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Impact of obstructive sleep apnea risk on prognosis and treatment responses of lung cancer

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ABSTRACT

Aims: Obstructive sleep apnea (OSA) may affect oncogenic processes in a specific way for each tumor type. This study was conducted to reveal the relationship between OSA risk and prognosis and treatment responses in patients with lung cancer.

Methods: This prospective study included stage III and IV lung cancer patients aged between 18 and 75 years. Patients with poor performance status, cranial metastasis, congestive heart failure, surgery history, and positive airway pressure device use were excluded. STOP-BANG questionnaire was used to assess the OSA risk. The primary end-point was the differences in the survival and treatment responses of patients at intermediate/high risk of OSA compared with those at low OSA risk. Data from the patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were analyzed separately.

Results: Ninety-eight patients (34 SCLC and 64 NSCLC), mostly male (85.7%), with a mean age of 59.3±8 were included in the analysis. Overall survival was similar in the groups. However, in the SCLC group, those at low OSA risk had a shorter progression-free survival (PFS) than those at intermediate/high risk (105±31.8 days, vs 272±16.2 days, p=0.001). Cox regression analysis showed that low OSA risk was an independent risk factor for PFS in only the SCLC group (HR:4.9 CI:1.6-14.7, p=0.005).

Conclusion: Our results showed that low OSA risk was an independent poor prognostic factor for PFS in SCLC regardless of the tumor stage.

Keywords: Lung cancer, obstructive sleep apnea, overall survival, progression-free survival, STOP-BANG questionnaire

INTRODUCTION

There has been an increased research interest in the relationship between obstructive sleep apnea (OSA) and cancer recently.[1] However, it is difficult to clarify this relationship because of the established risk factors such as age and obesity.[2] Intermittent hypoxia (IH), the characteristic feature of OSA, has an important role in carcinogenesis.[3] After the carcinogenic effects of IH were demonstrated in cell culture and animal studies.[1,3] Human studies of the OSA-cancer link gained momentum. In addition to its local effect on tumor cells, IH causes an increase in the release of inflammatory and angiogenic molecules and accelerates oncogenic processes systemically.[3,4] In addition, OSA-associated IH is believed to be responsible for resistance to cancer therapy.[5] Sleep disruptions, immune deregulation, and circadian rhythm changes caused by OSA were also shown as important factors in tumorigenesis.[6,7]

However, some epidemiological studies revealed conflicting results with the aforementioned animal studies.[8,9] Additionally, it has been revealed that the oncogenic effect of IH decreases with aging and obesity.[10,11] These oncogenic properties of OSA may also vary according to the tumor cell type. Some evidence suggests that the incidence of breast, rectum, prostate, and colon cancer decreases with OSA.[12] In a large cohort including various types of cancer, the incident and prevalent cancers were not associated with OSA severity in terms of apnea-hypopnea index (AHI) and sleep time spent with oxygen saturation <90%. The cancer incidence was associated with nocturnal oxygen desaturation in only smoking-related cancers.[8]

The studies about the lung cancer-OSA relationship mostly include non-small cell lung cancer (NSCLC) patients. In a study conducted on a hospital database containing mostly adenocarcinoma cases, it was seen that the overall survival (OS) was shorter in moderate-to-severe OSA patients than in the mild OSA group.[13] Current evidence indicates that OSA can have differential effects on different histological

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cancer types. The impact of OSA risk on each type of lung cancer needs to be evaluated. This study was conducted to show the impact of OSA risk on prognosis and treatment responses in patients with NSCLC and small cell lung cancer (SCLC) separately.

METHODS

This prospective observational study comprised lung cancer patients at locally advanced or metastatic stages aged between 18-75 years. Data of the patients who were admitted to our pulmonology clinics between 1.6.2019 and 31.12.2020 before or during the first-line standard chemotherapy and agreed to participate in the study were collected. The study was approved by the Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.05.2019, Decision No: 1905). The study protocol was registered at ClinicalTrials.gov with protocol number 1905 (ClinicalTrials.gov Identifier: NCT04003961). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The exclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≥2, cranial metastasis, congestive heart failure (ejection fraction≤%50), surgery history, treatment refusal, incomplete treatment (≤2 cycles), and the use of positive airway pressure device. The clinical data from 10 patients who were followed up by another hospital and 4 patients who did not complete the questionnaires were missing. Four patients enrolled in the other studies for immunotherapy drugs were also excluded (Figure 1). As general health insurance in Turkiye does not reimburse immunotherapy for the first-line treatment of lung cancer, all the patients enrolled in the study were on platinum-doublet systemic chemotherapy or concurrent/sequential chemoradiotherapy. The patients were assessed for the risk of obstructive sleep apnea (OSA) with the STOP-BANG questionnaire and excessive daytime sleepiness (EDS) with the Epworth sleepiness scale (ESS).

The 8th tumor node metastasis (TNM) staging system of the International Association for the Study of Lung Cancer (IASLC) was used for staging NSCLC.[14] For the staging of SCLC, a two-stage (limited/extensive) staging scheme belonging to the "Veterans' Administration Lung Study Group (VALSG)", which has been used in clinical practice since the 1950s, was used.[15]

Demographic and clinical data of the patients grouped according to OSA risk, overall/progression-free survival, and treatment side effects were evaluated comparatively. The variables included in the data set can be listed as: 1-Demographic information of the patients (age, gender, smoking history), anthropometric measurements (body mass index, neck circumference), 2-clinical information

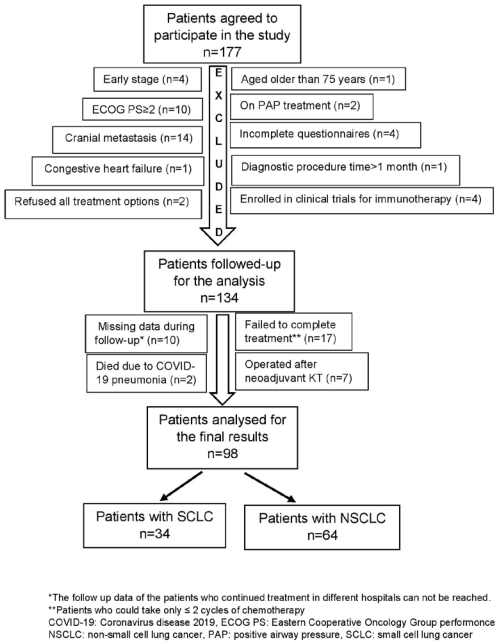

Figure 1. Flowchart of the study

(radiological TNM stages, diagnosis method, date of diagnosis, Patients' general medical condition, treatment outcomes, albumin, lactate dehydrogenase level, complete blood count results, and the results of Epworth sleepiness scale and STOP-BANG questionnaires) The radiotherapy related side effects (esophagitis and/or radiation pneumonia) were also recorded. The systemic inflammatory index (SII) value was calculated from the absolute neutrophil, lymphocyte, and platelet counts (NxP/L) in the complete blood count at the time of diagnosis.[16] The risk for OSA was assessed according to the results of the STOP-BANG survey as stated below.[17]

Evaluation of the STOP-BANG Survey Results

OSA-low risk: 0-2 positive responses to questions

OSA-intermediate risk: 3-4 positive responses to questions

OSA-high risk: 5-8 positive responses to questions or yes to at least 2 of 4 STOP questions and yes to at least 2 of 4 STOP questions and male patients, BMI≥35 kg/m^2 or neck circumference ≥43 cm for men, ≥41 cm for women.

In the follow-ups performed at 3-month periods after the treatment (please rephrase), the radiological response evaluation criteria in solid tumors (RECIST guideline version 1.1 criteria) was used to determine progression.[18] The patients with progression according to RECIST 1.1 in the first follow-up were considered as the early progression group. This study was conducted in accordance with the Declaration of Helsinki. The patients who approved informed consent for the usage of their data were included.

The primary endpoint of this study is to reveal the impact of OSA risk on the prognosis and treatment responses in

patients with lung cancer. To address prognosis, overall survival (OS) and Progression-free survival (PFS) were used. OS was calculated as the time (in days) from the date of pathological diagnosis to the date of death or the end of the study (31.12.2021). PFS was calculated as the time (in days) between the date of pathological diagnosis and the date of progression, date of death, or date of study termination.

As a secondary endpoint, the impact of OSA risk on radiotherapy-related side effects was investigated.

Statistical Analysis

SPSS 21 for Windows was used for data analysis. Descriptive statistics were stated as mean±standard deviation for normally distributed variables, median [IQR] for non-normally distributed variables, and the number of cases and (%) for nominal variables.

The t-test and Mann-Whitney U test were used to test differences in normally distributed and non-normally distributed variables, respectively. The ratios were compared using the 'Pearson Chi-Square or Fisher Exact test'.

The Kaplan-Meier survival estimates were calculated. The effect of the variables on survival was investigated using the log-rank test. The univariate analysis revealed OSA risk, smoking history, stage, and neck circumference as the possible risk factors for survival. OSA risk was highly correlated with neck circumference. The parameters including OSA risk, smoking history, and stage were entered into the Cox regression analysis with the Backward selection method to determine independent predictors of survival. Schoenfeld and Martingale analysis was used to assess the proportional hazards assumption and model fit. The results were considered statistically significant when the p-value is <0.05.

RESULTS

Out of 177 patients who agreed to participate in the study, 98 patients were included in the final analyses. The participants were mostly male, with a mean age of 59.3±8. The SCLC group included 34 and the NSCLC group included 64 patients. The flowchart for exclusion criteria is illustrated in Figure 1. The patients were divided into 2 groups according to the STOP-BANG score: low OSA risk and intermediate-high OSA risk. An endobronchial fine needle biopsy was performed in 24 patients (24.5%). Fiberoptic bronchoscopy was performed in 46 patients (46.9%). Computed tomography-guided transthoracic fine needle aspiration biopsy was performed in 23 patients (23.5%), cryobiopsy in 3 patients (3.1%), cell block cytology of pleural effusion in one patient (1%), and pleural biopsy in one patient (1%).

The statistical analysis was performed in SCLC and NSCLC groups separately. Five patients (14.7%) with SCLC and 23 (35.9%) patients in the NSCLC group were at low risk for OSA according to the STOP-BANG score. In both SCLC and NSCLC patients, the low-risk and intermediate/high-risk groups were similar for age, gender, comorbidities, active smoking percentage, Epworth sleepiness score, stage, and treatment. Laboratory values including systemic inflammatory index, white blood cell count, and lactate dehydrogenase at the time of diagnosis were also similar in the two groups. The components of the STOP-BANG score including neck circumference and BMI values were higher in the intermediate/high-risk group. Unlike the SCLC group, the albumin value was lower in the low OSA risk group among NSCLC patients (Table 1, 2).

All patients underwent platinum-based doublet chemotherapy regimens. While 67.3% (n=23) of the patients with SCLC received etoposide-cisplatin chemotherapy, the remaining 11 (32.7%) were treated with the etoposide-carboplatin regimen. The majority of the patients in the NSCLC group (n=48, 75%) were treated with a paclitaxel carboplatin regimen. The other treatment regimens given to the NSCLC group were as follows: Paclitaxel-cisplatin for 6 patients (9.4%), pemetrexed-cisplatin for 6 patients (9.4%), gemcitabine-cisplatin for 3 patients (4.7%), and docetaxel carboplatin for 1 patient (1.6%).

The SCLC patients with limited stage (n=17) and extensive stage who responded to the first-line chemotherapy (n=5) received sequential/concurrent radiotherapy. Among this study population with SCLC, radiotherapy-induced esophagitis and/or radiation pneumonia developed in 5 patients with intermediate/high OSA risk. In the low-risk group, no patient reported RT-related side effects. However, this difference was not statistically significant (0% vs 26.3%, p=1.000). The rate of early progression (progression in the first 3 months) was statistically higher in patients with low OSA risk in the SCLC group (80% vs 17.2%, p=0.012).

In the NSCLC group, 9 out of 30 patients who received sequential/concurrent chemoradiotherapy were at low risk for OSA. In this group, only 1 patient (11.1%) developed esophagitis due to radiotherapy. Radiotherapy-induced esophagitis and/or radiation pneumonia were recorded in 5 patients (23.8%) among 21 NSCLC patients with moderate-high risk of OSA (p=0.64). The low and intermediate/high OSA risk groups were similar for early progression rates in NSCLC patients (Table 2).

Table 1. Demographic and clinical characteristics of the patients with SCLC

	OSA RISK		
	Low n=5	Medium-High n=29	p-value
Age, years, mean±SD	54.6±13.9	60.1±7.4	0.435
Gender, male, % (n)	60 (3)	89.7 (26)	0.146
Smoking, active, % (n)	(n=5) 40 (2)	(n=23) 65.2 (15)	0.353
BMI, kg/m², median (IQR)	23.4 (3)	26.1 (4.4)	0.010
Neck circumference (cm)	38 (3)	41 (3)	0.001
Comorbidity, % (n) Asthma/COPD	0	20.7 (6)	0.556
DM	20 (1)	6.9 (2)	0.400
HT	20 (1)	31.0 (9)	1.000
CVD/arrhythmia	0	10.3 (3)	1.000
Stage, % (n)			
Limited	40 (2)	51.7 (15)	1.000
Extensive	60 (3)	48.3 (14)	
Treatment, % (n)			
CT	40 (2)	34.5 (10)	1.000
CRT	60 (3)	65.5 (19)	1.000
Early progression, % (n)	80 (4)	17.2 (5)	0.012
RT-related side effects, % (n)	(n=3) 0	(n=19) 26.3 (5)	1.000
WBC (x10count/L), median (IQR)	6990 (3495)	9430 (4165)	0.296
SII (cells/L), median (IQR)	882 (864)	848.5 (1434)	0.942
Hg (g/dl), mean±SD	13.9±1.8	14.5±1.8	0.452
Albumin (g/dl), mean±SD	(n=5) 38.4±3.3	(n=22) 39.8±4.9	0.548
LDH (U/L), median (IQR)	(n=5) 298 (169)	(n=22) 254 (138)	0.492
ESS Score, median (IQR)	6 (4)	2 (4)	0.065

SCLC: Small cell lung cancer, OSA: Obstructive sleep apnea, BMI: Body-mass index, IQR: interquartile range COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, HT: Hypertension, CVD: cardiovascular disease, CT: chemotherapy, CRT: chemoradio-therapy, RT:radiotherapy, WBC: White blood cell count, SII: Systemic inflammatory index, Hg:Hemoglobin, LDH: Lactate dehydrogenase, ESS: Epworth sleepiness scale

Table 2. Demographic and clinical characteristics of the patients with NSCLC

	OSA RISK		
	Low n=23	Medium-High n=41	p-value
Age, mean±SD	56.8±8.9	60.8±7.1	0.053
Gender, male, % (n)	87 (20)	85.4 (35)	1.000
Smoking, active, % (n)	(n=19) 47.4 (9)	(n=29) 44.8 (13)	1.000
BMI, median (IQR)	(n=23) 23.5 (4)	(n=40) 27.9 (6)	0.001
Neck circumference (cm), median (IQR)	38 (3)	40 (5)	0.001
Comorbidity, % (n)			
Asthma/COPD	13 (3)	9 (22)	0.510
DM	13 (3)	24.4 (10)	0.342
HT	13 (3)	34.1 (14)	0.059
CVD/ arrhythmia	8.7 (2)	12.2 (5)	1.000
Stage, % (n)			
Locally advanced	43.5 (10)	56.1 (23)	0.332
Metastatic	56.5 (13)	43.9 (18)	
Treatment, % (n)			
CT	60.9 (14)	48.8 (20)	0.409
CRT	39.1 (9)	51.2 (21)	
RT-related side effects, % (n)	(n=9) 11.1 (1)	(n=21) 23.8 (5)	0.640
Early progression, % (n)	43.5 (10)	35 (14)	0.505
WBC (x10 count/L), median (IQR)	9590 (3080)	9340 (2275)	0.386
SII, median (IQR)	1028.8 (1186)	996.7 (928)	0.471
Hg, g/dl, mean±SD	13.6±1.6	14.1±1.5	0.182
Albumin, g/dl, mean±SD	(n=19) 34.6±3.3	(n=32) 37.3±4	0.018
LDH, U/L, median (IQR)	(n=18) 247 (119)	(n=32) 208 (86)	0.656
ESS Score, median (IQR)	1 (3)	2 (5)	0.052

NSCLC: non-small cell lung cancer, OSA: Obstructive sleep apnea, BMI: Body-mass index, IQR: interquartile range COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, HT: Hypertension, CVD: cardiovascular disease, CT: chemotherapy, CRT: chemoradio-therapy, RT:radiotherapy WBC: White blood cell count, SII: Systemic inflammatory index, Hg:Hemoglobin, LDH: Lactate dehydrogenase, ESS: Epworth sleepiness scale

In the Cox regression analysis including disease stage and OSA risk, PFS was shorter in patients with SCLC having low OSA risk (Table 3). In log-rank analysis, the median PFS for the low-risk group with SCLC patients was 105±31.8 days, while it was 272±16.2 days in the medium/high-risk group (p=0.001, Figure 2). On the other hand, the groups were similar in terms of OS. Cox regression analysis in the NSCLC group showed that the advanced stage was a poor prognostic factor for both PFS and OS, regardless of OSA risk and albumin levels (Table 3).

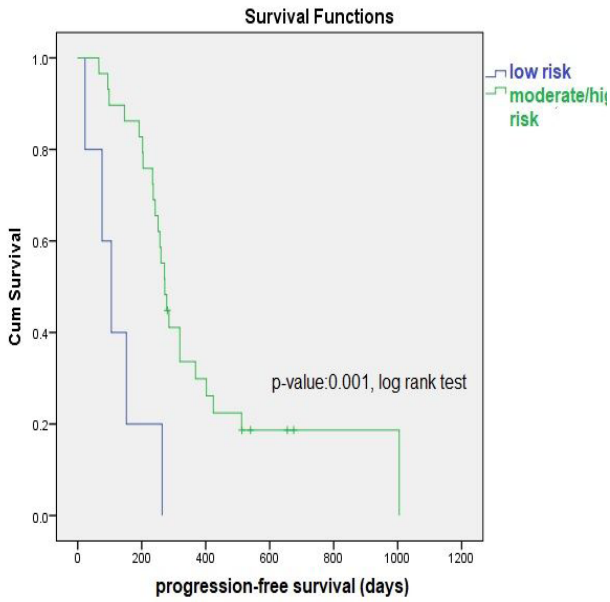

Figure 2. Graphs of Kaplan Meier analysis for progression-free survival of the patients with SCLC

Table 3. Cox regression analysis for survival (days)

OS for SCLC	**RR**	**95% CI**	**p-value**
Stage (extensive vs limited)	1.89	0.82-4.32	0.133
OSA risk (medium/high vs low)	0.59	0.19-1.82	0.361
PFS for SCLC	**RR**	**95% CI**	**p-value**
Stage (extensive vs limited)	1.63	0.42-6.44	0.480
OSA risk (medium/high vs low)	0.09	0.02-0.36	0.001
OS for NSCLC	**RR**	**95% CI**	**p-value**
Stage (advanced vs locally advanced)	2.95	(1.36-6.39)	0.006
OSA risk (medium/high vs low)	0.87	(0.41-1.83)	0.715
Albumin	0.95	(0.85-1.05)	0.280
PFS for NSCLC	**RR**	**95% CI**	**p-value**
Stage (advanced vs locally advanced)	2.49	(1.3-4.76)	0.006
OSA risk (medium/high vs low)	0.93	(0.49-1.78)	0.835
Albumin	0.99	(0.91-1.08)	0.879

OS: overall survival, RR: relative risk, SCLC: Small cell lung cancer, OSA: Obstructive sleep apnea, PFS: Progression-free survival, NSCLC: Non-small cell lung cancer,

DISCUSSION

This study reveals that PFS was shorter and the rate of early progression was higher among SCLC patients with low-OSA risk compared with intermediate/high OSA risk. On the other hand, we showed that OSA risk did not affect the prognosis of NSCLC patients. These results suggest that the effects of OSA may differ depending on histological type. Although not statistically significant, the result showing that RT-related adverse events were observed in only one patient in the low OSA risk group may prompt further research on this topic.

Current research on the OSA-cancer relationship includes animal experiments, cell culture studies, and human studies from non-specific databases. However, the results obtained so far are scientifically contradictory. In animal studies, mice are exposed to a model of IH in which the nadir of oxyhemoglobin saturation was reduced to the range of 65-72% by applying a 6% fraction of inspired oxygen (FiO_2) for 90 seconds, 20 times per hour, for 12 hours/day for 5 weeks.[19] This model represents a more severe and long-lasting form of IH than in many OSA patients. Besides, contrary to 5 week-period of IH in animal models, it is not possible to determine the exact onset of OSA in humans. Nonetheless, animal experiments showed that tumor growth is accelerated by intermittent hypoxia in melanoma, lung, renal, breast cancers, and myeloma.[3,20-23] Most of the animal experiments have defined tumor growth as the primary endpoint. However, only a few studies evaluated metastasis and invasion. Although rarely mentioned in these studies, another hallmark of OSA, sleep fragmentation, has been reported to promote cancer progression.[3,6]

Human studies have been made using databases or records of the general population that are not specific to OSA. In these analyses, the severity of IH, confounding factors, and the effects of OSA treatment were not fully assessed. Study populations typically included all cancer types, but specific analyses for single cancer types were lacking. The incidence of cancer in some studies was also too low to yield solid evidence.[24] Christensen et al.[25] found that those with OSA-related symptoms had a higher incidence of smoking-related cancers. In studies reporting polysomnographic or polygraphic data, the percentage of night-time with SpO^2<90% (Tsat90%) was associated with high incidence in all cancer types and cancer-related mortality.[10] This effect was even more pronounced when positive airway pressure (PAP) therapy-compliant patients were excluded.[26,27] The previous studies also showed that the association between cancer incidence/mortality and OSA was stronger for males, younger (aged <65 years), leaner, and less sleepy patients.[11,26] Our study population includes only PAP therapy-naïve patients with smoking-related cancer and the majority of participants were male. The median BMI of our study group was below 30 kg/m^2 and the median ESS score was below 10. These clinical characteristics of our study population may lead to an expectation for a strong effect of OSA risk for poor prognosis in lung cancer patients. However, we revealed a negative effect of intermediate/high OSA risk on the PFS of the patients with SCLC.

Only a few studies have focussed on the relationship between an individual tumor type and OSA so far.

The first human study on melanoma was published by Martínez-García et al.[28] The authors demonstrated a correlation between aggressiveness factors of melanoma (such as the Breslow index, presence of ulceration, and mitotic index), AHI, and oxygen desaturation index. It was reported that the incidence of head and neck tumors and histological aggressiveness of renal tumors were higher in OSA patients.[20,29,30] There is also a growing body of evidence for the OSA-lung cancer relationship. A meta-analysis including four studies revealed a 30% increase in the incidence of lung cancer for patients with OSA.[31] In a murine lung cancer model, IH was shown to be a factor that increases tumor growth and metastatic processes.[32] Recent studies including mostly NSCLC patients have pointed out that IH aggravated the proliferation, invasion, migration, and drug resistance of tumor cells.[33] Unlike previous studies SCLC patients of our study population were analyzed separately.

In another study of 23 cases from the Asian population, severe OSA was found to increase cancer-related mortality in lung cancer patients with stages 3 and 4.[34] On the other hand, in an analysis comparing 7 patients with lung cancer and comorbid OSA and 45 patients with lung cancer and no OSA, no significant correlation was reported between mortality rate and OSA.[35] These conflicting results may be related to the severity of OSA or histologic type of lung cancer. Similarly, Gozal et al.[12] provided epidemiological evidence from a nationwide cohort including 5.6 million individuals proving that the effect of OSA depends on cancer type and lacks any associations with an increased risk of metastatic cancer or cancer-related deaths. In this study, it was found that the incidence of lung cancer was lower in OSA patients when compared to the non-OSA group. Despite the correlations between the hypoxia-inducible factor (HIF) signaling pathway and tumorigenesis and therapy resistance, variations in recruiting this pathway may lead to divergent results in different types of cancer. It was shown that HIF activity may vary in cancer cell lines under the same level of hypoxia.[36] Furthermore, it was found that hypoxia does not effect etoposide-induced apoptosis in lung cancer cell lines while it reduces p53 activity in hepatoma cells.[37] These findings and our results suggest the existence of cancer-type specific intrinsic reactions to hypoxia.

In our study, the groups defined by OSA risk were similar in terms of confounding factors such as age, smoking rate, treatment modality WBC, SII, hemoglobulin, and LDH levels. Therefore, we performed comparisons in homogenous groups with a specific histologic type of cancer. Additionally, the STOP-BANG questionnaire provides more concrete evidence of OSA risk compared to a symptom-based study.[25] Nevertheless, the lack of polysomnographic data is the major limitation of our study. On the other hand, the sensitivity of the STOP-BANG test for patients with AHI>5 is 0.93.[38] Considering its high sensitivity, our results can be regarded as a basis for future studies. In 2019, Marhuenda et al.[39] published a remarkable study in which they exposed NSCLC cell cultures with different oncogenic mutations to different severity (moderate and severe) and types (intermittent vs sustained) of hypoxia. The authors reported that epithelial cell adhesion molecule and cell proliferation were not changed in some cell types when compared with normoxic cultures, and different results were obtained according to the type of IH. Likewise, our analysis yielded different results for NSCLC and SCLC. The poor PFS in the low-risk group with SCLC patients may be associated with the genetic and epigenetic characteristics of the tumor and the severity of OSA, which could not be determined in the current study.

CONCLUSION

This study shows that each histological subtype of lung cancer may have a unique response to OSA risk. OSA risk may also alter the side effects of cancer treatment. Larger future studies that include polysomnographic and genetic data to explore the metastatic processes, treatment responses, and side effects in the OSA-SCLC overlap are warranted.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.05.2019, Decision No: 1905).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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