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Title: The impact of clustering of oral symptoms in the pathogenesis of radiation caries: A systematic review.

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Short title: Clustering of oral symptoms in radiation caries

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Abstract

Radiation-related caries (RRC) is a disease with a high potential for destruction of the dentition, which impairs quality of life in head and neck cancer (HNC) patients who undergo radiotherapy. In light of the recently described “clustering of oral symptoms theory”, the present systematic review (PROSPERO CRD42019132709) aimed to assess the Head and Neck (HN) and Gastrointestinal (GI) symptom clusters among HNC patients and discusses how these indirect effects of cancer therapy have a pivotal role in the pathophysiology of RRC. The search was performed at Pubmed, Scopus and Embase and resulted in 11 studies that met the inclusion criteria. Data extraction was performed regarding the presence of HN/GI symptom clusters among HNC patients. The methodological data of the included studies was assessed using the MAStARI and GRADE instruments. The most prevalent reported HN symptoms were dysphagia, xerostomia and pain. Taste alterations and fatigue were also commonly reported by the patients. Loss of appetite and weight loss was regularly reported by the studies, as well as nausea and vomiting. The results of the present study suggest that HNC treatment generates clusters of oral symptoms, leading to dietary changes, deficient oral hygiene, enamel fragility and a highly cariogenic oral environment, which may impact the risk for RRC. A better understanding of the clustering of oral symptoms could be of considerable clinical significance for the oral health and quality of life of HNC patients. Therefore, RRC contemporary protocols of prevention must take into account this broader treatment scenario of cluster of oral side effects.

Introduction

Radiation-related caries (RRC) is a chronic side effect of head and neck radiotherapy (HNRT), and has a high potential for tooth destruction. Its causes are still not fully understood and the ability of HNRT to cause direct radiogenic damage to the dentition leading to RRC is a major topic for discussion in oral oncology [Lieshout & Bots, 2014; Morais-Faria et al., 2014].

Recent publications have linked the elevated risk of the clinically aggressive RRC in head and neck cancer (HNC) patients to the indirect effects of cancer therapies [Santos-Silva et al., 2015; Sroussi et al., 2017], which were reinforced by increasing evidence that "symptoms clusters" may have a pivotal role in several head and neck chemoradiotherapy (CRT) toxicities [Xiao et al., 2013; Xiao et al., 2014]. The so-called "clustering of oral symptoms" has been previously described and is composed of concurrent mucositis, taste changes, oral infections, oral pain, trismus, hyposalivation, altered saliva composition and shifts in the composition of the oral microbiota, which lead to significant dietary changes, deficient oral hygiene and the development of a highly cariogenic oral environment, working in synergy to increase the risk for RRC development and progression [Ribeiro et al., 2013; Xiao et al, 2013; Xiao et al. 2014; Santos-Silva, et al., 2015; Madrid et al., 2017; Gomes-Silva et al., 2017].

Therefore, the aim of this article is to present a systematic review of the recently described "clustering of oral symptoms" [Xiao et al., 2013; Xiao et al., 2014] associated with HNC treatment toxicities in an attempt to emphasize that RRC pathophysiology may be inserted into a broader and multifactorial setting than has been previously suggested.

Material and Methods

Study design

The present systematic review was conducted following the Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Supplementary Table 1) [Moher et al., 2009] and was registered at the PROSPERO platform CRD42019132709 (Palmier et al., 2019). The research question was: Is there a specific clustering of oral symptoms associated with HNC treatment that could impact the pathogenesis of radiation caries?

Studies that assessed the presence of treatment-related symptom clusters among HNC patients were selected. The inclusion criteria followed the PICOS strategy: Patients – HNC patients; Intervention – HNRT or CRT; Comparison – Head and neck specific toxicities (HN) and gastrointestinal toxicities (GI); Outcomes – Presence and cluster of symptoms from HNC treatment; Study design - clinical trials, descriptive and observational studies.

Studies were excluded for one of the following reasons: (1) Non-HNC symptoms; (2) Psychological/psychiatric disorders symptoms; (3) Respiratory system symptoms (4) Cardiovascular symptoms, and (5) Other reasons such as studies assessing molecular features of toxicities, studies assessing symptoms of other disorders such as fibromyalgia, among others.

Electronic and systematic searches of scientific studies that assessed the presence and cluster of symptoms from HNC treatment were conducted in April 2019 (Last update June 2019). English language restriction was applied, and there was no restriction to publication year. Medline/PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com/login) and Scopus (https://www.scopus.com) databases were screened. Related MeSH (Medical subjects headings) as well as free-terms were combined on different search strategies to find the articles. The process was repeated in each database to ensure that any relevant result would not be missed during the identification phase. Two combinations were performed at each database. Complete searching strategies are presented in Supplementary Table 2. Additional searches were conducted by reading reference lists from all selected studies to detect other potentially eligible reports that could meet the inclusion criteria.

Study Selection and data collection

All titles were systematically organized in Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, Washington, USA). They were verified and counted to exclude duplicated items. The articles were selected in two phases. In phase 1, 2 authors independently reviewed the titles and abstracts and selected those that apparently met the inclusion criteria. In phase 2, the same authors read the full texts of the selected articles at phase 1 and excluded those that did not meet the inclusion criteria (Supplementary Table 3). Any disagreements in the first or second phases were

resolved by discussion and mutual agreement between the two authors. Studies were classified into the following categories: duplicated, excluded by title, excluded by abstract, excluded by methodology and included studies. In the end, reports assessed for eligibility were downloaded from databases in full text version and they were read in detail in PDF formatted files. Studies that omitted relevant methodological information were also excluded from the current review.

The process for methodological data collection involved two investigators (AFGV and NRP). Data were independently extracted by each investigator and then compared; any disagreements were solved by discussion between the two investigators. Methodological data extracted from selected studies were related to first author name, year, country and journal of publication, type of study, number of patients, tumour topography, stage of disease, cancer treatment, mean radiation dose, type of radiotherapy, chemotherapy medications, chemotherapy cycles, treatment-related toxicities, time of assessment, HN specific symptoms, GI and general symptoms, toxicities assessment criteria and criteria for inclusion of toxicities in the Results section. The presence of the reported symptoms per included manuscript was assessed.

Risk of bias within studies

Methodologically, the authors appraised all included studies according to a checklist based in Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) [The Joanna Briggs Institute, 2014]. The reviewers (AFGV and NRP) independently answered nine questions for descriptive studies and eight questions for Cross-sectional studies as Y for “yes,” N for “no,” U for “unclear,” and NA for “not applicable” (Supplementary Table 4).

After that, the risk of bias was categorized as high when the study reached up to 49% of a “yes” score, moderate when the study reached 50–69% of a “yes” score, and low when the study reached more than 70% of a “yes” score. Disagreements were solved by discussion between the two authors.

Risk of Bias Across Studies

Quality of evidence and grading of recommendation was assessed by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) instrument. The assessment was based on radiation-related symptoms clusters evaluated

by different study designs. The criteria included the number of studies, study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations such as publication bias and confounding factors. Impact, certainty and importance were graded based on the assessed criteria and the quality of evidence was characterized as high, moderate, low, or very low for each outcome. The GRADE was assessed using tools from the following website http://gradepro.org.

Data analysis

Primary outcome was to assess the presence of HN specific symptoms cluster. Secondary outcome was to assess the presence of GI symptoms cluster. Tertiary outcome was to assess the possible impact of symptoms cluster in the pathogenesis of RRC. There was homogeneity in the research purpose among the studies but a great variability in time of assessment of toxicities and criteria used for the assessment of treatment-related toxicities. A detailed qualitative synthesis of the results was performed considering the presence of patient-reported symptoms among the included studies.

Results

Study selection and characteristics

A flow diagram summarizing the selection process is shown in Figure 1. A total of 4,611 studies were identified through the search strategies on three databases (PubMed, Embase and Scopus). After the first review process, 1,682 studies were excluded due to inter-database duplication. One study was added from the search on the reference list of the included studies. The total of 2,919 studies were excluded because they did not meet the inclusion criteria, resulting in 11 studies being eligible for the review. **Table 1** shows the main methodological aspects from the 11 included studies.

Seven studies (63.6%) assessed patients with heterogeneous HN topographies [Murphy et al., 2010; Xiao et al., 2013; Rosenthal et al., 2014; Kirka and Kutluturkan, 2016; Barnhart et al., 2018; Chiang et al., 2018; Ridner et al., 2018], two studies (18.2%) assessed patients with oropharynx/larynx tumours [Haisfield-Wolfe et al., 2012; Eraj et al., 2017] and two studies (18.2%) assessed patients with nasopharynx tumours [Xiao et al., 2017; McDowell et al., 2018]. Eight studies (72.2%) reported clarified information on patients' stage of disease, from which six (54.5%) assessed

patients with clinical stage of disease I to IV [Haisfield-Wolfe et al., 2012; Rosenthal et al., 2014; Kirka and Kutluturkan, 2016; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018] and two (18.2%) assessed patients with advanced clinical stage of disease III/IV [Xiao et al., 2013; Chiang et al., 2018].

Information on treatment modalities were also retrieved from the included studies: seven studies (63.6%) assessed patients treated with either RT or CRT protocols [Haisfield-Wolfe et al., 2012; Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Ridner et al., 2018], two studies (18.2%) assessed patients submitted to RT [Kirka and Kutluturkan, 2016; Chiang et al., 2018] and two studies (18.2%) assessed patients submitted to CRT protocols [Murphy et al., 2010; Xiao et al., 2013]. Four studies (36.3%) reported the use of the Intensity Modulated Radiation Therapy (IMRT) technique for radiation delivery [Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018], one study (7.1%) reported the use of IMRT and the 3D Conformational Radiotherapy (3DRT) [Barnhart et al., 2018] and one study (7.1%) compared the outcomes of the Accelerated Fractionation Radiotherapy (AFR) and Standard Fractionation Radiotherapy (SFR) [Xiao et al., 2013]. For the studies that assessed CRT protocols as treatment modality, cisplatin was the main medication used [Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018].

Considering the treatment-related toxicity assessment, five studies (45.4%) assessed patients both during RT and after RT completion [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Kirka and Kutluturkan, 2016; Barnhart et al., 2018], three studies (27.3%) assessed patients after the conclusion of RT [Eraj et al., 2017; McDowell et al., 2018; Ridner et al., 2018] and three studies (27.3%) assessed patients during the course of RT [Rosenthal et al., 2014; Xiao et al., 2017; Chiang et al., 2018]. For the classification of the observed toxicities, five studies (45.4%) used the M. D. Anderson Symptom Inventory [Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018; Chiang et al., 2018], two studies (28.2%) used The Memorial Symptom Assessment Scale [Haisfield-Wolfe et al., 2012; Kirka and Kutluturkan, 2016], one (9.1%) used the NCI Common Toxicity Criteria (CTC) 2.0 [Xiao et al., 2013], one (9.1%) used the Vanderbilt Head and Neck Symptom Survey [Murphy et al., 2010], one (9.1%) used the Vanderbilt Head and Neck Symptom

Survey version 2.0 [Ridner et al., 2018] and one (7.1%) characterized the toxicities as present or absent [Barnhart et al., 2018]

Results of the risk of bias assessment are shown in Figure 2. Six studies (54.5%) were classified as moderate risk of bias [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Rosenthal et al., 2014; Kirka and Kutluturkan, 2016; Barnhart et al., 2018; Ridner et al., 2018] and five studies (45.4%) were classified as low risk of bias [Xiao et al., 2013; Eraj et al., 2017; Xiao et al., 2017; McDowell et al., 2018; Chiang et al., 2018].

Since meta-analysis was not feasible due to the heterogeneity across studies, the quality of evidence was reported in a narrative summary of findings of GRADE and based on study design of included papers (**Supplementary Table 5**). The nine descriptive studies provided weaker scientific evidence and had heterogeneous methodologies, resulting in a serious level of inconsistency. Also, moderate risk of bias in most studies downgraded it to a serious rate, leading to a low quality of evidence. The second outcome included only two studies and had fewer patients; however, they represented stronger level of evidence (cross-sectional), had minor inconsistency across them and had low risk of bias, leading to a moderate quality of evidence. Based on these results, further research may have an important impact on the estimate of these effects.

Synthesis of Results

From the selected studies, all 11 (100%) reported the symptoms of difficult swallowing/dysphagia, dry mouth/xerostomia and pain [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Chiang et al., 2018; Ridner et al., 2018], eight studies (72.7%) reported taste alterations [Murphy et al., 2010; Xiao et al., 2013; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; Ridner et al., 2018], seven studies (63.6%) reported fatigue [Xiao et al., 2013; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Chiang et al., 2018], five studies (45.4%) reported sore mouth [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017], six studies (54.5%) reported problems with the presence of mucous on the mouth/throat [Murphy et al., 2010; Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018; Ridner et al., 2018], four studies (36.3%) reported

chewing problems [Rosenthal et al., 2014; Xiao et al., 2017; Eraj et al., 2017; McDowell et al., 2018], three studies (27.3%) reported teeth/gum problems - dental caries [Barnhart et al., 2018 McDowell et al., 2018; Ridner et al., 2018], three (27.3%) with radiodermatitis [Haisfiel-Wolfe et al., 2012; Xiao et al., 2013; Xiao et al., 2017], two studies (18.2%) reported problems related to oral mucositis [Xiao et al., 2013; Ridner et al., 2018], , two studies (18.2%) reported trismus [Barnhart et al., 2018; Ridner et al., 2018] and finally, one study (9.1%) reported smell alterations [Ridner et al., 2018]. Results of the distribution of HN specific symptoms among the studies are shown in Supplementary Figure 1.

Results of the analysis of the presence of GI symptoms are shown in Supplementary Figure 2. Eight studies (72.7%) reported loss of appetite [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017; Barnhart et al., 2018; Chiang et al., 2018; Ridner et al., 2018], five studies (45.4%) reported weight loss [Murphy et al., 2010;; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Kirca and Kutluturkan, 2016; Ridner et al., 2018], four studies (36.3%) reported nausea and vomiting [Xiao et al., 2013; Rosenthal et al., 2014; Xiao et al., 2017; Chiang et al., 2018] and one study (9.1%) reported dehydration [Xiao et al., 2013].

The high heterogeneity in reporting the results observed in the included studies made it impossible to assess frequency and prevalence of treatment-related toxicities among HN cancer patients. Nevertheless, four studies (36.3%) reported frequency values for HN and GI symptoms (Figures 3 and 4) [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Barnhart et al., 2018; Chiang et al., 2018]. Swallowing problems/dysphagia were reported by three studies with a mean frequency of 97.7% for 243 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Barnhart et al., 2018]. Dry mouth/Xerostomia was reported by all studies with a mean frequency of 94.75% for 343 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Barnhart et al., 2018; Chiang et al., 2018]. Pain was reported by three studies with a mean frequency of 91.3% for 151 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Chiang et al., 2018]. Taste alterations were reported by three studies with a mean frequency of 89.6% for 243 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Barnhart et al., 2018]. Fatigue was reported by three studies with a mean frequency of 92.2% for 322 patients [Xiao et al., 2017; Barnhart et al., 2018; Chiang et al., 2018]. Mucous was reported by one study

with a frequency of 99.2% for 130 patients [Xiao et al., 2017]. Sore mouth was reported by two studies with a mean frequency of 83.5% for 151 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017]. Chewing problems were reported by one study with a frequency of 98.5% for 130 patients [Xiao et al., 2017]. Teeth/gum problems - dental caries were reported by two studies with a mean frequency of 48.8% for 222 patients [Xiao et al., 2017; Barnhart et al., 2018]. Radiodermatitis was reported by two studies with a mean frequency of 73.9% for 151 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017]. Trismus was reported by one study with a frequency of 14.1% for 92 patients [Barnhart et al., 2018]. Four studies reported lack of appetite with a mean frequency of 90.9% for 343 patients [Haisfield-Wolfe et al., 2012; Xiao et al., 2017; Barnhart et al., 2018; Chiang et al., 2018]. One study reported weight loss with a frequency of 91% for 21 patients [Haisfield-Wolfe et al., 2012]. Two studies reported nausea and vomiting with a mean frequency of 87.8% and 74.3%, respectively, for 230 patients [Xiao et al., 2017; Chiang et al., 2018]. No studies reported frequency values for OM, smell alterations and dehydration. Detailed information of reported results from included studies are available in Supplementary Table 6.

Symptom clusters in patients with head and neck cancer

Results from the present systematic review described several clusters of symptoms following HNC treatment, which include specific HN conditions, such as dry mouth, dysphagia, pain, taste disturbances, fatigue, oral mucositis, radiodermatitis, and GI manifestations, such as nausea, vomiting, and dehydration [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Rosenthal et al., 2014; Kirca and Kutluturkan, 2016; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Chiang et al., 2018; Ridner et al., 2018]. These clustering of oral symptoms using contemporary concepts brought new ideas for the analysis of RRC pathogenesis and the impact of dietary changes, deficient oral hygiene, and the highly cariogenic oral environment on the dentition of HNC survivors **(Figure 5)**.

Discussion

HNRT is known to cause several acute and chronic toxicities to the oral cavity. Within the first 3 weeks, patients undergoing HNRT experience a series of symptoms that burden, evolve and overlap. They often develop oral mucositis (OM), radiation

dermatitis, edema, dysgeusia and a shift in the oral microbiota composition [Murphy et al., 2010; Xiao et al., 2013; Chiang et al., 2018; Ridner et al., 2018]. Additionally, these patients may develop associated pain, copious mucous production, hyposalivation, xerostomia, and acute tissue swelling, which contribute to acute dysphagia [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Chiang et al., 2018; Ridner et al., 2018]. Late effects include skin and salivary gland fibrosis, lymphedema and damage to neural structures, hyposalivation, trismus, dysphagia, RRC and osteoradionecrosis [Kielbassa et al., 2006; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018]. Adverse effects of cancer treatment represent profound and long-lasting alterations on function and diminished quality of life, which is composed of a complex network of inter-related factors that include functional, biological, psychological and social components [Murphy et al., 2007; Murphy and Gilbert, 2009; Vanderbilt et al., 2018].

The symptoms experienced by HNC patients are broad in scope and encompass both local and systemic symptoms. Furthermore, instead of occurring in isolation, results observed in the present systematic review indicate that they occur in clusters, exacerbating the overall symptom experience. ‘Symptom clusters’ are defined as groups of at least two or three concurrent symptoms that are synergistically interrelated [Murphy et al., 2007; Xiao et al., 2013; Dong et al, 2014]. Two main distinct and stable clusters were described for HNC patients, identified through factor modelling among 10 identified treatment-related symptoms: HN specific symptoms cluster (encompassing mucositis; radiodermatitis; pain; dysphagia; taste disturbances; dry mouth and fatigue) and GI cluster (nausea, vomiting and dehydration) [Aguiar et al, 2009; Silva et al., 2009; Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Xiao et al., 2017; Eraj et al., 2017; Barnhart et al., 2018; McDowell et al., 2018; Chiang et al., 2018; Ridner et al., 2018]. These clustered symptoms may be associated with the development of a highly cariogenic oral environment and the lack of proper oral hygiene leading to onset and development of RRC [Cohen et al., 2016].

Dysphagia is defined as difficulty in swallowing and can be an acute or late result of HNRT. Acute dysphagia is associated with mucosa and soft tissue damage within the treatment field particularly because of OM, radiation dermatitis, and edema of the soft tissues. Pain, hyposalivation associated with thickened and more viscous mucous production, and tissue swelling contribute to acute dysphagia. Late dysphagia is

the result of tissue fibrosis and stiffness due to the ongoing inflammatory cytokine cascade effects, as well as to lymphedema and radiation-induced damage to neural structures. Patients suffer aspiration, choking, and may consciously or unconsciously alter the type and consistency of food that they eat, resulting in nutritional deficiencies and an oral environment favourable for RRC onset and progression [Murphy et al., 2007; Nevens et al., 2017; Santa Cruz et al., 2018; Ridner et al., 2018].

Dry mouth, or xerostomia, observed in HNC patients is caused by hyposalivation due to radiogenic effects on salivary glands. It has a rapid onset and it is the most common persistent oral side effect for patients receiving HNRT [Sciubba and Goldenberg, 2006]. Saliva becomes scant and thicker causing difficulties in speaking; and induces taste alteration, as well as distress in chewing and swallowing. This scenario has an influence on dietary alterations, leading to the intake of softer and more carbohydrate-rich food [Aguiar et al., 2009]. Besides the quantitative effects, qualitative changes to saliva also occur unleashing an imbalance in its ionic composition. In this way, its buffering and tooth remineralization capacity are reduced, leading to loss of the demineralization/remineralization equilibrium and facilitating the more rapid loss of minerals from dentin and enamel following RT [Marsh, 2003; Murphy and Gilbert, 2000; Barnhart et al., 2018; Ridner et al., 2018].

In addition, an imbalance in both salivary organic components (glycoproteins and proteins) and in adaptive and innate immunity occurs following HNRT, altering the establishment and selection of the oral microbiota present on oral hard and soft tissues. Also, the frequent sugar and carbohydrate-rich food intake creates regular conditions of low pH within the dental biofilm and selects for acidogenic and aciduric bacteria such as mutans streptococci and lactobacilli, predisposing the enamel – which is known for being highly porous and permeable after HNC treatment [Madrid et al., 2017] – to the rapid onset and progression of RRC. In other words, a real “ecological catastrophe” occurs in the oral cavity of cancer patients following HNRT, due to the disruption of the natural balance that normally exists in the mouth between the microbiota and the host, and which drives dysbiotic changes in the composition of the biofilm, thereby creating a favourable environment for RRC [Marsh, 2003].

Pain is a ubiquitous problem faced by all HNC patients both due to the tumour before therapy begins and up to 76% of patients suffer severe pain related to acute therapy toxicities such as OM and radiodermatitis, despite the use of opioids [Murphy et

al, 2007]. After treatment completion, they experience pain when doing several basic physical functions due to fibrosis, muscular loss, neck dissection and neural impairment. Pain significantly impacts on function, with high percentages of patients reporting difficulties in swallowing, eating, drinking, talking, sleeping and maintaining basic self-day-care such as oral hygiene [Murphy and Gilbert, 2000; Xiao et al., 2017; Ridner et al., 2018; Chiang et al., 2018; Vanderbilt et al., 2018].

All HNC patients undergoing cancer therapy experience taste disturbances. It is caused by a multitude of other toxicities including OM, deficient oral hygiene, a shift in their oral microbiota, taste buds and oral neural structure impairment, medications or chemotherapies intake and especially salivary flow decrease [Sciubba and Goldenberg, 2006; Murphy et al. 2007; Barnhart et al., 2018; Ridner et al., 2018]. It importantly impairs a patient's quality of life, leading to decreased food intake and a switch to sweeter foods (the most maintained flavour, reported by the patients). Unfortunately, intake of carbohydrate-rich foods and sweeter foods provide a highly cariogenic environment and fosters RRC development and rapidly progression [Aguiar et al., 2009].

Fatigue is another well-documented side-effect observed in patients undergoing radiation therapy. The lack of appetite, mainly due to the presence of chemosensory dysfunctions such as taste and smell dysfunctions, can result in patients general deconditioning which may lead to profound weight loss, with a decrease in lean and fat body mass, and individuals experiencing weakness and fatigue [Murphy et al., 2010; Haisfield-Wolfe et al., 2012; Xiao et al., 2013; Kirca and Kutluturkan, 2016; Ridner et al., 2018]. This occurs due to chemotherapy and radiation metabolic changes; impaired food intake caused by pain, tumour-related factors dysphagia, socio-economic difficulties impairing the purchase of nutritional supplements and even depression [Murphy et al., 2007; Murphy et al. 2009]. All of these events compound a complex network leading to a decrease in physical functioning and loss of the ability to conduct daily activities such as proper oral hygiene, further propitiating RRC.

HNC patients that undergo radiotherapy will develop OM, especially when radiation treatment is associated with concurrent chemotherapy. The site of OM development depends on the tumour site, size and treatment planning, but in any case it produces mucosal pain and swelling, leading to bleeding, difficulty in speaking; sleeping; mouth opening; dysphagia and anorexia. In addition, it leads to dietary

adaptations with a switch to softer and carbohydrate-rich foods, with their intake at an increased frequency. This fact, associated with an impaired or absent oral hygiene, produces an environment conducive to RRC onset [Murphy and Gilbert, 2000; Aguiar et al., 2009; Xiao et al., 2013; Ridner et al., 2018].

Radiodermatitis causes wounds, pain and a burning sensation on the skin included in the treatment field. The radiogenic soft tissue damage may also affect the local lymphatic structures and muscles, being associated in the long-term with lymphedema, cutaneous and muscular fibrosis and consequent trismus. In this way, besides the swallowing difficulties, patients present distress on opening the mouth and must change their dietary habits to softer and more cariogenic food, which combined with the additional impairment of proper oral hygiene due to pain and trismus, increases their risk of RRC [Murphy and Gilbert, 2009; Nevens et al., 2017; Santa Cruz et al., 2018; Ridner et al., 2018].

Systemic symptoms cluster associated with HNC treatment toxicities were described by Xiao et al, in 2013, as a stable identified GI cluster involving nausea, vomiting and dehydration, often induced by CT or CRT. We go further and suggest that this “GI cluster” may have a significant impact on RCC pathophysiology, especially due to recurrent vomiting, which may result in dehydration and intensifies hyposalivation, lowering the protective salivary effects against caries. In addition, vomiting may produce a lower oral pH, leading to elevated risk of enamel and dentin dissolution. All of the side effects associated with nausea create an additional obstacle for proper oral hygiene in HNC patients, and represent a favourable environment for the onset and development of RRC.

Lastly, it is relevant to mention that most of the oral cancer patients are poorly educated, low-income individuals, with minimal oral hygiene and level of dental awareness. Many of these patients had never undergone dental treatment and previous studies have demonstrated that nearly all the HNC patients examined just before HNRT need extensive dental care due to advanced periodontal disease, residual roots, and caries **(Figure 6)** (Jham et al., 2008). These complex psychosocial and behavioural features of HNC patients create a poor oral health scenario even before HNRT (Jham et al., 2008), which might be considered another pillar to the development and rapidly progression of RRC.

Strengths and Limitations

Main strengths of this systematic review were rigorous searching and assessment methods and homogeneity in study objectives. Nonetheless, we found limitations such as heterogeneity of studies that met inclusion criteria regarding the methodology and criteria for toxicity assessment and report of observed results.

Conclusions

This review is the first to explore symptom clusters in HNC patients and their possible impact on RRC development and progression. HNC patients seldom present with a single oral symptom; thus the understanding and managing of the specific conditions of the HN and GI manifestations symptoms clusters may be paramount for the preservation of cancer survivor's quality of life. Remarkably, there is evidence that the observed HN and GI symptom clusters may indirectly contribute to RRC onset and progression. This scenario composes a much more complex panorama than what has been previously suggested in terms of RRC pathogenesis, and should be considered pivotal for RRC progression. Therefore, contemporary protocols of RRC prevention and treatment must take into account this broader HNRT-associated clustering of toxicities scenario.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

Adriele Ferreira Gouvêa Vasconcellos, Natália Rangel Palmier and Alan Roger Santos-Silva performed the systematic review methodology process and wrote the manuscript in consultation with Adriana Franco Paes Leme and Philip Marsh. Ana Gabriela Costa Normando and Mario Fernando de Goes performed risk of bias analysis within and across studies (GRADE). Thaís Bianca Brandão, Marcio Ajudarte Lopes, and Ana Carolina Prado Ribeiro designed the study. Karina Morais Faria, Wagner Gomes-Silva and Aljomar José Vechiato Filho drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript.

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Legends

Table 1. Main methodological data extracted from the included studies about the presence of radiation-related symptoms clusters.

NI - Not informed; CRT - Chemoradiotherapy; HNC - Head and Neck Cancer; RT - Radiotherapy; IMRT - Intensity modulated radiotherapy; Gy - Grays; AFR - Accelerated fractionation radiotherapy; SFR - Standard fractionation radiotherapy; NA - Not applied.

Figure 1. Flow diagram that summarizes selection process (PRISMA format).

Figure 2. Risk of bias in included studies about the symptoms cluster among Head and Neck Cancer patients.

a: MAStARI critical appraisal tools for Descriptive/Case series

b: Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies

Figure 3. Frequency (%) of Head and Neck specific symptoms reported included studies.

Figure 4. Frequency (%) of Gastrointestinal symptoms reported included studies.

Figure 5: Flow chart presenting the interactions between the head and neck and the gastrointestinal symptoms clusters in RRC pathogenesis. Green: head and neck specific symptoms cluster. Blue: gastrointestinal symptoms cluster.

Figure 6: Oral health status in two head and neck cancer patients examined before radiotherapy resembling radiation-related caries patients. a. Note the poor oral hygiene, extensive carious lesions, brown-blackish colour pigmentation due to smoking habit and extensive teeth loss. b. Presence of extensive periodontal disease, teeth loss, several caries and multiple residual roots – one of them (in the lower right mandibular area) presenting sign of apical periodontitis.

Supplementary Table 1: PRISMA Checklist

Supplementary Table 2. Search strategy in the databases.

Supplementary Table 3. Phase 2 excluded manuscripts and reasons for exclusion

Supplementary Table 4. Risk of bias assessed by Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI)1 critical appraisal tools. Risk of bias was categorized as High when the study reaches up to 49% score "yes", Moderate when the study reached 50% to 69% score "yes", and Low when the study reached more than 70% score "yes".

MAStARI critical appraisal tools for Descriptive/Case series. *Y=Yes, N=No, U=Unclear, M=Moderate, H=High, L=Low. [1]Meta Analysis of Statistics Assessment and Review Instrument (MAStARI). Joanna Briggs Institute Reviewers Manual. Australia: The Joanna Briggs Institute, 2014.

Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies

*Y=Yes, N=No, U=Unclear, M=Moderate, H=High, L=Low.

[1]Meta Analysis of Statistics Assessment and Review Instrument (MAStARI). Joanna Briggs Institute Reviewers Manual. Australia: The Joanna Briggs Institute, 2014

Supplementary Table 5: Question: Is there a specific clustering of oral symptoms associated with HNC treatment that could impact the pathogenesis of radiation caries?

Explanations

a. Most studies were categorized as having a moderate risk of bias.

b. Symptoms were measured, analyzed and reported heterogeneously across studies.

Supplementary Table 6. Results reported from the included studies, total number of assessed patients and criteria for assessment and results report

NI: Not informed; X: Not assessed. *Vanderbilt: Vanderbilt Head and Neck Symptom Survey; **CTC: NCI Common Toxicity Criteria (CTC) 2.0; ***MDASI: M. D. Anderson Symptom Inventory; ****MSAS: Memorial Symptom Assessment Scale. Except from the 4 studies that reported frequency values as percentage numbers, all other included studies reported mean values of response to Questionnaire-based assessment.

Supplementary Figure 1. Distribution of Head and Neck specific symptoms among the included studies.

Supplementary Figure 2. Distribution of Gastrointestinal symptoms among the included studies.

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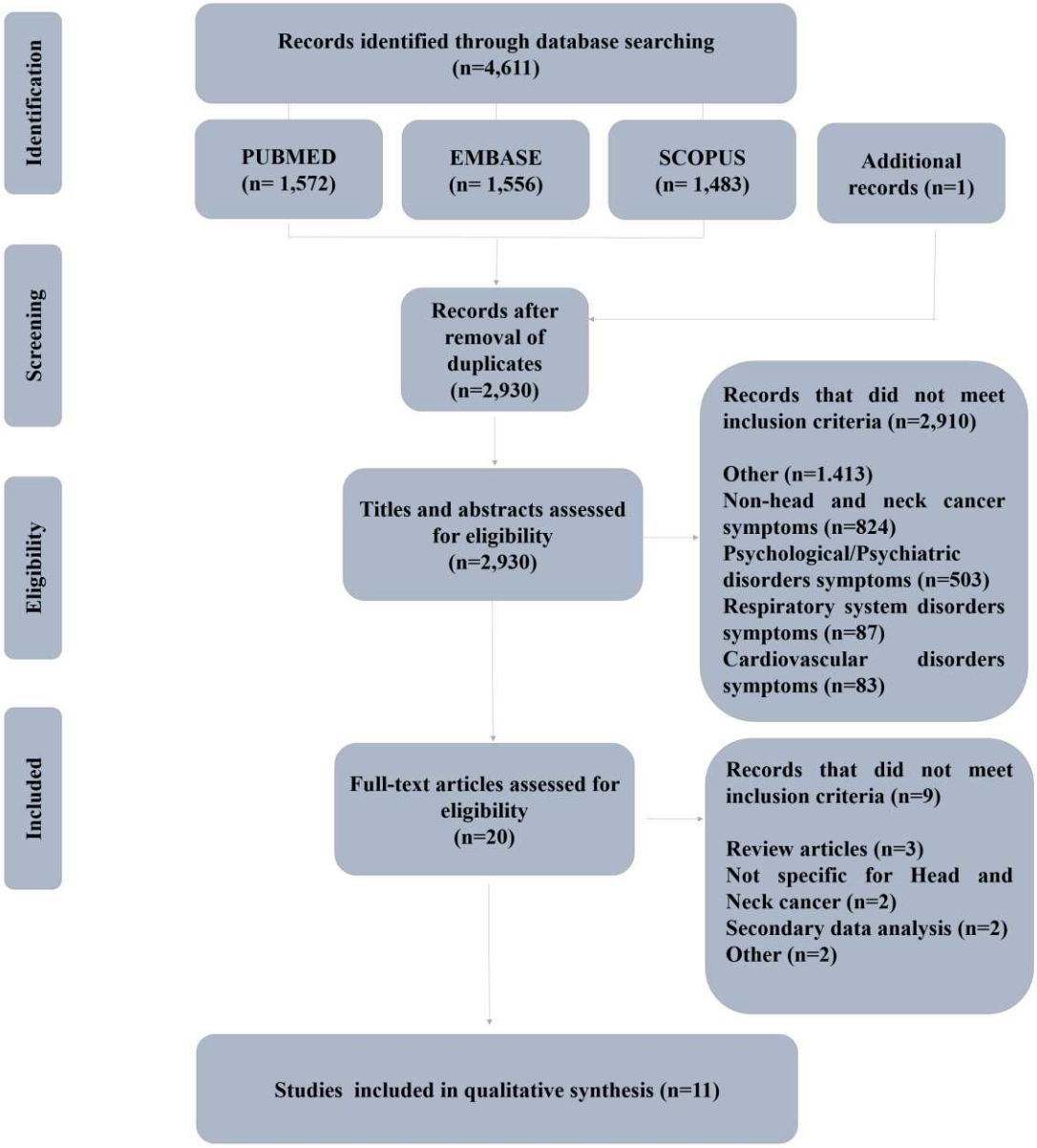

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740 Figure 2.

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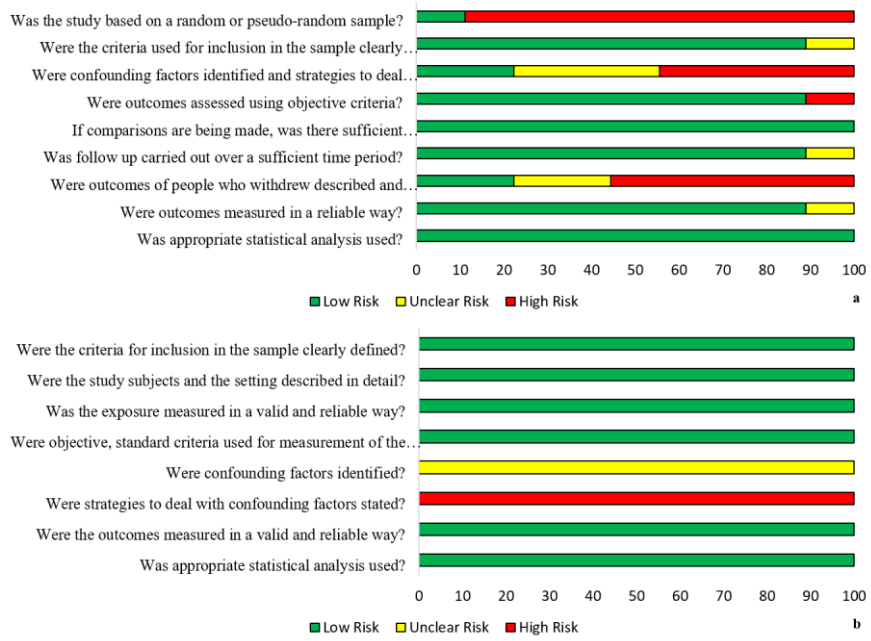

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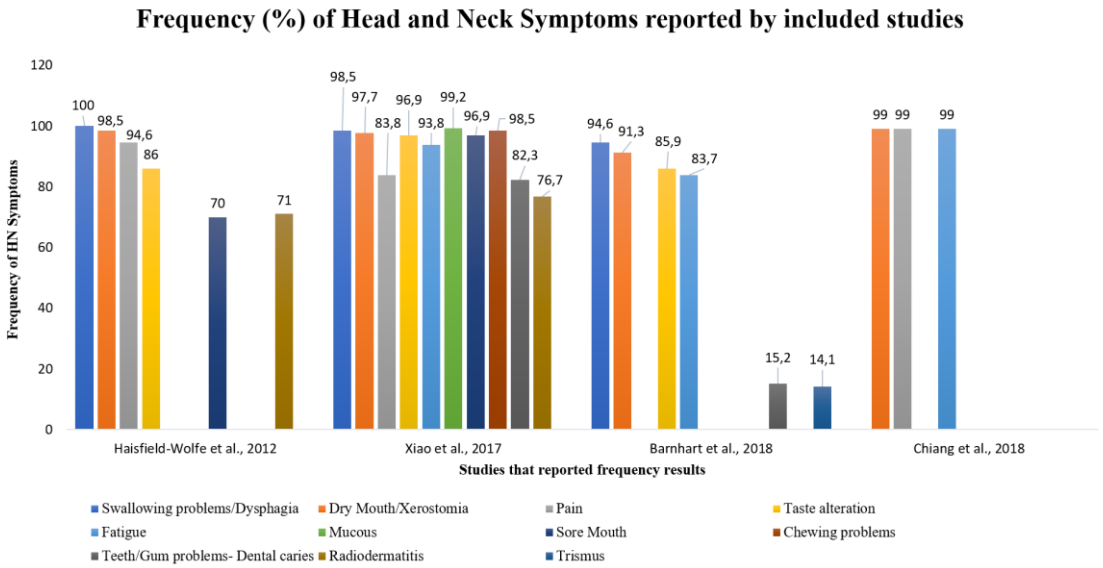
745 Figure 3.



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749 Figure 4.

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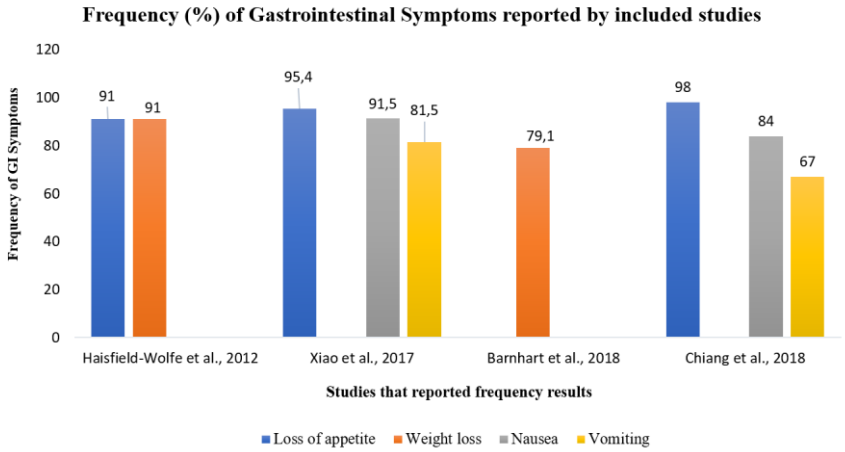

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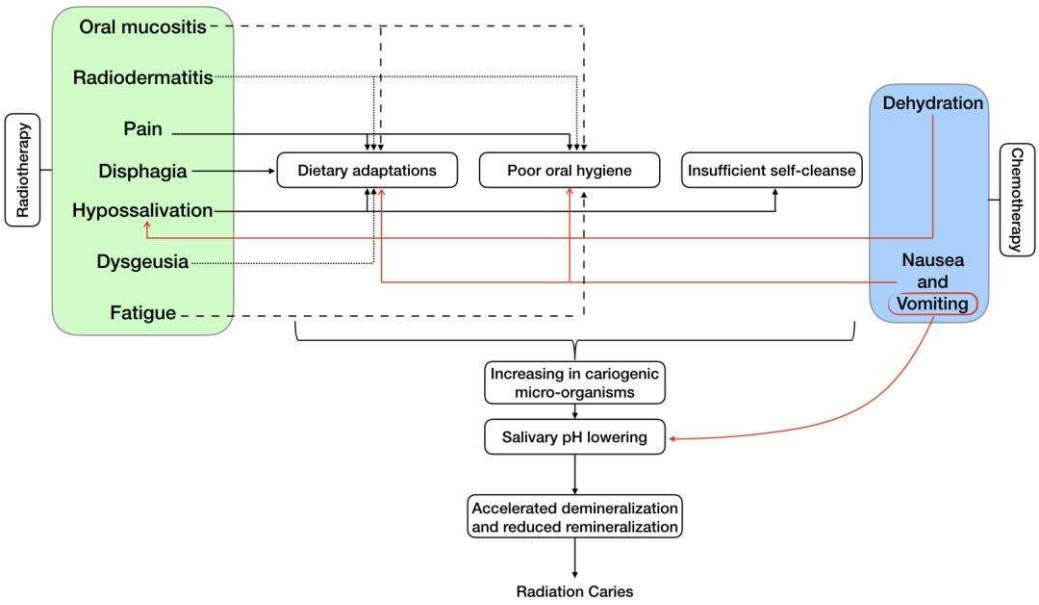
Figure 5.


Oral mucositis
Radiodermatitis
Pain
Disphagia
Hypossalivation
Dysgeusia
Fatigue
Radiotherapy
Dietary adaptations
Poor oral hygiene
Insufficient self-cleanse
Dehydration
Nausea
and
Vomiting
Chemotherapy
Increasing in cariogenic micro-organisms
Salivary pH lowering
Accelerated demineralization and reduced remineralization
Radiation Caries

760 Figure 6.

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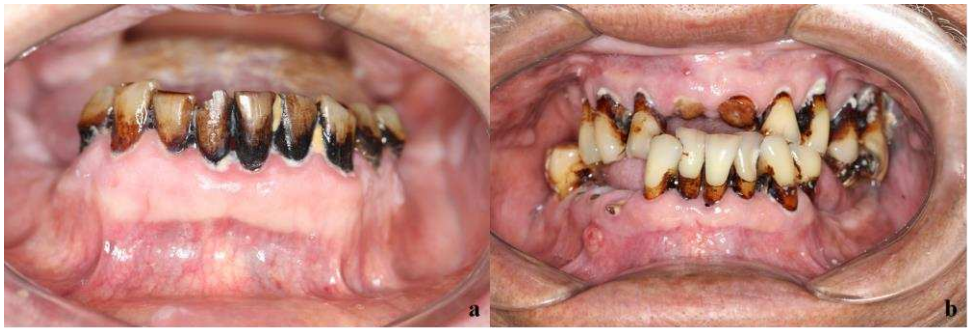

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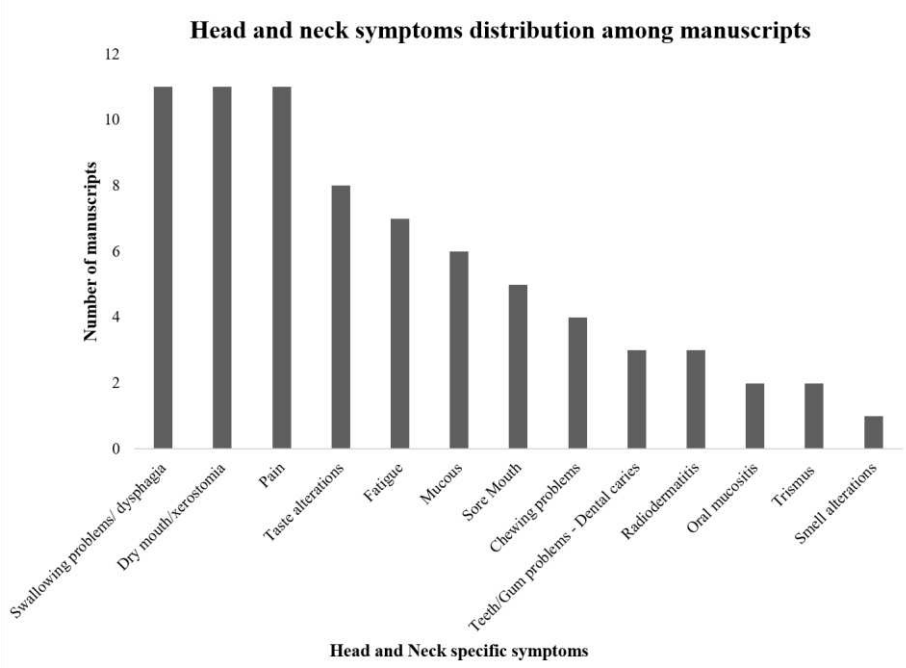
Supplementary Figure 1.



Supplementary Figure 2.