Editorial

Head and neck cancer radiotherapy and obstructive sleep apnea

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The incidence of head and neck cancer (HNC) continues to increase worldwide since the 90's. With lifestyle habits like tobacco and alcohol use being the most important risk factors, HNC now ranks sixth in the most common cancers worldwide (1). Since HNC can affect areas of utmost importance for swallowing and respiratory functions, the quality of life of patients during treatment is a priority. Hence, the use of treatments like induction chemotherapy, definitive radiation therapy (RT) or chemoradiotherapy (CRT) are essential for organ preservation, maintaining function and quality of life. However, the side effects of these radiation treatments can be critical and include, among others, weight changes, appetite loss, xerostomia, cognitive problems and recently, a high incidence of obstructive sleep apnea (OSA) in patients who underwent RT was noted (2).

OSA is a multisystem disease caused by the collapse of the pharyngeal airway resulting in interrupted breathing during sleep. OSA is associated with sleep fragmentation and oxygen desaturations. Typically, OSA patients complain of a variety of symptoms including daytime somnolence, fatigue, memory and attention problems just to cite a few. OSA is also a risk factor for (3) multiple cardiovascular diseases. It has been estimated that 2% of women and 4% of men in the general population are affected by OSA with male gender, obesity, menopause, upper airway anatomy and craniofacial abnormalities being risk factors for OSA (3). It has also been reported that 2.4% of patients who complain of snoring, have airway tumor and cysts (2). Furthermore, it was reported that increased BMI and neck circumference are important risk factors for OSA. In fact, Peppard *et al.* reported that a 10% weight gain predicted a 6-fold increase in chances of developing sleep-disordered breathing and a 10% weight loss predicted 26% decrease in the severity of OSA (4). Another study by Davies and Stradling, showed a significant correlation (r=0.63) between neck circumference and OSA (5).

In this issue of *Annals of Palliative Medicine*, Inoshita *et al.* report a prospective study on the impact of radiotherapy for HNC on OSA (2). The study was conducted on 32 patients treated for nasopharyngeal, oropharyngeal, hypopharyngeal and laryngeal cancers at the Jutendo University hospital. The radiation dose used in patients was of 70 Gy in 35 fractions except one patient who received a 60 Gy radiation dose in 30 fractions. Out of the 32 patients, 11 did not consent to do the post-tests because the tests were more painful than expected or because the side effects of radiation were too major. The 21 remaining patients included 20 men and 1 woman with ages varying between 45 and 80 years old. The authors did not discuss the socio-economic status nor the ethnicity of the patients. The exclusion criteria included patients under 20, patients treated for sleep-disordered breathing, patients who underwent surgery for HNC, patients with a history of lung or neuromuscular disease and patients with distant metastases. Additionally, in contrast to average OSA patients, the patients in this study were not obese before the treatments; 96.9% of the participating patients had a BMI under 30 kg/m^2.

Previous studies already showed an increased incidence of OSA following RT treatment for HNC. Huyett *et al.* found that 50% percent of patients treated with RT for HNC showed evidence of OSA (6). Piccin *et al.* published two cases of severe obstructive sleep apnea induced by neck radiotherapy (7). Friedman *et al.* showed that patients treated by RT for HNC had an incidence of OSA that is much higher that the normal middle aged population (8). Patients with pharyngeal or laryngeal cancer seem to be particularly at risk of OSA; they all had OSA after treatments in Friedman's study. Lin *et al.*'s issue targeted patients with nasopharyngeal carcinoma and the study showed that RT did not influence clinical features of OSA (9).

Also, some anatomical changes are common in HNC patients who undergo RT treatments. Machtay *et al.* reported that pharyngeal edema often causes respiratory airway narrowing (10) and Nömayr *et al.* showed that mucosal edema, showed by a thickened epiglottis on MRI, is also a typical side effect of radiation (11). In many studies, it is hypothesized that the most important factor that increases OSA is the effect of radiation on the pharyngeal dilator muscle. This can lead to reduced upper airway compliance and increased resistance, which makes these patients more likely to develop OSA. Xerostomia and dysphagia that often occur after RT also contribute to OSA. Despite all this data, Inoshita *et al.*'s study is the first prospective one to measure the impact of RT on HNC and to investigate the pathogenesis of OSA in all areas of the pharynx and larynx after RT by using magnetic resonance imaging (MRI) and sleep test parameters (2).

Many observations on the effect of RT on OSA were revealed in Inoshita *et al.*'s study (2). First, it was found that even before radiotherapy, patients with HNC have a higher prevalence of OSA compared to the general population. In fact, 81.3% of patients diagnosed with HNC presented with OSA. The pre-treatment results of the severity of OSA were very variable with a mean AHI 20.8±19.0 events/hr. Additionally, in previous reports, OSA was found in 76% of patients with oropharyngeal cancer and 72% of patients with nasopharyngeal cancer. In this study, the prevalence of OSA was measured with polysomnography (PSG) and WatchPat 200 portable sleep-testing device (WP) and these tests revealed a higher prevalence of pre-treatment OSA: 81.25% (26 of 32 patients). This study brings questions on whether it is the treatment itself that leads to OSA or if these patients are at risk of OSA independently.

Furthermore, after RT, the prevalence of OSA increased to 85.7% (18 of 21 patients) with one more patient being diagnosed. AHI was higher after treatment for 57.1% (12 of 21) of the patients. In fact, the severity of OSA after treatment increased from 33.3% to 38.1%, for patients with mild OSA, it decreased from 28.6% to 19.0% for patients with moderate OSA and for patients with severe OSA, the severity increased from 19.0% to 28.6%. However, all these differences were not statistically significant.

Third, BMI and neck circumference that are important risk factors for OSA were measured before and after treatment. The results showed an important decrease in both factors. This could be explained by reduced intakes because of sore throat and nausea associated with the treatments. This would generally mean a decrease in the prevalence of OSA according to previous studies like Peppard *et al.*'s (4). However, the prevalence of OSA was not statistically different before and after treatments. Considering this, the authors suggest that the post-treatment OSA could be explained by xerostomia, and laryngeal dysfunction associated with irradiation.

Fourth, MRI was conducted on patients before and after treatment to study the laryngopharyngeal structures of patients in the midsagittal plane. The retroglossal pharyngeal area showed a significant expansion compared to pre-treatment data. This could be explained by the post-treatment oedema. Additionally, there was no statistically significant difference in other head and neck areas measured.

Fifth, the research team measured the time where oxygen levels were under 90%. They also measured the oxygen desaturation index (ODI) which was defined as 4% meaning that the number of events where the oxygen saturation going below 4% compared to the base line is divided by the total monitoring time. Similar results were observed when comparing the different devices. Pre-treatment, the mean SO_2 was 89.0%±7.0% and post-treatment it was 86%±8.5%. For ODI, before radiation, the mean value was 5.0±10.4 events/h and after the treatment it was 4.8±19.8 events/h. So overall SO_2 and ODI were not significantly altered after the treatment.

The authors of this study revealed many of its limitations that could have introduced bias in the results. The first is the important heterogeneity of the patients concerning the severity of OSA, the OSA risk factors, the tumor location, the cancer stage, and the treatments received. A major limitation is also the low retention rate for sleeps tests. Indeed, because of the physical and mental distress associated with the sleep tests, only 21 of the 32 patients accepted the post-treatments tests. This significantly reduced the study power to detect differences. Also, there could be bias due to possible differences in the outcomes amongst patients who refused these tests. In addition, the patients were evaluated up to two months after treatment which happens to be in the acute phase of the treatment. However, follow-up after this acute phase should also be envisaged. Moreover, since the obstruction site causing OSA is yet to be determined, it would be relevant to conduct a swallowing videoendoscopy and/or videofluorography.

This Inoshita *et al.*'s study intended to compare the effect of HNC RT on OSA clinical parameters and MRI results (2). This prospective study was the first to attempt to elucidate the pathogenesis of OSA in all areas of the pharynx and larynx after RT. Radiation treatments are considered nowadays as standard care for the management of HNC according to the NCCN guidelines and can contribute to highly improve the quality of life of patients by avoiding invasive surgery. However, many side effects including OSA can result of these radiation treatments. In fact, the prevalence of OSA is very high, and the severity is comparable before and after radiation treatment even if the risk factors like obesity and neck circumference are reduced. Based on the findings of these studies, how can QOL be improved in patients who suffer from OSA after HNC? Is OSA an inevitable consequence of RT that must be managed? The authors state considering that OSA routine testing might improve the quality of life of patients with advanced HNC. Further studies with a larger sample might compare the effect of different radiation dosages in the severity of the OSA. Further studies might also use other technology like swallowing videoendoscopy and/or videofluorography to locate the site of obstruction in patients affected by OSA to clarify the pathogenesis. This could help improve the management of OSA after radiation treatments.

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