Pretreatment body mass index as a prognostic predictor in patients with oral squamous cell carcinoma

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Abstract

Objectives To evaluate whether low body mass index (BMI) is a potential adverse prognostic factor in patients with oral squamous cell carcinoma (OSCC).

Material and methods This cross-sectional study included 320 patients with OSCC who underwent therapeutic surgical treatment in Taiwan. The pretreatment BMI was measured as a common indicator of the pretreatment nutritional status to calculate the overall survival in Kaplan-Meier method. The adverse histopathological features of margin status, depth of invasion (DOI), lymphovascular invasion (LVI), perineural invasion (PNI), and extranodal extension (ENE) were analyzed using the Cox regression model.

Results Low BMI (underweight), DOI > 5 mm, and ENE were identified as detrimental prognostic factors. On multivariate Cox regression analysis, the low BMI group (odds ratio [OR] = 1.683; 95% confidence interval [95% CI] 1.116–2.539; *P* = 0.022), DOI > 5 mm (OR = 2.399; 95% CI 1.459–3.943; *P* = 0.001), and ENE (OR = 2.467; 95% CI 1.540–3.951; *P* = 0.000) yielded reduced survival rate.

Conclusions The lower BMI had an important and significant effect on the survival of patients with oral cancer and their surgical outcomes. In addition to the adverse histopathological features, a DOI > 5 mm and positive ENE were also identified as the most important prognostic factors.

Clinical relevance Underweight patients with low BMI, DOI of > 5 mm, and positive ENE should receive more intensive nutritional supplementation and postoperative adjuvant therapy.

Keywords BMI · Nutrition · Oral squamous cell carcinoma · Adverse features

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most prevalent type of malignancy worldwide, and the most frequently occurring malignant tumor of the oral cavity [1]. In Taiwan,

OSCC is the fourth most prevalent cancer among men, and the sixth most prevalent cancer overall. Accordingly, the number of annual deaths attributed to OSCC has been increasing rapidly among Taiwanese men [2].

Current guidelines for the treatment and management of OSCC recommend resection, either alone or in combination with concurrent adjuvant chemoradiotherapy. These guidelines have not been updated in the past 10 years; therefore, the 5-year OSCC survival rate has not improved significantly in recent decades [3]. Conventionally, long-term prognoses and selective treatment decisions are based on the tumor, node, metastasis (TNM) staging and adverse features [4]; however, we sought to identify other adverse prognostic factors and individual patient conditions as interesting research targets.

The adverse outcomes of surgical treatment for OSCC may induce facial muscle dysfunction and cause defects in the chewing apparatus [5]. Consequently, patients who have undergone surgical resection for OSCC may experience more difficulty in coping with the negative effects of both the disease and its treatment [6]. Although surgical resection is

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undertaken to excise the primary lesions from the oral cavity, both the preoperative tumor size and surgical outcomes can lead to insufficient food intake and malnutrition [7, 8].

The adverse features were important prognostic factors in the choice of postoperative adjuvant therapy [9]; these features included positive margin, perineural invasion (PNI), lymphovascular space invasion (LVSI), depth of invasion (DOI), and extranodal extension (ENE). ENE and positive margin were indicated as the high-risk factors of poor prognosis in a US intergroup trial, Radiation Therapy Oncology Group (RTOG) 9501 [10]. Presence of PNI and LVSI were indicative of the high-risk of OSCC from the study of European trial, European Organization for Research and Treatment of Cancer (EORTC) 22931 [11]. Moreover, the DOI and ENE were important prognostic factors, and the American Joint Committee on Cancer (AJCC) included two factors in the 8th edition of the Cancer Staging Manual [12].

The World Health Organization (WHO) presented the utilization of the following cutoff points for the classification of nutritional status in adults [13]: underweight with BMI, < 18.5 kg/m²; normal weight with body mass index (BMI), 18.5–24.9 kg/m²; overweight with BMI, > 25 kg/m²; and obesity with BMI, > 30 kg/m². Previous studies have addressed the effects of nutritional status on BMI in patients with gastric cancer; patients with a higher BMI experienced prolonged survival [14], whereas those with head and neck cancer who had a higher BMI tolerated additional treatment complications.

To date, no other study has addressed the effects of nutritional markers of BMI on oral cancer prognoses. Accordingly, this study aimed to investigate the preoperative BMI of patients with OSCC in Taiwan. These parameters were further investigated to explore the simple clinical predictors of survival in patients with oral cancer.

Materials and methods

Patients

In this retrospective study, the medical records of patients with oral cancer, who were treated at the Tri-Service General Hospital between 2002 and 2015, were evaluated. The study inclusion criteria were as follows: (1) previously untreated oral cancer, (2) histologically proven squamous cell carcinoma, (3) an Eastern Cooperative Oncology Group performance status of 0 or 1, and (4) surgical resection and curative surgery with or without adjuvant postoperative therapy. The exclusion criteria were as follows: (1) unavailable data of BMI parameters before curative surgery, (2) identification of distant metastasis at the initial visit, (3) history of treatment for other cancers, (4) contraindication to undergo curative surgery, and (5) final event of death and recurrence caused by an event of non-cancerous etiology. In our study, 389 patients met the inclusion criteria; of

these, 69 were excluded because of insufficient data or death due to non-cancer causes. Accordingly, the data on 320 patients were obtained and analyzed in this study. These patients were followed-up regularly at our single-unit medical center, and except in cases of death, all of them were followed-up for at least 2 years, until December 2015.

Treatments

All patients with primary OSCC underwent, at the minimum, selective neck lymphatic node dissection and resection with margins. Adjuvant radiotherapy or concurrent chemoradiotherapy was administered after cancer staging, if adverse features were present. All patients were followed-up and registered in an institutional database that was corrected and updated to include patients' latest treatment conditions. The Ethical Committee of the Tri-Service General Hospital (Taipei, Taiwan) approved this retrospective study (institutional review board protocol no.: 2-106-05-082), and all patients provided written informed consent.

Data collection

Definitive tumor staging relied on pathological features in accordance with the AJCC staging guidelines. Definitive nodular staging was based on the pathological analysis of specimens from selective neck dissections. BMI was evaluated within 2 weeks before curative excision and lymphatic dissection.

Nutritional analyses

Data were separated into different groups based on preoperative BMI values. Patients were separated into three BMI groups according to the WHO guidelines as follows [13]: underweight (BMI, < 18.5 kg/m²), normal weight (BMI, 18.5–25 kg/m²), and overweight (BMI, > 25 kg/m²).

Statistical analyses

The relationships between the patients' clinical characteristics and their BMI were examined using a chi-square test. The Kaplan-Meier method was used to estimate the overall survival (OS) and progression-free survival (PFS). OS was measured from the date of therapeutic surgery to the date of death or last follow-up, which was registered by the cancer recording group. PFS was measured from the date of surgery to the date of tumor recurrence, which was defined as locoregional or distant metastasis. OS and PFS were measured according to different BMI categories. Furthermore, OS analysis included the adverse features and BMI categories, and the multivariate Cox proportional hazard regression analysis was performed to evaluate the odds ratio of OS and to identify the prognostic

factors affecting OS among other individual factors. Statistical analyses were conducted using SPSS statistical software (IBM SPSS, version 20.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Data from 320 patients were obtained and analyzed in this study (Table 1). The 320 patients included 294 men and 26 women with a median age of 51 years (range, 23–84 years). The primary tumor sites were the lip, retromolar region, gingiva, tongue, buccal mucosa, floor of mouth, and palate. The survivors were followed-up for a median of 3.7 years (range, 0.0–11.5 years).

Patient nutritional markers

An overall mean (standard deviation) value of 23.9 (3.9) kg/m² was calculated for BMI. The patients were subsequently divided by the previous cutoff values into three sub-groups per parameter for further analyses. Results showed that 28 (8.8%) patients were underweight, 168 patients (52.5%) had normal weight, and 124 patients (38.8%) were overweight.

To examine the correlations among BMI, we compared the patients' characteristics with regard to the sub-groups classified by BMI (Table 2). No significant differences were observed with regard to BMI.

Survival analysis

Three hundred and twenty patients were followed-up for a mean (standard deviation) of 50.9 (34.1) months. Kaplan-Meier analysis yielded 1-, 3-, and 5-year OS rates of 87.2%, 74.1%, and 62.2%, respectively, and corresponding PFS rates of 74.2%, 57.8%, and 49.4%, respectively. Figure 1 presents the OS and PFS curves according to the pretreatment BMI, based on previously defined cutoff values. In summary, the BMI values of overweight patients correlated significantly with superior OS and with PFS. For continuous variables, the survival group showed both higher BMI (24.6 ± 3.7 kg/m² vs. 22.7 ± 4.0 kg/m²; t -value = -4.4 ; $P = 0.000$).

Cox proportional hazard model

Multivariate Cox proportional hazard regression model analyses indicated that the independent prognostic factors for OS included tumor stage, and adverse pathological features (Table 3). Patients with the underweight had a poorer prognosis than those who were normal or overweight ($P = 0.022$) and compared with the overweight group (OR = 1.963; CI = 1.090–3.535; $P = 0.025$). Patients with the normal weight

had a poor prognosis than those who were overweight (OR = 1.683; CI = 1.116–2.539; $P = 0.013$). In comparison with the histopathological status, such as surgical margin, DOI, PNI, LVSI, and ENE, poor prognoses was observed only with DOI (OR = 2.399; CI = 1.459–3.943; $P = 0.001$) and ENE (OR = 2.467; CI = 1.540–3.951; $P = 0.000$).

Discussion

In this multifactorial study, the pretreatment BMI value was found to be associated with the OS of patients with OSCC. Although all patients who enrolled in this study underwent resection, with or without adjuvant therapy, those with a low BMI (< 18.5 kg/m²) were considered underweight with regard to their nutritional status [13]. Moreover, the adverse features were analyzed by univariate and multivariate Cox regression and only DOI and ENE were identified as having prognostic importance. Furthermore, the result was similar to that reported by other studies in literature.

A cancer patient's nutritional status greatly influences OS. Malnutrition frequently affects patients with head and neck cancer, with a prevalence rate of 60% prior to diagnosis [15]. Previous evaluations of poor nutritional status among patients with oral cavity cancer were based on dynamic changes in various parameters including body weight, dysphagia, and even cachexia [7, 16, 17]. However, individual pretreatment nutritional status is also a useful parameter, and along with other related factors, could serve as an early marker preceding oral cavity cancer diagnosis, as well as a target for the prevention and reduction in the risk of oral cavity cancer among undernourished populations [18].

Our study demonstrates that nutritional factor of BMI was associated with OSCC outcomes. According to the categorization of BMI in the literature [19], underweight is below 18.5 kg/m², normal weight is 18.5 to 25 kg/m², overweight is 25 to 29.9 kg/m², and obese is over 30 kg/m². In our study, a BMI below 18.5 kg/m² indicated an underweight status, whereas a BMI above 25.0 kg/m² indicated an overweight or obese status. On survival analysis, the survival group showed a higher BMI value than the non-survival group on t test with continuous variables, and the overweight sub-group with BMI > 25.0 kg/m² showed higher survival rate in a Kaplan-Meier OS plot; thus, pretreatment BMI may indicate a better nutritional status to ensure that patients are better prepared for lengthy therapeutic periods, which may eventually prolong survival [20]. Patients with a low preoperative BMI had lower OS rates than those with higher (overweight) BMI values. This result is in agreement with the findings of previous studies [19, 21], as well as a large case-control study in which the odds ratio (OR) for poor survival was elevated in both the lower BMI and obese groups [22]. However, obesity by itself acts as an adverse prognostic factor, as obese patients were

Table 1 Demographic characteristics of patients

Characteristics		No. of patients	Percentage (%)
Sex	Men	294	91.9
	Women	26	8.1
Mean age (years)	52.2 (range, 23–84)	320	100.0
Tobacco consumption	No	60	18.8
	Yes	260	81.3
Alcohol consumption	No	81	25.3
	Yes	239	74.7
Betel nut consumption	No	70	21.9
	Yes	250	78.1
Overall TNM ^d stage	I	83	25.9
	II	73	22.8
	III	49	15.3
	IV	115	35.9
T classification	1	100	31.3
	2	106	33.1
	3	34	10.6
	4	80	25.0
N classification	N0	210	65.6
	N1	43	13.4
	N2a	2	0.6
	N2b	55	17.2
	N2c	10	3.1
Depth of invasion	≤ 5 mm	93	29.1
	> 5 mm	227	70.9
Perineural invasion	Negative	264	82.5
	Positive	56	17.5
Lymphovascular invasion	Negative	290	90.6
	Positive	30	9.4
Extranodal extension	Negative	269	84.1
	Positive	51	15.9
Surgical margin	≥ 5 mm	220	68.8
	< 5 mm	89	27.8
	Positive	11	3.4
Treatment	Surgery only	82	25.6
	Surgery + RT ^c	45	14.1
	Surgery + CT ^b	51	15.9
	Surgery + CCRT ^a	142	44.4
Anatomical site	Lip	2	0.6
	Retromolar trigone	15	4.7
	Gingiva	40	12.5
	Tongue	135	42.2
	Palate	6	1.9
	Buccal mucosa	111	34.7
	Mouth floor	11	3.4
Follow-up duration for all patients (months)	Mean 50.9 ± 34.1	320	100.0
	Median 44		
	Range 0–138		

^a CCRT, concurrent chemoradiotherapy; ^b CT, chemotherapy; ^c RT, radiotherapy; ^d TNM, tumor, node, metastasis

Table 2 Characteristics of the total number of patient and the sub-groups, stratified by body mass index, serum uric acid, and serum albumin cutoff values

		BMI ^a (kg/m ²)				
			< 18.5	≥ 18.5 < 25.0	≥ 25.0	
Variable	Total	No. of patients				<i>P</i> value
Age (years)						0.289
≥ 60	< 60	248	25	129	94	0.236
		72	3	39	30	
Sex						0.481
	Men	294	28	154	112	
	Women	26	0	14	12	
Stage						0.124
	I	83	4	41	38	
	II	73	6	38	29	0.385
III		49	5	24	20	
	IV	115	13	65	37	
Tobacco consumption						0.193
	No	60	8	25	27	
	Yes	260	20	143	97	
Betel nut consumption						0.193
	No	70	8	32	30	
	Yes	250	20	136	94	
Alcohol consumption						0.193
	No	81	11	39	31	
	Yes	239	17	129	93	

*Indicates a significant difference ($P < 0.05$)

^aBMI, body mass index

previously found to have significantly poor OS rates than overweight patients [23].

Pathological TNM staging, which is based on lesion size and the number of metastatic nodes, is critical to

determine the appropriate adjuvant treatment for oral cancer. When used alone, the conventional TNM staging category for OSCC is insufficient for survival analysis; a combination of adverse features and other nutritional factors is required. With regard to adverse features, insufficient surgical margin, lymph node metastasis with ENE, PNI, LVSI, and a large tumor invasion depth are well-known indicators of poor prognoses of OSCC. These adverse features that may shorten patients' survival period [24–26]; this data were presented in our study with the univariate analysis. However, on multivariate Cox regression analysis, only BMI influenced patient survival. In terms of adverse features, only DOI and ENE remained as prognostic factors, a result that corresponded with the change in the 8th edition AJCC staging system [27]. Because of their importance as prognostic factors, DOI and ENE were included by the 8th edition AJCC staging system. In summary, nutritional factors were found to be important prognostic factors in patients with OSCC, and pretreatment BMI was shown to have more influence than other adverse features, such as surgical margin, PNI, and LVSI, in our study.

This study has some limitations. The sample size was limited by patients' enrollment and poor compliance with follow-up. Accordingly, a larger number of patients should be enrolled in future studies, along with the inclusion of other pathological patterns of oral cancer. Future studies should also consider and compare several pathological factors as potential predictive factors for the prognosis of OSCC. For instance, ENE, as an essential independent adverse prognostic factor could be sub-grouped according to the ENE severity, based on the number of ENE [28]. Despite these limitations, age, sex, carcinogen exposure, and cancer sub-site distributions of the patients in our study were very similar to those observed in majority of the oral cancer cases diagnosed in Taiwan [29].

Fig. 1 Univariate analysis of the effects of pretreatment BMI on overall and progression-free survival. BMI body mass index

Table 3 Univariate and multivariate analyses of the prognostic factors related to 5-year overall survival

Variables (<i>n</i> , %)	5-year survival (%)	OS ^d			
		Univariate analysis <i>P</i> value	Multivariate analysis <i>P</i> value	Adjusted OR ^c	95% CI ^b
Sex					
Male (294, 91.9)	61.4	0.444			
Female (26, 8.1)	72.9				
Age (years)					
< 60 (248, 77.5)	63.8	0.291			
≥ 60 (72, 22.5)	56.2				
BMI^a (kg/m²)					
≥ 25.0 (124, 38.8)	73.8	0.006*	0.022*	1.000	
≥ 18.5, < 25.0 (168, 52.5)	54.4			1.683	1.116–2.539
< 18.5 (28, 8.8)	53.3			1.963	1.090–3.535
Tobacco consumption					
No (60, 18.8)	63.2	0.524			
Yes (260, 81.2)	62.0				
Betel nut consumption					
No (70, 21.9)	54.7	0.537			
Yes (250, 78.1)	64.1				
Alcohol consumption					
No (81, 25.3)	61.0	0.960			
Yes (239, 74.7)	62.4				
Surgical margin					
≥ 5 mm (220, 68.8)	65.9	0.000*	0.191		
< 5 mm (89, 27.8)	60.0				
Positive (11, 3.4)	13.6				
DOI^e					
≤ 5 mm (93, 29.1)	84.6	0.000*	0.001*	1.000	
> 5 mm (227, 70.9)	53.1			2.399	1.459–3.943
PNI^f					
Negative (264, 82.5)	68.4	0.000*	0.410		
Positive (56, 17.5)	30.5				
LVSI^g					
Negative (290, 90.6)	66.2	0.000*	0.322		
Positive (30, 9.4)	17.3				
ENE^h					
Negative (269, 84.1)	68.6	0.000*	0.000*	1.000	
Positive (51, 15.9)	26.0			2.467	1.540–3.951

*Indicates a significant difference, $P < 0.05$

^a BMI, body mass index; ^b CI, confidence interval; ^c OR, odds ratio; ^d OS, overall survival; ^e DOI, depth of invasion; ^f PNI, perineural invasion; ^g LVI, lymphovascular invasion; ^h ENE, extranodal extension

Conclusions

In conclusion, preoperative low BMI was found to correlate significantly with poor survival among patients with OSCC, and the adverse features of ENE and DOI > 5 mm were also influential in the analysis of overall survival. The finding suggests that an underweight status before treatment underweight status is a key factor in reducing the OS time in patients with oral cancer, and that patients in this condition should receive more intensive nutritional supplementation and cautious treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Ethical Committee of the Tri-Service General Hospital (Taipei, Taiwan) approved this retrospective study (institutional review board protocol no.: 2-106-05-082).

Informed consent Informed consent was obtained from all the individual participants included in the study.

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