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3D radiotherapy in the parotid gland and its dosimetric relationship with salivary flow and quality of life in patients with head and neck cancer

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Aim: Hyposalivation and dry mouth affect the quality of life in patients with Head and Neck Cancer, who did the treatment with radiotherapy. Thus this study has the objective to evaluate the dosimetric relationship between 3D radiotherapy and changes in salivary flow, xerostomia and quality of life in patients with head and neck cancer according to the volume of the irradiated parotid gland. **Methods:** 23 patients with cancer in the head and neck area and in need of 3D radiotherapy were followed up during radiotherapy treatment, and the parotid gland (PG) design was also performed in radiotherapy planning. Questionnaires were carried out to determine xerostomia and quality of life, while the salivary flow was determined through calculations regarding the collection and weighing of saliva. Such data were collected in three moments: before the beginning of the radiotherapy treatment (D0), in the middle of the treatment (D1) and at the end of it (D2). The numerical variables are represented by measures of central tendency and measures of dispersion. **Results:** when associating the salivary flow, the xerostomia questionnaire and the OHIP-14, a statistically significant difference was found (p-value <0.001), as well as when comparing some volumes of irradiated PG with the OHIP-14. However, no relationship was found between dosimetric data, xerostomia and hyposalivation. **Conclusion:** patients undergoing 3D radiotherapy for malignant neoplasms in the head and neck region had decreased salivary flow, increased complaints of dry mouth and decreased quality of life. However, it was not possible to establish a statistically significant correlation between these findings and the volumes of irradiated parotids.

Keywords: Parotid gland. Radiotherapy. Xerostomia. Quality of life.

Introduction

Head and Neck Cancer (HNC) is the fifth most common type of cancer in Brazil, representing approximately 5% of all malignant tumors[1]. This group includes tumors that affect the upper aerodigestive tract, representing important anatomical structures, such as the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, nasal cavity, paranasal sinuses, thyroid gland and salivary glands[2]. In the oral cavity alone, it is estimated that about 15,190 new cases arise between the 2020-2022 biennium[3]. According to data from Globocan 2020, all around the world, only in the lip and oral cavity the incidence of new cases in men is 264,211 and in women 113,502 with mortality rates of 125,022 and 52,735 respectively[4].

Surgery, radiotherapy and chemotherapy are alternative therapies commonly used in the treatment of HNC patients. These are recommended according to the stage of the pathology in question[3]. In the three-dimensional radiotherapy treatment, the non-specificity of the radiation beam also affects healthy cells that are closely related to the structures of radiotherapy interest. The control of the disease, as well as the toxicity caused by radiotherapy, can vary according to the type of radiotherapy treatment used, the dose used, the volume, the irradiated area and the intrinsic peculiarities of the patient's response[5].

Thus, the types of radiotherapy consist of: conventional radiotherapy or 2D radiotherapy (2DRT), performed by delimiting the area to be irradiated on simple radiographs, making it impossible to visualize the target volume; Intensity modulated radiotherapy (IMRT), multiple beams of non-uniform intensity are delivered to the patient to create a uniform dose distribution; three-dimensional (3D) radiation, uses three-dimensional anatomical information to create a dose distribution that adapts to the target as closely as possible[6].

Findings frequently found in patients with HNC, who underwent radiotherapy (RT) in PG area, are hyposalivation and dry mouth affecting their quality of life[3,6-7]. Thus, knowing that xerostomia may result from radiation-induced injury to the salivary glands, it is considered an important complication of RT as it has a great impact on patients' quality of life[8,9]. Brouwer et al.[10] 2015 carried out a systematic review through the MEDLINE® database, looking for scientific evidence that related the organs in the head and neck area submitted to radiotherapy as a major risk factor for dosimetric and anatomical changes (n = 80 articles). Most of the studies found included the anatomical and dosimetric study of PG, due to complaints of xerostomia observed in patients who underwent RT. Such studies were able to report significant anatomical changes in PG, up to 20% loss of volume, but did not collect data referring to xerostomia.

Thus, the degree of xerostomia depends on the intensity of exposure of the glandular tissue to radiation. In this way, the partially irradiated glands present a more intense salivary flow than the totally irradiated glands[11]. Such a decrease in salivary flow can lead to impairments in the oral cavity, such as decreased perception of taste and lubrication, changes in the stages of swallowing and digestion[12-13]. The maintenance of an effective barrier against external injuries and integrity of the

teeth, through the process of mineralization and demineralization, can also be compromised[12]. In addition to the quantitative change, there is also a qualitative change in salivary constituents, with a decrease in amylase activity, buffering capacity, pH, and consequent acidification[12].

As a prevention to minimize the effects of xerostomia in patients undergoing radiotherapy treatment in the head and neck region, the use of intensity-modulated radiation - IMRT, which irradiates the glandular zones in a smaller amount[9]. So, in patients with HNC, special attention should be given to the PG during radiotherapy treatment planning, since it is closely related to the structures of radiotherapy interest of these patients and is responsible for about 60% of saliva production , avoiding that unnecessary radiation doses reach it and impair its physiology[6-7]. Therefore, this study aimed to evaluate the dosimetric relationship between 3D radiotherapy and changes in salivary flow, xerostomia and quality of life of patients with head and neck cancer according to the volume of the irradiated PG.

Materials and methods

The study was a prospective cohort study with a quantitative approach. The study population consisted of 23 cancer patients from a Reference Hospital in Oncology in the state of Pernambuco, who underwent 3D conformational radiotherapy in the head and neck region and were followed up at this hospital's Dentistry outpatient clinic. This study included patients older than 18 years of age, diagnosed with Squamous Cell Carcinoma in the head and neck, whose therapeutic indication involved exclusive conformational radiotherapy, concomitant with chemotherapy or as an adjunct to surgery. Those with Performance Status below 70 were excluded according to Karnofsky score, diagnosis of HNC from other locations (skin lesions or metastases), cognitive impairment or refusal of the Informed Consent Form (ICF).

The sample was calculated based on the calculation technique of a simple random sample. The significance level was 95%. The sample calculation took into account the investigated population, margin of error, reliability, sampling error and confidence level according to the following formula:

$n = NZ^2p(1-p)(N-1)e^2+Z^2p(1-p)$

n = the calculated sample size;

N = size of universe;

Z = the deviation from the mean value that is accepted to reach the confidence level;

e = maximum margin of error that is allowed;

p = proportion expected to be found.

After signing the ICF, radiotherapy planning was carried out, the constraints used were those described in QUANTEC (Quantitative Analyzes of Normal Tissue Effects in the Clinic); dosimetric parameters were evaluated using dose-volume histograms. In determining and classifying xerostomia, the Xerostomia Inven-

tory[14] and the table proposed by Eisbruch et al.[13] (2003) that evaluates a subjective factor with grades from 1 to 3 and another objective related to the salivary flow rate (not stimulated) also with a grade that varies from 1 to 3. Then, sialometry was performed.

The main researcher was responsible for performing the sialometry. To determine the Salivary Flow at Rest (SFR), the technique described by Sreebny and Vissink (2010)[15] was used. The technique of collecting the saliva chosen was "Spitting": patients were instructed to remove any type of oral prosthesis, to be seated in a chair with their head slightly lowered, to swallow the first saliva as soon as the researcher instructs to start the collection of saliva, in disposable cups, for 5 minutes. With this technique it was possible to determine the SFR. All containers were weighed before starting and after collecting saliva on a precision electronic scale. To calculate the total SFR, and assuming that 1 g of saliva corresponds to 1 ml, the conversion formula was used[16-18].

$$\text{SFR (ml / min)} = \frac{\text{Weight of the post tube (g)} - \text{Weight of the pre tube (g)}}{\text{Collection period (min)}}$$

SFR was recorded in three moments:

D0 - before starting RT treatment

D1 - in the middle of RT treatment (approximately 17th session)

D2 - At the end of RT treatment

After sialometry was performed, a form with questions addressing sociodemographic aspects was used in order to present a patient profile, and the *Oral Health Impact Profile - OHIP 14* questionnaire was used to assess the impact on oral health. seven dimensions: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and disability[18]. There are five answer options with a code for the 14 questions: Never (0), Rarely (1), Sometimes (2), Repeatedly (3), and Always (4). In OHIP-14, the scale ranges from 0 to 56 points, and the higher the score, the worse the quality of life classification[17-18].

The follow-up and dental treatment that the patients participating in the research received, did not differ, from what is already done in a standard way for all head and neck patients who are submitted to RT. Having the patients been evaluated and adequate pre-radiotherapy, and followed up throughout the treatment period, according to protocols adopted in the Dentistry department.

Data were analyzed through descriptive analysis of patient data, their respective RT dosimetric data, sialometry results, xerostomia questionnaire and OHIP-14. All tests were applied with 95% confidence and the results are presented in a table with their respective absolute and relative frequencies. Numerical variables are represented by measures of central tendency and measures of dispersion. Having used as a method for repeated measures: the mixed linear regression model, which takes into account the possible correlation between the values of the variable response that constitute repeated measures.

Results

Twenty-three patients who underwent RT in the head and neck area participated in the research at the Pernambuco Cancer Hospital. Of these, 73.9% were male and 26.1% female. Minimum age of 35 and maximum of 73 years. Stratified into age groups, 52.2% were less than 60 years old and 47.8% were between 60 and 73 years old. Most of the patients came from the inland of Pernambuco (52.2%), with 17.4% residing in Recife and the other 30.4% in the Metropolitan Region of Recife (MRR). Regarding the tumor area, most tumors were located in the oral cavity (47.8%), followed by 39.1% in the larynx and 13% in the parotid. As for the clinical aspects of the patients, all had histology of Squamous Cell Carcinoma, 34.8% of which had a very different grade. According to the degree of tumor staging, 43.5% of patients were diagnosed with grade IV. 56.7% of the patients had cervical metastasis. Of the 23 investigated patients, 73.9% underwent chemotherapy and 52.2% underwent surgery prior to radiotherapy (Table 1).

Table 1. Sociodemographic data of the patients, the tumor area, histological type, presence or absence of cervical metastasis, tumor staging and type of cancer treatment of the research patients.

Variables	n	%
GENDER		
Male	17	73.9
Female	6	26.1
ORIGIN		
Recife	4	17.4
MRR	7	30.4
Inland	12	52.2
IDADE		
< 60	12	52.2
≥ 60	11	47.8
TUMOR AREA		
Larynx	9	39.1
Oral cavity	11	47.8
Parotid	3	13.0
SQUAMOUS CELL CARCINOMA		
Well	8	34.8
Moderate	7	30.4
Little	8	34.8
PESCOÇO		
Yes	13	56.5
No	10	43.5

Continue

Continuation		
DEGREE STAGING		
Estadium 1	2	8.7
Estadium 2	4	17.4
Estadium 3	7	30.4
Estadium 4	10	43.5
CHEMOTHERAPY		
Yes	17	73.9
No	6	26.1
SURGERY		
Yes	12	52.2
No	11	47.8

The following graphs (1.1 and 1.2) show the quality of life related to oral health through the use of OHIP-14 at times D0 and D2, respectively. In which we can evidence the growing increase in complaints of functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and disability from the beginning to the end of RT.

In table 2, in the analysis of the SFR, we obtained a statistically significant difference (p-value <0.001), such that when comparing D0, D1 and D2 we obtained a decrease in the SFR during the RT: in D0 (0 , 82 ± 0.70 ml/min), in D1 (0.44 ± 0.35 ml/min) and in D2 (0.29 ± 0.24 ml/min). In the data related to the OHIP-14 quality of life questionnaire, we can observe increasing scores according to the progress of radiotherapy treatment: in D0 (27.65 ± 11.83), D1 (37.65 ± 9.51) and D2 (41.48 ± 7.70), thus indicating a decrease in the quality of life of these patients. While, in the data related to the xerostomia inventory, we also found an increasing increase in complaints during RT: in D0 (27.83 ± 9.06), in D1 (35.35 ± 7.85) and in D2 (39 , 04 ± 7.72). And when crossing the data related to SFR, OHIP-14 and xerostomia inventory, it is possible to observe a statistically significant difference (p-value <0.001) in all analyzed variables of SFR (of 0.82 ml/min in D0 at 0.29 ml/min in D2), OHIP-14 (from 27.65 in D0 to 41.48 in D2) and in the xerostomia inventory (27.83 in D0 at 39.04 in D2), in moments (D0, D1 and D2).

Table 2. Average values of salivary flow, OHIP-14 and xerostomia inventory.

VARIABLES	MOMENTS			p-value *
	D0	D1	D2	
	Mean ± DP	Mean ± DP	Mean ± DP	
SFR	0.82 ± 0.70	0.44 ± 0.35 [A]	0.29 ± 0.24 [AB]	< 0.001
OHIP-14	27.65 ± 11.83	37.65 ± 9.51 [A]	41.48 ± 7.70 [AB]	< 0.001
XEROSTOMY INVENTORY	27.83 ± 9.06	35.35 ± 7.85 [A]	39.04 ± 7.72 [AB]	< 0.001

(*) Repeated measures
(A) Statistically significant difference in relation to moment D0
(B) Statistically significant difference in relation to moment D1

In table 3, according to the classification proposed by Eisbruch et al.[13] (2003), it is possible to notice the classification of xerostomia through subjective and objective factors, with Degree ranging from 1 to 3. Thus, we can infer that the degree of xerostomia increased according to the progression of RT: in D0 no patient had grade 3 of xerostomia in an objective way, while at the time D2 26.1% of patients had SFR <0.1 mL / min, configuring grade 3 of xerostomia. In the subjective classification, 39.1% of the patients had complaints that qualified them in grade 3 xerostomia in D0, while in D2 78.3% of the patients in the sample had such complaints.

Table 3. Classification of xerostomia through subjective and objective factors.

VARIABLES (Xerostomy)	n	%
OBJECTIVE D0		
Degree 1	21	91.3
Degree 2	2	8.7
Degree 3	0	0
OBJECTIVE D1		
Degree 1	15	65.3
Degree 2	7	30.4
Degree 3	1	4.3
OBJECTIVE D2		
Degree 1	14	60.9
Degree 2	3	13.0
Degree 3	6	26.1
SUBJECTIVE D0		
Degree 1	1	4.3
Degree 2	13	56.6
Degree 3	9	39.1
SUBJECTIVE D1		
Degree 1	1	4.3
Degree 2	8	34.8
Degree 3	14	60.9
SUBJECTIVE D2		
Degree 1	1	4.3
Degree 2	4	17.4
Degree 3	18	78.3

Table 4 shows that there was a statistically significant correlation between most of the results of the oral health-related quality of life questionnaire "OHIP-14" with the volume of "Parotid D" (In bold). It can also be noted that, although the volumes of irradiated PG did not have a statistically significant correlation with salivary flow or

with the xerostomia inventory, there was a decrease in salivary flow and an increase in xerostomia questionnaires in the three moments of the research (D0, D1 and D2). Thus evidencing that, during RT, complaints of xerostomia and decreased salivary flow significantly increased, thus evidencing that during RT, complaints of xerostomia and decreased salivary flow significantly increased.

Table 4. Association between the volumes of parotids irradiated with SFR, OHIP-14 and xerostomy inventory.

Variables[A]	RT/Gy	SFR D0	SFR D1	SFR D2	OHIP-14 D0	OHIP-14 D1	OHIP-14 D2	Xerostomy inventory D0	Xerostomy inventory D1	Xerostomy inventory D2
Vol total Parotid R	-0.170	-0.138	-0.299	-0.095	-0.004	0.068	0.157	-0.045	0.061	0.085
Parotid R V10	30.2	0.100	-0.126	-0.161	**0.476 ***	**0.663 ***	**0.723 ***	0.121	0.151	0.212
Parotid R V20	27.1	0.114	-0.115	-0.144	**0.449 ***	**0.636 ***	**0.716 ***	0.150	0.194	0.255
Parotid R V30	25.7	0.103	-0.113	-0.149	**0.437 ***	**0.624 ***	**0.703 ***	0.121	0.175	0.239
Parotid R V40	24.7	0.140	-0.080	-0.126	0.395	**0.578 ***	**0.658 ***	0.104	0.158	0.228
Parotid R V50	19.6	0.139	-0.081	-0.129	**0.441 ***	**0.616 ***	**0.686 ***	0.141	0.180	0.235
Parotid R V60	18.8	0.122	-0.100	-0.145	**0.436 ***	**0.607 ***	**0.680 ***	0.132	0.174	0.227
Parotid R V70	14.0	0.123	-0.098	-0.151	0.382	**0.577 ***	**0.645 ***	0.137	0.177	0.225
Parotid R V80	14.8	0.169	-0.076	-0.142	0.335	**0.579 ***	**0.652 ***	0.185	0.260	0.314
Vol total Parotid L	-0.047	-0.076	-0.187	-0.013	-0.061	0.116	0.179	-0.070	0.073	0.163
Parotid L V10	26.9	0.074	0.176	0.299	0.141	0.208	0.352	-0.230	0.278	0.187
Parotid L V20	23.6	0.070	0.187	0.309	0.118	0.179	0.314	-0.223	0.278	0.189
Parotid L V30	24.7	0.038	0.123	0.213	0.101	0.175	0.308	-0.264	0.215	0.140
Parotid L V40	24.9	0.040	0.144	0.225	0.103	0.164	0.306	-0.253	0.215	0.149
Parotid L V50	21.7	0.033	0.144	0.226	0.061	0.094	0.240	-0.258	0.216	0.157
Parotid L V60	20.6	-0.033	0.055	0.140	-0.054	-0.009	0.149	-0.313	0.181	0.148
Parotid L V70	21.7	-0.038	0.076	0.158	-0.154	-0.093	0.079	-0.338	0.196	0.191
Parotid L V80	16.5	-0.089	0.022	0.108	-0.212	-0.127	0.033	-0.320	0.200	0.196

Discussion

As a result of the projection of the aging of the world population, it is estimated that in 2040 there will be more than 28.4 million new cases of cancer. Such incidences

are highlighted in countries with low human development index (HDI) in 95% and in 65% in those with medium HDI[4]. Only in the head and neck area, according to GLOBOCAN estimates, the incidence of cases for 2020 has an average of 699.84 new cases are expected. A commonly used treatment for HNC is radiotherapy[4]. However, due to the proximity to noble structures, the complaints that arise during this treatment are intense and may remain throughout the individual's life. Among these, xerostomia and hyposalivation stand out because they are associated with a decrease in the quality of life of these individuals.

Messmer et al.[19] (2011) through a prospective study with 121 patients undergoing RT found no significant decrease in the complaint of xerostomia in these patients over a period of five years after RT. In the current study, patients were followed from the beginning to the end of RT, and it was possible to notice a significant difference in salivary flow, which was an average of 0.82 ml/min at the first moment of collection at 0.29 ml/min. min at the end of the RT. As well as, the increase in xerostomia questionnaire values from 27.83 in the first collection to 39.04 in the last collection. Such data were useful to classify xerostomia subjectively and objectively[13]. Thus, it is possible to infer that the number of patients with a more severe xerogenic degree increased, as well as, consequently, there was a statistically significant decrease in quality of life during RT (p-value <0.001).

According to INCA data, oral cavity cancers represent the fifth most common type of cancer in Brazilian men[1], but they are not included in the list of the ten most common types of cancer in women, either in the INCA or the *American Cancer Society*[1,20-21]. Corroborating the findings of the current study, where the number of male patients represents 73.9% of the sample. And due to the higher incidence of squamous cell carcinoma in the head and neck area[21], the present study had the other tumor histological classifications as exclusion criteria. It showed that: most of the research subjects (47.8%) had tumors in the oral cavity area; that 43.5% of the tumors were in advanced stages (stage IV); of the 23 patients, 56.7% had cervical metastasis at the beginning of cancer treatment; 52.2% of the individuals underwent surgery for tumor excision and 73.9% were treated with chemotherapy. Corroborating with epidemiological surveys that show that more than half of these tumors, in patients with the same profile, are diagnosed in advanced tumor stages and require aggressive surgery and /or the association with chemotherapy[22,23]. Thus, these data point to a gap, whether in the time expected to seek specialized care and / or the absence of effective health promotion and prevention measures.

As an objective criterion, no patient had grade 3 xerostomia before the start of radiotherapy, while 26.1% had grade 3 xerostomy at the end of RT. In the subjective classification, the percentage varied in Grade 3 from 39.1% in D0 to 78.3% at the end of RT. Making it possible to show in a statistically significant way (p-value <0.001), that when D0 was compared to D1 and D2, there was a gradual decrease in SFR and an increase in xerostomia complaints. As well, the increase in OHIP-14 values, from 27.65 in D0 to 41.48 in D2, showing an increase in the number of patients with more severe xerogenic degree and a decrease in quality of life during RT statistically significant (p-value <0.001).

In a study by Sanguinete et al.[24] (2015), it was noted that patients submitted to an average dose above 35.7Gy reported greater physical complaints and related to xerostomia, as well as an average reduction of 19.6% in the total volume of PG. In the current study, we could see that a statistically significant association (p-value <0.001) between physical complaints and patients' oral health, through OHIP-14, has already occurred when patients were submitted to an average dosage of 14Gy in the V70 of irradiated right PG. And that, comparing the three moments of collection, all patients had an impact on the seven dimensions of the questionnaire. Such findings demonstrated that the repercussions on quality of life are relevant and cannot be ignored, corroborating with Barkokebas et al.[22] (2015) and McMillan et al.[25] (2004) who also applied the same questionnaire to cancer patients and found an impact on their quality of life, thus showing, the contribution of OHIP-14 in the prognosis and treatment of these individuals.

Through the MEDLINE® database, it was not possible to find studies that associated xerostomia, quality of life and hyposalivation with irradiated PG volumes. In the current study, uwe were able to perform such a correlation, however it was not statistically significant (p-value> 0.001). As a limitation of the study, it can be pointed out that the sample was composed of individuals with HNC in different locations. Thus, studies are necessary to compare individuals separated by groups that contemplate the same tumor location, in order to identify if there are significant differences correlate with xerostomia, quality of life and hyposalivation with the volumes of irradiated PG with other types of radiation therapy.

Conclusion

It can be inferred that patients undergoing 3D radiotherapy for malignant neoplasms in the head and neck region had decreased salivary flow, increased complaints of dry mouth and decreased quality of life, but it was not possible to establish a statistically significant correlation between these findings and volumes of irradiated parotids.

Data availability

Datasets related to this article will be available upon request to the corresponding author.

Conflict of interests

None.

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Author Contribution

Ana Waleska Pessôa Barros de Aguiar: contributed to the development and writing of the project, execution of data collection, patient care, software design, data tabulation, data analysis and article writing and article correction.

Luiz André Nadler Lins: contributed to the development of the project and article correction.

Ana Luíza Fassizoli da Fonte: contributed to the development of the project, article correction and calibration of the design in software,

Raylane Farias de Albuquerque: execution of data collection and data analysis.

Jair Carneiro Leão: contributed to the development of the project and article correction.

Igor Henrique Morais Silva: contributed to the development and writing of the project, patient care, data tabulation, data analysis and article correction.

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