Overexpression of CD164 in oral cavity squamous cell carcinoma predicts a favourable prognosis

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Abstract. The aim of the present study was to investigate the association between cluster of differentiation (CD) 164 expression with clinicopathological parameters and prognosis among patients with oral cavity squamous cell carcinoma (OSCC). The present study retrospectively reviewed 70 patients with OSCC who underwent curative primary surgery. A number of patients subsequently received postoperative chemoradiotherapy although the specimens were not exposed to radiation or chemotherapy prior to anti-CD164 antibody immunohistochemical staining. CD164 overexpression was arbitrarily defined as exhibiting an H-score of ≥120. Univariate and multivariate analyses were performed for sex, age, American Joint Committee on Cancer stage, tumour location, histological grade, surgical margin and H-score. The 5-year overall survival rate was 54.4% and the median follow-up time was 46 months for surviving patients. Univariate analyses revealed that a low overall survival rate was associated with advanced-stage disease (P<0.001), buccogingival tumour location (P=0.038) and a CD164 H-score of <120 (P=0.016). Multivariate Cox's regression analyses revealed that poor overall survival rate was associated with advanced-stage disease (P=0.001) and a CD164 H-score of <120 (P=0.04). CD164 overexpression in OSCC was associated with favourable survival rate. Thus, CD164 expression may be a clinically useful predictor of prognosis in patients with OSCC.

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Introduction

Oral cavity cancer represents ~2.6 and 1.5% of all malignancies among males and females, respectively and is a major global public health problem (1). The 2012 cancer registry report from the Taiwan Health Promotion Administration of the Ministry of Health and Welfare indicated that the incidence of oral cavity cancer was 20/100,000 and the annual mortality rate was 11/100,000, making it the fifth most common cause of cancer-related mortality in Taiwan. On the basis of histological data, oral cavity squamous cell carcinoma (OSCC) accounts for >90% of all oral cavity cancer cases; this histological subgroup is characterized by increased rates of tumour cell migration, invasion and metastasis (2).

Marked progress has been made in the treatment of OSCC. Wide excision of the tumour with neck dissection is the primary form of treatment with concurrent postoperative chemoradiotherapy improving outcomes for operable cases of locally advanced OSCC (3,4). However, despite the availability of multidisciplinary treatment, the survival rate for oral cavity cancer over the last decade has remained poor and remains a major cause of mortality (5,6). Furthermore, radiotherapy may lead to side effects including trismus and xerostomia (7,8). Therefore, several studies have attempted to identify prognostic pathological markers, including human papillomavirus (HPV) infection, which may help to decrease radiation doses in patients with favourable prognostic factors for head and neck cancer (9,10).

Cluster of differentiation (CD) 164, a glycoprotein and type I integral transmembrane sialomucin that is also known as endolyn or MGC-24 is encoded by the *CD164* gene located on human chromosome 6q21 (11). Three isoforms of CD164 have been identified (12-14). CD164 serves important roles in regulating proliferation, adhesion and differentiation in progenitor and hematopoietic stem cells as well as negative regulation of haematopoiesis (15). However, few cancer-associated studies have examined this protein and, to the best of our knowledge, no studies have considered it in the context of head and neck cancer (16-22). Therefore, the present study aimed to investigate the association of CD164 expression

with clinicopathological parameters and prognosis in patients with OSCC.

Materials and methods

Patients. The present study retrospectively reviewed 70 patients who were diagnosed with malignant OSCC between January 2000 and December 2010 at the Tri-Service General Hospital (Taipei, Taiwan). This sample only included patients with OSCC who underwent planned curative primary surgery with or without adjuvant chemoradiotherapy. Patients with other histological diagnoses including acinic cell carcinoma, adenoid cystic carcinoma, verrucous carcinoma, adenocarcinoma, sarcoma and mucoepidermoid carcinoma were excluded. Patients with metastatic oral cavity cancer, synchronous oral cancers or a history of malignancy or treatment at other hospitals were also excluded.

The present study was approved by the institutional review board of Tri-Service General Hospital (TSGH1-105-05-012) and the methods were carried out in accordance with the approved guidelines. Informed written consent was obtained from all subjects. The 70 eligible patients included 63 males and 7 females with an age range of between 29 and 72 years (median, 51 years). Pathological stages were classified in all 70 cases according to the 2010 staging criteria of the American Joint Committee on Cancer (AJCC) (23).

Treatment. All patients underwent standard primary surgery according to their clinical stage (5,6). Wide excision with supraomohyoid neck dissection was performed for early-stage cases; wide excision with ipsilateral modified radical neck, ipsilateral radical neck or bilateral radical neck dissection was performed for locally advanced cases. The majority of patients required flap reconstruction due to the large wound that was created by the surgical procedures.

A total of 21 patients (30%) underwent surgery alone, with the remaining 49 patients (70%) undergoing postoperative radiotherapy with or without chemotherapy. The radiation fields included the tumour bed, the ipsilateral upper neck for early-stage cases and the ipsilateral whole neck or bilateral neck for locally advanced cases. The radiation technique was intensity modulated radiotherapy with prescribed doses of between 60 and 66 Gy for the tumour bed and upper neck, and between 50 and 54 Gy for the lower neck with a daily fraction size of between 1.8 and 2.2 Gy.

All 43 cases of stage III-IV disease underwent postoperative concurrent chemoradiotherapy. The early standard for chemotherapy was previously cisplatin (80-100 mg/m^2 per day on days 1, 22 and 43) during the radiotherapy (24). However, since 2007, weekly cisplatin chemotherapy (30-40 mg/m^2) has also been considered a treatment option during radiotherapy (6,25). Following the concurrent chemoradiotherapy, 3 cycles of monthly adjuvant chemotherapy were administered to high-risk patients (cisplatin at 80 mg/m^2 on day 1 and fluorouracil at 1,000 mg/m^2 on days 1-4 as a 96 h infusion for each cycle). Overall survival time was defined as the time from the date of diagnosis to the date of mortality from any cause.

Tissue specimens and immunohistochemistry. Tumour specimens were soaked in 10% v/v formalin solution at room temperature for 24 h, and then the specimens were embedded in paraffin. The paraffin-embedded tumour tissues from the 70 patients prior to chemoradiotherapy treatment were obtained from the department of pathology, and a tissue microarray slide was constructed. To construct the tissue microarray, one core of 2 mm in diameter was taken from a selected area of each paraffin-embedded tumour tissue. The tissue microarray slide showed uniform staining as the original paraffin-embedded specimens. Serial 4 μm sections were excised and stained by a Leica autostainer XL (Leica Biosystems, Nussloch, Germany) for standard hematoxylin and eosin staining. Briefly, the procedure of hematoxylin and eosin staining included xylene 16 min, absolute alcohol 4 min 30 sec, wash out 1 min 30 sec, hematoxylin 4 min, wash out 3 min, 0.1% HCL 40 min, wash out 5 min, absolute alcohol 2 min, eosin 30 sec, absolute alcohol 5 min 10 sec and xylene 4 min 20 sec. The histopathological diagnosis of OSCC was confirmed by two experienced pathologists. On the basis of the histopathological grading, 17 tumours (24%) exhibited good differentiation, 37 tumours (53%) exhibited moderate differentiation and 16 tumours (23%) exhibited poor differentiation. The immunohistochemical staining for CD164 was performed according to the standard protocol (21). The sections were dried overnight at 37°C and were deparaffinized using xylene. All sections were treated using an antigen retrieval solution (Target Retrieval; Dako; Agilent Technologies, Inc., Santa Clara, CA, USA) at 95°C for 15 min before incubation overnight at 4°C with a polyclonal sheep anti-human CD164 antibody (1:100; R&D Systems, Inc., Minneapolis, MN, USA). A dilution of 1:100 purified rabbit anti-human CD164 antibody (HPA010636; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) was set for 60 min at room temperature, and secondary biotin-linked sheep anti-immunoglobulin antibody (B3275; Sigma-Aldrich; Merck KGaA) for 30 min at room temperature. The sections were developed using diaminobenzidine and counterstained using haematoxylin. These were incubated in horseradish peroxidase-conjugated streptavidin (Dako; Agilent Technologies, Inc.) for 2 min at room temperature. All slides were examined using Olympus BX51 (magnification, x400) and scored independently by the two pathologists, who were blinded to the patients' clinical information.

As staining intensity and distribution varied, cytoplasmic staining was scored using a 4-point scale (0, no staining; 1+, light staining at high magnification; 2+, intermediate staining; 3+, dark staining of linear membrane at low magnification; Fig. 1). Additionally, the percentage of stained cells was estimated for each intensity. The percentage of CD164-stained cells for each intensity was multiplied by the corresponding intensity score to obtain an immunostaining score (H-score) that ranged between 0 and 300 (26).

Statistical analysis. SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. Pearson's χ^2 test and Fisher's exact test were used to evaluate the association of CD164 expression with the patients' clinicopathological characteristics. Cumulative survival rate was evaluated using Kaplan-Meier estimator analysis and the log-rank test. All the independent factors were further tested using Cox's regression for multivariate comparison. P<0.05 was considered to

Table I. Associations between H-score and patient characteristics.

Characteristic	H-score <120, n (%)	H-score ≥120, n (%)	P-value
All cases	42 (60)	28 (40)	
Sex			
Male	37 (88)	26 (93)	0.515
Female	5 (12)	2 (7)	
Age, years			
<51	28 (67)	15 (54)	0.324
≥51	14 (33)	13 (46)	
AJCC stage			
I-II	31 (38)	12 (39)	0.270
III-IV	50 (62)	21 (42)	
Tumour location			
Buccal-gingival	24 (57)	12 (43)	0.241
Others	18 (43)	14 (57)	
Histopathological grade			
1	10 (24)	7 (25)	0.972
2	22 (52)	15 (54)	
3	10 (24)	6 (21)	
Surgical margin			
Negative	36 (86)	27 (96)	0.143
Positive	6 (14)	1 (4)	

AJCC, American Joint Committee on Cancer.

indicate a statistically significant difference for all known confounding factors, although P<0.025 was used to evaluate the significance of CD164 expression as its clinical relevance was unclear.

Results

A total of 9 patients (13%) had stage I disease, 18 patients (26%) had stage II disease, 16 patients (23%) had stage III disease and 27 patients (38%) had stage IV disease. None of the patients exhibited distant metastases at their presentation. The tongue was the most commonly affected site [30 patients (43%)] followed by the buccal mucosa [29 patients (41%)], gingiva [7 patients (10%)], tonsils (2 patients), palate (1 patient) and lip (1 patient). At the last follow-up, 34 patients (49%) had succumbed and 36 patients (51%) remained alive. The median follow-up for the surviving patients was 46 months (range, 4-120 months). Among all patients, the 5-year locoregional control and overall survival rates were 48.0 and 54.4%, respectively.

CD164 was primarily detected in the cytoplasm and cell membrane of the cancer cells and in the lymphocytes surrounding the tumours. A total of 17 patients (24%) exhibited a CD164 staining intensity of 3+, compared with 42 patients (60%) for 2+ and 11 patients (16%) for 1+. The median H-score was 106.5 (range, 23-243) and the samples were arbitrarily classed as having low CD164 expression (H-score <120) or
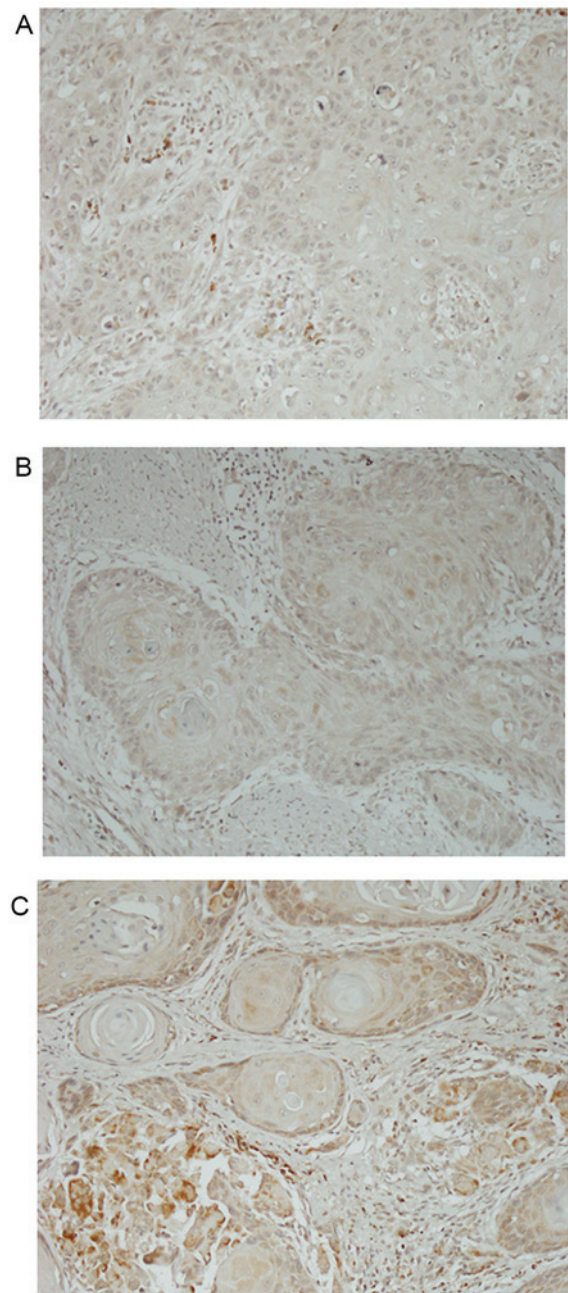

Figure 1. Immunohistochemical staining for CD164 in oral cavity squamous cell carcinoma tissues. Cytoplasmic staining was observed at distinct intensities: (A) 56% of the tissues exhibiting an intensity of 1+; (B) 66% of the tissues exhibiting an intensity of 2+; and (C) 26% of the tissues exhibiting an intensity of 3+. CD164 staining was also observed in the cell membrane and in lymphocytes surrounding the tumour cells. CD, cluster of differentiation.

high CD164 expression (H-score ≥120). Table I indicates that the H-score was not significantly associated with known prognostic factors including sex (P=0.515), age (P=0.324), AJCC stage (P=0.27), tumour location (P=0.241), histopathological grade (P=0.972) or surgical margin (P=0.143).

Univariate analyses revealed that no factors were significantly associated with locoregional control (Table II). However, poor overall survival rate was associated with advanced AJCC stage, buccogingival tumour location and low CD164 expression. The 5-year overall survival rates were 84.7% for patients with stage I-II disease and 35.9% for patients with stage III-IV

Table II. Patient characteristics and prognostic factors identified using univariate analysis.

Characteristic	n (%)	5-year locoregional control rate		5-year overall survival rate	
		%	P-value	%	P-value
Sex			0.544		0.871
Male	63 (90)	46.8		54.2	
Female	7 (10)	57.1		57.1	
Age, years			0.553		0.702
<50	30 (43)	56.2		59.8	
≥50	40 (57)	42.4		50.1	
AJCC staging			0.327		<0.001
I-II	27 (39)	61.7		84.7	
III-IV	43 (61)	39.3		35.9	
Tumour location			0.604		0.038
Buccal-gingival	36 (51)	52.8		44.4	
Others	34 (49)	44.3		65.7	
Histological grade			0.975		0.265
1	17 (24)	47.1		70.6	
2	37 (53)	47.6		47.0	
3	16 (23)	53.0		54.5	
Surgical margins			0.507		0.170
Negative	63 (90)	26.8		55.9	
Positive	7 (10)	49.8		38.1	
H-score			0.203		0.016
<120	42 (60)	41.8		42.0	
≥120	28 (40)	57.1		74.2	

AJCC, American Joint Committee on Cancer.

disease (P<0.001; Fig. 2). Buccogingival tumour location was associated with a significantly decreased 5-year overall survival rate (44.4%) compared with the other sites (65.7%) (P=0.038; Fig. 3). The 5-year overall survival rate was 42.0% for a low H-score compared with 74.2% for a high H-score (P=0.016, Fig. 4). All the independent factors were incorporated into the multivariate analyses which revealed that poor survival rate was only associated with AJCC stage III-IV disease (P=0.001) and a low H-score (P=0.040).

Discussion

To the best of our knowledge, the present study is the first to demonstrate that a low CD164 H-score was associated with poor overall survival rate in patients with OSCC. Therefore, CD164 expression may be a useful marker for predicting prognosis in these patients as it is independent of other known clinicopathological parameters including AJCC stage and histopathological grade. Previous studies have attempted to identify parameters that may facilitate decreases in dose- and treatment-associated side effects in head and neck cancer (9,10).

Matsui *et al* (22) evaluated 92 patients with advanced colorectal carcinoma and analysed the association of CD164 expression with metastatic potential, demonstrating that lower CD164 expression in colon carcinoma was associated with a trend towards invasion into the lymphatic vessels. McGuckin *et al* (27) identified that CD164 and CD34 exhibit marked co-localization patterns in cells that express the two antigens, suggesting a functional link between the two sialomucins; it was concluded that CD164 and CD34 act as negative regulators of cell proliferation in the transplantation area. Jorgensen-Tye *et al* (28) also demonstrated that CD164 was a negative regulator of haematopoiesis. Therefore, the results cited above may support the hypothesis that CD164 protects against cell proliferation.

However, other studies have demonstrated that CD164 serves a distinct role in other solid and haematological malignancies. For example, Tang *et al* (17) examined specimens from human colorectal, breast and ovarian cancer cell lines and revealed that decreased CD164 expression in a human colon cancer cell line significantly inhibited cell proliferation, mobility and metastasis. Thus, it was concluded that CD164 may be a useful target for diagnosing and treating colon cancer. Havens *et al* (18) analysed the role of CD164 in prostate cancer cell lines and identified that blocking CD164 impaired the ability of prostate cancer cells to adhere to bone marrow endothelial cells and invade extracellular matrices. They also stained human tissue microarrays for CD164 and
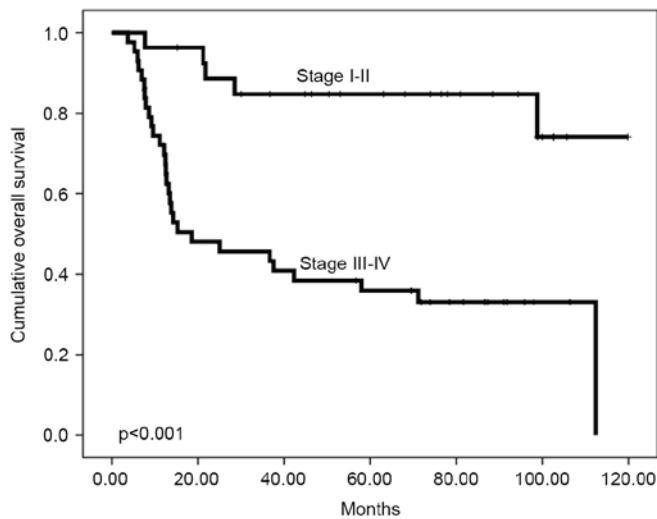
Figure 2. Calculated 5-year overall survival rates were 84.7 and 35.9% for patients with stage I-II and III-IV disease, respectively (P<0.001).
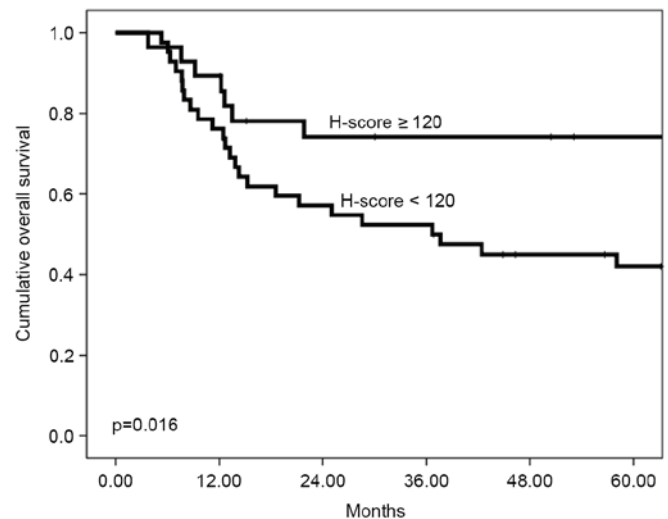

Figure 4. Calculated 5-year overall survival rates were 42.0% for a low H-score (<120) compared with 74.2% for a high H-score (≥120; P=0.016).
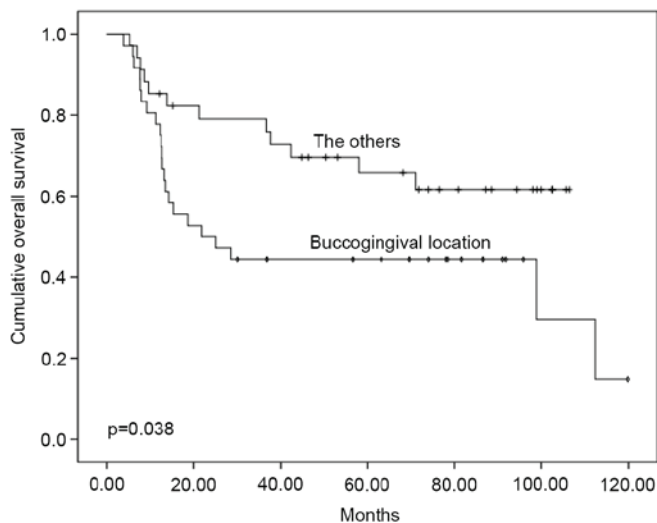

Figure 3. Calculated 5-year overall survival rates were 44.4% for patients with buccogingival tumour location compared with 65.7% for patients with tumours located in alternative sites (P=0.038).

observed a positive association with prostate-specific antigen levels which led to the conclusion that CD164 participates in the localization of prostate cancer cells to the bone marrow and is involved in tumour metastasis. Huang *et al* (21) evaluated the role of CD164 in ovarian surface epithelial cells from 97 cases and identified that high CD164 expression was significantly associated with high-grade ovarian tumours, advanced-stage disease and tumour metastasis. Thus, they suggested that increased CD164 expression is involved in ovarian cancer progression through the stromal cell-derived factor 1a/C-X-C chemokine receptor type 4 axis, which promotes tumourigenicity. Wysocka *et al* (20) evaluated 6 patients with Sézary syndrome and 3 healthy donors, and identified that CD164 could be used to diagnose and monitor cases of the disease. This potential diagnostic role was also observed by Guenova *et al* (19) who investigated CD164 expression in malignant T-cells from 8 patients with

Sézary syndrome and revealed that CD164 expression on CD4+ lymphocytes was significantly increased compared with healthy controls. The role of CD164 is ambiguous and remains unclear in the aforementioned studies; the results of the present study support the hypothesis that CD164 inhibits cell proliferation (17-22,27,28).

The present study has several limitations that warrant consideration. First, the sample size was small and a larger cohort study is required to validate the results. Secondly, having used a retrospective design, it is impossible to accurately consider all potential confounding factors (e.g., smoking status, alcohol consumption and paan consumption). Thirdly, H-scores <120 were arbitrarily defined as low based on a median score of 106.5, and a larger cohort is required to determine a more accurate and sensitive threshold value. Fourthly, the present study did not consider the cellular and molecular basis of the association of CD164 expression with patient survival rate, although this issue is currently being investigated by the present authors. Fifthly, as a consequence of betel chewing, the majority of OSCC occurs on the tongue, buccal mucosa and gingiva in Taiwan (5,6). However, the three most common sites worldwide for OSCC are the tongue, floor of the mouth and retromolar trigone (29). Owing to this disparity, it remains unknown whether the results of the present study are applicable to other countries or patients with OSCC who do not chew betel.

In conclusion, the results of the present study revealed that CD164 overexpression in patients with OSCC was associated with favourable overall survival rates. Therefore, in addition to the known prognostic factors, CD164 may be another clinically useful parameter.

Acknowledgements

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