Asia-Pacific Journal of Oncology Nursing 9 (2022) 100136

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Original Article

Impact of free flap reconstruction on obstructive sleep apnea in patients with oral and oropharyngeal cancer

Fu-Hsin Liao [a,1], Chan-Chi Chang [b,c,1], Yu-Cheng Lu [d], Cheng-Yu Lin [a,b,*], Wei-Shu Lai [e,*]

[a] Sleep Medicine Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[b] Department of Otolaryngology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[c] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[d] Singsin Ear, Nose and Throat Clinic, Tainan, Taiwan
[e] Department of Nursing, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ARTICLE INFO

Keywords:
Oral and oropharyngeal cancers
Free flap reconstruction surgery
Obstructive sleep apnea
Polysomnography

ABSTRACT

Objective: Little is known about the association between obstructive sleep apnea (OSA) and oral and oropharyngeal cancers (OOCs). This study aims to investigate the incidence and severity of OSA in patients with OOCs before and 6 months after free flap reconstruction (FFR), as well as identify the factors that affect the severity of OSA.

Methods: A prospective cohort study was designed. We recruited patients aged ≥ 20 years who were newly diagnosed with OOC and underwent FFR surgery at a medical center. Demographic data, cancer characteristics, and objective full-night polysomnographic parameters were collected. The Spearman rank correlation coefficient or the Kruskal–Wallis test was used for analyses.

Results: In the 23 included patients, the incidence of OSA was 91.3% before surgery and 95.6% as of 6 months after surgery. The proportion of patients with moderate OSA (apnea-hypopnea index (AHI) 15–29) or severe OSA (AHI ≥ 30) had increased from 52.2% to 78.3%, and the AHI was significantly increased (23.3 ± 17.6 vs. 34.6 ± 19.3, $P = 0.013$) as of 6 months after surgery. Neck circumference and treatment type were significantly correlated with preoperative and 6-month postoperative AHI, respectively.

Conclusions: Patients with OOCs had a high incidence of OSA before and after surgery. OOC survivors should undergo early OSA assessment and receive pre- and post-FFR OSA management to improve their quality of life.

Introduction

Oral and oropharyngeal cancers (OOCs) are the most common malignant tumors of the head and neck.[1] According to the GLOBOCAN estimates in 2020, approximately 377,713 people were newly diagnosed with lip/oral cancer, 98,412 people were diagnosed with oropharyngeal cancer, and the incidence of both continues to increase annually.[2] A recently published study demonstrated that sleep disorders are common among patients with head and neck cancer, which may affect cancer survivors' well-being and exacerbate the burden of disease.[3] However, the causes of sleep disturbances among patients with head and neck cancer are unclear and have not been well studied. Obstructive sleep apnea (OSA) is a common sleep disorder characterized by the repetitive collapse of the upper airway during sleep, leading to the intermittent cessation or reduction of airflow (apnea and hypopnea, respectively) and dips in arterial oxygen saturation during sleep.[4] The oral cavity and oropharynx are the parts of the head and neck that are the closest to the respiratory tract.[5] The prevalence of OSA in patients with head and neck cancers is 12%–95%, with a weighted mean of 59.78, which is higher than that in patients without these cancers (3.7%–50%).[6,7] Cao et al[8] conducted a systematic review and meta-analysis that focused on the relationship between cancers and OSA; they found that the overall prevalence of OSA in individuals with cancer was 46% (95% CI, 27%–67%), and the prevalence of cancers was 1.53 (95% CI, 1.01–2.31) times higher in patients with OSA than in individuals without OSA. However, these data could have been underestimated because some patients may not seek medical attention. If OSA is not diagnosed and treated in time, the incidence of cardiovascular, cerebrovascular, and metabolic diseases

* Corresponding author.
E-mail addresses: yu621109@ms48.hinet.net (C.-Y. Lin), weisue@mail.ncku.edu.tw (W.-S. Lai).
[1] These authors contributed equally to this work as joint first author.

https://doi.org/10.1016/j.apjon.2022.100136
Received 20 June 2022; Accepted 23 August 2022

increases and the mobility of the tissue can even increase in the long-term.[9–12] Sleep apnea or hypopnea may cause snoring, wakefulness, intermittent hypoxia, and increased carbon dioxide levels, which affect sleep and result in symptoms that negatively influence the patient's quality of life, such as daytime fatigue, lethargy, and decreased concentration, and these can change the patient's memory capacity.[13] Moreover, hypoxia may worsen the cancer prognosis. Hypoxia is a typical feature of the tumor microenvironment that stimulates cancer cells to initiate a series of gene regulatory responses, triggering rapid tumor growth and leading to drug resistance, metastasis, and progression.[14]

The common treatments for OOCs include surgery, radiotherapy, and chemotherapy. Surgery, which includes resection of the tumor and reconstruction of the defect with a soft tissue flap, is usually the first line of treatment.[15,16] For patients with large tumors or deep cancer cell invasion, free flap reconstruction (FFR) is needed after tumor resection. FFR uses a flap that is not taken from a neighboring structure; for example, an anterolateral thigh flap or a medial sural artery perforator fasciocutaneous flap may be used in FFR. The inevitable replacement of dynamic structures with static ones may alter the flexibility of tissue in the oral and oropharyngeal cavities. In addition, the flap size is decided according to the extent of tissue resection. Changes in the structure of the respiratory tract may increase the incidence of OSA.[16–19] Few studies have reported sleep parameters in patients with OOCs before and after FFR, and the cause of OSA secondary to FFR is unclear as well. Without this information, it can be difficult to discern whether we are healing OOC patients in a manner that does not harm them.

Most of the available studies that evaluated patients with OOC and OSA used a cross-sectional design while very few studies included OOC survivors in the follow-up.[17–20] However, during treatment, the physical condition of these patients may fluctuate. Single-time-point measurements cannot comprehensively reveal the true prevalence of OSA among patients with OOCs. Furthermore, few studies have examined the prevalence of patients with OSA in OCC before and after surgery. Therefore, we hypothesized that specific clinical variables and receiving FFR would affect OSA incidence and severity in patients with OOCs in ways that might worsen the underlying disease and impact the quality of life after the completion of therapy. Thus, in the present study, we longitudinally explored the changes in the OSA incidence and severity in patients with OCC before and 6 months after they received FFR, and we identified the factors affecting the OSA severity.

Methods

Research design and participants

This prospective cohort study was approved by the Institutional Review Board (B-ER-106-324) of the National Cheng Kung University Hospital. Patients who were newly diagnosed with OOCs, aged $\geq$ 20 years, expected to receive FFR, had no other comorbid cancers, and had not been diagnosed with any sleep disorders were recruited from a 1193-bed, single tertiary metropolitan medical center in an urban area of southern Taiwan from April 2019 to December 2020. Participants were excluded if they were diagnosed with a mental illness or were unable to cooperate with the examination. All potentially eligible individuals were invited to participate in the present study and provided their written informed consent.

Procedure

The participants were asked to provide their general information before and 6 months after the surgery and to undergo polysomnography (PSG). All pretreatment PSG measurements were performed within 1 month after the diagnosis of OOC. The pretreatment assessments were performed to determine the patients' baseline OSA statuses and the relative locations of the tumors before the tumor resection and respiratory tract structure alteration surgeries, whereas the 6-month post-treatment assessments were performed to determine the patients' actual daily statuses because by 6 months, the patients surgical wounds would have healed, the patients would be more stable, and the patients who received combined chemoradiotherapy would have completed their treatment.

FFR uses muscles or fascial flaps with vessels from other parts of the body to reconstruct the exposed tendon in the wound site. In our patients, the treatment specialist conducted a professional evaluation to determine the flap harvest site.

Data collection

General information

The patients' demographic characteristics (eg., gender, age, height, weight, and neck circumference) and cancer characteristics (eg., diagnosis, clinical staging, tumor size, and type of treatment) were collected both before surgery and 6 months after surgery.

Objective full-night polysomnographic parameters

Full-night PSG was performed at the Sleep Medicine Center of the National Cheng Kung University Hospital. The examination room that was used for the PSG was a single suite under a suitable temperature and with sound control. For the monitoring and interpretation standards that we used in this study, we referred to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications Version 2.4, issued in 2017 (Berry et al). We collected the following data using standard techniques: electroencephalography, electrooculography, chin electromyography, leg electromyography, electrocardiography, oronasal thermal flow (measured with an oronasal thermal airflow sensor/thermistor), nasal pressure (Npress, measured with a nasal pressure transducer), abdominal and chest breathing movements, oxygen saturation (SPO_2), snoring severity, and body positions.

The apnea-hypopnea index (AHI) is defined as the total number of apnea and hypopnea episodes per hour of electroencephalographic sleep. Apnea was defined as a decrease in the amplitude of the oronasal thermal airflow by $\geq$ 90% compared with the reference amplitude and a decrease in the airflow amplitude for $\geq$ 10 s. Hypopnea was defined as a decrease in the amplitude of the nasal pressure airflow by $\geq$ 30% compared with the reference amplitude, as well as a decrease in the airflow amplitude for $\geq$ 10 s and a decrease in the SPO_2 by $\geq$ 3% or by the presence of an electroencephalography arousal. A patient with an AHI of $\geq$ 5 was diagnosed as having sleep apnea.

The outcomes assessed were sleep-related indices: the percentage of light sleep (Stages 1 and 2 [S1 + S2]), percentage of deep sleep (Stage 3), percentage of rapid eye movement (REM) sleep, sleep latency, sleep stage percentage, sleep efficiency, and arousal index. The sleep-breathing-related indices that were measured were the AHI, apnea index (AI), hypopnea index (HI), obstructive apnea index (OI), AHI in the supine position, AHI during REM sleep, mean SPO_2, minimum SPO_2, oxygen desaturation index (ODI), and snoring index. The PSG data were scored by experienced sleep technicians according to the standard criteria and interpreted by a sleep physician approved by the Board of Sleep Medicine in Taiwan.

Data analysis

Percentages were used to describe the baseline demographic categorical variables. The continuous demographic variables were described using the mean and standard deviation (SD). The pretreatment and post-treatment data were compared using the Wilcoxon signed-rank test for paired data or the Fisher exact test when appropriate; $P < 0.05$ was considered statistically significant. All correlation analytical results are presented as nonparametric statistics. The Spearman rank test was utilized to analyze the correlation of the continuous variables. The

Table 1
Baseline demographic and clinical characteristics (Mean ± SD or *n* [%]).

Variable	Before treatment ($N = 26$)	6-month after treatment ($N = 23$)[a]
Age (years)	55.4 ± 8.4	54.7 ± 8.5
Gender		
Male	26 (100.0)	23 (100.0)
Female	0	0
Tumor size (2.4–54.0 cm^2)	17.1 ± 13.6	N/A
Tumor location		
Oral cavity (buccal mucosa)	8 (30.8)	8 (34.8)
Lower gingiva	2 (7.7)	2 (8.7)
Behind the molars	2 (7.7)	2 (8.7)
Tonsils	2 (7.7)	2 (8.7)
Floor of the month	1 (3.8)	1 (4.3)
Tongue	7 (26.9)	5 (21.8)
Soft palate	3 (11.6)	2 (8.7)
Oropharynx	1 (3.8)	1 (4.3)
Tumor stage		
1	2 (7.7)	2 (8.7)
2	6 (23.1)	5 (21.7)
3	8 (30.7)	8 (34.8)
4	10 (38.5)	8 (34.8)
Type of treatment	N/A	
Surgery		10 (43.5)
Surgery + Chemotherapy		0
Surgery + Radiotherapy		4 (17.4)
Surgery + Chemoradiotherapy		9 (39.1)

N/A, not applicable.
[a] We recruited 26 patients who met the inclusion criteria, 23 of whom completed both of the pretreatment and 6-month post-treatment examinations.

Kruskal–Wallis test was used to examine the correlation of two groups of categorical variables.

Results

A total of 26 patients with OOCs met the criteria, 23 of whom completed both pretreatment and 6-month post-treatment examinations (attrition rate: 12%). Of the three patients who did not complete the examinations, one developed cancer recurrence during the follow-up period, one experienced a cerebral stroke after the surgery, and one died due to cancer progression after the surgery.

Demographic and clinical characteristics of subjects

The participants' baseline characteristics are presented in Table 1. In the 26 included patients, their mean age was 55.4 years (SD = 8.4), and they were all men. Eight participants had a tumor in the oral cavity (buccal mucosa) (30.8%). The mean tumor size was 17.1 cm^2 (SD = 13.6), and 10 participants (38.5%) had stage 4 cancer. Furthermore, for the 23 patients who completed the 6-month postoperative follow-up, 10 patients (43.5%) had surgical treatment, 4 patients (17.4%) had surgery with radiotherapy, and 9 patients (39.1%) had surgery with chemoradiotherapy.

Pretreatment and post-treatment sleep-related indices for patients with OOCs

The participants' pretreatment and post-treatment data are presented in Table 2. Compared with the pretreatment data, at 6 months after the surgery, the mean BMI of the patients was significantly lower (24.4 [4.5] vs. 22.9 [3.0], $P = 0.039$); their mean neck circumference did not significantly change; the percentage of patients with no OSA (AHI < 5) or mild OSA (5 ≤ AHI < 15) had decreased from 47.8% to 21.7%; the number of patients with moderate OSA (15 ≤ AHI < 30) or severe OSA (AHI ≥ 30) had increased from 52.2% to 78.3%; and the patients' AHI, AI, and OI were all significantly higher (AHI: 23.3 [17.6] vs. 34.6 [19.3], $P = 0.013$; AI: 3.1 [5.8] vs. 9.0 [11.4], $P = 0.006$; OI: 3.0 [5.9] vs. 8.2 [10.4], $P = 0.005$). The overall minimum SPO_2 of the patients was decreased, and the increase in the ODI was non-significant. The percentage of time that the participants were in different stages of sleep did not change significantly; however, the patients' arousal indexes had significantly increased from 37.5 (19.9) to 48.5 (18.2) ($P = 0.039$).

Correlation of OSA among patients with OOCs before and 6 months after surgery

The correlation analysis that analyzed the patients' OSA severity (AHI) correlation with the other physiological indices before the surgery and 6 months after the surgery are presented in Table 3; we observed that

Table 2
Pretreatment and post-treatment polysomnographic data for patients with OOCs.

Variable ($N = 23$)	Before treatment (Mean ± SD)	6-month after treatment (Mean ± SD)	*P* value
BMI (kg/m^2)	24.4 ± 4.5	22.9 ± 3.0	0.039
Neck size (cm)	37.5 ± 3.2	37.7 ±2.9	0.567
Sleep efficiency (%)	78.1 ± 14.1	71.9 ± 17.7	0.196
Sleep latency (min)	15.3 ± 15.6	17.6 ± 19.2	0.294
Arousal index (/h)	37.5 ± 19.9	48.5 ± 18.2	0.039
S1+S2 (%)	77.0 ± 13.5	76.1± 12.4	0.465
S3 (%)	7.8 ± 8.3	9.1 ± 8.2	0.509
REM (%)	15.2 ± 7.9	14.9 ± 8.7	1.0
AHI (/h)	23.3 ± 17.6	34.6 ± 19.3	0.013
AI (/h)	3.1 ± 5.8	9.0 ± 11.4	0.006
HI (/h)	20.0 ± 14.9	25.5 ± 13.0	0.110
OI (/h)	3.0 ± 5.9	8.2 ± 10.4	0.005
AHI (supine) (/h)	29.9 ± 21.2	39.4 ± 27.5	0.097
AHI (REM) (/h)	27.1 ± 24.8	37.1 ± 24.0	0.149
Mean SPO_2 (%)	94.7 ± 1.8	94.6 ± 1.9	0.752
Minimum SpO_2 (%)	84.0 ± 9.8	79.8 ± 11.7	0.130
ODI (/h)	13.0 ± 15.1	17.6 ± 15.9	0.191
Snoring index (/h)	150.3 ± 159.4	89.9 ± 116.3	0.191
Patients with OSA, *N* (%)	21 (91.3)	22 (95.6)	
Mild, *N* (%)	9 (39.1)	4 (17.4)	
Moderate, *N* (%)	4 (17.4)	6 (26.1)	
Severe, *N* (%)	8 (34.8)	12 (52.2)	
N/A, *N* (%)	2 (8.7)	1 (4.3)	

AHI, apnea-hypopnea index; AI, apnea index; BMI, body mass index; HI, hypopnea index; ODI, oxygen.
Desaturation index; OI, obstructive apnea index; REM, rapid eye movement; S1 + S2, stages 1 and 2 (percentage of light sleep); S3, stages 3 (percentage of deep sleep).

Table 3
Correlation of OSA among patients with OOCs before and 6 months after surgery.

Variable	Pretreatment OSA severity (AHI)			6-month post-treatment OSA severity (AHI)		
	$N = 26$ n (%)	Correlation coefficient /mean of rank sum/χ^2	P value	$N = 23$ n (%)	Correlation coefficient /mean of rank sum/χ^2	P value
Age		0.13	0.538		0.17	0.431
BMI		0.38	0.057		0.36	0.89
Neck circumference		0.51	0.008		0.39	0.064
Tumor size		0.03	0.887		N/A	N/A
Tumor staging		2.59	0.459		2.11	0.55
Stage 1	2 (7.7)	6.25		2 (8.7)	6.0	
Stage 2	6 (23.1)	15.83		5 (21.7)	12.6	
Stage 3	8 (30.8)	14.50		8 (34.8)	11.5	
Stage 4	10 (38.4)	12.75		8 (34.8)	13.63	
Type of treatment	N/A	N/A	N/A		6.04	0.049
Surgery				10 (43.5)	9.3	
Surgery + Chemotherapy				0	–	
Surgery + Radiotherapy				4 (17.4)	9.0	
Surgery + CCRT				9 (39.1)	16.33	

AHI, apnea-hypopnea index; BMI, body mass index; CCRT, concurrent chemo-radiotherapy; N/A, not applicable.

neck circumference ($r = 0.51$, $P = 0.008$) had a significant and positive correlation with the pretreatment AHI. The AHIs of the participants between the different types of treatment groups were significantly different 6 months after surgery ($\chi^2 = 6.04$, $P = 0.049$), and the patients who received surgery with chemoradiotherapy had the highest AHI among the treatment types. The other physiological indices had no significant correlation with the pretreatment and post-treatment AHI.

Discussion

This pioneering study in Taiwan used PSG to explore the changes in the incidence and severity of OSA in patients with OOC before and 6 months after FFR; this study also identified the factors that affected OSA severity. The detection of factors that may influence the well-being of OOC survivors is becoming increasingly important for healthcare systems to improve follow-up care for these patients. In this study, we discovered that the incidence of OSA among patients with OOCs before surgery was 91.3%, which was considerably higher than that in individuals without such cancer.[6,7] According to an epidemiological survey on OSA,[6] the prevalence of OSA for men and females in European and American countries was 17%–26% and 9%–50%, respectively; in Asian countries, it was 8.8%–37.4% and 3.7%–16%, respectively; and globally, it was 22% and 17%, respectively. This may be because the tumor in the respiratory tract narrows the respiratory tract, thereby increasing airflow resistance. However, the tumor size had no significant correlation with the OSA severity. Among the physiological indices, only the neck circumference had a significant and positive correlation with the OSA (AHI value) ($r = 0.51$, $P = 0.008$), which is consistent with previous studies.[10,21–23] This may be because an increase in the neck circumference implied an increase in the amount of fat or edema around the pharynx, causing a narrowing of the pharynx and respiratory tract. Tumor hypoxia is a well-known contributor to poor cancer prognoses.[14,24] For example, chronic intermittent tissue hypoxia resulting from OSA in patients with OOC may cause radioresistance and thereby worsen therapeutic outcomes. Future studies may need to further explore the impact of high AHI values on recurrent disease and cancer-related mortality as clinical oncological outcomes.

The incidence of OSA for patients with OOCs 6 months after surgery was 95.6%. According to a recent systematic review by Ralli et al,[7] the prevalence of OSA among patients with head and neck cancers ranged from 12% to 95.8%, with a weighted mean of 59.78. The incidence of OSA in the present study was higher. The AHI ($P = 0.013$), AI ($P = 0.006$) and OI ($P = 0.005$) were all significantly worse after surgery for OOCs. We analyzed the possible factors that could be contributing to this situation and noted that the type of treatment was significantly correlated with the AHI ($\chi^2 = 6.04$, $P = 0.049$). The participants who underwent surgery with chemoradiotherapy had the highest AHI, followed by those who received only surgery. The participants who received surgery with radiotherapy had the lowest AHI. Although their surgical wounds were more stable 6 months after surgery, the structure of their respiratory tracts had changed after the FFR. The uneven flap that was protruding from the respiratory tract had increased their airway resistance. In addition, performing lymph node dissection might damage both the carrying capacity and the efficiency of the lymphatic transport mechanism, causing secondary head and neck lymphedema and compression of the respiratory tract.[25,26] Furthermore, some of the participants also received adjuvant chemoradiotherapy. Chemotherapy might cause respiratory tract inflammation, leading to mucosal swelling and increased secretions. Radiotherapy destroys the mucin in the salivary gland. Because mucin serves as a mucosal lubricant, mucin-related surface tension plays a role in the upper airway luminal patency, which affects the upper airway compliance and resistance.[27] In addition, the cicatricial effects of radiotherapy on the superior pharyngeal constrictor muscle may act to pull the tongue posteriorly and decrease the distance between its base and posterior pharyngeal wall.[28] The impairment of the neuromuscular regulation of the pharyngeal dilator muscle and the impact of radiation on the surrounding tissues around the respiratory center may be additional contributing factors that can aggravate OSA.[28] However, there have been inconsistent findings in the previous studies evaluating if radiation has a beneficial effect in tightening any redundant soft tissue in the upper airway or if any excessive tongue base tissue can be reduced, which has a positive impact on OSA.[29] The impacts of oral and oropharyngeal radiation on OSA need to be further explored in future studies. The incidence of OSA after treatment among the patients in the present study was substantially higher than the 25.5% in the study that was conducted by Loth et al,[18] which indicated that the incidence of OSA in patients treated with surgery was 30% and the incidence of OSA in patients treated with combined chemoradiotherapy was 24.39%. Future studies must use increased sample sizes to validate our findings.

Regarding the changes in the stages of sleep, the percentage of time in light sleep (S1+S2) and deep sleep (S3+REM), the sleep latency, and the sleep efficiency of the patients before and after surgery showed no significant differences. However, the patients' sleep efficiencies before and after surgery were generally low, and the proportion of time that they spent in light sleep was high. This implied that the participants had a poor sleep quality,[30] and their arousal index values were significantly higher at 6 months after the surgery ($P = 0.039$). One possible reason for such an increase was the aggravation of OSA. Clinically, patients with poor sleep are mostly treated with insomnia therapy; the risk of OSA is often initially ignored. Taking muscle relaxants and hypnotic drugs may reduce muscle tension during sleep and increases the effects of sedative treatments. Nevertheless, a Cochrane systematic review indicates that no consensus

has been reached on whether the use of opioids, sedatives and hypnotic drugs significantly increases the severity of sleep apnea. These drugs should be prescribed and dosed with caution in patients with OSA due to the specific physiological changes that these patients undergo post-operatively.[4] Before administering sedative-hypnotics, muscle relaxants, or anxiolytics to patients, healthcare providers should cautiously assess the cause of the patient's poor sleep to avoid relaxing the posterior glossopharyngeal muscle and thus aggravating the patient's OSA symptoms, which can be counterproductive. Patients should lie on their side or adopt a comfortable reclining posture with their head elevated off the bed during sleep. These sleeping positions can partially resolve patients' breathing difficulties during sleep.[10,31] Six months after surgery, healthcare providers should actively assist the patients in a self-assessment of whether the relevant symptoms have worsened or have affected their daily life; additionally, the healthcare providers should educate patients' families to pay attention to the patients' sleep patterns and safety, and they should arrange for a PSG to estimate the severity of the patient's OSA if necessary. Our results may suggest that an appropriate assessment of sleep quality should be performed in OOC survivors because prompt sleep treatment is crucial for the overall improvement of patients' quality of life.

Limitations and future directions

The findings of the current study should be received with caution due to some limitations. (1) This was a prospective cohort study without a control group; therefore, we were unable to estimate the relative risk of OSA among patients with OOCs. (2) The sample size was relatively small, and the recruited participants were all men from a single institute, which precluded geographical generalization and slightly compromised the power of the analyses. (3) The attrition rate was 12% (3/26), with various reasons for withdrawal (eg. cancer recurrence, cerebral stroke and death) during the 6-month follow-up period; therefore, the prevalence of OSA in patients with OOCs may have been underestimated. (4) The follow-up period was limited to 6 months, and although we acknowledge that PSG remains the gold standard for diagnosis, only objective sleep-related indices as opposed to subjective sleep quality were investigated in this study; therefore, additional measurement systems should be incorporated to verify our findings. Nevertheless, this study provided new insights into the changes in OSA severity before surgery and 6 months after surgery in patients with OOCs after undergoing FFR, and this study evaluated the characteristics of these changes. Further studies should investigate the contribution of these findings to the patients' overall quality of life and postoperative morbidities by conducting a long-term follow-up. Future studies with large sample size are needed so that researchers can control for tumor location, the type and subsite of the free flap, and the potential effect of opiates on sleep architecture in order to achieve generalizability.

Implications for practice

FFR has been regarded as a standard procedure following head and neck cancer resection. Its technique has progressed considerably over time; its success rate is now 91%–99%,[32] leading to the lowering of indications for this surgical strategy, which might lead to the inclusion of patients who would not have been considered candidates elsewhere. This study should increase clinical awareness of OSA in OOC patients treated with FFR, as we showed that they have an increased risk of developing OSA. Since OSA has a negative impact on quality of life, we suggest that routine screening for OSA be required when patients complain of OSA or severe daytime sleepiness or when chronic fatigue remains present after FFR; in this way, treatment options can be discussed. We hope that this study and its results can act as a springboard for future work; the early identification and treatment of OSA may be important considerations in the comprehensive management of patients with OOCs.

Conclusions

Our data indicated that the incidence of OSA for patients with OOC was high before FFR surgery and was even higher at 6 months after surgery. This high incidence of OSA may be attributable to the neck circumference and complexity involved in the treatment process. Neck circumference is a surrogate marker of airway patency and the collapsibility of tissue during sleep, and it also represents the tumor mass and radiation-induced edema after FFR in this subset of OOC patients. Furthermore, neck circumference is easily measured in a clinical setting to assess the need for PSG. Clinicians should assess the risk factors and clinical symptoms of OSA early, be aware of this condition when presented with complaints of sleep disturbance among patients with OOCs and provide timely and relevant referrals to ensure individualized and appropriate care.

Acknowledgments

The authors are grateful to Chung-Yi Li, Chih-Hui Hsu and Wan-Ning Chen of the Biostatistics Consulting Center, National Cheng Kung University Hospital, for providing statistical consulting services; the authors also thank the family members of the patients who were willing to participate in the research. This study could not have been completed without their assistance.

Author contributions

Fu-Hsin Liao: Conceptualization, Methodology, Software, Writing-Original draft preparation. Chan-Chi Chang: Data curation, Data interpretation. Yu-Cheng Lu: Investigation. Cheng-Yu Lin: Validation, Supervision, Final Approval. Wei-Shu Lai: Methodology, Supervision, Writing-Reviewing and Editing, Final Approval.

Declaration of competing interest

None declared.

Funding

The authors gratefully acknowledge the support of the National Cheng Kung University Hospital Research Project (Grant No. NCKUH-10703035).

Ethics statement

Ethics approval was sought and received from the National Cheng Kung University Hospital (Approval No. B-ER-106-324).

Data availability statement

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

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca - Cancer J Clin*. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin*. 2021;71(3):209–249. https://doi.org/10.3322/caac.21660.
3. Gasparro R, Calabria E, Coppola N, et al. Sleep disorders and psychological profile in oral cancer survivors: a case-control clinical study. *Cancers*. 2021;1855(8):13. https://doi.org/10.3390/cancers13081855.
4. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane*

Database Syst Rev. 2015;7:1465–1858. https://doi.org/10.1002/14651858.CD011090.
5. Colin SP, Kerstin MS. Overview of the diagnosis and staging of head and neck cancer, 2021 http://www.uptodate.com/; 2021. Accessed July 1, 2021.
6. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. *J Thorac Dis*. 2015;7(8):1311–1322. https://doi.org/10.3978/j.issn.2072-1439.2015.06.11.
7. Ralli M, Campo F, Angeletti D, et al. Obstructive sleep apnoea in patients treated for head and neck cancer: a systematic review of the literature. *Medicina (Kaunas)*. 2020;399(8):56. https://doi.org/10.3390/medicina56080399.
8. Cao Y, Ning P, Li Q, Wu S. Cancer and obstructive sleep apnea: an updated meta-analysis. *Medicine*. 2022;10(e28930):101. https://doi.org/10.1097/MD.0000000000028930.
9. Aurora RN, Collop NA, Jacobowitz O, Thomas SM, Quan SF, Aronsky AJ. Quality measures for the care of adult patients with obstructive sleep apnea. *J Clin Sleep Med*. 2015;11(3):357–383. https://doi.org/10.5664/jcsm.4556.
10. Epstein LJ, Kristo D, Strollo Jr PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263–276. https://doi.org/10.5664/jcsm.27497.
11. Kingman PS. Overview of obstructive sleep apnea in adults. http://www.uptodate.com/; 2017. Accessed November 1, 2019.
12. Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clin Proc*. 2011;86(6):549–555. https://doi.org/10.4065/mcp.2010.0810.
13. Berry RB, Brooks R, Gamaldo C, et al. AASM scoring manual updates for 2017. *J Clin Sleep Med*. 2017;13(5):665–666. https://doi.org/10.5664/jcsm.6576 (Version 2.4).
14. Shih JW, Chiang WF, Wu A, et al. Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1α co-activator driving oral cancer progression. *Nat Commun*. 2017;15874:8. https://doi.org/10.1038/ncomms15874.
15. American Joint Committee on Cancer. AJCC cancer staging atlas. http://link.springer.com/book/10.1007/978-1-4614-2080-4/page/1/; 2017. Accessed May 12, 2020.
16. Bruce EB, Kerstin MS, Shiyu S. Overview of treatment for head and neck cancer. http://www.uptodate.com/; 2021. Accessed March 1, 2021.
17. Huyett P, Kim S, Johnson JT, Soose RJ. Obstructive sleep apnea in the irradiated head and neck cancer patient. *Laryngoscope*. 2017;127(11):2673–2677. https://doi.org/10.1002/lary.26674.
18. Loth A, Michel J, Giorgi R, et al. Prevalence of obstructive sleep apnoea syndrome following oropharyngeal cancer treatment: a prospective cohort study. *Clin Otolaryngol*. 2017;42(6):1281–1288. https://doi.org/10.1111/coa.12869.
19. Payne RJ, Hier MP, Kost KM, et al. High prevalence of obstructive sleep apnea among patients with head and neck cancer. *J Otolaryngol*. 2005;34(5):304–311. https://doi.org/10.2310/7070.2005.34502.
20. Steffen A, Graefe H, Gehrking E, Konig IR, Wollenberg B. Sleep apnoea in patients after treatment of head neck cancer. *Acta Otolaryngol*. 2009;129(11):1300–1305. https://doi.org/10.3109/00016480802613113.
21. Cheng CH, Huang YC, Jih KS. Anthropometric measurements and sleep-related features in relation to obstructive sleep apnea syndrome. *Thorac Med*. 2003;18(3):187–193. https://doi.org/10.29806/TM.200306.0001.
22. Paul EP, Terry Y, Jodi HB, Mari P, Erika WH, Khin MH. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006–1014. https://doi.org/10.1093/aje/kws342.
23. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA*. 2004;291(16):2013–2016. https://doi.org/10.1001/jama.291.16.2013.
24. Huppertz T, Horstmann V, Scharnow C, et al. OSA in patients with head and neck cancer is associated with cancer size and oncologic outcome. *Eur Arch Oto-Rhino-Laryngol*. 2021;278(7):2485–2491. https://doi.org/10.1007/s00405-020-06355-3.
25. Anand A, Balasubramanian D, Subramanian N, et al. Secondary lymphedema after head and neck cancer therapy: a review. *Lymphology*. 2018;51(3):109–118.
26. Ridner SH. Pathophysiology of lymphedema. *Semin Oncol Nurs*. 2013;29:4–11.
27. Rada R. Obstructive sleep apnea and head and neck neoplasms. *Otolaryngol Head Neck Surg*. 2005;132(5):794–799. https://doi.org/10.1016/j.otohns.2004.12.002.
28. Lin HC, Friedman M, Chang HW, Fang FM, Lin MC, Su MC. Impact of head and neck radiotherapy for patients with nasopharyngeal carcinoma on sleep-related breathing disorders. *JAMA Otolaryngol Head Neck Surg*. 2014;140(12):1166–1172. https://doi.org/10.1001/jamaoto.2014.2953.
29. Friedman M, Landsberg R, Pryor S, Syed Z, Ibrahim H, Caldarelli DD. The occurrence of sleep-disordered breathing among patients with head and neck cancer. *Laryngoscope*. 2001;111(11 Pt 1):1917–1919. https://doi.org/10.1097/00005537-200111000-00008.
30. Ohayon M, Wickwire EM, Hirshkowitz M, et al. National sleep foundation's sleep quality recommendations: first report. *Sleep Health*. 2017;3(1):6–19. https://doi.org/10.1016/j.sleh.2016.11.006.
31. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110–114. https://doi.org/10.1093/sleep/7.2.110.
32. Chen KH, Kuo SCH, Chien PC, Hsieh HY, Hsieh CH. Comparison of the surgical outcomes of free flap reconstruction for primary and recurrent head and neck cancers: a case-controlled propensity score-matched study of 1,791 free flap reconstructions. *Sci Rep*. 2021;11(2350):1–6.