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Original Article

A Comparison of Clinicopathological Differences and Survival Rates in Oral Squamous Cell Carcinoma between Middle Age and Old Age in Taiwan

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SUMMARY

Background: It is unclear whether age plays a crucial role in the oral cancer prognosis. We aimed to compare the clinicopathological parameters, outcomes, and trends of patients aged < 65 years (middle age, MA) and ≥ 65 years (old age, OA) with oral squamous cell carcinoma (OSCC).
Methods: Data of 862 OSCC patients who underwent surgery at the Taipei MacKay Memorial Hospital between 1997 and 2017 were obtained. The patients were divided into MA and OA groups. Tumor size, nodal invasion, tumor location, radiotherapy status, pathological features, and prognosis were compared. The chi-square test was used for statistical analysis. We calculated the hazard ratios and 95% confidence intervals of all-cause mortality risk between the two groups.
Results: Significant differences were noted in sex, tumor location, and survival rate between the groups. Sex, late-stage cancer, positive nodal invasion, and moderate differentiation significantly increased the mortality risks in the OA group compared to those in the MA group. In addition, OA group patients without diabetes mellitus (DM), perineural invasion, lymphovascular invasion, recurrence, secondary primary cancer, and distant metastases also showed a higher mortality risk than other patients.
Conclusion: Aging could be a predictive prognostic factor for OSCC, particularly for tumor location and survival rate. Radiotherapy after surgery could increase the survival rate of OA patients with nodal invasion.

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1. Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most prevalent type of cancer in Taiwan. It is most commonly diagnosed in patients in their 60s or 70s and is often associated with a history of heavy betel quid chewing, tobacco smoking, and alcohol drinking.[1] However, more patients are being diagnosed with OSCC at a younger age worldwide.[2] Data estimates from 2009 to 2015 showed that individuals aged 55–64 years (median age: 63 years) were frequently affected by oral cancer in the United States. Over 93% patients are diagnosed at the age of ≥ 45 years.[3] Oral cancer is frequently diagnosed in patients aged 50–70 years. The incidence of OSCC in younger patients has been increasing worldwide in recent years. However, the differences in clinical courses and prognoses between younger and older OSCC patients are controversial. Some studies have reported that the 5-year overall survival is higher in those aged < 40 years,[4] while other studies have reported that tumors in patients aged > 35 years are more aggressive, suggesting the need for more radical treatment modalities.[5]

Cancer is considered an age-related disease as the incidence of most cancer types increases with age. It can also be considered a part of the natural biological process of senescence. However, old age does not necessarily lead to cancer.[6] More than half of all cancer types occurred in adults aged ≥ 65 years in 2009. By 2030, approximately 70% of all cancer types will occur among adults aged ≥ 65 years.[6] In this study, we compared two groups of individuals with OSCC categorized according to age (< 65 and > 65 years) in Taiwan. We aimed to compare the clinicopathological parameters and outcomes with or without radiotherapy and determine the trends between middle age (MA) and old age (OA) groups.

2. Materials and methods

The records of 862 patients with OSCC who underwent tumor resection and neck dissection at the Taipei MacKay Memorial Hospital from 1997 to 2017 were retrospectively collected. Patients with surgery-related morbidities and mortalities were excluded. This study was approved by the Mackay Memorial Hospital Institutional Review Board (21MMHIS189e) and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participating adults, and their rights were clearly defined. All OSCC patients were divided into the MA (< 65 years) and OA (≥ 65 years) groups. The following clinical parameters were evaluated: sex, age, tumor location, radiotherapy status, recurrence status, and secondary primary and distant metastases. Pathological

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parameters, such as tumor size, tumor cell differentiation, and perineural, lymphovascular, and lymph node invasion, were subcategorized according to the American Joint Committee on Cancer 7th edition. Each variable was analyzed using descriptive statistics. Survival was evaluated using the Kaplan-Meier method and compared statistically using the log-rank test. The mortality rates in both groups were determined, and the risks was compared using Cox proportional hazards models. Prognostic factors were analyzed using the chi-square test, and statistical significance was set at $p < 0.05$.

3. Results

In total, 862 patients were enrolled and categorized into the MA group (n = 696, 80.7%, 649 men and 47 women) and the OA group (n = 166, 19.3%, 134 men and 32 women).

The analyzed clinical and pathological parameters are shown in Table 1. In the MA group, 124 (17.8%), 182 (26.1%), 57 (8.2%), and 333 (47.9%) patients had T1, T2, T3, and T4 tumors, respectively. Approximately 48%, 45.4%, and 6.6% tumors were well differentiated, moderately differentiated, and poorly differentiated, respectively.

Table 1
Characteristic parameters of oral cavity cancers between the MA and OA groups.

	Age (< 65 years)	Age (≥ 65 years)	p value
Numbers	696	166	
Age	27–64 (50.44 ± 8.27)	65–90 (71.42 ± 5.68)	
Sex			
Male	649 (93.2%)	134 (80.7%)	< 0.001***
Female	47 (6.8%)	32 (19.3%)	
Tumor size			
T1	124 (17.8%)	20 (12.1%)	0.329
T2	182 (26.1%)	44 (26.5%)	
T3	57 (8.2%)	16 (9.6%)	
T4	333 (47.9%)	86 (51.8%)	
Nodal invasion			
(-)	429 (61.6%)	111 (66.9%)	0.211
(+)	267 (38.4%)	55 (33.1%)	
Stages			
I	107 (15.4%)	12 (7.2%)	0.036*
II	127 (18.2%)	34 (20.5%)	
III	80 (11.5%)	21 (12.7%)	
IVa	353 (50.7%)	96 (57.8%)	
IVb	29 (4.2%)	3 (1.8%)	
Locations			
Buccal	303 (43.5%)	57 (34.3%)	0.005**
Tongue	189 (27.2%)	39 (23.5%)	
Gum	131 (18.8%)	43 (25.9%)	
Palate	40 (5.7%)	12 (6.0%)	
Lip	15 (2.2%)	12 (7.2%)	
Mouth floor	18 (2.6%)	5 (3.0%)	
Differentiation			
Well	334 (48.0%)	74 (44.6%)	0.253
Moderate	316 (45.4%)	75 (45.2%)	
Poor	46 (6.6%)	17 (10.2%)	
Perineural invasion			
(-)	574 (82.5%)	134 (80.7%)	0.597
(+)	122 (17.5%)	32 (19.3%)	
Lymphovascular invasion			
(-)	611 (87.8%)	143 (86.1%)	0.113
(+)	85 (12.2%)	12 (13.9%)	
DM			
(-)	501 (71.9%)	110 (66.3%)	0.145
(+)	195 (28.1%)	56 (33.7%)	
Radiation therapy			
(-)	287(41.2%)	83 (50.0%)	0.040*
(+)	409(58.8%)	83 (50.0%)	
Recurrence			
(-)	511 (73.4%)	136 (81.9%)	0.023*
(+)	185 (26.6%)	30 (18.1%)	
Secondary primary			
(-)	666 (95.7%)	164 (98.8%)	0.087
(+)	30 (4.3%)	2 (1.2%)	
Distant metastasis			
(-)	675 (97.0%)	163 (98.2%)	0.395
(+)	21 (3.0%)	3 (1.8%)	
Prognosis			
Survival	447 (64.2%)	93 (56.0%)	0.049*
Expired	249 (35.8%)	73 (44.0%)	

MA, middle age (< 65 years); OA, old age (≥ 65 years).
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The buccal region was the most common tumor location, followed by the tongue and gums, with the lips as the least affected region. In the OA group, 20 (12.1%), 44 (26.5%), 16 (9.6%), and 86 (51.8%) patients had T1, T2, T3, and T4 tumors, respectively. The ratios of well-and moderately differentiated tumors were similar (44.6% vs. 45.2%). Similarly, the most common tumor location was the buccal region, followed by the gums, tongue, and mouth floor. Significant differences were noted in parameter distributions, such as sex (less male predilection in OA patients, $p < 0.001$), proportion of advanced stage tumors (more advanced stage tumors in OA patients, $p = 0.036$), tumor location (higher occurrence in the gum and lip regions in the OA group, $p = 0.005$), receipt of radiotherapy (OA patients favored conservative treatments, $p = 0.040$), recurrence rates ($p = 0.023$), and survival rates ($p = 0.049$), between the groups. No age-related differences were found in the histopathological parameters of OSCC, such as tumor size distribution, nodal invasion, perineural invasion, lymphovascular invasion, and types of tumor cell differentiation, between the groups. The Kaplan-Meier method showed a significantly lower survival rate in the OA group than in the MA group ($p < 0.005$; Figure 1).

Table 2 shows a comparison of the overall mortality rates and hazard ratios (HRs) between the groups. The following parameters significantly increased the mortality risks in the OA group: sex (male, $p = 0.013$; female, $p = 0.035$), tumor size (T3, $p = 0002$), positive nodal invasion ($p < 0.001$), late-stage cancer (stage III, $p = 0.009$; stage IV, $p = 0.005$), tumor location (tongue: $p = 0.015$; gum: $p = 0.048$), moderate differentiation ($p = 0.015$), and with/ without radiotherapy ($p = 0.004$; $p = 0.002$). In addition, patients without perineural invasion ($p = 0.002$), lymphovascular invasion ($p = 0.019$), diabetes mellitus (DM) ($p = 0.001$), recurrence ($p = 0.001$), secondary primary tumor ($p = 0.001$), and distant metastases ($p = 0.001$) showed mortality risks than other patients. The OA group with T3 tumors had 3.65 times higher risk of mortality (HR = 3.65, 95% CI: 1.63–8.15) than the MA group. The OA group with positive nodal invasion had a significantly higher mortality rate than the MA group (HR = 2.15, 95% CI: 1.50–3.07, $p < 0.001$).

There were significant differences in the mean survival rates of patients without DM ($p = 0.009$), recurrence ($p = 0.015$), secondary primary cancer ($p = 0.025$), and distant metastases ($p = 0.037$) as well as those who did not receive radiotherapy ($p = 0.013$) between the groups. Therefore, we screened patients after major surgery with and without radiotherapy and compared their mortality rates according to factors presented in Tables 3 and 4. We excluded the effects of radiotherapy and determined the significant difference in mortality rates associated with different clinicopathological factors between the groups. In the patients receiving postoperative radiotherapy, the HR of mortality in the OA group also increased by 1.49-fold (95% CI: 1.06–2.09) with sex, by 4.32-fold (95% CI: 156–12.00) with tumor size (T3), and by 2.22-folds (95% CI: 1.49–3.32) with positive nodal invasion. Unlike patients not receiving radiotherapy, the HR of mortality did not significantly increase in the OA group with T3 tumors. Tumor location (tongue, HR = 2.70, 95% CI: 1.43–5.09; gum, HR = 1.92, 95% CI: 1.06–3.47; shift to buccal region, HR = 2.70, 95% CI: 1.17–6.24) significantly increased the mortality risk in the OA group, regardless of whether patients received radiotherapy. Furthermore, the risk factors associated with moderate differentiation and absence of DM, perineural invasion, lymphovascular invasion, recurrence, and secondary primary and distant metastases significantly increased the mortality rates in the OA group, regardless of whether patients received radiotherapy.

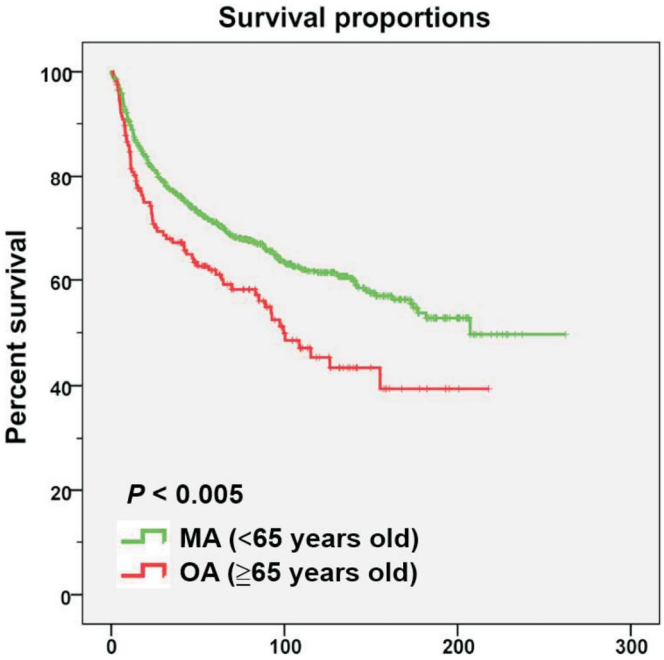

Figure 1. There is significant difference in overall survival proportions between MA and OA groups in OSCC by Kaplan-Meier method with Log-Rank test. * $p < 0.05$ was defined as significant difference.

4. Discussion

In the previous investigation, habitual cigarette smokers, alcohol consumers, and betel quid chewers had a higher risk of developing OSCC,[7,8] and these cohorts predominantly included men in Taiwan. Aging may also predispose body tissues to cancer through several mechanisms — (1) tissue accumulation of cells in the late stages of carcinogenesis; (2) alterations in homeostasis, particularly alterations in the immune and endocrine systems; and (3) telomere instability linked with aging and increased cancer risk.[9] In this study, the OA group had less male predilection, which might be explained by the accumulation of genetic-related carcinogens. The carcinogenic gaps relating to personal habits (alcohol consumption, betel nut chewing, and smoking) between men and women were narrowed in this study.

As shown in Table 1, men were predominantly diagnosed with OSCC. However, only 80.7% OSCC patients were men in the OA group, while 93.2% OSCC patients were men in the MA group. The decline in the percentage of men with OSCC, a trend observed in this study, could be explained by the deaths of patients in the MA group who did not survive beyond the age of 65 years. At diagnosis, both age groups mostly progressed through stage IVa (50.7% and 57.8% in the MA and OA groups, respectively).

In tumor location analysis, the OA group had a higher proportion of patients with gum and lip cancer, consistent with the results of Hernández-Guerrero et al.'s study.[10] According to Hernández-Guerrero et al.,[10] detection of OSCC is associated with pain or functional disturbances in the affected location. In tongue cancer, the movement of the tongue against the teeth causes discomfort. In contrast, lip and gum carcinomas only cause intense pain at advanced stages, which prevents patients from seeking medical or dental attention for a long period of time. Therefore, attention should be paid to the gums and lips in OA patients during oral screening.

In Ramos-Garcia's systematic review and meta-analysis, oral cancer patients with DM had a higher mortality risk than control patients.[11] In our study, there was no significant difference in the

Table 2
Clinicopathological parameters stratified by survival status in the MA and OA groups (N = 862).

Stratification variables	MA (< 65 years)	OA (≥ 65 years)	HR (95% CI)	pvalue
	Deaths (mortality rate)	Deaths (mortality rate)		
Sex				
Male	235 (36.2%)	58 (43.3%)	1.44 (1.08–1.91)	0.013*
Female	14 (29.8%)	15 (46.9%)	2.23 (1.06–4.71)	0.035*
Tumor size				
T1	15 (12.1%)	4 (20.0%)	2.57 (0.93–7.11)	0.068
T2	46 (25.3%)	13 (29.5%)	1.35 (0.73–2.50)	0.342
T3	16 (28.1%)	10 (62.5%)	3.65 (1.63–8.15)	0.002**
T4	172 (51.7%)	46 (53.5%)	1.22 (0.88–1.70)	0.225
Nodal invasion				
(-)	120 (28.0%)	34 (30.6%)	1.31 (0.89–1.91)	0.170
(+)	129 (48.3%)	39 (70.9%)	2.15 (1.50–3.07)	< 0.001***
Stages				
I	8 (7.5%)	1 (8.3%)	1.22 (0.15–9.79)	0.850
II	25 (19.7%)	5 (14.7%)	0.85 (0.32–2.22)	0.734
III	23 (28.7%)	11 (52.4%)	2.66 (1.28–5.55)	0.009**
IVa	174 (49.3%)	56 (58.3%)	1.54 (1.14–2.08)	0.005**
IVb	19 (65.5%)	1 (33.3%)	0.564 (0.08–4.24)	0.578
Locations				
Buccal	122 (40.3%)	24 (42.1%)	1.17 (0.76–1.80)	0.478
Tongue	55 (29.1%)	16 (41.0%)	2.00 (1.14–3.51)	0.015*
Gum	52 (39.7%)	23 (53.5%)	1.64 (1.01–2.69)	0.048*
Palate	11 (27.5%)	4 (40.0%)	1.78 (0.57–5.62)	0.324
Lip	2 (13.3%)	4 (33.3%)	4.81 (0.83–27.92)	0.080
Mouth floor	7 (38.9%)	2 (40.0%)	0.942 (0.19–4.71)	0.942
Differentiation				
Well	102 (30.5%)	24 (32.4%)	1.29 (0.83–2.01)	0.265
Moderate	126 (39.9%)	38 (50.7%)	1.57 (1.09–2.24)	0.015*
Poor	21 (45.7%)	11 (64.7%)	1.97 (0.95–4.11)	0.069
Perineural invasion				
(-)	192 (33.4%)	56 (41.8%)	1.60 (1.19–2.15)	0.002**
(+)	57 (46.7%)	17 (53.1%)	1.13 (0.66–1.95)	0.657
Lymphovascular invasion				
(-)	201 (32.9%)	54 (37.8%)	1.43 (1.06–1.93)	0.019*
(+)	48 (56.5%)	19 (82.6%)	1.67 (0.97–2.86)	0.063
DM				
(-)	142 (28.3%)	45 (40.9%)	1.77 (1.26–2.48)	0.001**
(+)	107 (54.9%)	28 (50.0%)	1.09 (0.72–1.65)	0.675
Radiation therapy				
(-)	48 (16.7%)	24 (28.9%)	2.18 (1.34–3.54)	0.002**
(+)	201 (49.1%)	49 (59.0%)	1.58 (1.16–2.16)	0.004**
Recurrence				
(-)	144 (28.2%)	53 (39.0%)	1.71 (1.25–2.34)	0.001**
(+)	105 (56.8%)	20 (66.7%)	1.31 (0.81–2.12)	0.270
Secondary primary				
(-)	226 (33.9%)	71 (43.3%)	1.57 (1.12–2.04)	0.001**
(+)	23 (76.7%)	2 (100.0%)	2.37 (0.54–10.41)	0.252
Distant metastasis				
(-)	231 (34.2%)	70 (42.9%)	1.56 (1.20–2.04)	0.001**
(+)	18 (85.7%)	3 (100.0%)	2.25 (0.64–7.8)	0.206

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MA, middle age (< 65 years); OA, old age (≥ 65 years).
Statistical analysis was carried out by Cox proportional hazards models.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

distribution of OSCC patients between the MA group and OA group as well as the mortality rate of OSCC patients between the MA group and OA group with DM, although the OA group had more DM patients. However, the mortality risk was higher in the OA group without DM, regardless of whether they received radiotherapy (with radiotherapy, $p = 0.001$; without radiotherapy, $p = 0.026$), suggesting that DM is not related to the mortality rates of the MA and OA groups. The same interpretation applies to OSCC patients without recurrence, secondary primary, and distant metastases in our study.

Head and neck radiotherapy may result in several early (mucositis and loss of taste) and late (xerostomia, dysphagia, trismus, and osteoradionecrosis) side effects.[12] In addition, these side effects may lead to decreased nutritional intake, weight loss, and aspiration pneumonia.[12,13] These sequential complications could be dose limiting and have a tremendous impact on patients' quality of life. Thus, in OA groups, oncologists and patients are less likely to choose aggressive treatments, such as radiotherapy, and choose relatively conservative adjuvant therapies.

In general, the MA group had better survival rates than the OA group. Some investigators have proposed that a more favorable clinical outcome in young adults should be expected, with an average 5-year survival rate of ≥ 65%,[14] consistent with our study results. The

Table 3
Clinicopathological parameters stratified by survival status in the MA and OA groups receiving radiotherapy (N = 492).

Stratification variables	MA (< 65 years)	OA (≥ 65 years)	HR (95% CI)	p value
	Deaths (mortality rate)	Deaths (mortality rate)		
Sex				
Male	191 (49.4%)	41 (58.6%)	1.49 (1.06–2.09)	0.021*
Female	10 (45.5%)	8 (61.5%)	2.33 (0.89–6.11)	0.085
Tumor size				
T1	8 (36.4%)	2 (50.0%)	2.23 (0.45–11.12)	0.330
T2	31 (41.9%)	9 (60.0%)	1.68 (0.80–3.53)	0.174
T3	12 (35.0%)	6 (66.7%)	4.32 (1.56–12.00)	0.005**
T4	150 (53.8%)	32 (58.2%)	1.36 (0.93–1.99)	0.117
Nodal invasion				
(-)	83 (43.5%)	18 (41.9%)	1.15 (0.69–1.92)	0.581
(+)	118 (54.1%)	31 (77.5%)	2.22 (1.49–3.32)	< 0.001***
Stages				
I	1 (10.0%)	0 (0.0%)	-	
II	12 (46.2%)	1 (20.0%)	0.30 (0.04–2.34)	0.252
III	18 (36.7%)	6 (50.0%)	2.32 (0.89–6.00)	0.084
IVa	152 (51.4%)	41 (65.1%)	1.74 (1.23–2.47)	0.002**
IVb	18 (64.3%)	1 (33.3%)	0.60 (0.08–4.53)	0.621
Locations				
Buccal	108 (57.1%)	16 (59.3%)	1.17 (0.69–1.97)	0.570
Tongue	41 (42.3%)	13 (68.4%)	2.70 (1.43–5.09)	0.002**
Gum	35 (41.7%)	16 (59.3%)	1.92 (1.06–3.47)	0.031*
Palate	10 (41.7%)	2 (66.7%)	3.71 (0.73–18.78)	0.113
Lip	0 (0.0%)	2 (40.0%)	-	
Mouth floor	7 (63.6%)	0 (0.0%)	-	
Differentiation				
Well	79 (47.0%)	17 (45.9%)	1.28 (0.76–2.17)	0.357
Moderate	104 (50.5%)	23 (65.7%)	1.73 (1.10–2.72)	0.018*
Poor	48 (51.4%)	9 (81.8%)	2.32 (1.04–5.19)	0.041*
Perineural invasion				
(-)	151 (50.2%)	36 (62.1%)	1.73 (1.20–2.49)	0.003**
(+)	50 (46.3%)	13 (52.0%)	1.14 (0.62–2.10)	0.679
Lymphovascular invasion				
(-)	158 (47.6%)	34 (52.3%)	1.46 (1.01–2.12)	0.046*
(+)	43 (55.8%)	15 (83.3%)	1.63 (0.89–2.99)	0.115
DM				
(-)	108 (40.3%)	30 (53.6%)	1.99 (1.32–2.99)	0.001**
(+)	93 (66.0%)	19 (70.4%)	1.05 (0.64–1.73)	0.838
Recurrence				
(-)	108 (39.4%)	35 (53.8%)	1.87 (1.27–2.74)	0.001**
(+)	93 (68.9%)	15 (77.8%)	1.17 (0.67–2.06)	0.584
Secondary primary				
(-)	182 (47.2%)	48 (58.8%)	1.61 (1.17–2.21)	0.003**
(+)	19 (82.0%)	1 (100.0%)	5.23 (0.58–46.84)	0.139
Distant metastasis				
(-)	184 (47.3%)	46 (57.5%)	1.60 (1.15–2.27)	0.005**
(+)	17 (85.0%)	3 (100.0%)	2.07 (0.59–7.27)	0.256

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MA, middle age (< 65 years); OA, old age (≥ 65 years).
Statistical analysis was carried out by Cox proportional hazards models.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

survival between the MA group and OA group with OSCC was significantly different according to the Kaplan-Meier method (Figure 1). Positive nodal invasion, negative perineural invasion, negative lymphovascular invasion, and absence of radiotherapy treatment were significantly associated with the mortality rate (Table 2). The results are not surprising in terms of risk factors, including positive nodal invasion.[15] The presence of lymphovascular invasion in primary tumors was highly related to the development of cervical metastasis. In contrast, the poorest 5-year survival rate was observed in patients with nodal invasion and extranodal extension.[16] Aggressive treatment should be performed to prevent neck recurrences in older patients, and accelerated chemoradiation therapy should be considered. However, due to the greater incidence of radiotherapy in older OSCC patients, the number of patients in the OA group willing to receive radiotherapy is lower than that in the MA group.

There was a significant difference in the mortality rates of patients receiving adjuvant radiotherapy between the groups. However, a difference in mortality rate was observed (HR = 2.18, 95% CI: 1.34–3.54) when patients did not undergo adjuvant radiotherapy (p = 0.002), and the mortality risk was lower (HR = 1.58, 95% CI: 1.16–2.16) in patients who underwent adjuvant radiotherapy (p = 0.004). In addition, the mortality rate in the OA group was significantly higher than that in the MA group, with and without radiotherapy (Table 3, 4). The HR of most parameters decreased in the radiotherapy group than in the non-radiotherapy group, indicating that radiotherapy may decreasing the risk of mortality. However, tumor

Table 4
Clinicopathological parameters stratified by survival status in the MA and OA groups not receiving radiotherapy (N = 370).

Stratification variables	MA (< 65 years)	OA (≥ 65 years)	HR (95% CI)	p value
	Deaths (mortality rate)	Deaths (mortality rate)		
Sex				
Male	44 (16.8%)	18 (28.1%)	1.97 (1.14–3.42)	0.016*
Female	4 (16.0%)	7 (36.8%)	2.76 (0.81–9.46)	0.106
Tumor size				
T1	7 (6.9%)	3 (18.8%)	3.04 (0.79–1.76)	0.108
T2	15 (13.9%)	4 (13.8%)	1.19 (0.39–3.64)	0.757
T3	4 (17.4%)	4 (57.1%)	3.72 (0.92–15.00)	0.065
T4	22 (40.7%)	14 (45.2%)	1.37 (0.70–2.68)	0.366
Nodal invasion				
(-)	37 (15.5%)	16 (23.5%)	1.82 (1.01–3.27)	0.048*
(+)	11 (22.4%)	9 (60.0%)	3.63 (1.48–8.90)	0.005**
Stages				
I	7 (7.2%)	1 (8.3%)	1.18 (0.15–9.58)	0.879
II	13 (12.9%)	4 (13.8%)	1.32 (0.42–4.10)	0.634
III	5 (16.1%)	5 (55.6%)	3.90 (1.12–13.52)	0.032*
IVa	22 (38.6%)	15 (45.5%)	1.57 (0.81–3.04)	0.183
IVb	1 (100.0%)			
Locations				
Buccal	14 (12.3%)	9 (30.0%)	2.70 (1.17–6.24)	0.020*
Tongue	14 (15.2%)	3 (15.0%)	1.40 (0.40–4.92)	0.603
Gum	17 (36.2%)	7 (43.8%)	1.38 (0.57–3.37)	0.481
Palate	1 (6.3%)	2 (28.6%)	4.92 (0.45–54.29)	0.193
Lip	2 (18.2%)	2 (28.6%)	4.45 (0.40–49.94)	0.227
Mouth floor	0 (0.0%)	2 (66.7%)	-	
Differentiation				
Well	23 (13.9%)	7 (18.9%)	1.59 (0.68–3.73)	0.282
Moderate	22 (20.0%)	16 (40.0%)	2.42 (1.27–4.63)	0.007**
Poor	3 (27.3%)	2 (33.3%)	1.45 (0.24–8.71)	0.682
Perineural invasion				
(-)	41 (15.0%)	21 (27.6%)	2.24 (1.32–3.80)	0.003**
(+)	7 (50.0%)	4 (57.1%)	0.90 (0.26–3.09)	0.869
Lymphovascular invasion				
(-)	43 (15.4%)	21 (26.9%)	2.10 (1.24–3.55)	0.005**
(+)	5 (62.5%)	4 (80.0%)	1.21 (0.32–4.58)	0.777
DM				
(-)	34 (14.6%)	15 (27.8%)	1.99 (1.09–3.66)	0.026*
(+)	14 (25.9%)	10 (34.5%)	2.93 (1.12–6.17)	0.026*
Recurrence				
(-)	36 (15.2%)	19 (26.8%)	2.02 (1.16–3.53)	0.013*
(+)	12 (24.0%)	6 (50.0%)	2.99 (1.12–8.00)	0.029*
Secondary primary				
(-)	44 (15.7%)	24 (29.3%)	2.20 (1.34–3.62)	0.002**
(+)	4 (57.1%)	1 (100.0%)	-	
Distant metastasis				
(-)	47 (16.4%)	25 (30.1%)	2.21 (1.36–3.60)	0.001**
(+)	1 (100.0%)	25 (30.1%)	–	

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MA, middle age (< 65 years); OA, old age (≥ 65 years).
Statistical analysis was carried out by Cox proportional hazards models.
* $p < 0.05$, ** $p < 0.01$.

size (T3), IVa stage, tumor location (tongue and gum), and poor differentiation had a reverse effect in the radiotherapy group compared to that in the non-radiotherapy group. Whether radiation therapy increases the mortality risk in patients from different age groups does not seem to have a significant effect on such parameters. Hence, additional studies on these parameters are required to confirm whether these results can be applied.

Postoperative radiotherapy alone or in combination with chemotherapy is the gold standard treatment for advanced OSCC. Table 4 shows a comparison of survival rates by risk factors between the MA and OA groups, excluding radiation therapy as a factor. Among non-radiotherapy patients, the mortality rates increased by 3.63-fold (HR = 3.63, 95% CI: 1.48–8.90) in the OA group with positive nodal invasion ($p = 0.005$). Increasing the N-stage is associated with the development of distant metastases[17] and further decreases the overall survival rate. In our study, especially in the OA group, nodal invasion appeared to be a crucial risk factor for patient survival in those who did not receive postoperative radiotherapy.

In conclusion, aging could be a predictable and prognostic factor for OSCC, particularly in terms of sex, tumor location, and survival rate. Previously, we chose a relatively conservative adjuvant therapy for older patients. In this study, radiotherapy after surgery could considerably decrease the mortality rate in OA patients with nodal invasion. OSCC patients may benefit from effective surgical resections based on modern reconstructive methods, radiotherapy, and chemotherapy, with fewer side effects.[18] According to the cur-

rent studies,[19] surgery and radiotherapy are feasible, effective, and well tolerated by older patients, who seem to recover well without severe comorbidities.

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Conflicts of interest

The authors declare no conflict of interest.

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