Systematic Review
Endodontic Therapy

Does radiotherapy treatment alter the pulp condition in patients with head and neck cancer? A systematic review

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Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

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https://doi.org/10.1590/1807-3107bor-2023.vol37.0079

Submitted: July 4, 2022
Accepted for publication: February 6, 2023
Last revision: May 8, 2023

Abstract: The main purpose of this study was to answer the question: "Can radiotherapy cause changes in the dental pulp condition of patients treated with irradiation in the head and neck region?" Clinical observational studies in adults with head and neck cancer undergoing treatment with ionizing radiation, longitudinal or cross-sectional follow-up to measure oxygen saturation (SpO_2), and/or pulp sensitivity test to cold stimulation, were considered eligible. A systematic literature search was performed in six different databases, including the gray literature, and in article references. Two independent evaluators selected the studies, extracted the data, recorded the data on electronic spreadsheets, and then evaluated the methodological quality using the Checklist for Quasi-Experimental Studies tool devised by JBI. The data were assessed qualitatively using the Synthesis Without Metanalysis (SWiM) guidelines. After removing the duplicate articles, carefully analyzing the titles and abstracts, and reading the papers in full, seven studies were included. Four of the studies evaluated applied the cold sensitivity test, two associated pulse oximetry and cold sensitivity, and only one used just pulse oximetry. Evaluation using the cold sensitivity test and pulse oximetry in the initial periods before radiotherapy showed a decrease in the sensitive response and in SpO_2 levels during a maximum period of 1 year. However, analyses thereafter indicated a normal response in both tests from 5 to 6 years after the end of radiotherapy treatment. Radiotherapy causes changes in pulp behavior patterns in the short term; however, recovery and return to average values occurs after long periods.

Keywords: Dental Pulp; Dental Pulp Test; Oximetry; Radiotherapy; Systematic Review.

Introduction

Cancer ranks as one of the leading world public health problems of the 20th and 21st centuries, and its diagnostic rates increase yearly.[1] The malignant neoplasms located in the head and neck region rank 6th in incidence, and have been showing greater propensity for afflicting lower income countries.[2,3] The epidemiological aspects of the disease indicate that male patients between the fourth and seventh decade

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of life, with established habits such as alcohol consumption and smoking, are more propense to neoplastic development.[4]

The oral cavity is composed of important structures, and the functional and structural complexity of this region indicate using ionizing radiation as the main treatment approach to combat tumor cells.[5] Although radiation is less invasive and has the potential to preserve healthy tissues, compared with tumor resection surgery, high-energy radiation from X-rays causes changes in the tissues which surround the tumor, and may affect both the patient's quality of life, and the functioning of tumoral organs.[6] The main side effects reported across the region of the craniocervical complex are episodes of trismus, dysphagia, dysgeusia, pain, erythema, mucositis, and changes in dental and bone tissues.[5,7-10] It is not uncommon for the teeth to be included in the radiation zone of ionizing beams in head and neck cancer (HNC) treatments, and hence also submitted to the negative effects of high doses of energy. Thus, although pulp tissue is protected by structures such as enamel and dentin, it can suffer injury from radiation, resulting in decreased vascular supply, tissue fibrosis, decreased sensitive response, increased metabolites, inflammatory changes, and even atrophy.[11,12]

The correct endodontic diagnosis of HNC is determined a priori by the professional's evaluation of the pulp conditions, according to his skills and to tools affording high power of accuracy.[13] Most of the current devices determining pulp status consider the patient's pain response subjectivity to the stimulus applied to the tooth.[14] However, several factors can interfere with the response, such as the patient's emotional state, mineralized structures, coronary restorations, and the lack of test standardization. In the thermal tests performed at low temperatures, and those using electrical current stimulation, the degree of pulp disease can interfere with the response, depending on blood supply, level of inflammation, presence of fibrosis, and pulp stones.[15] More objective methods, such as pulse oximetry, have been studied to afford more assertive methods of diagnosing the pulp condition, based on levels of peripheral oxygen saturation (SpO_2) circulating in different dental groups; in addition, studies have been conducted to understand how pulp tissues influence the reading of pulse oximeter results.[16,17]

The high risk of osteoradionecrosis in surgical procedures makes preservation of the dental elements in radiotherapy patients of essential importance.[5] Therefore, periodic evaluations and referrals of patients to the dental team must be carried out constantly to check the oral health of radiotherapy patients. In addition, pulp sensitivity should always be measured to monitor and plan interventions to remove possible sources of infection.[18] However, several studies have shown incompatibility between pulp behavior and tissue health status, such as decreased oxygen saturation levels after administering the radiotherapy treatment, despite no presence of pulp necrosis.[19] Despite the incompatibility issues, methodological differences in the treatment periods evaluated did not clarify whether or not low levels of SpO_2 permanently persist in teeth subjected to ionizing radiation.[20,21] Furthermore, pulp cell behavior determined by thermal and electrical tests cannot draw any conclusions, because of the intrinsic differences among the studies in the literature. [20,22]

Therefore, a better understanding of the pulp tissue condition in patients undergoing radiotherapy (RT) is essential. This can be achieved by comparing different diagnostic methods and evaluating patient behavior over time. In this sense, clinical decision-making for endodontic treatment can be better directed with more accurate tools and within an ideal follow-up period. Therefore, the objective of this study was based on the problem question for accomplishing this systematic review, namely, "Is RT capable of causing changes in the tooth pulp condition in patients irradiated in the head and neck region during treatment?"

Methodology

Study design and eligibility criteria

Based on the PICO strategy, the review question reads as follows: Is RT (I) capable of causing changes in the tooth pulp condition (O) in irradiated

patients in the head and neck region (P) during treatment (C)?

The studies included in the systematic review were observational clinical studies (OCS) that evaluated pulp sensitivity and vitality in the head and neck region of RT patients, based on thermal tests and SpO_2 measured by pulse oximetry. There was no specific time frame for the search.

The inclusion criteria were:

a. OCS with patients aged over 18 years, diagnosed with malignant tumors in the head and neck region;
b. OCS with patients whose main treatment approach was using ionizing radiation in the head and neck region;
c. OCS with patients who underwent RT using ionizing radiation in fractional doses until reaching the recommended dose for treating the tumor;
d. OCS with patients having sound teeth, free from periapical pathosis, or not submitted to previous endodontic treatment;
e. OCS that performed thermal pulp sensitivity tests and/or pulse oximetry to determine the SpO_2 in the dental pulp;
f. Studies that used before and/or after RT analysis as a comparison among the parameters, or between non-irradiated and irradiated groups.
g. The exclusion criteria were:
h. Articles with laboratorial methodologies (e.g. histological analysis of extracted human teeth, analysis of slides, animal studies);
i. Studies such as literature reviews, clinical case reports, case series, opinion articles, book chapters, editorials, abstracts of scientific conferences;
j. OCS with HNC patients who did not report pulpal outcomes related to pulpal behavior (sensitivity or SpO_2);
k. OCS with HNC patients who underwent surgery to remove tumors in areas where there were teeth;
l. OCS with HNC patients who had undergone RT and endodontic treatments during cancer therapy;
m. OCS with no control group;
n. OCS with patients submitted to incomplete RT treatment;
o. Studies written in languages that had an alphabet which could not be translated using online simultaneous translation applications.

Therefore, the main purpose of the present systematic review was to investigate whether RT causes changes in the pulp condition of patients diagnosed with and treated for cancer in the head and neck region, at different follow-up periods.

Research and information sources

The literature search was performed using PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), and EMBASE electronic databases, followed by parallel gray literature databases (Google Academic and Open Grey). The search strategy used the descriptors of the Descriptors in Health Science (DeCS) and Medical Subject Headings (MeSH) databases, adapted according to each database. Use of the Boolean operators AND and OR enhanced the search for the combination of terms in different ways. The search was complemented by manual searches in the references used by the selected articles. The survey was carried out during August 2021 and December 2022 (Table 1). All the references were exported to the Mendeley™ manager software (London, UK), and the files identified as duplicates were removed.

Selection of studies

An independent and parallel search was performed by two reviewers (T.E.R and M.L.L.S.); in the case of disagreements, a third reviewer (D.A.D.) assisted in reaching an agreement by discussion, and by applying the pre-defined inclusion and exclusion criteria. First, the titles were read, and those outside the scope of the present study were excluded. The evaluators were not privy to the authors of the studies or the names of the journals in which the articles were published. Then, the abstracts were read and analyzed independently by the two reviewers; the studies that did not meet the inclusion criteria were excluded, including literature reviews, case reports, annals of scientific seminars, opinion articles, and laboratory methodologies. The titles that met the eligibility criteria, but had abstracts which did not

Table 1. Search strategies used in the different electronic databases.

Database	Search strategy (August/2021 and December/2022)	Results
PubMed (https://www.ncbi.nlm.nih.gov/pubmed/)	((((((Cancer of the Head and Neck) AND (Radiation Treatment)) OR (Radiation, Ionizing)) AND (Time)) AND (Dental Pulp Test)) OR (Tooth Sensitivity)) OR (Dental Pulp Devitalization)	7730
Scopus (http://www.scopus.com/)	(ALL("Cancer of the Head and Neck") AND ALL("Radiation, Ionizing") OR ALL (Radiation Therapy) AND ALL(Time) AND ALL(Dental Pulp Test) OR ALL(Tooth Sensitivity) OR ALL(Dental Pulp Devitalization))	568
Embase (http://www.embase.com)	('cancer of the head and neck' AND 'radiation treatment' OR 'ionizing radiation') AND 'time' AND 'dental pulp test' OR 'tooth sensitivity' OR 'dental pulp devitalization'	632
Web of Science (http://apps.webofknowledge.com/)	((((((TS=(cancer of the head and neck)) AND TS=(radiation treatment)) OR TS=(radiation, ionizing)) AND TS=(time)) AND TS=(dental pulp test)) OR TS=(tooth sensitivity)) OR TS=(dental pulp devitalization)	254
LILACS (lilacs.bvsalud.org/)	"Neoplasias de Cabeça e Pescoço" AND "Radioterapia" AND "Polpa Dentária"	11
Google Scholar (https://scholar.google.com.br/?hl =pt)	Cancer of the Head and Neck AND Radiation Ionizing AND Dental Pulp Sensitivity Treatment OR Dental Pulp Test	100
Open Grey (http://www.opengrey.eu/)		0

conform to the inclusion criteria of this review were also excluded. The remaining articles were read in full, and reference lists were evaluated to identify other studies that may have been omitted from the databases. The data were collected in a paired and independent manner by the reviewers, and were recorded in a spreadsheet for data extraction at a later date, or to check the data collected and merge the characteristics obtained by each evaluator at the end.

Data processing and collection

After reading the manuscripts in full, the two reviewers (T.E.R. and M.L.L.S.) evaluated each article individually, and then collected, extracted and recorded the data on electronic spreadsheets organized using Excel software (Microsoft Corporation, New Mexico, USA), according to the following information: author/year, country, study type, study population, groups (intervention), chemotherapy treatment, radiation dose, RT technique, tumor location and type, group of teeth, total number of teeth, evaluation period, primary outcomes (SpO_2 and/or test response), secondary outcomes (recovery and recovery time) and notes. The data were obtained and classified by both raters, T.E.R. and M.L.L.S. Any disagreements were clarified by discussion with a third evaluator (D.A.D.).

Methodological quality of the studies

The methodological quality of the studies was determined using the Checklist for Quasi-Experimental Studies tool developed by JBI for Systematic Reviews (https://jbi.global/criticalappraisal-tools). Each topic was evaluated by two independent reviewers (T.E.R. and M.L.L.S.) according to the PRISMA 2020 protocol recommendations. The studies were evaluated by assigning scores to each topic presented by the tool; a positive response received a score of 1, and a negative response had a score of 0. A score of 0 was also given if the descriptions were considered unclear or insufficiently detailed. Questions not applicable to the study were designated as N/A. The studies were classified according to their score, namely low (when the scores were between 0 and 3), moderate (scores between 4 and 6), or high methodological quality (scores between 7 and 9).

Effect measures

The primary outcome was defined as the change in the behavior pattern of the pulpal response, the patient's sensitivity to cold thermal testing, and the changes in the SpO_2 rates in the pulse oximetry of the test group versus the control group. The secondary outcomes that were established included the recovery

made to normal levels recorded before OCS RT treatment, achieved after longitudinal follow-up.

Summary of Results

The results were synthesized using SWiM (Synthesis Without Meta-analysis)[23] as the descriptor. Meta-analysis was not possible because of the high methodological heterogeneity of the studies, such as differences in the follow-up time and in the dental groups evaluated. Therefore, tabulation and narrative synthesis were used to summarize the reported outcomes.

Results

Study selection

The systematic search was carried out using 7 databases, including the gray literature. This search yielded 9,295 references, 2,353 of which were duplicates. No results were found in the Open Grey database. Removal of the duplicate files left the titles of 6,942 studies for analysis. Application of the exclusion criteria led to the elimination of another 6,929 references. Lastly, 13 articles were read in full and evaluated for their eligibility criteria. The references of the selected studies were assessed to identify studies not found in the databases of the original search. At the end of the selection process, 7 studies were included for qualitative analysis, according to the parameters adopted by the PICO strategy (Figure). The excluded articles were recorded, and the main reason for exclusion is described in Table 2. A final data collection table with the main characteristics of the included studies was prepared (Table 3). Analysis of the methodological quality was conducted using the tool provided by JBI, and yielded one study[8] presenting moderate quality, and the rest as having high methodological quality (Table 4). The main concerns toward this analysis were related to the lack of detail in the various comparisons, and the method of applying the cold sensitivity and the pulse oximetry tests.

The included studies were carried out in Brazil (4 studies) and India (3 studies), and had 368

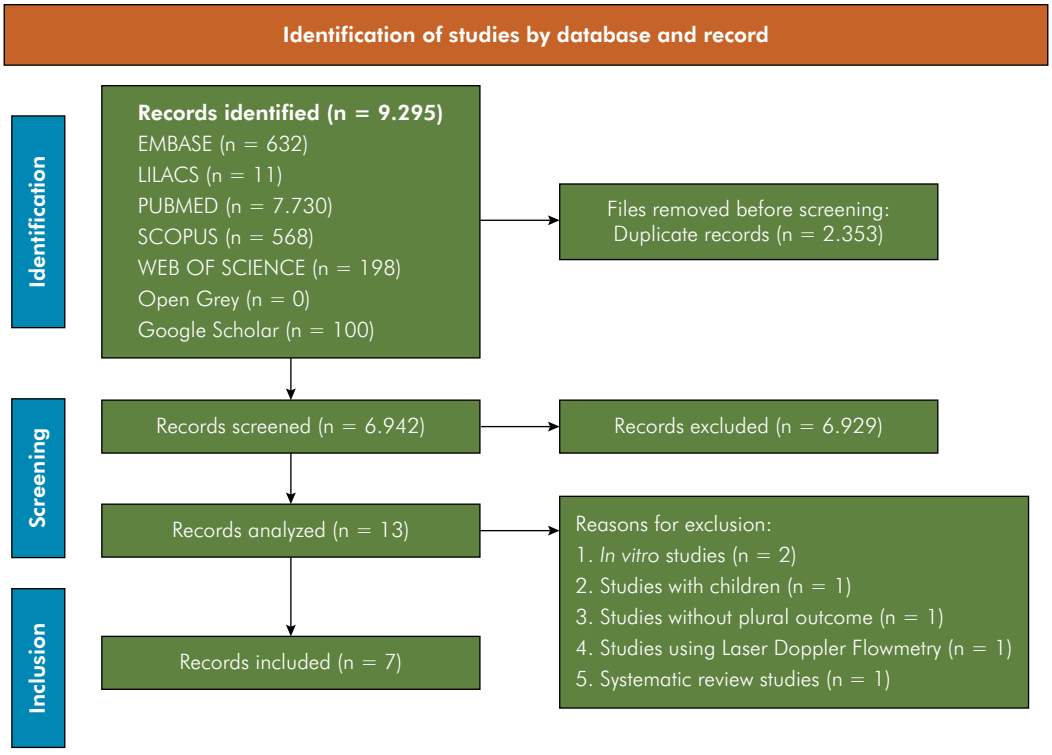

Figure. PRISMA diagram for study selection.

Table 2. Reasons for excluding articles after the full-text reading.

Author	Title	Reason for exclusion
Antic et al.[34]	Assesment of radiotherapy effects on the blood flow in gingiva and dental pulp - a laser Doppler flowmetry study	The study was carried using Laser Doppler Flowmetry study and the patients received varying doses of ionizing radiation
Cooperstein et al.[35]	Vanderbilt head and neck symptom survey version 2.0: Report of the development and initial testing of a subscale for assessment of oral health.	It did not assess pulp outcomes.
Faria et al.[30]	Micromorphology of the dental pulp is highly preserved in cancer patients who underwent head and neck radiotherapy.	The study was *in vitro*, and the analysis was performed in the form of histological slides.
Fônseca et al.[36]	Dentin-pulp complex reactions in conventional and radiation-related caries: A comparative study.	The study was *in vitro* and evaluated the dentinal changes.
Lopes et al.[21]	Evaluation of pulp vitality using a pulse oximeter in patients undergoing radiotherapy for rhabdomyosarcoma or rhinopharynxcarcinoma.	The study was carried out in a pediatric population.
Weissheimer et al.[26]	Head and neck radiotherapy effects on the dental pulp vitality and response to sensitivity tests: A systematic review with meta-analysis.	The study was a systematic review

participants of both genders, a minimum age of 35 and a maximum age of 74 years. A total of 2,148 teeth were evaluated, with a higher prevalence of anterior teeth, such as incisors and canines (1,660; 77.28%). The main types of tumors were those of the oral cavity and the oropharynx (Table 3). The meta-analysis could not be conducted because of the high heterogeneity of the groups evaluated, particularly the different follow-up times and techniques used to determine the pulpal health status. Therefore, the data were grouped and analyzed qualitatively, according to the type of test applied.

Five of the articles included were cohort studies, and two were cross-sectional studies. Four studies used only the cold sensitivity test to measure pulp behavior,[8,20,22,24] including one by Rodrigues et al.[8], who were the only authors to perform a short-term analysis. At 4.3 months after the end of RT, they found a positive response rate of 71.4%. The longitudinal follow-up of the other studies allowed the authors to obtain a 100% variation of positive responses. The pre-RT analyses of all the studies showed a 100% positive response, those made during the RT ranged between 6.7% and 38.1%, and the post-RT analyses revealed that none of the teeth responded positively to the cold stimulus. In the study by Gupta *et al.*[22], the analyses performed up to 1 year after the end of RT showed consistently null response rates. The results of the abovementioned studies[20,22,24] indicated a gradual decrease in pulpal response throughout the treatment, and for up to 1 year after completing the ionizing radiation treatment.

In two studies (28.57%), there was an association between the cold sensitivity and the pulse oximetry tests to determine the patients' pulp condition[11,19]. In the study by Kataoka et al.[11] the SpO_2 rate throughout the treatment ranged from 93% before initiation of RT to 77% at the end, and 85% at 4 to 5 months after treatment. Similar to other studies, 100% of those in the systematic review had positive responses to cold stimuli in the pre-RT period, and no teeth responded positively at the end of treatment. Moreover, Kataoka *et al.*[19] evaluated pulpal behavior 4 to 6 years after the end of RT, and found that the average SpO_2 value for the irradiated patients was 92.7%. Both studies demonstrated partial or complete recovery in SpO_2 levels, and the results were similar to non-irradiated teeth, in more extended periods of evaluation.

Finally, only one study analyzed pulse oximetry individually to determine pulp behavior.[25] The analysis was restricted to SpO_2 evaluation at three periods of time: average of 93.60% at pre-RT assessment, average of 75.12% at post-RT, and average of 81.04% at the six-month follow-up. The results highlight the recovery of SpO_2 levels in the short term after treatment was initiated.

Table 3. Studies included in the review and their main characteristics.

Author	Country	Study	Population	Groups	Rt type	Dose	Tumor	Tooth	Total teeth	Period	Tests	Outcome	
												Primary	Secondary
Rodrigues et al.[8]	Brazil	Cross-sectional Retrospective Observational	HNC patients submitted to RT. The mean age of patients was 54.4 years, ranging 40 to 74 years.	RT Group (n = 12) Control Group (n = 12)	-	Fractional Dose totaling at least 45 Gy and max 71.2 Gy.	Tumors are located in Tonsils, Tongue Edge, Soft Palate, Tongue Base, Tongue Belly, Anterior Pillar, Thyroid, Zygomatic Region, and Neck.	Lower, Superior Incisors and Canines	Control Group: 103 teeth RT Group: 91 teeth	The analysis was performed at the end of the RT, with an average time of 4.3 months.	Cold Sensitivity Test	In the RT Group, 28.6% of the teeth did not respond to the Thermal Test, while 71.4% showed a positive response. In the Control Group, the rate was 11% for negative responses and 89% for positive responses, with a statistically significant difference.	-
Kataoka et al.[11]	Brazil	Cohort Prospective	Patients with cancer in the oronasopharyngeal region. The mean age was 47.2 years, ranging 35 to 55 years.	RT Group (n = 20)	-	Fractional Doses totaling 60 to 70 Gy	Intraoral Malignant Neoplasms in the oronasopharynx	Incisors Lower, Superior	22 upper and 18 lower	Before the beginning of RT (TP1), during RT (between doses of 30 and 35 Gy) (TP2), at the end of RT (total doses between 60 and 70 Gy) (TP3), and 4 to 5 months after completing treatment (TP4).	Pulse Oximetry and Pulpal Cold Sensitivity Test	SpO_2 values in the study were 93% (TP1), 83% (TP2), 77% (TP3) and 85% (TP4). There were responses from TP1 to the Thermal Test (100%); however, only 9 continued to respond positively in TP2 (23%). No response was recorded in TP3 (0%) and TP4 (0%).	There was a recovery of SpO2 from oxygen in TP4, 4 to 5 months after the end of RT.

Continue

Continuation

Kataoka et al.[24]	Brazil	Cohort Prospective	Patients with oral and oropharynx cancer. The average age was 47.2 years, ranging 35 to 55 years.	IMRT Group (n = 12) 3D RT Group (n = 8)	IMRT 3D RT	Fractionated doses totaling 60 to 70 Gy	Oropharyngeal Cancer, Mouth Cancer.	Incisors Lower, Superior	22 upper and 18 lower	Before the beginning of RT (TP1), during RT (between doses of 30 and 35 Gy) (TP2), at the end of RT (total doses between 60 and 70 Gy) (TP3), and after 4 to 5 months of completion of treatment (TP4).	Cold Sensitivity Test	All 40 teeth showed positive responses to the TP1 Sensitivity Test (40/40, 100%). Nine teeth continued to respond positively in TP2 (9/40, 22.5%): 3 of 16 (18.8%) in the 3D-RT and 6 of 24 (25.0%) in the IMRT group.	During the RT, there was a decrease in the number of teeth that responded to the Sensitivity Test after doses greater than 30 to 35 Gy of radiation. There was no difference among the RT techniques
Garg et al.[20]	India	Cohort Prospective	Patients with HNC treated with chemoradiotherapy. The mean age was 52.5.	Group Chemotherapy (n = 20).	IMRT	Fractionated doses totaling 60 to 70 Gy	Oral or Oropharyngeal Cancer	Posterior	42 upper and 42 lower	Before the beginning of RT (TP1), during RT (between doses of 30 and 35 Gy) (TP2), at the end of RT (total doses between 60 and 70 Gy) (TP3), and after 4 to 5 months of completion of treatment (TP4).	Cold Sensitivity Test	All teeth showed positive responses to the thermal sensitivity test in PT1 (100%) and 25 (29%) in PT2. No teeth responded to the PT3 and PT4 sensitivity test (0%).	During the RT, there was a decrease in the number of teeth that responded to the sensitivity test after doses greater than 30 to 35 Gy of radiation. There was no difference among the RT techniques.

Continue

Continuation

Kataoka et al.[19]	Brazil	Cross-sectional Retrospective Observational	Patients with HNC submitted to RT. The average age of the patients was in 49.4 years for the RT Group, and 49.6 years for the control group was	RT Group (n = 90) Control Group (n = 90)	IMRT	Fractional doses of 2 Gy daily, totaling 66 to 70 Gy	Cancer in Oropharynx, Oral Cavity, Nasopharynx, and Hypopharynx.	Upper Incisors, Upper Canines, Lower Incisors, Lower Canines.	Total of 1386 teeth, being 693 teeth in the RT Group (240 maxillary incisors, 104 maxillary canines, 240 mandibular incisors, and 109 mandibular canines), and there were 693 (235 maxillary incisors in the control group, 115 maxillary canines, 225 mandibular incisors, and 118 lower canines).	The patients were rated from 4 to 6 years after the end of RT.	Pulse Oximetry and Cold Sensitivity Test	The mean SpO2% recorded in the RT group was 92.7%, and 92.6% in the Control Group. All the teeth showed positive responses to the Sensitivity Test.	There was a recovery of SpO2 levels 4 to 6 years after radiotherapy treatment.
Gupta et al.[22]	India	Cohort Prospective	Patients with oral or oropharyngeal cancer. The mean age was 58.5 years.	RT Group (n = 79).	IMRT	Fractionated doses totaling 60 to 70 Gy.	Oral or pharyngeal cancer	Posterior	288	Patients were evaluated before RT (TP1), at the end of radiotherapy treatment (TP2), 4 months after the end of RT (TP3), 6 months after RT (TP4), and finally 1 year after the end of RT (TP5).	Cold Sensitivity Test	All teeth (100%) responded to cold tests at TP1. In TP2 and TP3, only 23 (7.98%) and 6 (2.08%) teeth gave a positive response to the cold test. In TP4 and TP5, none of the teeth responded to the cold test.	There was no recovery of response levels, as sensitivity progressively decreased.
Daveshwar et al.[25]	India	Cohort Prospective	Patients with oropharyngeal cancer. The mean age was 46.04.	RT Group (n = 25)	-	Fractionated doses totaling 60 to 70 Gy	Oropharyngeal Cancer	1st Lower Premolar	25 tooth	Before initiation of RT (TP 1), immediately after RT (TP 2), and six months after RT (TP 3)	Pulse Oximetry	The mean SpO2 before RT (TP1) was 93.60, 75.12 after RT (TP2), and 81.04 six months later (TP3).	There was partial recovery at the end of the 6 months after completing RT (TP3); however, the values are still lower than those in TP1.

Table 4. Methodological quality assessment of the studies using the Checklist for Quasi-Experimental Studies tool developed by JBI.

Variable	Rodrigues et al.[8]	Kataoka et al.[11]	Kataoka et al.[24]	Garg et al.[20]	Kataoka et al.[19]	Gupta et al.[22]	Daveshwar et al.25
Does the study leave clear what the cause and what the effect are (i.e., no confusion about which variable comes first)?	1	1	1	1	1	1	1
Were the participants included in any similar comparisons?	0	1	1	1	1	1	1
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	0	1	1	1	1	1	0
Was there a control group?	1	1	1	1	1	1	1
Were there multiple measurements of the outcome, both pre and post intervention/exposure?	0	1	1	1	0	1	1
Was follow-up complete; if not, were differences among the groups in terms of follow-up adequately described and analyzed?	N/A	1	1	1	N/A	1	1
Were the outcomes of participants included in any comparisons measured in the same way?	1	1	1	1	1	1	1
Were outcomes measured in a reliable way?	1	1	1	1	1	1	1
Was appropriate statistical analysis used?	1	1	1	1	1	1	1
Methodological quality	Moderate	High	High	High	High	High	High

Only one study compared the different RT techniques, by analyzing Intensity Modulated Radiotherapy (IMRT) and Three-Dimensional Conformal Radiotherapy (3D RT) to determine the results of the pulp sensitivity test.[24] No significant differences were detected in the pulpal response alteration in patients irradiated with the different techniques. Radiation doses ranged from 60 to 71.2 Gy, with fractioned doses of 1.4 to 2 Gy daily until reaching the total radiation doses determined for the specific tumor types. Regarding the other studies, only four detailed the type of radiation used.[19,20,22,24] The lack of information about the irradiation technique can compromise the reproducibility of the studies.

Methodological quality assessment

The methodological quality assessment is described in Table 4.

Discussion

This systematic review aimed to clarify pulp tissue behavior in HNC patients submitted to RT. The results indicate that the pulp tissue undergoes short-term changes in SpO_2 levels, and responds to the cold sensitivity test. However, this response is similar to that of non-irradiated patients at more extended follow-up periods (greater than 12 months). No recovery of pulp sensitivity to the cold thermal test has been observed in evaluation periods between 6 months and 1 year after the end of numerous RT sessions.[8,11,20,22,24] Nevertheless, in regard to SpO^2 levels, studies reporting similar periods showed a partial return between 6 months and one year post-RT, compared to pre-RT levels, and right after conclusion of the RT sessions.[11,25] Concurrently, long-term pulse oximetry assessment up to 6 years after ionizing radiation

therapy has shown recovery of SpO_2 rates to normal levels.[19]

This study aimed to conduct qualitative and quantitative analyses to compare the results of several studies, and extract the utmost amount of information on the subject at issue, from these studies. It should be mentioned that no study included herein presented low methodological quality, according to the Checklist for Quasi-Experimental Studies tool developed by the JBI. However, the small number of studies included represents a limitation of this systematic review, even though a search was carried out in several electronic databases, a manual search was made by analyzing the references of the selected studies, and the gray literature was also researched.

The present systematic review should be compared with a recently published one on the same topic.[26] Several differences in the methodology and their application led to the inclusion of a further study in Portuguese in our review.[8] The inclusion of a non-English language strengthens our findings, which conclude that the effects of radiotherapy in the pulp tissues, based on responses to sensibility testing, should be considered reversible and not require endodontic intervention. Finally, quantitative synthesis was not carried out due to the methodological heterogeneity of the component studies and, in our opinion, the limited clinical translation of numeric scores obtained from electric pulp testing.

The criteria for normality of pulp tissue SpO_2 levels have already been the subject of previous studies, which include clinical studies of different dental groups researched to address the subjectivity and limitations of an endodontic diagnosis of sensory tests, such as the cold sensitivity test. Thus, parameters from these studies can be established for normal and healthy blood flow and physiology of the pulp tissue, in the different dental groups (such as incisors, canines, premolars, and molars). In different studies, the authors identified values between 85% and 87% as normal levels, compatible with the status of fully healthy pulp.[16,17,27] In the present systematic review, and in studies conducting a longitudinal follow-up with cancer patients, the analyses performed before RT initiation found SpO_2 levels of 93% and 93.6%. After completing RT, within a maximum period of 6 months after RT discharge, the same studies found values of 85% and 81.04%.[11,25] Although the initial values are not similar to those found by Estrela *et al*.[16] and Bruno *et al*.[27], a decrease can be observed in the SpO_2 rate after ionizing radiation for HNC treatment.

The cold sensitivity test is the most commonly used parameter for endodontic diagnosis in clinical routine, because it is convenient and easy to perform, despite its limited objectivity. It should also be borne in mind that, when this test is executed correctly, the patient's response to the application of a cold stimulus could imply either the relief or the worsening of painful conditions, hence indicating different stages of pulp injury. In the case of inflammation, there is a component change in the extracellular matrix of the dental pulp, leading to the formation of inflammatory exudates, which play an essential role in the healing process.[28] Current evidence shows that an inflammatory state makes the body tend to have an exacerbate response to stimuli, as a way of protecting the pulp-dentin complex. When in contact with the cold, A-delta and C nerve fibers detect low temperatures as harmful excitation.[29] Another important factor to be evaluated, in addition to the positive or negative response to sensitivity tests, is the time it takes for patients to report discomfort to the thermal stimulus, and the time required for any painful sensation to cease.[16,17] No study included in the present review addressed the patient's response time or delay, but only whether or not there was a stimulus.

The particularities of the pulp behavior response toward the different tests can be explained by the nature of the two tools recommended to determine pulp health status. Pulp sensitivity tests assess the response capability of the nerve endings in the dental pulp. Conversely, pulse oximetry determines the arrival of oxygen by the red blood cells carried to the pulp chamber. Regardless of which tool is used to assess the outcome, a change can be observed in the expected patterns of sound teeth in the irradiated field. A study carried out by Madani *et al*.[12] evaluated the changes in the pulp tissue of rats submitted to different doses of ionizing radiation after 60 days of irradiation. Results based on histological slides

showed areas with a hyaline substance, tissue inflammation, and congestion of blood vessels, especially in the group with the highest radiation dose. These findings may explain the decrease in the SpO_2 saturation levels of the RT patients in the present systematic review, attributed to vascular congestion that prevents blood flow and arrival of oxygen to the tissues.[11,25]

Another interesting factor to be borne in mind is the recovery of oxygenation levels and the response to the sensitivity tests after more extended evaluation periods. The assessment made by Faria *et al*.[30] of human teeth extracted months after completion of RT found patterns of normality in dental tissues under optical microscopy for nerve structures, blood vessels, and dental pulp cells. These findings corroborate the data from the studies included in this systematic review, especially from those with an assessment of 5 to 6 years after the RT sessions.[19] This restructuring of the dental pulp vascular tissues can be explained by the presence of stem cells in the dental pulp cellular matrix, and the differentiation of these cells into vascular tissue, to maintain the blood supply after the injury caused by ionizing radiation.[31] The current literature reports that dental pulp stem cells have high proliferative power, angiogenesis, and vasculogenesis properties, especially in younger teeth.[32] Overall, no study has been able to explain the changes in sensitivity to thermal stimuli in RT patients; however, it can be posited that ionizing radiation is not capable of modifying the microstructure of nerve fibers, hence allowing sensory recovery, especially after more extended periods of follow-up.[30]

It should be pointed out that the search for studies with standardized methodologies was not an easy task, mainly regarding the thermal sensitivity test. No detailed information was found in the articles as to the length of the cold stimulus application time, patient guidance for cold stimulus management during the test, and the beginning and end of the sensitivity reaction time. Therefore, it is recommended that greater care should be taken to report such important information more explicitly in future pulp behavior analysis studies, including the step-by-step instructions to carry out the tests, the thermal test performance timing, and the preparation of the area for stimulus application. In addition, it is essential to provide a reference to establish the operator calibration and performance specifications. Another critical factor observed about these studies was that the type of RT technique used on the patients was not described, or what apparatus was used. It is strongly recommended that these factors be detailed and explained in order to enhance the clinical description of the findings, to contribute toward study reproducibility, and to allow the performance of a quantitative synthesis of comparable data of similar studies.

Prospective studies with longer follow-up periods are needed, considering that only one study in the present systematic review used a six-month recall, and the outcome measured was solely SpO_2 values.[25] Furthermore, studies with longer evaluation periods should consider using cold sensitivity testing and pulse oximetry in association. Patient survival should also be considered, since it may affect the recall rates in studies with excessive follow-up expectations. Although root canal treatment was not the outcome of the study, it is often the only option to manage pulp and periapical diseases in patients at risk of osteoradionecrosis when a less conservative option is opted for. This should be looked into in future studies. Crucially, it should be reiterated that an altered response to pulp sensitivity testing does not mean that treatment is needed when there are no clinical findings to suggest the presence of an endodontic infection. Similarly, the role of non-odontogenic pain in assessing the pulpal status of HNC patients receiving RT must be better understood.

Conclusion

The synthesis of the results of the articles included in this systematic review leads us to conclude that there is a decrease in the pulp response to sensitivity and vitality tests during the RT treatment period in HNC patients, and that this response decreases further after successive sessions, and soon after all the sessions end. In addition, the SpO_2 levels of patients discharged from radiotherapy treatment after 4 to 6 years are similar to those of non-irradiated patients.

Acknowledgment

This study followed the standards recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA),[33] and the Cochrane Handbook guidelines for Systematic Reviews. The study protocol was duly registered at the International Prospective Register of Systematic Reviews (PROSPERO) platform, under number CRD42021276338.

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