Original Article

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Prognostic Significance of PD-L1 and mTOR Expression in Oral Squamous Cell Carcinoma

Nattinee Charoen, M.D.[1], Kitti Jantharapattana, M.D.[2], Paramee Thongsuksai, M.D.[1]

[1]Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

[2]Department of Otolaryngology Head and Neck Surgery, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

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Abstract:

Objective: Programmed cell death ligand 1 (PD-L1) and mammalian target of rapamycin (mTOR) are key players in host immune evasion and oncogenic activation, respectively. Evidence of the prognostic role in oral squamous cell carcinoma (OSCC) is conflicting. This study examined the associations of PD-L1 and mTOR expression with 5-year overall survival in OSCC patients.

Material and Methods: The expressions of PD-L1 and mTOR proteins were immunohistochemically evaluated on tissue microarrays of 191 patients with OSCC who were treated by surgery at Songklanagarind Hospital, Thailand from 2008 to 2011. Cox regression analysis was used to determine independent prognostic factors.

Results: PD-L1 expression was observed in 14.1% of cases while mTOR expression was present in 74.3% of cases. Females were more likely to have tumors with PD-L1 (p-value=0.007) and mTOR expressions (p-value=0.003) than males. In addition, lower clinical stage and well differentiated tumor are more likely to have mTOR expression (p-value= 0.038 and p-value<0.001, respectively). Cox regression analysis showed that age, tumor stage, nodal stage, combined surgical treatment with radiation or chemoradiation therapy, surgical margin status, PD-L1 expression and mTOR expression are independent prognostic factors. High PD-L1 expression (hazard ratio (HR) 3.14, 95% confidence interval (CI), 1.26–7.79) and high mTOR expression (HR 1.69, 95% CI, 1.00–2.84) are strong predictors of poor outcome.

Conclusion: A proportion of OSCC expressed PD-L1 and mTOR proteins. Expression of PD-L1 and mTOR proteins are strong prognostic factors of OSCC.

Keywords: oral squamous cell carcinoma, PD-L1, mTOR, prognosis

Contact: Assoc. Prof. Paramee Thongsuksai, M.D.
Department of Pathology, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand.
E-mail: tparamee@gmail.com

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Introduction

Cancer of the oral cavity is one of the common malignancies worldwide with an estimated 354,864 new cases and 177,384 deaths in 2018.[1] The incidence is varied in different countries, being higher in low socioeconomic countries. In Thailand, the age-standardized rate of oral cancer (9.1 per 100,000) is higher in the southern region than in other regions.[2] The majority of oral cancer is squamous cell carcinoma. Surgery and radiation and adjuvant chemotherapy significantly improve survival rates in the early stage.[2] However, the prognosis is still poor and 5-year overall survival rate is up to 60.0% in advanced stage.[3,4] Chemoradiation therapy is, however, associated with high morbidity. Currently, novel immune and targeted therapies including programmed cell death ligand 1 (PD-L1) and mammalian target of rapamycin (mTOR) inhibitors are being investigated in many cancer types.[5,6] Thus, evaluation of PD-L1 and mTOR expression and their prognostic significances are important in the provision of information on the potential benefits from the usage of these novel therapies.

PD-L1, a cell surface molecule, is a key player in the immune suppression pathway. Under physiologic conditions, PD-L1 ligand on antigen-presenting cells binds to the programmed death-ligand 1 receptor on activated T cells, leading to reduced proliferation of antigen-specific T cell.[7] This mechanism plays an important role in self-tolerance along with protection against autoimmunity. However, various tumor cell types can express PD-L1, enabling them to evade immune detection and therefore, elimination.[8] For clinical utility, the effectiveness of blocking agents against PD-L1 is being evaluated, and has shown a promising result.[9] PD-L1 expression on tumor cells has been found to be related with poor prognosis in many cancer types.[10-12] However, reports of prognostic significance in oral squamous cell carcinoma (OSCC) are controversial.[13-16]

mTOR protein is a key downstream molecule of the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway which involves in various cellular functions including cell proliferation, survival, and motility.[17] mTOR is frequently upregulated in many cancers and is related to poor prognosis,[18,19] However, clinical trials have shown only modest objective response rates, and so a combination of targeted therapeutic agents has been suggested as an alternative possibility.[20,21] Nevertheless, simultaneous evaluation of PD-L1 and mTOR expression in tumors with regards to clinical outcomes has rarely been reported. Therefore, this study aimed to examine the association of PD-L1 and mTOR protein expressions with 5-year overall survival (OS) in surgically resected OSCC patients.

Material and Methods

This cohort of patients had been included in our previous study.[22] They were patients who were diagnosed of OSCC and treated by surgery at Songklanagarind Hospital, Thailand, from January 2008 to December 2011. The Human Ethics Committee of the Faculty of Medicine approved our study protocol (REC. 59-295-05-01). Clinical data, lifestyle habits (smoking and alcohol drinking) and pathological information were retrieved from medical records and pathological reports. The patients were staged using the tumor, node, and metastasis (TNM) staging system, according to the guideline of the American Joint Committee on Cancer, 7th edition, 2010. Date of death was acquired from the civil registration system

Treatments given to the patients were of curative intent. The decision on individual treatment resulted from multidisciplinary tumor board recommendations, which were on the oncologic principles of oral cancer treatment. For the early stage, a single treatment modality, such as surgery, was given primarily. If there was an adverse pathological result such as lymphovascular invasion or

inadequate resection of the primary tumor, adjuvant radiation or chemoradiation was administrated. For advanced stages, a combined treatment modality was applied. Adjuvant chemoradiation using a Platinum-based regimen was indicated in cases of incomplete resection margins and/or extranodal extensions. Patients were deemed to have local tumor recurrence if a histologically proven cancer reappeared at the site of first occurrence after completion of treatment for 6 months.

Tissue microarray (TMA) construction

TMAs were constructed as previously described.[22] Briefly, the histologic slides were reviewed, then, the area having abundant viable tumor cells were circled. Then, the corresponding areas on the paraffin-embedded tissue blocks were outlined with a felt tip marker. A TMA having two 2-mm cores from each case was constructed using Quick Ray® manual tissue microarrayer (Unitma, Seoul, Korea).

Immunuhistochemistry and staining evaluation

Immunohistochemistry for PD-L1 expression was performed in EnVision FLEX visualization system on Autostainer Link 48 (Dako, California, United States of America). The 3-μm-thick sections were deparaffinized with xylene and rehydrated in graded alcohol. Antigen was retrieved via PT Link (Dako PT109) using EnVision™ FLEX Target Retrieval Solution according to manufacturer's instruction. Following FLEX peroxidase blocking for 5 minutes, the sections were incubated with primary antibodies against PD-L1 (monoclonal mouse anti-PD-L1, clone 22C3, Dako). Diaminobenzidine (DAB) was used as a chromogen for color development. The slides were then counterstained by EnVision FLEX hematoxylin (Code K8008).

Immunohistochemistry for mTOR expression was performed in an automated immunostainer (Leica BOND-MAX, Melbourne, Australia). Antigens were retrieved in the Tris-EDTA buffer (Bond Epitope Retrieval Solution 2, Leica Biosystem, Newcastle Upon Tyne, United Kingdom), pH 9, in a pressure cooker at 95 °C for 4 mins. The sections were then incubated with bond peroxidase-blocking reagent (Bond Polymer Refine Detection, Leica Biosystem, Newcastle Upon Tyne, United Kingdom). The sections were then incubated with primary antibodies against mTOR (polyclonal PAB26759, Abnova; dilution 1:50). Antibody reactions were detected by use of a bond polymer refine detection kit (Leica) and visualized by the methods described above.

Immunostaining was independently evaluated under light microscope (Olympus CX41) by N.C. and P.T. who did not know the patients' outcome at the time of evaluation; whereas in discordant cases, a consensus was achieved by discussion. The tissue core contained less than 10.0% of viable tumor cells were not evaluated. PD-L1 expression was evaluated according to the manufacturer protocol by using a Tumor Proportion Score (TPS), this being the percentage of tumor cells showing partial or complete membrane staining at any intensity. The cases were considered to have a low PD-L1 expression if TPS was 1.0-49.0% or a high PD-L1 expression if the TPS $\geq$ 50.0%. For mTOR expression, the total immunoreactivity score was determined by multiplication of intensity score (0-3) by the percentage of positive stained tumor cells. mTOR expression was categorized into three groups according to the quartile values as: negative expression (score $\leq$15), low expression (15 < score $\leq$60) and high expression (3rd & 4th quartile, score >60).

Percentages for categorical variables and mean for continuous variable are presented as descriptive statistics. Relationship between clinicopathological characteristics and protein expressions were assessed by chi-square or Fisher's exact test as appropriate. OS time was interval from date of diagnosis to date of death from any cause

or to date of last follow-up. Censored observations were defined as patients who were alive at the time of last follow-up (June 2016). Kaplan-Meier survival probability was estimated and the difference among the survival curves was tested by log-rank test. The Cox proportion hazard model was used to evaluate independent prognostic parameters. P-value less than 0.05 was set as statistical significance. Intercooled Stata 6.0 was used an analysis software.

Results

Patients' characteristics

A total of 191 cases from 202 eligible patients had adequate tissues for immunohistochemistry assessment. Table 1 presents the clinical and pathological characteristics of the patients. The mean age of the patients was 61 years. Less than half of the cases (45.5%) were stage I-II disease. The highest number of patients (49.7%) was treated by surgical resection with post-operative radiotherapy, 33.0% were treated by surgical resection alone, and 17.3% by surgery coupled with chemoradiation therapy.

Protein expressions and association with clinicopathological characteristics

Two tissue cores were examined in 178 cases and only one core in 13 cases (nine cores of tissue loss and four cores of inadequate tumor cells). PD-L1 expression was noted as membrane staining and mTOR expression as cytoplasmic and membrane staining (Figure 1). The majority of cases (164, 85.9%) showed negative PD-L1 expression and 19 (9.9%) and 8 (4.2%) cases showed low and high PD-L1 expressions, respectively. The median total score of mTOR immunoreactivity was 60 (inter-quartile range 15, 120). Negative, low and high mTOR expression was noted in 49 (26.7%), 47 (24.6%) and 95 (49.7%) tumors, respectively.

Table 1 Clinicopathological characteristics of 191 oral cancer patients

Variables	Category	Number (%)
Gender	Female	69 (36.1)
	Male	122 (63.9)
Age (years)	≤65	113 (59.2)
	>65	78 (40.8)
Smoking	Never	64 (33.5)
	Habitual	103 (53.9)
	Unknown	24 (12.6)
Alcohol drinking	Never/social	81 (42.4)
	Habitual	78 (40.8)
	Unknown	32 (16.7)
Tumor site	Tongue	91 (47.6)
	Floor of mouth	34 (17.8)
	Gum	22 (11.5)
	Buccal mucosa	21 (11.0)
	Others	23 (12.0)
T stage	T1-T2	114 (59.7)
	T3-T4	77 (40.3)
N stage	N0	129 (67.5)
	N1- N3	62 (32.5)
Clinical staging	I	35 (18.3)
	II	52 (27.2)
	III	30 (15.7)
	IV	74 (38.7)
Treatment	Surgery alone	63 (33.0)
	Surgery + RT	95 (49.7)
	Surgery + CCRT	33 (17.3)
Tumor recurrence	No	165 (86.4)
	Yes	26 (13.6)
Tumor differentiation	Well	142 (74.3)
	Moderate	43 (22.5)
	Poor	6 (3.1)
Surgical margin status	Free of tumor	157 (82.2)
	With tumor	34 (17.8)
Lymphovascular invasion	Absence	177 (92.7)
	Presence	14 (7.3)
Perineural invasion	Absence	173 (90.6)
	Presence	18 (9.4)

RT=radiotherapy, CCRT=concurrent chemoradiation therapy

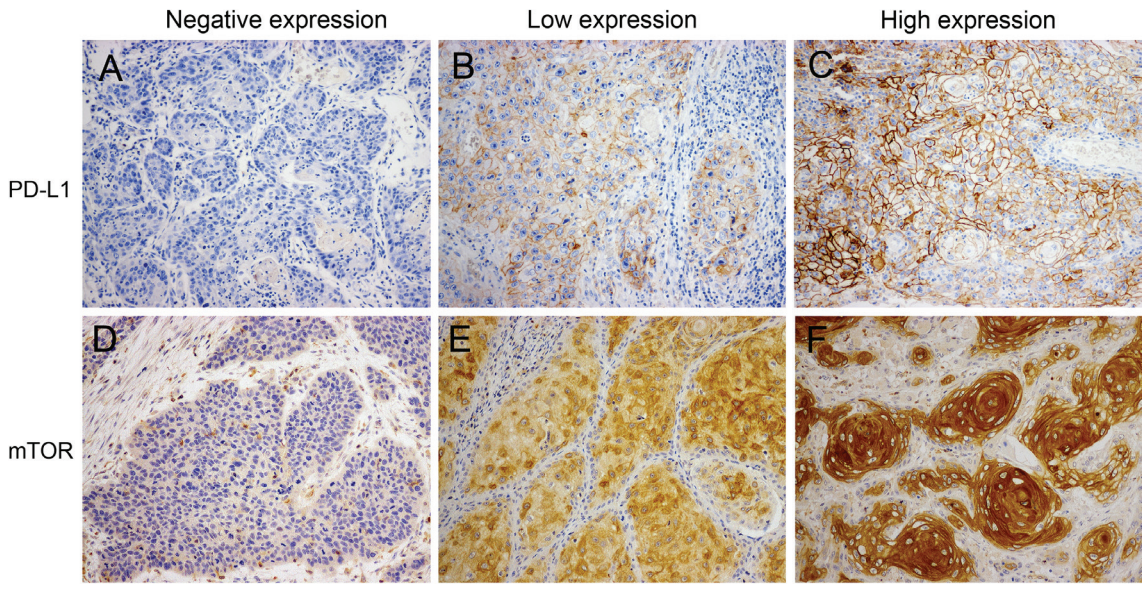

Figure 1 Immunohistochemical staining of the representative cases for PD-L1 expression; negative (A), low (B) and high expression (C) and for mTOR expression; negative (D), low (E) and high expression (F) Original magnification, 200x

The association of PD-L1 and mTOR expressions is shown in Table 2 and Table 3, respectively. Due to the small number of cases, low and high PD-L1 expressions were grouped as positive PD-L1 expression. Only gender was associated with PD-L1 expression while gender, clinical stage and tumor differentiation were associated with mTOR expression. Females were more likely to have tumor with PD-L1 and mTOR expressions than males. High mTOR expression was seen more frequently found in lower clinical stage and well-differentiated tumor. The remaining clinical variables were not found to be associated with either PD-L1 or mTOR expressions.

Association of PD-L1 and mTOR expression with 5-year overall survival

Median survival time was 49.8 months (range 3.1 to 101.5 months). The 5-year OS was 45.5% (95% confidence interval (CI), 38.3-52.4). Figure 2 shows the Kaplan-Meier curves stratified by PD-L1 and mTOR expression level. Increased level of PD-L1 expression was associated with poorer survival (p-value=0.055), while mTOR expression level showed no difference of survival probability (p-value=0.134).

Results of Cox regression analyses are shown in Table 4. Age, T stage, N stage, treatment and PD-L1 expression were significantly associated with poor survival in univariate analysis. In multivariable analysis, all of these five factors and two additional variables including surgical margin and mTOR expression were significant prognostic factors. Both PD-L1 and mTOR expression were associated with poorer prognosis compared to negative expression. In addition, increasing level of PD-L1 expression was associated with worsening prognosis in stepwise manner [low PD-L1, HR 1.87 (95% CI, 1.03-3.38); high PD-L1, HR 3.14 (95% CI, 1.26-7.79)]. We did not evaluate combined expression of both proteins, as the amount of positive PD-L1 was too limited.

Table 2 Association of PD-L1 expression with clinicopathological variables in 191 oral cancer patients

Variables	PD-L1 expression		p-value
	Negative	Positive	
	Number (%)	Number (%)	
Age (years)			
≤65	98 (59.8)	15 (55.6)	0.681
>65	66 (40.2)	12 (44.4)	
Gender			
Male	111 (67.7)	11 (40.7)	0.007
Female	53 (32.3)	16 (59.3)	
Smoking			
Never	57 (34.8)	7 (25.9)	0.660
Habitual	87 (53.0)	16 (59.3)	
Unknown	20 (12.2)	4 (14.8)	
Alcohol drinking			
Never	70 (42.7)	11 (40.7)	0.909
Habitual	66 (49.2)	12 (44.4)	
Unknown	28 (17.1)	4 (14.8)	
T stage			
T1-T2	99 (60.4)	15 (55.6)	0.637
T3-T4	65 (39.6)	12 (44.4)	
N stage			
N0	110 (67.1)	19 (70.4)	0.735
N1-N3	54 (32.9)	8 (29.6)	
Clinical staging			
I-II	76 (46.3)	11 (40.7)	0.588
III-IV	88 (53.7)	16 (59.3)	
Treatment			
Surgery	53 (32.3)	10 (37.1)	0.573
Surgery + RT	84 (51.2)	11 (40.7)	
Surgery + CCRT	27 (16.5)	6 (22.2)	
Tumor differentiation			
Well	123 (75.0)	19 (70.4)	0.610
Moderate-poor	41 (25.0)	8 (29.6)	
Surgical margin			
Free of tumor	134 (81.7)	23 (85.2)	0.662
With tumor	30 (18.3)	4 (14.8)	
Lymphovascular invasion			
Absence	152 (92.7)	25 (92.6)	0.987
Presence	12 (7.3)	2 (7.4)	
Perineural invasion			
Absence	149 (90.9)	24 (88.9)	0.746
Presence	15 (9.1)	3 (11.1)	

PD-L1=programmed cell death ligand 1, RT=radiotherapy, CCRT=concurrent chemoradiation therapy

Table 3 Association of mTOR expression with clinicopathological variables

Variables	mTOR expression			p-value
	Negative	Low	High	
	Number (%)	Number (%)	Number (%)	
Age (years)				
≤65	30 (61.2)	26 (55.3)	57 (60.0)	0.818
>65	19 (38.88)	21 (44.7)	38 (40.0)	
Gender				
Male	41 (83.7)	29 (61.7)	52 (54.7)	0.003
Female	8 (16.3)	18 (38.3)	43 (45.3)	
Smoking				
Never	12 (24.5)	19 (40.4)	33 (34.8)	0.529
Habitual	31 (63.3)	22 (46.8)	50 (52.6)	
Unknown	6 (12.2)	6 (12.8)	12 (12.6)	
Alcohol drinking				
Never	16 (32.6)	19 (40.4)	46 (48.4)	0.117
Habitual	26 (53.1)	22 (46.8)	30 (31.6)	
Unknown	7 (14.3)	6 (12.8)	19 (20.0)	
T stage				
T1-T2	28 (57.1)	25 (53.2)	61 (64.2)	0.414
T3-T4	21 (42.9)	22 (46.8)	34 (35.8)	
N stage				
N0	27 (55.1)	31 (65.9)	71 (74.7)	0.056
N1-N3	22 (44.9)	16 (34.1)	24 (25.3)	
Clinical staging				
I-II	17 (34.7)	18 (38.3)	52 (54.7)	0.038
III-IV	32 (65.3)	29 (61.7)	43 (45.3)	
Treatment				
Surgery	13 (26.5)	13 (27.7)	37 (38.9)	0.183
Surgery + RT	25 (51.0)	29 (61.7)	41 (43.2)	
Surgery + CCRT	11 (22.5)	5 (10.6)	17 (17.9)	
Tumor differentiation				
Well	22 (44.9)	35 (74.5)	85 (89.5)	<0.001
Moderate-poor	27 (55.1)	12 (25.5)	10 (10.5)	
Surgical margin				
Free of tumor	36 (73.5)	37 (78.7)	84 (88.4)	0.065
With tumor	13 (26.5)	10 (21.3)	11 (11.6_	
Lymphovascular invasion				
Absence	44 (89.8)	43 (91.5)	90 (94.7)	0.525
Presence	5 (10.2)	4 (8.5)	5 (5.3)	
Perineural invasion				
Absence	44 (89.8)	40 (85.1)	89 (93.7)	0.252
Presence	5 (10.2)	7 (14.9)	6 (6.3)	

mTOR=mammalian target of rapamycin, RT=radiotherapy, CCRT=concurrent chemoradiation therapy

Table 4 Univariate and multivariate cox regression for overall survival of oral cancer patients

Variables	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (years)				
≤65	1		1	
>65	1.59 (0.09–2.31)	0.015	2.64 (1.68–4.16)	<0.001
Sex				
Male	1			
Female	1.35 (0.92–1.97)	0.122		
Smoking				
Never	1			
Habitual	1.25 (0.83–1.89)	0.279		
Unknown	0.87 (0.46–1.65)	0.672		
Alcohol drinking				
Never				
Habitual	1.31 (0.88–1.96)	0.177		
Unknown	0.77 (0.43–1.35)	0.358		
T stage				
T1–T2	1		1	
T3–T4	2.86 (1.95–4.18)	0.000	1.97 (1.28–3.04)	0.002
N stage				
N0	1		1	
N1	1.98 (1.19–3.29)	0.012	2.41 (1.36–4.29)	0.003
N2–N3	1.84 (1.15–2.96)	0.648	1.71 (1.02–2.84)	0.041
Treatment				
Surgery	1		1	
Surgery + RT	3.06 (1.89–4.96)	0.000	2.64 (1.53–4.56)	0.033
Surgery + CCRT	2.58 (1.42–4.70)	0.002	2.19 (1.07–4.51)	<0.001
Differentiation				
Well	1			
Moderate-poor	1.11 (0.72–1.69)	0.648		
Surgical margin				
Free of tumor	1		1	
With tumor	1.34 (0.84–2.16)	0.222	2.09 (1.19–3.66)	0.011
Lymphovascular invasion				
Absence	1			
Presence	1.58 (0.82–3.03)	0.168		
Perineural invasion				
Absence	1			
Presence	1.08 (0.57–2.08)	0.802		
PD-L1 expression				
Negative	1		1	
Low	1.49 (0.85–2.62)	0.166	1.87 (1.03–3.38)	0.038
High	2.35 (1.03–5.37)	0.044	3.14 (1.26–7.79)	0.014
mTOR expression				
Negative	1		1	
Low	1.56 (0.93–2.59)	0.091	1.98 (1.15–3.41)	0.014
High	1.06 (0.65–1.73)	0.831	1.69 (1.00–2.84)	0.049

HR=hazard ratio, CI=confidence interval, RT=radiotherapy, CCRT=concurrent chemoradiation therapy, PD-L1=programmed cell death ligand 1, mTOR=mammalian target of rapamycin

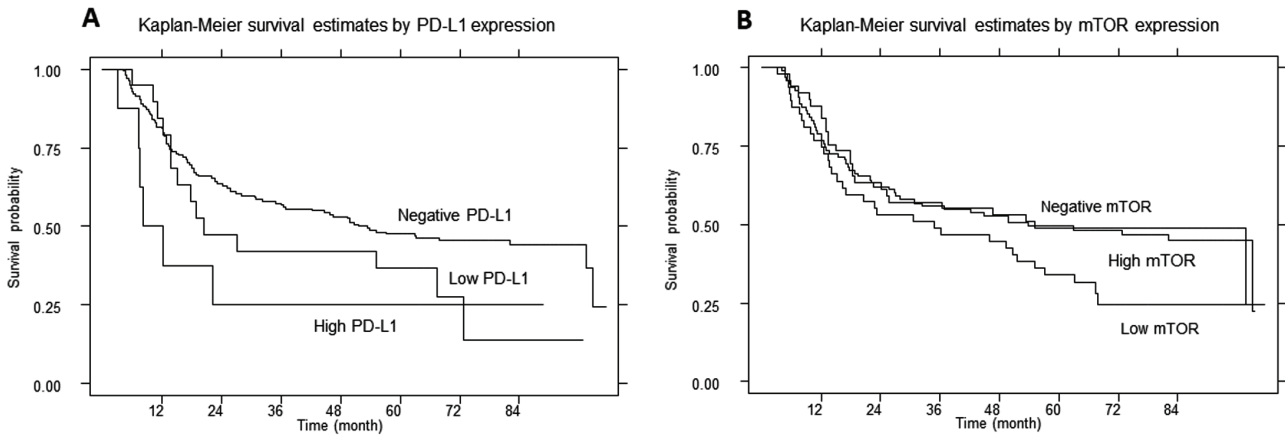

Figure 2 Kaplan-Meier curves of overall survival in patients with oral squamous cell carcinoma according to PD-L1 (A) and mTOR expression (B)

Discussion

Capabilities of immune evasion as well as enhancing proliferative signaling are two important hallmarks of cancer that enable tumor development, progression and dissemination. PD-L1 and mTOR are, respectively, key players in these two processes. In this study, we found that 14.0% of OSCC expressed PD-L1 and 74.3% expressed mTOR protein. In addition, tumors with PD-L1 or mTOR expression were significantly associated with poor prognosis.

We found 14.0% of tumors expressed PD-L1, while other studies reported a frequency of 46.0-87.0%.[13,15,16,23,24] These conflicting results may be due to various factors, including patient characteristics and immunohistochemistry technique. Hanna et al.[16] confined their study to young patients aged ≤45 years and Kogashiwa et al.[15] included patients with advanced disease (stage III-IVa). By contrast, we included patients of any age and any stage, and nearly half of them were stage I-II. Regarding immunohistochemistry, various antibodies (monoclonal and polyclonal) and scoring strategies of PD-L1 expression were applied. We used PD-L1 22C3 pharmDx which is a FDA-approved diagnostic antibody used for selecting lung cancer patients for anti-PD-L1 therapy.[9] This antibody and its evaluation criteria have been reported to have a high inter-observer reproducibility.[25] By contrast, Ngamphaiboon et al.[24], who also studied in Thai patients, used SP142 assay in 203 head and neck squamous cell carcinoma (HNSCC) and found a very high (80.0%) PD-L1 expression.

Prognostic role of PD-L1 expression in OSCC or HNSCC have been reported. However, many studies have not found the significant association of PD-L1 with survival outcome.[13,23,26] Besides, some studies reported a better survival in OSCC with PD-L1 expression[15,27,28] which is reverse to the functional roles of PD-L1 as immune invader and tumor enhancer. A pooled analysis of these studies reported in the form of meta-analysis shows non-significant results (HR 0.60, 95% CI 0.33-1.10) with a high rate of heterogeneity among studies.[29] All of these studies except of Lin et al.[13] have a small number of study subjects (less than 100). By contrast, our study found that either low or high PD-L1 expressions were significantly related to poor survival in OSCC. High PD-L1 showed comparable or even stronger prognostic factors as compared to nodal stage which is a well-known strong predictor. Our results are consistent with the studies by Moratin et al.[30] and

Ngamphaiboon et al.[24], both of which have included a considerable large sample size (n=175 and n=203, respectively. The latter study is also from Thailand, performed in a tertiary hospital in the central part of the country.

Most HNSCC are found to have an activated PI3K/Akt/mTOR signaling pathway.[17,31] Based on recent meta-analysis in 12 studies of HNSCC, the frequency of expression of the pathway proteins stands at 74.4% (95% CI 63.3-84.0).[19,32] Consistent with this, our study also found that the majority of cases (70.0%) expressed an mTOR protein which is slightly higher than previous studies (range 53.0-64.0%).[33,34] This discrepancy may be due to the different clonality of antibodies and/or different expression scoring systems. We used polyclonal antibodies, coupled with an H-score system, while Monteiro et al.[33] used monoclonal antibody and a summation of intensity and percentage of positive tumor cells.

In our study, low mTOR expression was related to higher clinical stage. Besides, based on Kaplan-Meier curves, low mTOR expression group seems to have poorer survival than the high expression group, although it was not statistically significant. This is inconsistent with the theoretical expectation, as mTOR activation is likely to be associated with aggressive tumor behavior. As known, mTOR is one of the protein kinases in PI3K/AKT signaling pathway which interacts with many upstream and downstream molecules. The aforementioned relationship between mTOR and clinical stage, may therefore, be influenced by other molecules of the related pathways.

Regarding the association of mTOR expression and survival in OSCC, the Kaplan-Meier analysis and log rank test demonstrated no significant association of mTOR expression with overall survival (p-value=0.134). However, mTOR expression turns to be an independent prognostic factor in multivariate analysis. This is likely because the confounding effect on the relationship between mTOR and survival had been eliminated. The confounder here is likely to be clinical stage and nodal stage, as shown in Table 3 where these two variables are significantly associated with mTOR expression. We also performed subgroup analysis stratified by clinical stage - another strategy to determine confounder. The results showed significant HR of mTOR expression in stage III-IV group, but not in stage I-II group (data not shown). Our multivariate results are consistent with other authors, which reported that mTOR expression is significantly increased risk of death (HRs were 2.19[33] and 2.08[35]). Therefore, our study supports the importance of the mTOR pathway in the progression of OSCC.

Certain limitations have to be noted in this study. The retrospective nature of the study may have made it subject to selection and/or follow-up bias. In addition, we included patients who treated by surgical resection, and thus may have under-represented patients who could not tolerate surgical resection. Another important limitation is that we did not evaluate the prognostic role of combined PD-L1 and mTOR expression as the number of cases in each combined category was too small.

Conclusion

In summary, a proportion of OSCC expressed PD-L1 and mTOR proteins. PD-L1 and mTOR expressions were strong independent prognostic predictors in OSCC. These results may provide preliminary evidence for the potential benefit of novel therapy against PD-L1 and PI3K/Ark/mTOR pathway in the treatment of OSCC.

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Conflict of interest

All authors declare there is no conflict of interest.

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