Orofacial Pain and Snoring/Obstructive Sleep Apnea in Individuals with Head and Neck Cancer: A Critical Review

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Aims: *(1)* To summarize current knowledge on the prevalence, intensity, and descriptors of orofacial pain and snoring/obstructive sleep apnea (OSA) before and after head and neck cancer (HNC) treatment; and *(2)* to propose future directions for research. **Methods:** The median prevalence for each condition was estimated from the most recent systematic reviews (SRs) and updated with new findings retrieved from the PubMed, Web of Science, Embase, and Cochrane databases up to December 2021. **Results:** The prevalence of HNC pain seems relatively stable over time, with a median of 31% before treatment in three studies to a median of 39% at 1 month to 16 years after treatment in six studies. HNC pain intensity remains mild to moderate. There was a threefold increase in temporomandibular pain prevalence after surgery (median 7.25% before to 21.3% after). The data for snoring prevalence are unreliable. The OSA/HNC prevalence seems relatively stable over time, with a median of 72% before treatment in three studies to 77% after treatment in 14 studies. **Conclusion:** With the exception of temporomandibular pain, the prevalence of HNC pain and OSA seems to be stable over time. Future studies should: *(1)* compare the trajectory of change over time according to each treatment; *(2)* compare individuals with HNC to healthy subjects; *(3)* use a standardized and comparable method of data collection; and *(4)* assess tolerance to oral or breathing devices, since HNC individuals may have mucosal sensitivity or pain. *J Oral Facial Pain Headache 2022;36:85–102. doi: 10.11607/ofph.3176*

Keywords: *head and neck cancer, orofacial pain, prevalence, sleep apnea, snoring*

Head and neck cancer (HNC), including oropharyngeal cancer (OPC), is a life-threatening condition[1] that has been increasing in the last decade.[2,3] Importantly, HNC patients who receive radiotherapy (RTH) or chemotherapy (CTH) or who undergo surgery complain of orofacial pain, poor sleep quality, and snoring or cessation of breathing (eg, obstructive sleep apnea [OSA]).

In daily practice, when a patient complains about oral or facial pain, it is a challenge for dentists to exclude any possible association with HNC or brain cancer. Indeed, oral pain can be a prodromal sign of an oral cancer and a major diagnostic challenge.[4–6] Many publications report that orofacial pain associated with OPC/HNC may be present before diagnosis and may increase during treatment and decrease after treatment, with values fluctuating from 19% to 66%.[4–8] Such a large prevalence range and variation over time are also reported in systematic reviews (SRs).[6,9,10] The abundance of descriptive comprehensive reviews relating to the management and mechanisms of pain support the perception that OPC/HNC conditions are not optimally managed.[11–18] Dentists routinely screen for oral lesions that may indicate a risk of cancer and refer for biopsy when indicated. Oral pathologists are experts in interpreting oral biopsies and refer patients to oncologists for appropriate management when necessary. The dominant oral cancer is squamous cell carcinoma. The main traditional risk factors for OPC are tobacco and alcohol, but younger and otherwise healthy individuals are more often presenting with OPC due to human papillomavirus–augmented propagation. Both men and women can present with lesions

in the oropharyngeal area. The malignant potential, dominant in males, is a subject of debate; nonetheless, survival is a concern over 5 years.[1–3,19] Clinically, OPC is recognized as a persistent ulcer with a size of 1 to 3 cm. Although mostly asymptomatic, it is a serious health hazard due to the risk of malignant transformation. Complaints associated with the onset of OPC include difficulty chewing, swallowing, or speaking, with or without oral mucosa pain or other orofacial pains. Symptoms such as ulcers located on the tongue, tonsils, postpharyngeal walls, and/or soft palate indicate the need for biopsy. From an observational hospital chart review of 1,412 cancer patients, including HNC cases, the sites and type of pain first reported are (in decreasing order of frequency): sore throat (38%); the tongue and mouth (with pain when swallowing; 11% to 14%); dental pain, earache, pain in the palate and gingiva, and burning mouth (2% to 6%); and pain when chewing/neck and facial pain (around 1%).[4] Although these values are informative, extrapolation of these results requires caution, as the data were obtained from a retrospective chart review and are therefore not systematically structured. In addition to biopsies, visual screening of the oropharynx, larynx, hypopharynx, and sinus-nasal tract is done by otorhinolaryngologists.

According to a hospital chart review of only 40 patients, most HNC pain is located near the tumor site in 52% of cases. The pain was classified as nociceptive and neuropathic or as nociceptive alone (identified in the majority of cases); myofascial pain was only present in about 10% of the patients, and neuropathic pain alone in 7.5%.[20] Systematic reviews indicate that the prevalence of HNC pain is a critical issue, but it is not clear whether the pain persists after treatment or how this varies among individuals.[6,9,10] Pain intensity was reported to be low to severe across the course of treatment.[6,9,21,22] It seems that the intensity of pain decreases in the months after treatment and that opioids are used by almost 40% of OPC patients in this period.[6,22] The second focus of the present review is on sleep breathing disturbance complaints, snoring, and obstructive sleep apnea (OSA), which are frequently noted in the authors' clinic in relation to HNC treatments. It was elected not to cover insomnia (ie, difficulties initiating and maintaining sleep) since it was not a frequent complaint from the patients in stomatology-oncology. Insomnia is a complex psychophysiologic condition.[23] Its prevalence in adults in the US is about 27%, with a co-occurrence with fibromyalgia and arthritis in ratios of 1:3 and 1:5, respectively.[24] Insomnia seems to be exacerbated by cancer and related treatment, but findings are not easy to interpret. Insomnia symptoms are known to be prevalent before treatment in 59% of breast, gynecologic, and prostate cancers, and to drop after surgical treatment to 36%.[25] An SR and meta-analysis of HNC revealed how complex it is to summarize the changes in insomnia before and after treatment. Its prevalence, measured using many tools to estimate self-reported insomnia, rose from 29% before to 40% after HNC surgical and RTH treatments.[26] As highlighted by the authors of the latter study, the high heterogeneity observed in that SR suggests that caution must be exercised in interpretation. Furthermore, when insomnia was assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, the pooled estimates were 21% and 23% before and after treatment, respectively.

Snoring is frequent in the general population, and its prevalence increases with population age.[27,28] Snoring is caused by reduction of the soft palate and pharyngeal dilator muscle tone during sleep and may be secondary to a progressive neuropathy.[29] Excessive snoring may be a risk factor for sleep apnea, which can be a threat to health with respect to a number of comorbidities and increased mortality.[30–34] OSA (ie, cessation of breathing for 10 seconds or more) and oxygen desaturation (hypoxia) have been estimated to be present in about 10% to 49% of adult men and 3% to 23% of adult women in studies carried out in the USA, Switzerland, and Brazil.[31,35–37] Estimates of the prevalence of OSA vary widely depending on the populations studied and the methods and definitions (eg, higher cut-off for apnea/hypopnea index [AHI] of 15 and over) used, but it has been shown to exceed 50% in some countries and may affect up to 1 billion people globally.[38] Like snoring, OSA is present in about 50% of individuals over 60 years of age and is associated with major health risk factors, meaning that clinicians should not overlook the complaint.[36] The association of snoring or OSA with HNC before and after treatment is challenged by recent SRs and other publications.[26,39,40]

Therefore, considering the importance of these issues, the objectives of the present critical review were to: *(1)* summarize current knowledge on the prevalence, intensity, and descriptors of orofacial pain and snoring/OSA before and after HNC treatment; and *(2)* To propose future research directions with respect to HNC.

Materials and Methods

This research aimed to find relevant SRs including meta-analyses, randomized controlled trials, and observational studies (case-control, cohort, and cross-sectional studies) using the PubMed, Web of Science, Embase, and Cochrane databases. To be included, papers had to report the prevalence and intensity/frequency of HNC pain, orofacial pain,

temporomandibular pain, snoring, and/or OSA. First, a search was undertaken to identify relevant SRs. The following search words were used to find papers of interest: "head and neck"; "cancer"; "oropharyngeal cancer with orofacial pain"; "temporomandibular disorder"; "snoring"; and "sleep apnea". Conference abstracts, commentaries, editorials, narrative reviews, case reports, treatment reports, randomized clinical trials, and papers not specific to HNC were excluded. Studies pooling data on the prevalence or intensity of pain and frequency of snoring or OSA before and after treatment were also excluded.[41] Two authors (P.H. and G.L.) reviewed the papers relevant to this review. An agreement was found 9 times in 10. A third author validated the selected papers (C.D.F.). The publication range searched was from 1960 until the end of December 2021.

The rareness of the studies on the topics of interest, the large variability of tools selected, and the nonexistence of a standardized protocol (see Table 1 for HNC and pain as an example), supported the decision not to conduct an SR or meta-analysis and instead to pursue a more flexible approach that could allow for the inclusion of SRs and original research. Most of the papers that met the selection criteria to present this critical update were clinical reports or clinical data collected retrospectively from clinical charts or prospectively using validated questionnaires or tools to assess the outcomes of interest.

Results and Critical Appraisal

Research Results

As expected, most of the literature on HNC-related pain and sleep disturbance prevalence was based on observational studies, with very little research comparing before- and after-treatment complaints. The search was about five times more productive using the search term "head and neck cancer" or its abbreviation than when using the term "oropharyngeal cancer."

The search of papers followed the usual four steps:

- Identification: A total of 678 papers related to HNC pain or sleep breathing disturbances were identified using the words listed in Materials and Methods.
- Screening: After reading the abstracts and removing duplicates, 51 SRs and clinical reports relevant to the topic of interest were selected.
- Eligibility: For HNC and orofacial pain, 3 SRs and 11 papers were selected; 1 paper that presented polled data before and after HNC treatment was eliminated.[41] For HNC and snoring, 1 SR and 5 papers were selected. Snoring data from the selected SR were not used in the calculation, as these were secondary to OSA and were based on 3 low-quality studies.[26] For HNC and OSA, 3 SRs and 3 papers were selected.
- Included: For HNC and orofacial pain, 3 SRs[6,9,10] and 10 new papers published since 2012 were included (Table 1). These 10 papers are moderately useful as evidence due to the nature of the study designs, as they are noncontrolled cohort/follow-up or cross-sectional studies. Based on the 2020 criteria of the Oxford Centre for Evidence-Based Medicine, 6 of the 10 papers were level 3 prospective cohort studies,[8,42–46] of which 2 were based on chart reviews and 2 on a secondary analysis of a previously published study. The other 4 studies were level 4 cross-sectional/case series.[7,21,22,47] No randomized controlled studies and no clear comparisons to normal populations (with the exception of literature comparisons) were found. Although these papers provide data with respect to before and after HNC treatment, none of them state whether the clinical data collection and analysis were done blinded to treatment (RTH, surgery, or chemotherapy).
- For snoring, four informative clinical reports were selected to raise the critical issue of snoring assessments.[48–51] An SR based on studies reporting only data after HNC treatment was also referred to.[26]
- For OSA, three relevant and recent SRs, one in 2020 and two in 2021, were available.[39,40,52] The level of evidence in the papers included in these SRs was rated in one publication at level 2 to 4.[40] One recent paper related to the objectives of the present review was added to provide a concise update.[53]

Pain and OPC-HNC

Systematic reviews on HNC pain.

Three HNC SRs were selected to summarize the knowledge available before 2012. This search did not identify any recent SRs related to the present objectives. These 3 SRs were based on 33 to 52 papers reporting data on orofacial pain and HNC up to 2011. A 2007 systematic review based on 52 studies over 40 years reported that about 50% of all cancer patients report pain, a prevalence that increased to 70% for individuals with HNC.[10] Among the individuals with HNC, one-third reported moderate to severe pain and pain reduction after treatment. The other 2 SRs, from 2010 and 2012, revealed that orofacial pain was present before HNC treatment in 50% of patients, increased during treatment, and dropped to about 30% after treatment.[6,9] Although these SRs

Table 1 Summary of Papers Reporting Pain Prevalence and Intensity in HNC Individuals

Reference	Study type	Sample size (M/F), mean ± SD age	Country	Site of pain	Clinical environment	Pain scale
Rogers et al,[7] 2012	Cross-sectional prospective	177 (112/65), 62 ± 12 y	UK	Head and neck pain	Oncology	University of Washington Quality of Life Questionnaire, version 4
Shuman et al,[46] 2012	Cohort prospective	559 (433/126), 58.4 ± 10.7 y	USA	General bodily pain	3 oncology centers	SF-36 Bodily Pain Score (cut-off < 75/100 = worse pain; lower score indicates worse pain)
Pegoraro et al,[42] 2016	Prospective	22 (19/3), 58.9 ± 9.4 y	Brazil	Temporomandibular pain	Oncology	Helkimo Questionnaire (yes/no): discomfort of muscle pain with chewing; pain in the face when awake; Mild TMD symptoms
Terkawi et al,[21] 2017	Cross-sectional survey	102 (59/42), 49.6 ± 14.8 y	Saudi Arabia	Head and neck pain	Oncology	BPI (0–10); NPQ-SF (0–100); PCS (5 points with Likert scale with 13 descriptors)
Cho et al,[22] 2019	Cross-sectional	H&N cancer: 708 (613/95), 54.7 ± 10.0 y Control group (other cancer): 2,581 (1,278/1,303), 58.0 ± 12.8 y	Taiwan	Head and neck pain	16 oncology centers	BPI (0–10); Cut-off > 1 = for presence of pain Cut-off > 4 = for moderate to severe pain
Pauli et al,[8] 2019	Prospective	89 (57/32) 59.2 y (no SD available)	Sweden	Temporomandibular pain	Oncology	1–3: GTQ (0–100) 4, 5: Palpation (self-reported tenderness)

Table 1 *(continued)* Summary of Papers Reporting Pain Prevalence and Intensity in HNC Individuals

Reference *(continued)*	Before treatment: Pain prevalence/ intensity	Follow-up: Pain prevalence/intensity	Treatment distribution	Note from the authors
Rogers et al,[7] 2012	25%/NA	12–47 mo: 38/NA	Surgery: 58% Surgery + RTH: 32% RTH + CTH: 10%	–
Shuman et al,[46] 2012	NA/60.5 ± 27.1	1 y: NA/65.1 ± 26.2*	RTH: 84% CTH: 62% Surgery: 38%	60.5 < 75 may correspond with mild pain on the SF-36 scale. *Significant compared to before treatment.
Pegoraro et al,[42] 2016	1. 1. 4.5%/NA 2. 2. 0%/NA 3. 3. 31.8%/NA	Data collection period unknown: 1. 22.7%/NA 2. 4.5%/NA 3. 59.1%*/NA	RTH: 100%	*Significant compared to before treatment.
Terkawi et al,[21] 2017	NA	3–72 mo: 30–42% chronic pain Intensity: 1. 3.4 ± 2.7/10 2. 63.0 ± 64.5/100 3. 15 ± 13.1	Surgery: 58% RTH: 43% CTH (adjuvant): 36.3%	In 38% of all participants, pain was the primary presentation at diagnosis.
Cho et al,[22] 2019	NA	Data collection period unknown 1. HNC: 50.4%/3.93 ± 1.95; Other cancers: 39.1%/3.85 ± 1.99 2. HNC: cut-off > 4 = 44.2%/NA; Other cancers: 38.7%/NA	NA	Patients with HNC had a higher demand for pain management than patients with other cancers.
Pauli et al,[8] 2019	Prevalence: 1. Moderate to severe pain in jaw muscles: 9.0% 2. Moderate to severe facial pain right now: 4.6% 3. Subjective TMD (from GTQ): 43% 4. Temporalis insertion: 17.3% 5. Masseter muscle 13.6% NA for intensity	Prevalence, 6–12 mo after end of treatment: 1. Moderate to severe pain in jaw muscles: 6 mo = 20.7%, 12 mo = 13.4% 2. Moderate to severe facial pain right now: 6 mo = 10.3%, 12 mo = 7.1% 3. Subjective TMD (from GTQ): 6 mo =78%*; 12 mo = 70%* 4. Temporalis insertion (bilateral tenderness): 6 mo = 57.9%*; 12 mo = 48.8%* 5. Masseter muscle (bilateral tenderness): 6 mo = 53.9%*, 12 mo = 40.2%*	RTH + CTH: 71.9% RTH: 14.6% RTH + surgery: 12.3%	Moderate to severe cut-off is not defined on the 0–100 scale; it was defined as impact of facial pain on social, leisure, and family activities, as well as the impact of facial pain on the ability to work. *Significant compared to before treatment.

BPI = Brief Pain Inventory; CTH = chemotherapy; GSS = General Symptom Survey; GTQ = Gothenburg Trismus Questionnaire; MDASI-H&N-C = Anderson Symptom Inventory, Head & Neck Module, Chinese version; NPQ-SF = Neuropathic Pain Questionnaire-Short Form; PCS = Pain Catastrophizing Scale; RTH = radiotherapy; SF-36 = Short Form-36; VHNSS = Vanderbilt Head and Neck Symptom Survey.

Table 1 Summary of Papers Reporting Pain Prevalence and Intensity in HNC Individuals

Reference	Study type	Sample size (M/F), mean ± SD age	Country	Site of pain	Clinical environment	Pain scale
Hu et al,[43] 2020	Prospective	105 (90/15), 60.3 ± 11.7 y	China	Head and neck pain	Oncology	MDASI-H&N-C (two subscales rated from 0–10)
Saghafi et al,[44] 2022	Prospective	217 (160/57), 61.6 ± 9.2 y	Sweden	Temporomandibular pain	Maxillofacial oncology	Clinical pain, TMD symptoms; Palpation (TMJ and masticatory muscles) (yes/no)
Lou et al,[45] 2021	Prospective	77 (53/24), 59.3 ± 10.1 y	USA	Mouth and throat	Oncology	1. McGill Pain Questionnaire (intensity: 0–100) 2. VHNSS 2.0 (0–10): cut-off > 4 for moderate to severe pain 3. GSS
Magaña et al,[47] 2021	Cross-sectional	31 (28/3), 64.0 ± 8.7 y	USA	Head and neck pain	Oncology	Pain score category (0–10), numeric pain scale

Table 1 *(continued)* Summary of Papers Reporting Pain Prevalence and Intensity in HNC Individuals

Reference *(continued)*	Before treatment: Pain prevalence/ intensity	Follow-up: Pain prevalence/intensity	Treatment distribution	Note from the authors
Hu et al,[43] 2020	43.8%/median (Q1, Q3), range = 0 (0, 3), 0–8	3–9 days after surgery: 91.4%*/median (Q1, Q3, range = 4 (3, 5), 0–7 1 mo after surgery: 28% (estimated from paper figure)/ median (Q1, Q3), range = 0 (0, 2), 0–7	Surgery: 100%	*Significant compared to before treatment.
Saghafi et al,[44] 2021	Jaw muscle symptoms + pain on palpation: 5.5% TMJ symptoms + pain on palpation: 0.9% Self-reported pain on chewing: 1.8%	Prevalence 12 months after treatment (intensity NA): Jaw muscle symptoms + pain upon palpation: 21.2%* TMJ symptoms + pain on palpation: 4.6%* Self-reported pain on chewing: 9.2%*	RTH + CTH: 90% RTH + CTH + surgery: 8% RTH: 2%	Brachytherapy was performed in 20% of participants. *Significant compared to before treatment.
Lou et al,[45] 2021	1. NA/median = 9/100 2. 31%/median = 1–2/10 (> 4 for moderate to severe pain) 3. 36%/NA	Immediately following treatment: 1. NA/median = 31/100 2. NA/median = 4.3/10 12 mo after treatment: 1. NA/median = 2/100 2. 40%/mild to moderate pain = 2/10, moderate to severe pain persisted in 9% of the individuals with pain level of 4–8/10 3. 47%/NA	RTH + CTH: 54.1% Surgery: 29.1% RTH + CTH + surgery: 12.5% RTH + surgery: 2.8% RTH: 1.4%	Chronicity of pain was established by 6 mo. Oral mucosal neuropathic pain was the most common chronic pain subtype.
Magaña et al,[47] 2021	NA	Mean 80 mo (4–192 mo): No pain (0–1/10): 55% Mild to moderate pain (2–4/10): 45%	CTH: 58.06% Surgery + adjuvant treatment: 41.94%	

BPI = Brief Pain Inventory; CTH = chemotherapy; GSS = General Symptom Survey; GTQ = Gothenburg Trismus Questionnaire; MDASI-H&N-C = Anderson Symptom Inventory, Head & Neck Module, Chinese version; NPQ-SF = Neuropathic Pain Questionnaire-Short Form; PCS = Pain Catastrophizing Scale; RTH = radiotherapy; SF-36 = Short Form-36; VHNSS = Vanderbilt Head and Neck Symptom Survey.

were based on a relatively high number of papers, the sample sizes of most of the studies were modest, reducing the strength of their results. Moreover, it should be considered that different methods of pain data collection, covering different time periods, from different countries and health care systems, were used in the studies.

In conclusion, about 50% of patients with HNC pain reported pain before any type of HNC treatment, with the prevalence decreasing after treatment. Furthermore, pain levels were high intensity.

New findings on orofacial pain in HNC.

To update the knowledge acquired on the association between pain and HNC after publication of the 3 SRs, 10 observational studies providing data after 2011 were identified. The 2012 paper by MacFarlane was the most recent systematic review, including studies up to December 2011.[9]

As listed in the Introduction, the study focused on three main outcomes: *(1)* HNC pain prevalence; *(2)* pain intensity; and *(3)* pain descriptors (both before and after treatment). Based on the available literature, the papers will be described in three main categories: *(1)* mucosal-related pain, *(2)* global head and neck pain, and (*3)* temporomandibular joint (TMJ) pain and orofacial muscle pain (with one paper on generalized body pain). Table 1 lists the studies by year of publication. In addition to the main outcomes of interest, secondary information (when available) related to pain interference on sleep, pain elsewhere than the head and neck region (eg, widespread pain), and pain medication use was also included. In the 10 papers selected, the sample size was varied, ranging from 22 to 708 for a total of 2,087 patients. The after-treatment period of observation had a very long duration, ranging from 1 to 192 months, which is a limitation of the study interpretation, as mentioned below.

Mucosal-related pain

In a 12-month prospective study (n = 77), Lou et al reported a slight increase in the prevalence of mouth- and throat-related pain from 31% before any treatment to 40% at 12 months after treatment.[45] It could not be confirmed whether such a difference was statistically significant. Treatments were mainly RTH and CTH followed by surgery, alone or in combination. Two validated questionnaires were used: *(1)* the McGill Pain questionnaire (MPQ), including 11 sensory and 4 affective word descriptors and average pain intensity rated on a 0- to 100-mm scale; and *(2)* the Vanderbilt Head-Neck Symptom Survey 2.0 (0 to 10 scale, with 10 indicating the worst symptoms).[53,54] The intensity of pain measured using the MPQ was low at baseline (9/100 mm) and reached a statistically significant value (31/100) at the immediate end of the treatment period (more than 70% of patients received RTH), dropping to 2 at the 12-month follow-up. At the end of treatment, both the intensity of pain and difficulty swallowing were high for the multimodality treatment group (RTH alone or with CTH): 6/10 on the Vanderbilt Head-Neck Questionnaire in comparison to 0 to 1/10 for the surgery-alone group. While mouth and sore throat pain dropped after 3 months in the majority of participants, moderate to severe pain ($\geq$ 4/10 on the Vanderbilt Head-Neck Questionnaire) persisted in 9% of individuals (7 of the 77) across the total observation period; the pain level was between 4/10 and 8/10 for that subgroup. The pain descriptors used were burning pain and mucosal sensitivity. Furthermore, Lou et al reported data on pain beyond the head and neck region and the use of pain medication; widespread pain was reported by 36% of patients before treatment and by 47% at the 12-month follow-up (a nonsignificant difference). Use of pain medication (type not specified) at baseline was reported by less than 50% of subjects, a value that nearly reached 80% at the end of treatment and then dropped to 40% over the following 6 to 12 months of observation. The study contained descriptive data only.

Global head-neck pain

In 2012, Rogers et al prospectively collected clinical characteristics of 177 HNC patients before treatment with a deep analysis of data 12 to 47 months after treatment.[7] According to the study, 25% of patients reported pain before treatment. After treatment, 38% of their sample reported significant pain, and 25% reported moderate to severe pain. The treatment distribution was 58% for surgery alone, 32% surgery and RTH, and 10% for RTH and CTH. The data were extracted from the University of Washington Quality of Life questionnaire (version 4), an indirect method of assessing pain with scoring in 5 categories.[56–58] Moderate to severe pain was rated using a Likert scale using 3 criteria: *(1)* patients with moderate pain requiring medication (eg, paracetamol); *(2)* severe pain controlled by prescription medicine (eg, morphine); and *(3)* severe pain not controlled by medication. Sleep was a major concern in the 25% of individuals comprising the moderate to severe pain group. Extrapolation from the findings of this study should be undertaken with caution, since many statistical comparisons were not made or reported, pain intensity was not directly assessed, opioid/nonopioid medication use was unclear, and pain descriptors and specific localization of head and neck pain were not available.

In 2012, a paper by Shuman et al provided indirect data on the intensity of pain in relation to neck dissection followed by RTH and CTH performed in three oncology departments.[46] The analyses were done by comparing data collected prospectively in a previous study of HNC cancer individuals before treatment to data from a subgroup of 559 patients after treatment who were accessible after 1 year. No prevalence for pain data is available. The pain index was indirectly extracted from a quality of life questionnaire (the Short Form-36 [SF-36]) using the Bodily Pain score. Ratings of pain before and after treatment were reported, with statistically significantly less pain after treatment. Interpretation of these scores needs to be done cautiously, as the difference was rather small. Furthermore, for multivariate prediction analyses, the sample size dropped to 374 subjects, which represented about 46% of the total sample of 811. Changes in sleep quality were assessed using the validated Medical Outcomes Study sleep measure (MOS-Sleep) with a cut-off of ≤ 73, with lower scores indicating poorer sleep.[59] From their analyses, significantly lower sleep quality was present in almost 50% of subjects, with a lower SF-36 pain score (52.4) in the worst sleepers and worse pain than in better sleepers (77.9). The Shuman et al paper requires attentiveness to data interpretation due to the inherent complexity of these data.

Terkawi et al assessed the burden of pain in 102 HNC individuals before treatment and 3 to 72 months after treatment.[21] Of the sample, 30% to 42% reported chronic persistent pain at the site of cancer/surgery after treatment. The cancer/pain sites were neck (46.7%), cheek or face (23.3%), jaw or mandible (16.7%), and throat or head (6.7%). For 38% of participants, pain was the primary HNC symptom at the time of diagnosis, and 41% of the patients had pain after treatment, suggesting an elevated persistence. The primary HNC treatment distribution was 58% for surgery, 43% for RTH, and 36% for CTH. Pain prevalence and intensity were estimated with the Arabic versions of the Brief Pain Inventory Short Form, the Neuropathic Pain Questionnaire Short Form, and the Pain Catastrophizing Scale questionnaires.[60–62] Pain scales were 0 to 10. The mean pain level after treatment was 3.4 ± 2.7/10, with a lowest value of 1.2 and a highest of 4.3. Pain duration was described as being intermittent or continuous at ratios of 2:3 and 1:3, respectively. The characteristics used to describe the pain were throbbing (16.7%), tender (33.3%), stabbing (16.7%), hot burning (26.7%), aching (13.3%), and sharp (3.3%). Sleep quality according to the Brief Pain Inventory was 3.5 times worse in patients with chronic pain compared to those without chronic pain (0.8 ± 2.2/10 to 2.8 ± 3.8/10, respectively), a small but statistically significant difference. The total score in the Neuropathic Pain QuestionnaireShort Form was significantly lower for patients without chronic pain compared to those with chronic pain (6.5 ± 20.6 vs 63.0 ± 64.5, respectively; $P <$ .001). Catastrophizing, rated using the rumination-magnification-helplessness domain, was also significantly higher in pain vs nonpain HNC patients (15.0 ± 13.1 vs 4.8 ± 7.3, respectively). In addition, patients with chronic pain reported significantly higher mood-related complaints in comparison to patients without chronic pain (3.8 ± 3.4/10 and 1.3 ± 2.6/10, respectively).

Cho et al collected pain data from 708 HNC patients seen after treatment in 16 oncology centers. They were able to compare the data to 2,581 patients presenting with other cancers (eg, breast, genital-urinary).[22] The HNC pain prevalence was extracted using the validated Brief Pain Inventory Questionnaire using a 0 to 10 scale.[60] Significantly more HNC patients reported cancer-related pain (50.4% vs 39.1% for HNC vs other cancers) or cancer treatment–related pain (23.4% vs 9.1% for HNC vs other cancers). No difference between groups was observed for the mean pain intensity (3.93/10 and 3.85/10 for HNC vs other cancer), and the values were between 2.4 and 5.9 for the lowest to highest pain. The cut-off for moderate to severe pain was set at ≥ 4/10, and no difference in prevalence was reported (44.2% vs 38.7% for HNC vs other cancer). Sleep quality was also similar between both groups, with a cut-off of ≥ 4/10 (56% and 60% for HNC vs other cancers) and for the mean intensity (4.4/10 and 4.8/10 for HNC vs other cancers). The use of analgesics was significantly higher in HNC patients (53.8%) vs other cancers (34.5%), as was the prevalence of use of weak or strong opioids (cumulative 44.2% vs 26.4% for HNC vs other cancer, respectively). It is unclear if the questionnaires were in English, in Taiwanese Mandarin, or in any of the other four languages used in Taiwan.

In a prospective study, Hu et al compared pain reports before, 3 to 9 days after, and 1 month after HNC surgery in 105 patients.[43] The distribution of the types of surgeries were: 50% tracheotomy, 46% lymph node dissection, and 18% flap transplantation, alone or in combination. Pain was reported by 43.8% of the patients before treatment, by 91.4% 3 to 9 days postsurgery, and by 28% 1 month after surgery (a value extracted from Fig 2 of that paper). Pain and sleep, as well as other variables, were assessed using the MD Anderson Symptoms Inventory Head and Neck module (Chinese version).[63] Scores were rated from 0 to 10, with 0 indicating "not present" and 10 "as bad as you can imagine." The median pain intensity was reported to be 0 before surgery, 4/10 at 3 to 9 days postsurgery, and 0 at 1 month. The

dominant pain descriptors included skin pain, burning, rash, numbness, and tingling. The median intensity seemed to significantly increase in the 3 to 9 days postsurgery. Disturbed sleep prevalence was present in 44% of patients before surgery and increased significantly in the 3 to 9 days postsurgery to 62%, then decreased to 35% 1 month after surgery. The interpretation of pain intensity and sleep data is challenging due to the nonnormal distribution.

Magaña et al assessed neck function in 31 individuals with HNC in addition to pain 1 to 16 years after treatment.[47] Pain was reported on a numeric scale of 0 to 10, with 2 to 4 being mild to moderate pain, 5 to 9 being distracting pain, and 10 being debilitating pain. Pain scores were between 2/10 and 4/10 in 45% of the group. Controlling for neck disability, 86% of individuals with neck disability reported a pain intensity of ≥ 2 in comparison to 14% of individuals without disability, a statistically significant difference. This study needs to be interpreted with caution, since the objective was to assess neck function, the sample size was small, and because of the fact that the very long follow-up period means that neck pain could be associated with other causes.

Orofacial muscle and TMJ pain

Pegoraro et al reported the prevalence of pain during the first days of RTH (1–5 days) and at the end of RTH in a short-term prospective study with a small sample size (n = 22).[42] The time scale in this study is very different compared to others reported in the present review, and the precise length of time after the treatment that the assessments were made could not be found, probably varying from individual to individual. The prevalence of jaw pain, listed as difficulty chewing or muscle pain when chewing, was 4.5% and 22.7%, and pain in the face when awake was 0% and 4.5% for the before and after time points, respectively. No difference in pain or in the prevalence of joint sounds was noted between the two time points. The global prevalence of HNC individuals presenting a "mild" temporomandibular disorder, derived from self-reports using the Helkimo index adapted for Brazilian Portuguese,[64] was 31.8% before and 59.1% after RTH, a statistically significant difference. The small sample size, the lack of precision with respect to the period of observation and the method of assessing pain (a dichotomic yes or no), and the lack of a clinical examination means that caution should be used when interpreting this study.

Pauli et al reported the pain prevalence of temporomandibular-related pain in a prospective observational study with 89 participants. Baseline data before treatment and at 6 and 12 months after RTH were available.[8] The prevalence of pain, based on self-report, was 9% for jaw muscles before RTH and 20.7% at 6 months post-RTH, dropping to 13.3% at 12 months. Facial pain was 4.6%, 10.3%, and 7.1% at the same time points. No significant difference was observed between time points. The tool used was the Gothenburg Trismus questionnaire,[65] which uses a scale ranging from 0 to 100. The intensity of facial pain was not given; however, it was rated to be moderate to severe (no cut-off was found in the paper) in 16.1% of the participants before RTH, and 25% and 10.3% at 6 and 12 months post-RTH, respectively. Again, no significant difference was observed between time points for facial pain prevalence or moderate to severe pain intensity. Facial pain was defined as moderate to severe when it had an impact on social, leisure, and family activities and the ability to work.

Furthermore, Pauli et al undertook clinical examinations to assess pain perception in the jaw muscles and TMJ palpation (no information on the specific pressure applied was found), as well as the range of mouth opening in relation to trismus (data not reported in the present paper). Although caution should be applied with respect to data extrapolation, it is noteworthy that some statistical difference was noted for temporalis insertion and masseter muscle pain, but not for joint pain. The percentage of participants reporting pain after manual palpation at baseline in the temporalis and masseter muscles was 17.3% and 13.6%, respectively, increased to 57.8% and 53.8% at 6 months, and then fell to 48.8% and 40.2% at 12 months, remaining statistically significant throughout. It is unclear whether the palpation data were reported dichotomously or on a scale. The cumulative, subjective, and objective prevalence of temporomandibular disorders signs (ie, pain or stiffness of the jaw and muscles of mastication, reduced ability to open mouth, and/or facial pain) increased significantly between baseline (68%) and 6 months post-RTH (94%), then fell slightly at 12 months (81%). The self-reported prevalence of TMJ sounds was associated with a significant increase from 7.9% at baseline to 20.7% at 6 months post-RTH, which fell to 12.3% at 12 months (no significant statistical difference from baseline to 12 months). It was assumed that Swedish was the language of the questionnaire.

A recent prospective study by Saghafi et al investigated the presence of temporomandibular symptoms identified from hospital charts of an HNC population (n = 217) comparing retrospectively subjective and clinical data collected before treatment to the time point 12 months after RTH, alone or in combination.[44] The prevalence of self-reported jaw muscle pain after manual palpation increased from 5.5% at baseline to 21.2% at 12 months. TMJ pain increased from 0.9% to 4.6% for the same two respective time points. Both increases were statistically significant.

Awareness of TMJ joint sounds was reported as 1% at both time points. Since no formal protocol or valid questionnaire was used, since pain was rated on a dichotomous scale of yes/no, and since 90% of the participants were on a supervised jaw exercise program with a trainer, the results of this study should be interpreted with caution.

Summary of the Pain and OPC-HNC Papers

In comparison to the 3 SRs, the papers published during the last 10 years are more in the domain of confirmatory findings, although they added more detail. The prevalence of pain in relation to mucosal or global HNC before treatment is in the range of 25% to 43.8% (7 papers). To further visualize the magnitude of this prevalence, the median and mean values were calculated based on 3 of the 10 studies with available data and were 31% and 33%, respectively. Although the prevalence seems to rise following RTH or surgical treatment (data not reported here, only 1 study), after 1 month, the pain prevalence dropped to a level similar to baseline and seemed relatively stable over time. The after-treatment values were in the range of 28% to 50.4%, with an estimated median of 39% and a mean of 38.6% in 6 studies. It should be noted that follow-up periods were quite variable, ranging from 1 month to 16 years (Fig 1). No standardized method was used to assess pain, but the pain intensity seemed to be low to moderate before treatment, with a peak in the days after treatment. When they were available, the words used to describe pain were more frequently in the domain of neuropathic pain: tingling, burning, numbness, triggered by touch (also assumed by food contact), and sharp (3/8 studies). Pain appears to be more commonly of an intermittent frequency than continuous (1 paper). Sleep, which was reported in 4 of 7 studies, was of a lower quality or disturbed in about half of the patients before treatment, with a peak after treatment before returning to levels similar to baseline. The description of pain medication was reported in 3 of the 7 studies and opioid prescription frequency in only one study; none of the studies mentioned an impact on sleep quality or breathing/OSA.

A few studies reported pain prevalence with respect to temporomandibular disorders (TMDs) that was low before treatment: 5.5% and 9% (median 7.25%, 2 studies), increasing to 13% to 22.7% (median 21.2%, mean 20%, 3 studies) after treatment (Fig 1). Although TMD-related pain prevalence values seem lower than the global or mucosal HNC estimates, the small number of studies prevents further extrapolation. The estimates of the presence of TMDs (including jaw limitation, joint sounds, etc) are large both before (39% and 68%) and after (59% and 81%) treatments. The fact that only 2 studies were available and that very different methods of data collection were used requires that caution be used in interpreting the results.

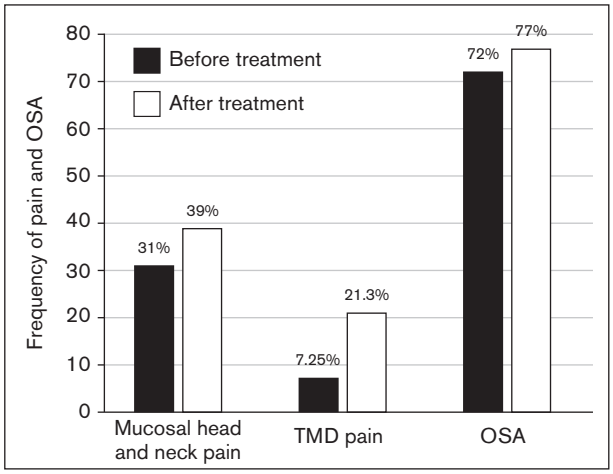

Fig 1 Median prevalence of mucosal-head and neck pain, TMD pain, and obstructive sleep apnea (OSA) before and after head and neck cancer treatment.

Snoring and OSA/HNC

Snoring and HNC

In a cross-sectional study, a sample of 105 patients with different types of cancers (the majority having breast or genitourinary cancer) completed the validated Oviedo Sleep Questionnaire. Snoring before receiving RTH was reported by 29% of the sample.[46,66] After HNC treatment, the prevalence of self-reported snoring or awareness based on complaint by the sleep partner seemed to be slightly higher, although the high heterogeneity and lack of pretreatment data prevent the drawing of a firm conclusion. In an SR of 14 studies on sleep breathing disturbances, snoring prevalence was estimated at 37% (from 3 studies).[26] A few papers revealed a large range of self-reported snoring (33% to 82%). A German study observed that 33% of 31 HNC patients report snoring after surgery.[67] A prospective posttreatment home sleep testing study done in France 54 months after treatment observed that snoring was present in 92.3% of OSA-positive cases (AHI over 10 hours in 25%) in comparison to 65.8% in HNC non-OSA cases.[51] The high prevalence of snoring reported after such a long period of time raises questions as to the specificity of the cause and challenges the conclusion that no difference was noted for AHI between the treatment groups, surgery (n = 10) or RTH + CTH (n = 41). Changes in lifestyle, health, body mass index, and aging may all have concurred with such a high prevalence. In another retrospective chart study, it was found that 82% of 56 HNC patients snored. This self-reported sleep symptoms and polysomnography

(PSG) study was done using a data bank of 1,025 patients from the University of Texas MD Anderson Cancer Center.[49] In the study, 79% of the individuals had received RTH before the PSG (one-third current, and for two-thirds, PSG was done 2 years after RTH), and the HNC was still active in 80%. In the PSG, 84% of the patients had OSA, with 22% presenting an AHI in the mild range (5 to 15 AHI), 32% in the moderate range (15 to 30 AHI), and 46% in the severe range (≥ 30). The use of a positive airway pressure (PAP) device was recommended for the majority (89% of 44 patients) and was used with high compliance (75%; usage was not clearly defined in the paper, but it seems to have been used for 4 hours per night), and an oral appliance was used by one patient.

Another way of estimating snoring perturbation is to assess the perception of a sleep partner. In a retrospective analysis of PSG recordings in patients with nasopharyngeal cancer (n = 18), the bed partner reports of the patient's snoring intensity were estimated with a 0- to 10-cm visual analog scale. Snoring intensity dropped significantly from 6/10 before to 2.8/10 at 6 months after RTH or CTH.[50] No snoring prevalence was reported.

Summary of the Snoring and HNC Papers

Subjective reports suggest that snoring is present in association with HNC in older patients (over 60 years of age), but a scarcity of data prevents any conclusions at this time. Studies with objective recordings of snoring before and after HNC treatment for specific treatment, such as RTH vs surgery, are required in parallel with the assessment of the impact of snoring on sleep partners.

OSA and HNC.

The present search identified 17 papers, including 3 recent SRs, related to HNC and OSA. The first, from 2020, identified 10 studies; the second from 2021 covered 14 studies; and the third, which was more focused on RTH and OSA risk, included 6 studies.[39,40,52] The other 14 papers were excluded due to different focuses of interest; eg, assessment of OSA as a cancer risk, insurance issues, biomarkers, and surgical techniques, among other factors. One clinical report that corresponded to the review objectives was added after the initial search and is briefly described below.[53] Ralli et al conducted an SR and concluded that OSA was more frequent in HNC (59%) than in the general population.[39] Gavidia et al published the second most recent SR and concluded that there is a potential association between HNC surgery and OSA, but the evidence is inconclusive.[40] To provide a rapid visualization of the data, the median and mean were calculated as a proxy to estimate the magnitude of the association. From the 14 papers listed in both SRs, a small and inconsistent difference was observed between the time point before treatment (median 72%, mean 68.3%; 3 studies) vs after treatment (median 77%, mean 63.8%; 14 studies) (Fig 1). It should be noted that all of the studies included in the paper by Ralli et al were also included in the study by Gavidia et al; however, Ralli et al did not include 4 papers contained in the study by Gavidia et al, probably due to different inclusion/exclusion criteria. These 4 papers were published from 2005 to 2014, all had more than 100 participants, and, in 3 of the 4, RTH was clearly included in the treatment list. Since the present review is not an umbrella SR, such issues will not be further explored here.

Another limitation with respect to the 14 papers cited by Gavidia et al is that a large range of AHI cut-offs was used. An AHI ≥ 5 was selected in 11 studies, ≥ 10 in one study, and ≥ 20 in two studies; the last excluded mild cases. When the median AHI was calculated with the very inclusive, but perhaps too low criterion of ≥ 5, a prevalence of OSA of 80% was estimated. However, when these values were estimated using the studies with a cut-off of ≥ 10 or 20, the median of the frequency dropped drastically, to 25.5%. Currently, it is suggested to use a continuum analysis with group clustering instead of a fixed cut-off criterion to be able to better delineate the specific association, or nonassociation, of OSA with other health conditions.[68]

As stated above, Gavidia et al found that the evidence of an association between RTH and OSA is inconclusive. This is supported by the third SR, by Tawfik et al, and clearly illustrated by a forest plot. Heterogeneity was low among the six studies selected, and the OR of 1.54 (95% CI = 0.66 to 3.6) was not statistically significant.[40,52] Tawfik et al reached this conclusion using five of the six papers included in Gavidia et al.

The most recent paper, which is not listed in any of the 3 SRs, is an observational retrospective chart analysis of 50 HNC patients.[53] OSA was suspected in 40% of the cohort. This report needs to be interpreted with caution since it is based on a chart review, and neither PSG nor home sleep testing recordings were used to confirm the diagnosis of OSA.

Summary of the OSA and HNC papers

The evidence for the OSA-HNC association is also weak, as most studies had small samples with results that are complex to interpret. Differences in the prevalence of OSA frequency were observed before treatment (median 72%, mean 68.3%; 3 studies) vs after treatment (median 77%, mean 63.8%; 14 studies). Although OSA seems to be highly prevalent in HNC patients, the lack of comparisons with age-matched controls, the monitoring of trajectory

changes over time, the use of different AHI cutoffs, and the high heterogeneity in most SR meta-analyses studies reduce the reliability of the evidence and the possibility of drawing any firm conclusions at this time.

Discussion and Future Avenues

The prevalence of pain related to HNC is rather stable before and after treatment, with about one-third of patients reporting mild to moderate pain, usually in the domain of mucosal or neuropathic pain. The frequency of the pain associated with TMDs seems to rise about two to threefold after treatment. Self-reported sleep quality also seems to change. Snoring seems to be more common after HNC treatment, but this cannot be confirmed due to the lack of data before treatment. The prevalence of OSA in HNC individuals is reported in about 7 out of 10 patients; however, this may not be due specifically to HNC or may be exacerbated by treatment, since age, gender, morphology of airway, and body mass index are all variables to take into consideration.

For all outcomes, the main problem is the lack of data for all stages of the disease, such as the lack of assessment of the change in trajectory. A case may stay the same, become worse, or improve over time and due to aging. The use of dichotomic yes or no ratings rather than an intensity pain score, the absence of clinical examination (muscle pain palpation with standardized protocols for pain pressure; oropharyngeal risk estimation such as retrognathia; Mallampati score; Friedman staging system for OSA) and/or objective validated measures (eg, snoring frequency, or, with respect to OSA, the AHI and oxygen desaturation index) reduces the strength of the putative search for any of the associations listed above. Furthermore, it is important to note that the studies included in this review were undertaken using an open data collection mode, often over a very long period of observation. Another major limitation is the lack of comparisons with healthy age- and gender-matched populations of the same study design and not from a referenced population. In addition, to properly investigate factors such as the specificity of pain, the association between snoring/OSA and HNC cancer, and its aggravation by treatment, more robust methods of data collection are required. It should also be remembered that no causality can be implied from the analyzed observational-association studies.

A few other issues remain to be considered regarding the use of a pain scale.

Most studies used validated pain scales, but one extracted intensity from the SF-36 bodily pain subscale, which was more difficult to interpret.[46] For temporomandibular/orofacial pain, no standardization was used in the three studies listed in Table 1; and, surprisingly, the validated orofacial-TMD research protocols, such as the Diagnostic Criteria for TMDs (DC-TMD), do not seem to have reached the field of HNC pain assessment.[69] Caution in interpreting pain intensity data is also recommended when repeated measures are used, as regression toward the mean is a well-known effect that may render observed small differences irrelevant.[70] Another concern is the precision of the numeric 100-mm scale marked by the participant that can be variable from 5 to 9 mm for acute pain measurements.[71,72]

A few issues also remain open to discussion in the field of sleep-disordered breathing assessments.

One of the variables that needs to be taken into consideration when comparing AHI data is the intrinsic night-to-night variability in the AHI index; eg, if AHI varies by 25% from night to night, then a single-night recording to assess a relationship between HNC and OSA may not suffice.[73,74] Whether AHI is a good predictor of health risk is another topic of debate. It has been suggested that other variables, such as hypoxia, may play a more important role, although this variable is also associated with a potential but debatable role with respect to mortality risk.[68,75] Nowadays, methods other than those used in randomized controlled trials (RCTs), such as the propensity score, may offer better bias protection and improve confidence in conclusions.[76–78]

The presence of OSA in HNC patients must therefore be considered according to each individual health condition and risk factors; eg, age, gender, anatomy, physiology, and complaint. It is notable that in all of the studies and SRs, the mean age of patients was over 60 years, with a high male to female ratio and elevated body mass index, and that all of these features are risk factors for OSA, which in older males has a prevalence of around 40%.[35–38,79] Specificity is then a critical issue to be clarified in comparison with the age and gender noncancer–matched group. Furthermore, the role of opioids frequently used in HNC patients probably needs to be taken into consideration, since it is reported that they can contribute to an increased risk of sleep breathing disturbances.[80,81] It must also be kept in mind that methods used to assess sleep disorders in a captive hospital cancer center may need adjustment in the presence of comorbidities or in their specificity related to HNC and breathing, both before and after RTH, CTH, and/or surgery. A recent paper challenged the poor relationship regarding OSA management between RCT-selected populations (namely PAP use for cardiovascular risk) and a clinical population; the sleep clinic OSA patients were "younger, sleepier, more likely to be female, and less likely to have

established cardiovascular" conditions than the participants selected for the RCT.[82] In other words, before importing a sleep technology or research methodology to a clinical population like the HNC group, concordance must be assessed to obtain relevance.

Study Limitations

The present review has some limitations. First, it is a critical analytic review, and thus does not reach the stringency of a usual SR. Second, as mentioned above, it is based on studies that depend on cohort or cross-sectional data collection that investigate the prevalence or association of HNC with pain, snoring, and/or OSA. Third, the absence of standardized protocols to collect pain and sleep data may have generated a higher heterogeneity, as seen by the large range in the prevalence reported for each outcome. Finally, it was nearly impossible to isolate the effect of RTH alone from surgery alone or from CTH alone, as most studies pooled data.

Future Directions

Future studies should use a standardized protocol with validated tools, which may contribute to stronger SRs and meta-analyses based on the higher methodologic standards of the papers (Table 2). This is advised by a recently published consensus and the validation of a pilot protocol in HNC cancer.[18,83] When assessing orofacial pain or TMDs, the use of a validated protocol such as the Diagnostic Criteria for Temporomandibular Disorders (DC-TMD) is recommended.[69] Currently, a structured interview with a questionnaire and a clinical examination are considered to be the gold standard.[84] For snoring, technologies can be used to improve objective data collection using devices that can help to quantify snoring frequency during sleep and that can be used at home or in the sleep laboratory. Such quality data collection is critical, since snoring may be a sign of OSA and has also been associated with "poorer" survival (hazard ratio [HR] of 1.3 to 2.1) in women if frequently present before the diagnosis ($\geq$ 5 nights/week). It is therefore essential to use objective data to assess snoring risk in HNC.[30,31,85–87] With respect to the presence of OSA in HNC patients, it is more accurate to assess the contribution of each individual health condition and risk factor; eg, age, gender, and anatomical and physiologic factors.[31,81,88] Furthermore, the use of validated screening tools, such as the Berlin or STOP-Bang questionnaires,[89–91] or even more advanced protocols that include a clinical examination,[92] will help to improve the accuracy of data collection. Although this may be time-consuming for clinical teams and patients, laboratory or home sleep testing done under medical supervision is the gold standard with respect to confirming the presence of breathing disorders.[31] In addition, it may be wise to use advanced breathing with oxygen (O_2) and carbon dioxide (CO_2) monitoring, since severe hypoxemia (O_2 desaturation) seems to be linked to the risk of mortality and CO_2 may play a role in HNC.[75,93] This is even more critical if opioids or other central nervous system depressive medications or illicit drugs are being used due to the higher risk of respiratory depression and central sleep apnea.[80,81,94]

Finally, as listed above, in the planning of future studies on HNC pain or sleep breathing disturbance with medication or devices, a method other than RCTs, such as the propensity score, may offer better bias protection and improve confidence in assessing conditions with high heterogeneity, such as HNC.[76–78]

Conclusions

With the exception of TMD pain, the prevalence of HNC pain and OSA seems to be stable over time. Future studies would help clarify many issues and should be directed to:

1. Compare the trajectory of change over time according to each treatment; eg, RTH may have a different and delayed effect on pain, snoring, or OSA than HNC rapid postoperative pain, with possible persistent consequences.
2. Compare individuals with HNC to healthy subjects matched for age and gender. The OSA prevalence observed was very close to normal population prevalence, questioning the specificity of the observations.
3. Use standardized and comparable method of data collection, which is essential for data comparison; however, such protocol requirements should not be so rigid as to prevent innovation.
4. Finally, assess tolerance to oral or breathing devices used for snoring or OSA management, since HNC individuals may have mucosal sensitivity or pain.

Clinical Implications

HNC individuals may present orofacial pain, snoring, and OSA before and after treatment. It is, however, unclear if the exacerbation of these conditions is specific to the cancer itself, its treatment, or aging. In the management of HNC oral pain or breathing disturbances, use of an oral appliance or PAP device needs to be done with caution due to the mucosal pain and dryness. So far, there is a lack of clear evidence on tolerance of such treatment in OPC-HNC patients.

Table 2 Future Directions Suggested for Research Assessing Pain and Sleep Disturbances in HNC Populations

Suggestions to improve the assessment of pain in HNC populations:
Evaluate pain using 0–100 or 0–10 scales for pain intensity and unpleasantness.
Ideally, add a descriptive word to assess the level of pain (mild, moderate or severe, or extreme). Some patients may rate pain as low on a numeric scale, but the pain may have a significant effect with respect to impairment. Pain is subjective and its impact personal to each patient.
Assess the power needed for the study and adjust sample size accordingly. The lowest sample size was 22, and the highest 708. Two studies with sample sizes of around 100, reported median pain values, suggesting that their data distribution was not normal.
Select a prospective design to assess pain parameters before, during, and after treatment and up to 3 to 12 months later.
Pain estimation on the days immediately postsurgery may be different at the end of the treatment assessment; eg, after 8 weeks of RTH. This was not clarified in most papers. Postsurgical pain and RTH pain are probably caused by different mechanisms; this is an issue that needs to be clarified.
Report the variability of data collected at each time point, as it is never as precise as might be desired; eg, patients may miss a visit and come back a few days later. It is important to collect data, but their variability has to be defined and reported.
Report any missing data for each time point. It is rare to get 100% participation during follow-up. This was not reported in most of the studies identified.
If long-term data collection is planned, provide the time of data collection and the distribution of subjects at each time point.
Data collection lasted up to 16 years, which is far too long a period, with smaller and smaller sample sizes toward the end of studies.
When considering long-term data, try to assess the contribution of other comorbidities.
Use a standardized and valid method to collect data on pain intensity, sites, and other induced disturbances (eg, sleep, chewing, swallowing).
Estimate differences between RTH, surgery, and CHT, alone or in combination. They may have different effects over time.
Monitor use of pain medication, nonopioids and opioids, and dose.
Add information related to concomitant physical therapy, psychotherapy, or other therapy and include frequency (eg, weekly or on demand).
In analyses, provide data on the differences between groups. Many of the studies reviewed failed to provide complete statistical information.
Recognize bias and also the fact that pain estimates have limitations, such as variability over time, and that they are sensitive to regression toward the mean. Additionally, the accuracy of a visual analog 0- to 100-mm scale can be 3–9%.
If oral appliances (eg, occlusal splints) are used to manage orofacial-temporomandibular pain, control for tolerance, since mucosal pain may alter adherence to treatment and the risk of OSA because a maxillary splint may exacerbate breathing disturbance in at-risk individuals.
Before and after treatment, collect data on pain elsewhere in body, such as widespread pain or headache, to distinguish head and neck pain from pain in other areas.
Suggestions to improve the assessment of snoring in HNC populations:
Self-reports of snoring are easy to collect but are dependent on many variables, such as the effect of memory distortion, and are most commonly based on data provided by a sleep witness.
Technologies can help to improve data quality collection using devices that quantify snoring frequency during sleep. This can be done at home using a smart phone or other device to record snoring, body position, and sleep duration. Other devices can be used to measure sleep at home, while the gold standard is the use of PSG in a sleep laboratory.
Since snoring may be a sign of OSA, it is essential to collect data on comorbidities (eg, hypertension, diabetes mellitus).
Assessment of OSA risk using screening tools such as the STOP-Bang or Berlin questionnaires would strengthen studies.
Clinical examinations can provide data on body mass index, sleepiness, fatigue, oropharyngeal obstruction (modified Mallampati score for tongue position and soft palate/pillars, Friedman score for tonsils), among other factors.
If indicated, clinical examinations should be followed by home sleep testing under medical supervision.
Advanced breathing and oxygen/CO_2 measures are highly recommended if opioids are being used to manage HNC pain due to the risk of respiratory depression and central sleep apnea.
Add an estimation of influence of other comorbidities such as insomnia.
Distinguish the impact or effect of RTH from surgery and CTH.
If oral appliances (eg, mandibular advancement devices) are used instead of PAP devices to manage snoring or OSA, mucosal pain should be considered, as it may affect the adherence to treatment. If medications are also being used, consideration should be given to potential hypoxia/hypercapnia, since opioids, benzodiazepine, and gabapentin can depress respiration in at-risk individuals.
Suggestions to improve assessment of OSA in HNC populations:
Estimate all health, anatomical, and physiologic risk factors that can influence OSA outcome measures. This should include the use of medications such as opioids, benzodiazepines, and gabapentin, etc, which can depress breathing.
Include measures of BMI, as increased BMI is a risk factor for OSA.
Report AHI and oxygen desaturation indices, and, if possible, CO_2 and arousal index. AHI is not the most important risk factor for morbidity and mortality.
As discussed in the text, the use of fixed AHI cut-offs, such as 10 or 5–15, may not be the best way to assess cause and effect with respect to OSA in HNC/RTH patients.
Ideally, estimate the impact of other variables, such as sleepiness and fatigue, etc.
Add an estimation of influence of other comorbidities, such as insomnia.
Distinguish the impact or effect of RTH from surgery and from CTH.
The role of opioids, benzodiazepines, or gabapentin, which are frequently used in HNC patients, must be taken into consideration since they can reportedly contribute to an increased risk of sleep breathing disturbances.
If oral appliances or breathing devices are used, see the above recommendations.

AHI = Apnea-Hypopnea Index; BMI = body mass index; CTH = chemotherapy; HNC = head and neck cancer; RTH = radiotherapy; OSA = obstructive sleep apnea; PAP = positive airway pressure.

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