region. We also constructed nomograms for DSS and OS predictions, which provide a tool for clinicians to predict the survival.

Disclosure of conflict of interest

None.

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References

[1] Albores-Saavedra J, Scoazec JC, Wittekind Sripa B. Tumours of the gallbladder and extr - hepatic bile ducts. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classifi- cation of tumours. Pathology and genetics of tumours of the digestive system. Lyon: IARC; 2000. pp. 203-217.

[2] Hoshimoto S, Hoshi S, Hishinuma S, Tomikawa M, Shirakawa H, Ozawa I, Wakamatsu S, Hoshi N, Hirabayashi K and Ogata Y. Adenosquamous carcinoma in the biliary tract: association of the proliferative ability of the squamous component with its proportion and tumor progression. Scand J Gastroenterol 2017; 52: 425-430.

[3] Hsu JT, Chen HM, Wu RC, Yeh CN, Yeh TS, Hwang TL, Jan YY and Chen MF. Clinicopathologic features and outcomes following surgery for pancreatic adenosquamous carcinoma. World J Surg Oncol 2008; 6: 95.

[4] Masoomi H, Ziogas A, Lin BS, Barleben A, Mills S, Stamos MJ and Zell JA. Population-based evaluation of adenosquamous carcinoma of the colon and rectum. Dis Colon Rectum 2012; 55: 509-514.

[5] Eguchi T, Basugi A, Kanai I, Miyata Y, Suzuki T and Hamada Y. Adenosquamous carcinoma development as a recurrence of squamous cell carcinoma in the oral floor: a case report. Medicine (Baltimore) 2019; 98: e17688.

[6] Kikuta S, Todoroki K, Seki N and Kusukawa J. Adenosquamous carcinoma in the midline dorsum of the tongue: a rare case report. J Oral Maxillofac Surg 2018; 76: 2131-2135.

[7] Rawal YB and Anderson KM. Adenosquamous carcinoma of the tongue. Head Neck Pathol 2018; 12: 576-579.

[8] Satomi T, Kohno M, Hasagawa O, Enomoto A, Abukawa H, Chikazu D, Yoshida M, Matsubayashi J and Nagao T. Adenosquamous carcinoma of the tongue: clinicopathologic study and review of the literature. Odontology 2017; 105: 127-135.

[9] Thanakappan P, Venkata NS, Amudala R and Botu M. Adenosquamous carcinoma of oral cavity. J Cancer Res Ther 2015; 11: 1034.

[10] Lee RJ, Lin T, Lee SA, Lee KK and Christensen RE. Importance of tumor extent in adenosquamous carcinoma of the head and neck: a retrospective cohort study. Oral Surg Oral Med Oral Pathol Oral Radiol 2017; 124: 114-120.

[11] Alos L, Castillo M, Nadal A, Caballero M, Mallofre C, Palacin A and Cardesa A. Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. Histopathology 2004; 44: 570-579.

[12] Allon I, Vered M, Kaplan I, Nahlieli O, Yahalom R, Shalmon B, Srouji S and Livoff A. Rare variants of head and neck squamous cell carcinoma-differential immunohistochemical profiles. Acta Histochem 2019; 121: 151444.

[13] Mehrad M, Trinkaus K and Lewis JS Jr. Adenosquamous carcinoma of the head and neck: a case-control study with conventional squamous cell carcinoma. Head Neck Pathol 2016; 10: 486-493.

[14] Karadaghy OA, Shew M, New J and Bur AM. Development and assessment of a machine learning model to help predict survival among patients with oral squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg 2019; 145: 1115-1120.

[15] Pointer KB, Ko HC, Brower JV, Witek ME, Kimple RJ, Lloyd RV, Harari PM and Baschnagel AM. Small cell carcinoma of the head and neck: an analysis of the National Cancer Database. Oral Oncol 2017; 69: 92-98.

[16] Yu CX, Yibulayin F, Feng L, Wang M, Lu MM, Luo Y, Liu H, Yang ZC and Wushou A. Clinicopathological characteristics, treatment and prognosis of head & neck small cell carcinoma: a SEER population-based study. BMC Cancer 2020; 20: 1208.

[17] Yan O, Xie W, Teng H, Fu S, Chen Y and Liu F. Nomograms forecasting long-term overall and cancer specific survival of patients with head and neck neuroendocrine carcinoma. Front Oncol 2021; 11: 619599.

[18] Patel NR, Sanghvi S, Khan MN, Husain Q, Baredes S and Eloy JA. Demographic trends and disease-specific survival in salivary acinic cell carcinoma: an analysis of 1129 cases. Laryngoscope 2014; 124: 172-178.

[19] Bjorndal K, Krogdahl A, Therkildsen MH, Overgaard J, Johansen J, Kristensen CA, Homoe P, Sorensen CH, Andersen E, Bundgaard T, Primdahl H, Lambertsen K, Andersen LJ and Godballe C. Salivary gland carcinoma in Denmark 1990-2005: a national study of incidence, site and histology. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 2011; 47: 677-682.

[20] Schwarz S, Zenk J, Muller M, Ettl T, Wunsch PH, Hartmann A and Agaimy A. The many faces of acinic cell carcinomas of the salivary glands: a study of 40 cases relating histological and immunohistological subtypes to clinical parameters and prognosis. Histopathology 2012; 61: 395-408.

[21] Wang YL, Zhu YX, Chen TZ, Wang Y, Sun GH, Zhang L, Huang CP, Wang ZY, Shen Q, Li DS, Wu Y and Ji QH. Clinicopathologic study of 1176 salivary gland tumors in a Chinese population: experience of one cancer center 1997-2007. Acta Otolaryngol 2012; 132: 879-886.

[22] Yibulayin F, Feng L, Wang M, Lu MM, Luo Y, Liu H, Yang ZC and Wushou A. Head & neck acinar cell carcinoma: a population-based study using the seer registry. BMC Cancer 2020; 20: 631.

[23] Fukumoto C, Ogisawa S, Tani M, Hyodo T, Kamimura R, Sawatani Y, Hasegawa T, Komiyama Y, Fujita A, Wakui T, Haruyama Y, Kobashi G and Kawamata H. Clinical characteristics, treatment methods and prognoses of patients with oral squamous cell carcinoma in Japanese population: a single institution retrospective cohort study. BMC Geriatr 2020; 20: 487.

[24] Iyer NG, Tan DS, Tan VK, Wang W, Hwang J, Tan NC, Sivanandan R, Tan HK, Lim WT, Ang MK, Wee J, Soo KC and Tan EH. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer 2015; 121: 1599-1607.

[25] Katsoulakis E, Leeman JE, Lok BH, Shi W, Zhang Z, Tsai JC, McBride SM, Sherman EJ, Cohen M, Wong R, Ganly I, Lee NY and Riaz N. Long-term outcomes in oral cavity squamous cell carcinoma with adjuvant and salvage radiotherapy after surgery. Laryngoscope 2018; 128: 2539-2545.

[26] Vigano A, De Felice F, Iacovelli NA, Alterio D, Facchinetti N, Oneta O, Bacigalupo A, Tornari E, Ursino S, Paiar F, Caspiani O, Di Rito A, Musio D, Bossi P, Steca P, Jereczek-Fossa BA, Greco A and Orlandi E. M. D. Anderson symptom inventory head neck (MDASI-HN) questionnaire: Italian language psychometric validation in head and neck cancer patients treated with radiotherapy +/- systemic therapy - A study of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Oral Oncol 2021; 115: 105189.

[27] Choi KH, Song JH, Kim YS, Kim JH, Jeong WJ, Nam IC, Kim JH, Ahn HK, Chun SH, Hong HJ, Joo YH, Eun YG, Moon SH and Lee JS. Recent treatment patterns of oropharyngeal cancer in Korea based on the expert questionnaire survey of the Korean Society for Head and Neck oncology (KSHNO). Cancer Res Treat 2021.

[28] Tasoulas J, Divaris K, Theocharis S, Farquhar D, Shen C, Hackman T and Amelio AL. Impact of tumor site and adjuvant radiotherapy on survival of patients with adenoid cystic carcinoma: a SEER database analysis. Cancers (Basel) 2021; 13.

[29] Zanoni DK, Montero PH, Migliacci JC, Shah JP, Wong RJ, Ganly I and Patel SG. Survival outcomes after treatment of cancer of the oral cavity (1985-2015). Oral Oncol 2019; 90: 115-121.

[30] Ivaldi E, Di Mario D, Paderno A, Piazza C, Bossi P, Iacovelli NA, Incandela F, Locati L, Fallai C and Orlandi E. Postoperative radiotherapy (PORT) for early oral cavity cancer (pT1-2,N0-1): a review. Crit Rev Oncol Hematol 2019; 143: 67-75.

[31] Han H, Luo XD and Shao LQ. A population-based analysis of adenosquamous carcinoma of the salivary gland. Gland Surg 2021; 10: 645-655.