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EVALUATION OF DAMAGE IN SALIVARY GLANDS OF PATIENTS WITH HEAD AND NECK CANCER BY IMRT: A LITERATURE REVIEW

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Abstract: Intensity Modulated Radiotherapy (IMRT) has been the radiotherapy modality of choice for the treatment of cancer patients with head and neck cancer (HNC). Significant side effects for head and neck treatment are still unavoidable due to the proximity of risk organs to the target volume. This study aims to evaluate the damage caused by irradiation to the salivary glands in patients with HNC undergoing IMRT. The methodology applied for the development consisted of an electronic search performed in the MEDLINE database to identify relevant studies published in the last five years (2017-2022). The search strategy resulted in 17 scientific documents related to the following MeSH terms: head and neck neoplasms, salivary gland and intensity-modulated radiotherapy. Based on this sample, after predetermined selection criteria, five studies were selected and reviewed, evaluating a total of 513 patients. Two selected studies reported that comprehensive protection of the salivary glands reduced xerostomia without compromising locoregional control. In another study, it was evaluated that the volumetric shrinkage of the submandibular gland persisted after radiotherapy. It was concluded that reduced salivary gland function is still a common side effect, even in times of IMRT, however restricting the average doses to be as low as possible significantly improves xerostomia.

Keywords: Head and neck cancer. Salivary gland. Intensity modulated radiotherapy.

INTRODUCTION

The salivary glands belong to the group of tissues that maintain an acute response to radiation, in contrast to the fact that the excretory cells in the salivary glands have a slow turnover. Although the cellular composition of the submandibular gland and the parotid gland are different, the radiosensitivity of both is comparable. Findings indicate that two separate mechanisms cause salivary gland dysfunction after irradiation: i) first, defects in cell functioning due to selective membrane damage; ii) later, due to the reduction of the population of acinar cells with adequate ability, due to cell death of progenitor cells and damage to the cell environment (KONINGS et al., 2005).

Salivary gland dysfunction is an "umbrella" term for the presence of xerostomia (subjective feeling of dryness) or salivary gland hypofunction (reduction in saliva production), considered a predictable side effect of radiotherapy in the head and neck region. neck, and is associated with a significant impairment of the patient's quality of life (RILEY et al., 2017). Assessment of salivary dysfunction is relatively subjective unless an individual baseline record of salivary flow has been established. About 30% of the population reports some degree of dry mouth, which indicates that it is not an infrequent patient complaint. Salivary gland dysfunction causes two effects related to the oral cavity: it reduces food preparation for digestion and taste and it increases the susceptibility of oral structures to disease (HUMPHREY; WILLIAMSON, 2001).

Radiotherapy is the treatment of cancer, which uses different equipment and techniques to irradiate areas of the human body, the total duration and the interval between fractions may vary according to the technique used, the purpose of the treatment and the radiotherapy regimen. The daily dose can vary from 1.8 to 2.0 Gy/day for conventional fractionation and from 2.0 to 4.0 Gy/day in a hypofractionation regime. The average treatment time is 4 to 5 weeks, and it is possible to use other fractionation regimens (INCA, 2021). Intensity Modulated Radiation Techniques (IMRT) refers to a technique of conforming the dose to the target volume that aims to maximize the radioprotection of the surrounding tissues. For this, a set of multidirectional fields is used, or even in a continuous arc, whose intensities and dimensions are planned to minimize the dose in healthy tissues, without compromising the delivery of the prescribed dose in the target volume (LEÃO, 2018). Currently, IMRT is mainly indicated for the treatment of prostate, head, neck, gynecological, gastrointestinal and central nervous system tumors.

This article is based on a literature review to answer the following clinical question: "Is IMRT effective in reducing salivary gland dysfunction in patients with head and neck cancer?" Despite technological advances, xerostomia is still a serious complication and has a great impact on the patient's quality of life. Salivary gland changes in irradiated patients were evaluated in three main aspects: i) salivary flow rate, ii) glandular volume, and iii) patient-reported outcome measures (PROMs).

METHODOLOGY

For the preparation of this review article, the PICO strategy (STONE, 2002) was used, which allows structuring a specific question with the appropriate focus of inclusion. P - Population: patients undergoing head and neck RT; I – Intervention: IMRT; C – Comparator: not applied; O – Outcome: salivary gland dysfunction.

An electronic search was performed (until April 13, 2022) in the MEDLINE database (http://www.ncbi.nlm.nig.gov/pubmed), with no language restriction, to retrieve relevant studies published in the last five years.

SEARCH STRATEGY

The MeSH terms used in the Pubmed advanced search engine were: head and neck neoplasms, salivary glands and intensity-modulated radiotherapy, whose strategy details are shown in Table 1.

SELECTION AND INCLUSION OF STUDIES

Observational studies were included in human beings with head and neck cancer undergoing treatment with IMRT alone or associated with chemotherapy, and which evaluated the salivary glands. Review studies, case study, clinical trial, study that it was not possible to access the full text, study in animals, studies that did not evaluate the salivary glands and study that did not focus only on IMRT were excluded. The study selection process was carried out by a reviewer and included, at first, the analysis of the titles and abstracts of the 17 studies retrieved by the search strategy; then, the complete reading of the 10 studies selected in the first analysis was performed. After evaluating the full text, according to the eligibility criteria, a final sample of five studies was obtained.

The most common reason for exclusion was the one that analyzed more than one type of radiotherapy (n = 5). Followed by a review study (n = 2), a study that analyzed a radiotherapy plan (n = 2), it was not possible to obtain the complete article (n = 1), a clinical trial (n = 1), a study that evaluated the treatment for clinical complications (n = 1).

RESULTS AND DISCUSSION

A total of five studies were included in this review. According to the established inclusion and exclusion criteria, all selected studies are prospective. The enrollment period of the participants occurred between September 2011 and November 2018, however, two studies, Hawkins et al., 2018 and Sim et al., 2018, did not report the enrollment period. The total number of participants analyzed was 513 patients, ranging in age from 11 to 91 years. Participants were predominantly male (n=407), corresponding to 79.34% of the sample. In each of the included studies, the following data were extracted and

	MeSH term	Query	Result
#1	Head and neck neoplasms	"head and neck neoplasms"[All Fields]	61.406
#2	Salivary glands	"salivary glands"[All Fields]	31.729
#3	Intensity-modulated radiotherapy	"intensity-modulated radiotherapy"[All Fields]	12.307
#4	#1 and #2	"head and neck neoplasms"[All Fields] AND "salivary glands"[All Fields]	926
#5	#4 and #3	"head and neck neoplasms"[All Fields] AND "salivary glands"[All Fields] AND "intensity-modulated radiotherapy"[All Fields]	61
#6	#5 and filter in the last 5 years	"head and neck neoplasms"[All Fields] AND "salivary glands"[All Fields] AND "intensity-modulated radiotherapy"[All Fields] AND (y-5[Filter])	17

Table 1 - Search details

Author / year of publication	Number of Patients	Objectives	Evaluation method	Radiation dose (Gy)
Hawkins et al., 2018	252	Investigate how preservation of all salivary glands affects PROMs	XQ HNQOL	50-80
Sim et al., 2018	24	Assess changes in xerostomia status, salivary characteristics, and salivary gland volume	XQ RTOG/EORTC salivary flow rate saliva pH buffer capacity CT	70
Teng et al., 2019	175	To analyze the protective effect of salivary glands by helical tomotherapy	XQ Salivary flow rate	70
Shi et al., 2019	30	Evaluate the function of the salivary glands using DW-MRI with gustatory stimulation	DW-MRI salivary flow rate XQ	-
Oba et al., 2021	32	To evaluate the correlation between acute side effects in the oral mucosa, salivary glands and general health status with QoL during IMRT	UW-QOL salivary flow rate KPS Weight	60-70

Table 1 - Characteristics of the included studies

CT: computed tomography; DW-MRI: diffusion-weighted magnetic resonance imaging; HNQOL: head and neck quality of life questionnaire; IMRT: intensity-modulated radiotherapy; KPS: Karnofsky performance scale; PROMs: patient-reported outcome measures; QL: quality of life; RTOG/EORTC: Cancer Therapy Group / European Organization for Cancer Research and Treatment; UW-QOL: standardized protocol and quality of life questionnaire; XQ: questionnaire related to xerostomia.

arranged in a comparative way: (1) author / year of publication; (2) number of patients; (3) objectives; (4) evaluation method; (5) radiation dose, as provided in table 1.

In Hawkins et al., 2018, the relationship between the scores reported in the questionnaire and the average doses in the bilateral parotid gland (GPb), in the contralateral submandibular gland (GSMc) and in the oral cavity (OC) glands were evaluated. The study included the largest number of participants, 252 patients with head and neck cancer, bilaterally irradiated in the neck. This study did not report where the research was carried out, although the origin of the institutions involved is American and Chinese. Of the five studies included, there was a predominance of institutions of Asian origin, of which three studies are of exclusively Asian origin, one study of North American and Asian origin, and one study of South American origin.

Teng et al., 2019, analyzed the effects of comprehensive protection of bilateral parotid glands (GPb), contralateral submandibular gland (GSMc) and accessory salivary glands in the oral cavity (OC) by IMRT with helical tomotherapy technique. A total of 175 patients with head and neck squamous cell carcinoma recruited from the Department of Radiotherapy of the General Hospital of the Chinese People's Liberation Army were included. Salivary glands (GPb, cGSM and CO) were analyzed by Teng et al., 2019, and by Hawkins et al., 2018.

In Sim et al., 2018, the changes that occurred in the status of xerostomia, in the salivary characteristic and in the volume of the parotid and submandibular glands were evaluated. We included 24 patients with nasopharyngeal carcinoma, referred from the National Cancer Center Singapore to the National Dental Center Singapore. Among the included studies, this one had the lowest number of participants. The study by Shi et al. 2019, used dynamic diffusion-weighted imaging (DW-MRI) to assess parotid, submandibular, and sublingual salivary gland function after IMRT. Thirty patients with nasopharyngeal carcinoma diagnosed and treated at the Department Radiotherapy of the Second Affiliated Hospital of Soochow University, China were included. Sim et al., 2018, used CT imaging to assess salivary gland volume, while Shi et al. 2019, used DW-MRI to assess salivary gland function.

In Oba et al., 2021, acute side effects (mucositis and xerostomia) involving the oral cavity, general health conditions and the patient's quality of life were evaluated. Thirty-two patients with head and neck cancer at the Hospital das Clínicas da Faculdade de Ribeirão Preto – USP, Brazil were included. Comparing with the included studies, Oba et al., 2021, was the only study that did not analyze patients in the post-treatment period, while Hawkins et al., 2018, was the only study that did not provide data prior to radiotherapy.

The duration of surveys and the interval of assessments in patients varied greatly between studies. In Hawkins et al., 2018, patients completed a questionnaire on xerostomia at follow-up appointments at 01, 03, 06, 12, 18, 24, 48 and 60 months. In Sim et al., 2018, all participants underwent diagnostic CT to assess response, performed at 3 months and two years after radiotherapy. In addition, clinician-reported and participant-reported assessments were determined before treatment, mid-treatment, 2 weeks after treatment, 3 months after treatment, and 24 months after treatment. In the study by Teng et al., 2019, through the xerostomia questionnaire, xerostomia was assessed before the beginning and at 01, 03, 06, 12 and 18 months after the end of treatment. In Shi et al. 2019, the three pairs of salivary glands underwent DWI, before and late after radiotherapy, at rest and after stimulation with lemon juice. In Oba et al., 2021, measurements were collected weekly using protocols and standardized questionnaires, immediately before the start of radiotherapy until the last week.

EVALUATION OF SALIVARY FLOW RATE

The salivary flow rate is considered an indicator of xerostomia for patients undergoing radiotherapy for head and neck cancer. According to Humphrey & Williamson, 2001, the acceptable range of normal flow for unstimulated saliva is above 0.1 mL/min, whereas for stimulated saliva, the minimum acceptable volume increases to 0.2 mL/min. On average, the unstimulated flow rate is 0.3 mL/min, while the maximum stimulated flow rate is 7 mL/min (EDGAR, 1990).

All participants were instructed not to eat or drink for one hour before saliva collection. For the collection of stimulated saliva, stimulation with acid or chewing gum is necessary. Of the three studies that evaluated stimulated saliva, each study used a different way. In Sim et al., 2018, patients chewed wax, in the study by Teng et al., 2019, patients used 2% citric acid solution, and in the study by Shi et al., 2019, participants used apple juice. lemon. The time at which saliva collection was performed was not mentioned in any of the studies. The collection time varied between 05 and 15 minutes.

ASSESSMENT OF SALIVARY GLAND VOLUME

The total volumes of the glands were calculated as the sum of the respective volumes of the right and left glands, in the study by Sim et al., 2018, therefore, all participants underwent diagnostic computed tomography, the resulting digital images were imported into the same treatment planning system, and the salivary glands were re-contoured and the volume measured. Mean doses of bypassed volumes were recorded from the dose volume histograms in the approved treatment plan. The mean GP and GSM radiation dose was derived from the mean of the respective mean doses of the right and left glands. The apparent diffusion coefficients of the parotid, submandibular and sublingual glands were calculated in the study by Shi et al. 2019, using diffusion-weighted magnetic resonance imaging, which allows the representation of molecular diffusion caused by Brownian motion in biological tissues, since the diffusion of the water molecule leads to signal attenuation and can be quantified as an apparent diffusion coefficient.

PATIENT REPORTED OUTCOME MEASURES (PROMS)

As xerostomia is primarily a symptom, patient self-report can be significant in assessing its severity, Meirovitz et al., 2006, concluded that self-reported measures by the patient must be used whenever the assessment of xerostomia is an important study objective. The use of a self-reported questionnaire, either to assess the severity of xerostomia and/or to assess the patients' quality of life, was used in all studies.

In Hawkins et al., 2018 and Sim et al., 2018, patients answered the xerostomia questionnaire, validated in the study by Eisbruch et al, 2001. In Shi et al. 2019, participants answered the xerostomia questionnaire established by the University of Michigan in the United States, described by Meirovitz et al., 2006. Patients rated each symptom on an ordinal 11-point Likert scale from 0 to 10, in which the highest scores indicate greater dryness or discomfort due to dryness, consisting of eight questions equally divided into: four items asking about dryness when eating or talking, and four items about dryness when not eating or chewing.

In Hawkins et al., 2018, patients also answered a questionnaire on head and neck quality of life (HNQOL) composed of several domains: eating, communication, emotion, pain, satisfaction and general discomfort, which was previously described by Terrell et al. al., 1997. This was the only study that used two different types of self-reported questionnaires, one to assess the degree of xerostomia and the other to assess the quality of life score that reflects the impact of radiation-induced side effects. In Sim et al., 2018, the clinician-rated xerostomia score was determined using the Radiation Therapy Oncology Group/ European Organization for the Research and Treatment of Cancer (RTOG/EORTC) radiation morbidity scoring criteria.

In Teng et al., 2019, xerostomia was investigated based on the self-reported questionnaire, validated by Amosson et al., 2003, consisting of 10 questions, each question divided into four degrees (“no”, “mild”, “moderate” and “severe”) according to the level of oral dryness. In Oba et al., 2021, the quality of life of patients was assessed using the questionnaire proposed by the University of Washington Quality of Life (UW-QOL), version 4, described in Pugh et al, 2017, the domains evaluated are divided into the physical-functional dimensions (appearance, mastication, swallowing, speech, taste and saliva) and socio-emotional (pain, activity, recreation, mood, muster and anxiety).

The proximity of the major salivary glands to the lymph nodes in the neck limits the ability to reduce the average dose in radiotherapy, mainly to the submandibular gland (SCRINGER et al., 2018). The relationship between comprehensive protection of the salivary glands and the risk of locoregional recurrence, when evaluated in the study by Hawkins et al., 2018, concluded that the dose restriction for cGSM of ≤ 39 Gy does not increase the risk of failure in the contralateral neck. A result corroborated in the study by Teng et al., 2019, when assessing the locoregional recurrence rate, found that comprehensive protection of the salivary glands significantly reduced the risk of developing severe xerostomia, without compromising locoregional control.

The evaluation of damage induced by salivary gland radiotherapy mainly consists of measuring salivary flow. Sim et al., 2018, observed that, two years after treatment, both resting and stimulated salivary flow rates and resting saliva pH remained significantly low, and xerostomia scores remained significantly higher compared to pretreatment levels. Considering these results, the authors suggest that study participants were still at risk of oral diseases related to hyposalivation. However, contrary results are reported in the study by Teng et al., 2019, stimulated and unstimulated saliva flow rates were restored to 69.5% to 77.4% of baseline at 12 months and 81.5 % to 91.7% in 18 months, respectively. Based on the results of the study, the authors concluded that patient-reported xerostomia significantly decreased when the mean dose threshold was maintained below 29.12 Gy, 29.29 Gy, 31.4 Gy for GPb, GSMc, CO, respectively.

The evaluation of the salivary glands in the study by Shi et al. 2019, using DW-MRI, showed that the apparent diffusion coefficients of the salivary glands increased after radiotherapy, both at rest and in the stimulated state, and correlated with the salivary flow rate and questionnaire scores for xerostomia. The authors consider the result of the stimulation with lemon juice an important finding, since an initial constant increase to the peak was observed during the first DWI exam (30 seconds) and a subsequent decrease in the apparent diffusion coefficients in all the glands before and after radiotherapy, suggesting a persistent ability of acinar cells to produce saliva after stimulation with lemon juice.

Oba et al., 2021, for the variable unstimulated total salivary flow rate, found a positive correlation with five domains evaluated in the UW_QOL and with general quality of life. The authors considered that glandular or nerve damage due to surgery (67% of patients underwent surgery) may have been responsible for the lower value for salivary flow found in the study. Although it was not the objective of the study, the authors tested the correlation between salivary flow rate and type of treatment and found a significant positive correlation between salivary flow rate and surgery.

Findings from the multivariate analysis, in Teng et al., 2019, showed that the mean dose of OC, mean dose of cGSM, age and tumor stage were important predictors of patient-reported xerostomia. Mouth dryness was restored more slowly with increasing age, while in young patients, xerostomia was restored to almost normal level within 1 year. A significant interaction between dose and time was observed in the study by Hawkins et al., 2018, with the effect of dose on xerostomia increasing over time. The lowest mean dose for each salivary structure was associated with lower (better) xerostomia questionnaire sum scores at each time point at follow-up. The xerostomia questionnaire sum scores in each dose group improved continuously during the initial 18 months after completion of treatment and then stabilized. Furthermore, the results indicate a correlation between GP dose and xerostomia, and show that the lowest rates of patient-reported xerostomia were achieved when the mean dose for GPb was < 26 Gy. The mean dose of CO was moderately correlated with the mean doses of GPb ($p < 0.001$) and GSMc ($p < 0.001$), and the latter two were moderately correlated with each other ($p < 0.001$). Furthermore, mean CO dose correlated moderately with overall tumor stage, as did mean doses of CO, cGSM, and GPb with stage N.

The effects on total WG and GSM volumes, in the study by Sim et al., 2018, were significant and remained so for two years after completion of radiotherapy. At 2 years after radiotherapy treatment, the GP presented partial volumetric recovery, however the GSM continued to present volumetric retraction, in 2 years, and was reduced to half of its original volume. The authors report that this fact can be explained by the high dose of radiation received by the GSM, since the values reported in the literature for the recovery of the GSM function, over time, were much lower than the 65 Gy received.

CONCLUSION

The function of the salivary glands of irradiated patients deteriorated with radiotherapy, but over time, when the radiation dose applied was not high, studies indicate partial recovery of the salivary glands, suggesting that the reduction of average doses for these structures reduces the risk of xerostomia and improves quality of life. IMRT is the recommended treatment for all primary cancers of the nasopharynx, oropharynx, hypopharynx, larynx, and oral cavity. Furthermore, IMRT resulted in excellent locoregional control when mean doses to glandular structures were constrained to be as low as possible in treatment planning. Currently, longitudinal studies and clinical trials in humans on the recovery of radiation-damaged salivary glands at the cellular and molecular level are promising approaches.

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