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Impact of moderate-to-severe obstructive sleep apnea on aggressive clinicopathological features of papillary thyroid carcinoma

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) may to be strongly associated with cancer mortality. The risk hazards of OSA regarding aggressive features of papillary thyroid carcinoma (PTC) remain unclear. The main objective of this study was to explore the relationship between OSA and aggressive features of PTC.
Methods: We prospectively studied 210 patients (54 men, 156 women; age 43 ± 13 years) with PTC. Indices of sleep respiratory disturbance and oxygen desaturation were determined by polysomnography with the apnea-hypopnea index (AHI) and lowest oxygen saturation (LSaO2), respectively. PTC aggressive features were assessed by postoperative histopathological analysis. Multivariant logistic regression models adjusting for demographic and OSA-related factors were generated to determine OSA risk hazards for aggressive PTC features.
Results: The prevalence of moderate-to-severe OSA (defined as AHI of >15) was 20% in PTC patients. Those in the moderate-to-severe OSA group had higher BMI and more aggressive PTC features. Moderate-to-severe OSA was associated with increased odds of larger tumor size (OR, 4.31; 95% CI, 1.79−10.37; $p = 0.001$), capsular invasion (OR, 2.96; 95% CI, 1.42−6.16; $p = 0.004$), multifocality (OR, 3.11; 95% CI, 1.52−6.39; $p = 0.002$), central (OR, 4.7; 95% CI, 1.77−12.49; $p = 0.003$) and lateral (OR, 5.94; 95% CI, 2.27−15.54; $p < 0.001$) cervical lymph node metastasis, and BRAF mutation (OR, 2.88; 95% CI, 1.31−6.31; $p = 0.008$). Moderate to severe hypoxemia did not correlated with aggressive PTC behaviors.
Conclusions: OSA is a common respiratory disturbance in PTC. Aggressive PTC features in patients with moderate-to-severe OSA implicate OSA as a cause of cancer progression. Respiratory disturbance events have a greater impact on PTC aggressiveness than hypoxia.

1. Introduction

Obstructive sleep apnea (OSA) is a chronic sleep disorder in patients who experience apnea or hypopnea caused by collapse of the upper airway during sleep, with intermittent hypoxemia, sleep fragmentation, and daytime sleepiness. It is estimated that almost 1 billion adults aged 30–69 years have OSA, with 425 million adults globally have moderate-to-severe OSA [1]. Mounting studies have shown that OSA is associated with the prevalence and progression of tumors [2–4]. Fox example, a meta-analysis, including 5 cohort studies with a total of 112 228 patients, revealed that the overall incidence of tumors in people with sleep disordered breathing (SDB), defined as apnea-hypopnea index (AHI) > 15, is 1.53 times that of those without SDB [5]. Another multicenter cohort study from Spain showed that in male patients younger than 65 years old, the overall tumor incidence was associated with the percentage of time in oxyhemoglobin desaturation [4]. In addition, a large cohort study from Wisconsin suggested that the presence of SDB is associated with an increased odds of tumor mortality [3]. Moreover, the severity of SDB has been independently associated with greater aggressiveness of cutaneous melanoma [6], as well as high Fuhrman grade in patients with clear cell renal cell carcinoma treated surgically [7].

Abbreviations: OSA, Obstructive sleep apnea; PTC, Papillary thyroid carcinoma; SDB, Sleep disordered breathing.

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The incidence of papillary thyroid cancer (PTC) has increased in most countries over the past three decades [8]. A three-fold increased incidence in the US, from 4.5 per 100 000 in 1974 to 14.4 per 100 000 population in 2013, has been reported [9]. In South Korea, the national screening program for tumors led to an epidemic of thyroid cancer, with a 15-fold increase in detection of PTC between 1993 and 2011 [10]. Approximately 16% of all PTCs diagnosed in 2013–2015 in the US were attributable to overweight or obesity [11]. Hence, the impact of OSA on the development of PTC should be considered. Although it has been reported that OSA increases the incidence of thyroid cancers development [12], the relationship between OSA and PTC aggressiveness remains unclear. Most PTCs are low-risk tumors and have a favorable prognosis, yet tumor recurrence and metastasis caused by the aggressive profiles of PTC are still a major and challenging public health problem, leading to substantial costs for health-care systems. Therefore, it is of great practical significance for the clinical management of thyroid cancer to study whether OSA is a risk factor for its aggressiveness.

Herein, we prospectively examined the association between OSA and aggressive pathological features of PTC, and assessed possible mechanisms of SDB in PTC aggressiveness.

2. Methods

2.1. Study participants

We prospectively enrolled 302 patients with PTC from our department between January 2016 to December 2017. The enrolled patients had a postoperative pathological diagnosis of PTC, were 18–72 years old, had full knowledge of their own disease, and agreed to complete an overnight polysomnography (PSG) prior to thyroidectomy. Subjects were excluded if they reported use a continuous positive airway pressure (CPAP) during the past 3 months. In addition, patients were excluded if they had difficulty breathing or underwent open tracheostomy. Patients with mental and psychological diseases, severe heart, kidney, and liver insufficiency, type II respiratory failure, past history of alcoholism, history of hypothyroidism and history of psychotropic drug use, were also excluded. Of the 302 patients with PTC, 23 refused to participate in the study, and 279 patients met the selection criteria for enrollment. After excluding 69 patients without sufficient tumor blocks for immunohistochemistry (IHC) analysis, 210 patients with PTC were selected as the study participants (Fig. 1). This study was approved by the ethics committee of our hospital and the informed consent was obtained from the participants.

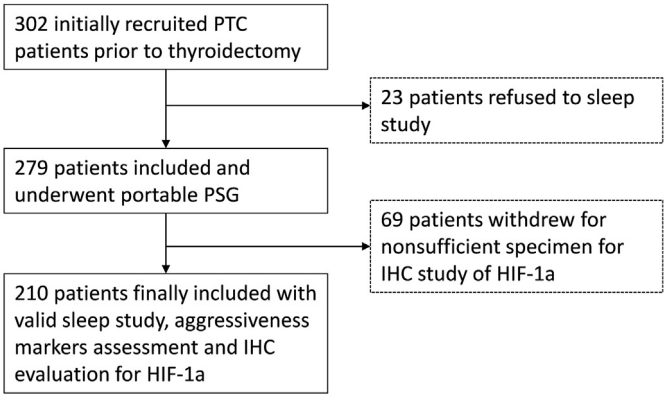

Fig. 1. Flow chart of the study. PTC, papillary thyroid carcinoma. PSG, polysomnography. IHC, immunohistochemistry. HIF-1α, hypoxia inducible factor-1α.

2.2. PSG

The participants were told to not drink any alcoholic beverages or to take any sedative drugs or stimulants on the night of PSG. Overnight PSG data were collected in the ward using a portable sleep apnea recording device (Alice PDx, Philips, USA). The signals recorded by the sleep recording mainly included airflow of the nose, finger pulse oximetry, thoracic and abdominal respiratory effort, and snoring. Randomized controlled trials have shown that portable recording devices and standard PSG can diagnose OSA comparably [13,14]. The data were evaluated by trained technicians and respiratory events were assessed according to standard criteria. Apneas (complete cessation of airflow) and hypopneas (discernible [>30%] reduction in airflow) were defined when occurring for 10 s or longer and accompanied by a 3% or greater oxygen desaturation. OSA was measured by the AHI (number of apnea plus hypopnea events per hour of sleep) and was graded as mild, moderate, or severe based on AHI of 5–15, 16–30, or > 30, respectively. The index of hypoxia was measured by the lowest oxygen saturation (LSaO2) of sleep and was graded as mild, moderate, or severe hypoxemia based on LSaO2 of 90%–85%, 84%–65%, and <65%, respectively.

2.3. Histopathology and IHC

For all 210 enrolled patients, specimens of paraffin-embedded tumor blocks were available for IHC analysis. All hematoxylin and eosin (HE)- stained sections were confirmed by histological review. IHC was performed to assess hypoxia inducible factor-1α (HIF-1α) expression in the tumors. Pathological staging was based on the postoperative pathological results of PTC according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system for thyroid cancer.

HIF-1α protein expression was assessed immunohistochemically in resected PTC samples after paraffin embedding according to a previously described method [15]. Sections were incubated with a mouse monoclonal anti–HIF–1α antibody (1:100 dilution; ab16066; Abcam, Cambridge, UK) in a humidified chamber overnight at 4 °C. Incubation with the secondary antibody mouse IgG (1:2000 dilution; ab150113; Abcam, Cambridge, UK) was carried out for 30 min at 25 °C.

Two independent pathologists who were blinded to the clinical status of the patients scored the stained sections under a microscope. Nuclear staining of HIF-1α expression was divided into the following semiquantitative grades: I, no cytoplasmic staining; II, rarely, at ≤10% cytoplasmic staining; III, moderate, staining >10% and ≤50%; and IV, strong, staining in >50% of the cytoplasm. Scores I and II were classified as the low HIF-1α expression group; scores III and IV were classified as the high HIF-1α expression group.

2.4. Statistical analysis

Continuous variables following a normal distribution are expressed as the mean and standard deviation, otherwise, they are expressed as the median and interquartile range (IQR). Qualitative variables are provided as absolute values and percentages. Normality in variable distribution was assessed by using the Kolmogorov-Smirnov test. The χ^2 test and t tests were applied to compare the baseline characteristics of the two groups of PTC patients with or without moderate-to-severe OSA. To determine the association of OSA and aggressive features of PTC, we first employed χ^2 tests to compare pathological characteristics between the PTC groups with and without moderate-to-severe OSA, as well as other indices of OSA and demographic factors. The indicated cofounders in accordance with clinical practices and literatures, were entered into multivariate logistic regression models to

examine the association between moderate-to-severe OSA and aggressive clinicopathological features of PTC. Multivariate models were adjusted for sex, age, body mass index (BMI), neck circumference, smoking status, alcohol status, and C-reactive protein (CRP) and thyroid-stimulating hormone (TSH) levels. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs), considering non-SDB PTC patients as the reference group. A p value of less than 0.05 was considered significant and 2-sided tests were utilized. All statistical analyses were performed using SPSS software version 25 (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics in PTC patients with or without moderate-to-severe OSA

Of the 210 PTC patients studied, most were female (n = 156, 74.3%), had a mean age of 43 years (standard deviation [SD], 13), 11% were smoker, and 11.9% were consumed alcohol. The mean BMI was 24.6 (SD, 2.4). The median AHI was 4.2 (IQR, 2.8–12.7) events per hour (40.5% with AHI >5, and 7.1% with AHI >30). Among the 210 patients with PTC, 42 (20%) met the criteria for moderate-severe OSA with AHI >15, and 63 (30%) met the criteria for moderate-severe hypoxemia with LSaO2 < 85% in sleep. Compared with the PTC patients without OSA or with mild OSA, those with moderate-to-severe OSA had greater BMIs, had slightly larger neck circumferences, and were less likely to smoke and drink alcohol, but did not differ in age, sex, CRP and TSH levels. PTC patients with moderate-to-severe OSA showed more aggressive tumor features, including larger primary tumor size, advanced tumor stages, prevalent central and lateral cervical lymph node metastases, capsular invasion, multifocality, and *BRAF V600E* mutation (Table 1).

3.2. Increased odds of aggressive features in PTC patients with moderate-to-severe OSA

In multivariate models, the presence of moderate-to-severe OSA was associated with increased odds of aggressive features of PTC, including larger tumor size (OR, 4.31; 95% CI, 1.79–10.37; $p = 0.001$), capsular invasion (OR, 2.96; 95% CI, 1.42–6.16; $p = 0.004$), multifocality (OR, 3.11; 95% CI, 1.52–6.39; $p = 0.002$), central (OR, 4.7; 95% CI, 1.77–12.49; $p = 0.003$) and lateral (OR, 5.94; 95% CI, 2.27–15.54; $p < 0.001$) cervical lymph node metastasis, and *BRAF* mutation (OR, 2.88; 95% CI, 1.31–6.31; $p = 0.008$) (Table 2 and Fig. 2).

We also investigated the relationship of hypoxemia and overweight with the risk of aggressive features of PTC. The results showed that moderate to severe hypoxemia (LSaO2 < 85%) had no impact. Moreover, overweight (BMI >24) was associated with vascular invasion (OR, 3.06; 95% CI, 1.10–8.55; $p = 0.033$), central (OR, 23.42; 95% CI, 5.19–105.63; $p < 0.001$) and lateral (OR, 21.18; 95% CI, 4.75–94.39; $p < 0.001$) cervical lymph node metastasis, and *BRAF* mutation (OR, 2.36; 95% CI, 1.26–4.40; $p = 0.007$) (Table 2).

3.3. Increased expression of HIF-1α in PTC specimens of patients with moderate-to-severe OSA, and its impact on PTC aggressive traits

Given that HIF-1α represents hypoxia in the tumor microenvironment, we explored the association of HIF-1α with OSA and hypoxemia in PTC by multivariate models. Representative immunohistochemical images of different HIF-1α expression intensities are depicted in Fig. 3. The results showed that PTC patients with moderate-to-severe OSA had higher levels of HIF-1α in tumors ($p = 0.015$). However, there was no significant association of HIF-1α expression with hypoxemia, or other baseline characteristics in PTC (data not shown). The results suggest that intermittent apnea, rather than long-term hypoxemia at night, has a great impact on the development of hypoxia in thyroid tumors. After adjustment for covariates, increased expression of HIF-1α correlated negatively with increased size of tumor (OR, 0.45; 95% CI, 0.25–0.81; $p = 0.008$), but not correlated with other aggressive features of PTC, suggesting HIF-1α, the sign of hypoxia in PTC microenvironment, plays a more active role on the initiation of PTC (Table 2).

4. Discussion

In the present study we found moderate-to-severe OSA to be associated with an increased risk of aggressive PTC features development. When OSA was expressed as the respiratory disturbance index, the presence of moderate-to-severe OSA correlated

Table 1
Baseline characteristics by moderate-to-severe OSA[a] status in patients with papillary thyroid carcinoma (n = 210).

Characteristic	Moderate-severe OSA		P Value
	No (n = 168)	Yes (n = 42)	
Age, mean (SD), y	43.1 (12.4)	43.4 (14.3)	.887
Male, No. (%)	40 (23.8)	14 (33.3)	.207
Body mass index, mean (SD)	24.0 (2.0)	27.2 (1.7)	<.001
Smoker, No. (%)	23 (13.7)	0 (0)	.011
Drinker, No. (%)	24 (14.3)	1 (2.4)	.033
Waist-hip Ratio, mean (SD)	0.93 (0.15)	0.98 (0.17)	.033
Neck Circumference, mean (SD), cm	34.0 (1.0)	34.5 (0.8)	.001
C-reactive Protein, mean (SD), mg/L	1.47 (0.25)	1.41 (0.26)	.215
TSH, mean (SD), mU/L	1.85 (0.26)	1.85 (0.22)	.945
Tumor Size, mean (SD), cm	1.2 (0.9)	1.7 (1.1)	.001
Tumoral Stage, T1/T2/T3/T4, No. (%)	149/16/2/1 (88.7/9.5/1.2/0.6)	28/12/1/1 (66.7/28.6/2.4/2.4)	.006
Central Neck Metastasis, No. (%)	29 (17.3)	26 (61.9)	<.001
Lateral Neck Metastasis, No. (%)	3 (1.8)	16 (38.1)	<.001
TNM Stage, I/II/III/IV, No. (%)	160/5/1/2 (95.2/3/0.6/1.2)	36/1/2/3 (85.7/2.4/4.8/7.1)	.024
Vascular Invasion, No. (%)	17 (10.1)	7 (16.7)	.233
Capsular Invasion, No. (%)	77 (45.8)	30 (71.4)	.003
Multifocality, No. (%)	45 (26.8)	24 (57.1)	<.001
BRAF V600E Mutation, No. (%)	60 (37.5)	30 (71.4))	<.001
HIF-1α Expression, No. (%)	98 (58.3)	33 (78.6)	.015

[a] Moderate-to-severe OSA was defined as apnea plus hypopnea index >15.

Table 2
Aggressive features of papillary thyroid carcinoma according to apnea/hypopnea and hypoxia in multivariant analysis.

Aggressive Features	Moderate-Severe OSA[a]		Moderate-Severe Hypoxemia[b]		Overweight[c]		HIF-1α Expression	
	No (n = 168)	Yes (n = 42)	No (n = 147)	Yes (n = 63)	No (n = 88)	Yes (n = 122)	No (n = 79)	Yes (n = 131)
Primary Tumor Size ≥ 1 cm								
No. (%)	85 (50.6)	35 (83.3)	75 (51)	45 (71.4)	42 (47.7)	78 (63.9)	34 (28.3)	86 (71.7)
P value		.001	.429		.288		.008	
OR (95% CI)	1	4.31 (1.79–10.37)					1	0.45 (0.25–0.81)
Capsular Invasion								
No. (%)	77 (45.8)	30 (71.4)	66 (44.9)	41 (65.1)	39 (44.3)	68 (55.7)	34 (43)	73 (55.7)
P value	.004		.633		.567		.175	
OR (95% CI)	1	2.96 (1.42–6.16)						
Vascular Invasion								
No. (%)	17 (10.1)	7 (16.7)	15 (10.2)	9 (14.3)	5 (5.7)	19 (15.6)	6 (7.6)	18 (13.7)
P value	.233		.394		.033		.175	
OR (95% CI)					1	3.06 (1.10–8.55)		
Multifocality[d]								
No. (%)	45 (26.8)	24 (57.1)	37 (25.2)	32 (50.8)	26 (29.5)	43 (35.2)	24 (30.4)	45 (34.4)
P value	.002		.286		.386		.553	
OR (95% CI)	1	3.11 (1.52–6.39)						
Central cervical Lymph Node Metastasis[e]								
No. (%)	29 (17.3)	26 (47.3)	25 (17)	30 (47.6)	2 (3.6)	53 (43.4)	13 (16.5)	42 (32.1)
P value	.002		.433		<.001		.130	
OR (95% CI)	1	4.70 (1.77–12.49)			1	23.42 (5.19–105.63)		
Lateral cervical Lymph Node Metastasis[f]								
No. (%)	3 (1.8)	16 (38.1)	1 (0.7)	18 (28.6)	0 (0)	19 (15.6)	1 (5.3)	18 (13.7)
P value	<.001		.831		<.001		.138	
OR (95% CI)	1	5.94 (2.27–15.54)			1	21.18 (4.75–94.39)		
BRAF Mutation								
No. (%)	63 (37.5)	30 (71.4)	53 (36.1)	40 (63.5)	25 (28.4)	68 (55.7)	28 (35.4)	65 (49.6)
P value	.008		.611		.007		.148	
OR (95% CI)	1	2.88 (1.31–6.31)			1	2.36 (1.26–4.40)		

[a] Moderate-severe OSA coded as apnea plus hypopnea index >15.
[b] Moderate-severe hypoxemia coded as lowest oxygen saturation <85% in sleep.
[c] Overweight coded as body mass index ≥24.
[d] High neck circumference (≥34 cm) is also the risk factor for multifocality in multivariant analysis (P value, .04; OR (95% CI), 1.88 (1.02–3.48)).
[e] Older than 43 years is also the risk factors for central cervical lymph node metastasis in multivariant analysis (P value, < .001; OR (95% CI), 0.12 (0.05–0.31)).
[f] Older than 43 years is also the risk factor for lateral cervical lymph node metastasis in multivariant analysis (P value, < .001; OR (95% CI), 0.12 (0.05–0.31)).

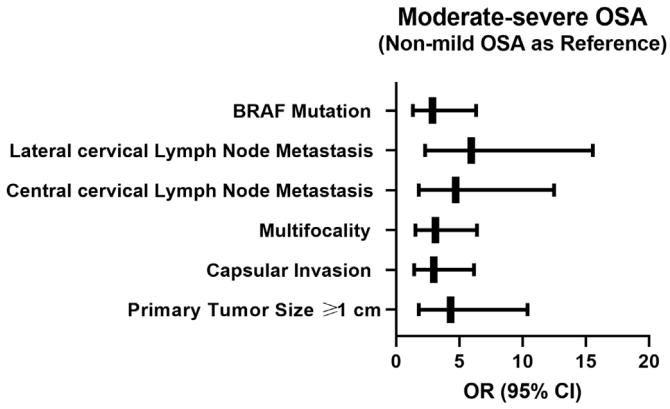

Fig. 2. Relationship between moderate-severe OSA and aggressive features of PTC.

positively with primary tumor size, capsular invasion, multifocality, central and lateral cervical lymph node metastasis, and BRAF mutation in PTC.

The presence of OSA has been reported in several conditions that are associated with the prevalence and mortality of cancers [3,16,17]. For example, based on 22-year mortality follow-up data, moderate-to-severe OSA was associated with total and cancer mortality in a dose-response fashion; in addition, severe OSA was related to an elevated relative hazard of cancer mortality [3]. Similarly, in another multicenter study enrolling 5427 patients with median follow-up of 4.5 years, high AHI was associated with an increased hazard ratio of 1.87 for cancer mortality in patients under 65 years of age [18]. An experiment study in a mouse model of sleep apnea showed that intermittent hypoxia enhances tumor volumes, induces melanoma lung metastasis [19,20] and was potentially related to enhancement of cancer stem cell-like properties [21], suggesting that tumor invasion and metastasis promoted by intermittent hypoxia may be responsible for SDB-related tumor mortality.

With regard to specific types of cancer, Martinez-Garcia et al. demonstrated a positive and independent association between SDB severity and cutaneous melanoma aggressiveness in a multicenter study [6], and Vilaseca et al. indicated that a history of OSA is associated with adverse features in clear cell renal cell carcinoma [7]. Our study focused on PTC due to the increasing prevalence of PTC in the past several decades, and because the high PTC diagnosis rate has emerged as a global public health concern [10,11]. In our initial study we found more aggressive features of PTC in patients who were overweight [22]. Thus, we sought to determine whether SDB also increases the aggressiveness of PTC. The results of this study support such a relationship and confirm that SDB can promote tumor aggressiveness. Overall, the promotion of tumor progression by SDB should be taken into account when considering the high PTC diagnosis and treatment rates when informing health policies.

The potential mechanisms involved in cancer progression by hypoxia have been investigated. In general, tumor growth is controlled by the vascular flow and oxygen tension inside a tumor [23], and the rate of growth is boosted by increased angiogenesis within the tumor microenvironment. Over-expression of HIF-1α, an

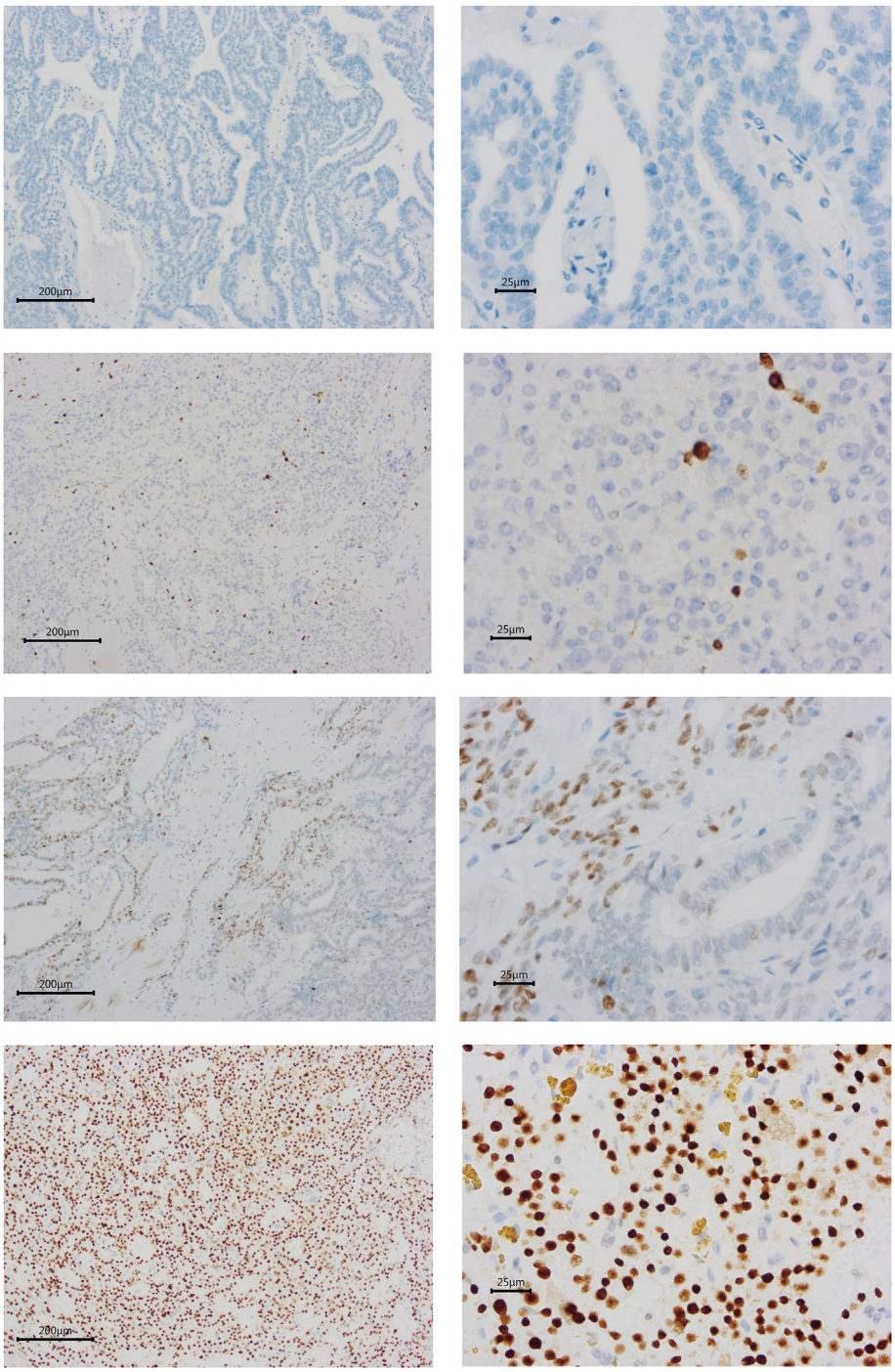

Fig. 3. Representative immunohistochemical images of HIF-1α expression with different staining intensities in papillary thyroid carcinoma with or without OSAHS. A, grade I, without cytoplasmic staining; B, grade II, staining in <10% of the cytoplasm; C, grade III, 10% ≤ staining ≤50% of the cytoplasm; D, grade IV, in >50% of the cytoplasm. The magnification is 100 times of small image in lower left corner and 400 times of large image, respectively.

index of tissue hypoxia, triggers upregulation of proangiogenic mediators, such as VEGF, in cancer cells. Furthermore, there is evidence of elevated serum VEGF concentrations in OSA patients [24], suggesting that HIF-1α-VEGF axis contributes to increased angiogenesis, leading to tumor progression. In this study, we also observed that overexpression of HIF-1α is positively associated with increased AHI, suggesting that OSA contributes to tumor progression in PTC potentially via HIF-1α expression. Nevertheless, when considering respiratory disturbance, hypoxemia and obesity as concomitant risks for PTC aggressiveness, we found that HIF-1α overexpression was not associated with PTC aggressiveness and that, the primary PTC size did not correlate positively with increased HIF-1α expression in PTC tissues. These observations indicate that the aggressive PTC features do not depend on the hypoxia, and the respiratory disturbances caused by OSA play an important role in the aggressive PTC features. Other mechanisms, such as abnormal expression of clock genes, decreased immunity, and melatonin release disruption caused by sleep disorders [25], may contribute to the aggressiveness of PTC, and need to be explored further.

In addition to the AHI, oxygen desaturation has been used to measure the long-term impact of OSA on a patient. Frequent oxygen desaturations and resaturations can lead to endothelial damage and create an inflammatory state in the circulation, which is related to heart and brain damage [26–29]. In this study, when the lowest oxygen saturation was used as the index of oxygen desaturation, hypoxemia was not as sensitive as respiratory events in determining the impact of OSA on aggressive PTC features, suggesting that respiratory disturbance contributes to PTC aggressiveness beyond the hypoxemia mechanism.

In a previous study, we found that increased BMI was strongly associated with extrathyroidal extension, multifocality, lymph node metastasis and advanced TNM stage in patients with PTC [22]. Given that increased BMI is a risk factor of OSA, we built a multivariate model incorporating OSA concomitant factors such as oxygen desaturation and BMI. According to the results, overweight (BMI $\geq$24 in Chinese individuals) remained a risk factor for capsular invasion and lymph node metastasis, suggesting that BMI is an independent risk factor for the aggressive features of PTC in the setting of OSA.

Because this study was a cross-sectional and lacked longitudinal outcomes such as survivals, the impact of moderate-to-severe OSA on PTC progression remains to be assessed. In addition, we used portable sleep apnea monitoring but not standard PSG to record sleep-disordered events, which led to incomplete data collection such as the presence of sleep fragmentation and sleep duration, thus, the effect of sleep fragmentation or arousal index on the development of aggressive PTC features could not be determined.

5. Conclusion

In this study, we found an increased risk of aggressive features of tumors among PTC patients with moderate-to-severe OSA. This relationship appears to be linked to sleep respiratory disturbance rather than to the long-term hypoxemia caused by OSA. Given the high prevalence of OSA among cancer patients, the possibility of an association between OSA and tumor progression has the potential for a large public health impact, and proactive treatment for OSA is recommended.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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