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Head and neck radiotherapy in patients with oral rehabilitation by dental implants: analysis of implant survival

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ABSTRACT

Radiotherapy (RT) plays an important role in the treatment of patients with head and neck cancer. Clinical changes in the surrounding healthy tissue are often inevitable. The deleterious effects on the bones of the jaws have been considered a contraindication for rehabilitation with dental implants. However, in recent years, the installation of implants in irradiated patients has been consolidated as a valuable treatment option. The aim of this study was to evaluate the effect of RT on the survival of osseointegrated dental implants in patients with head and neck cancer. The applied methodology involved an electronic search in the MEDLINE database during the last five years. We identified 67 scientific documents related to the keywords: "radiotherapy", "dental implants" and "head and neck cancer", four articles were selected and reviewed, composing this analysis. It is concluded that dental implants installed in irradiated bone in the oral cavity have a high survival rate, 96,26%, provided that rigorous monitoring is instituted in RT in order to be successful in the long term. The percentage of dental implant failures tended to be higher in the group of irradiated patients.

Keywords: **radiotherapy, dental implants, head and neck cancer.**

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1. INTRODUCTION

Head and neck cancer (HNC) is a collective term defined by anatomical basis to describe malignant tumors in the upper aerodigestive tract. This anatomical region corresponds to the nasal cavity and paranasal sinus, oral cavity, pharynx and larynx [1]. For Brazil, an estimated 11,180 new cases of oral cavity cancer in men and 4,010 in women, for each year of the 2020-2022 biennium, these values correspond to an estimated risk of 10.69 new cases per 100,000 men, and 3.71 per 100,000 women. The number of new cases expected for laryngeal cancer will be 6,470 in men and 1,180 in women, the estimated risk will be 6.20 new cases per 100,000 men and 1.06 new cases per 100,000 women. Cancer in the oral cavity occupies the fifth position and a percentage of 5% of all types of cancer in men [2].

The best-known risk factors for HNC include smoking and excessive alcohol consumption. Among other risk factors, there is unprotected sun exposure (important risk for lip cancer), excess body fat, human papillomavirus (HPV) infection (related to oropharynx cancer) and factors related to occupational exposure [2]. However, according to Castellsague et al. the classic risk factors for squamous cell carcinomas in the head and neck were smoking and excessive alcohol use, currently HPV infection, in a substantial and increasing way, presents high risk for the development of these tumors, originating mainly in the oropharynx and occurring particularly in the Western world [3].

The treatments used to combat HNC involve three modalities: surgery, radiotherapy (RT) and chemotherapy that can be administered exclusively or concomitantly. Patients undergoing tumor resection surgery for the HNC are potential candidates for implant-supported dental rehabilitation, since debilitating results and involvement of oral structures can be generated due to oncologic surgery, an acquired condition that often makes it impossible to use conventional prostheses. Moreover, and based on the concept of osseointegration advocated by Bränemark et al. [4], it should be considered that RT can cause changes in irradiated tissue and compromise the success of implant-supported rehabilitation.

The adverse side effects to bone tissue caused by ionizing radiation are very consistent with: (1) decrease in osteocytes numbers, (2) suppression of osteoblastic activity and (3) decreased vascularization. Bone regenerative capacity is affected due to reduced clonogenicity of osteoblasts, bone-formation cells, allowing osteoclastic cells responsible for bone resorption to act at the irradiated site, induced by the unbalance of cytokines and growth factors. Such events, over time, generate an imbalance between bone formation and resorption and may have a deleterious impact on implant osseointegration over time.

Dekker et al. did a quantitative study of bone marrow vascularization in irradiated human jaws [5]. The irradiated group consisted of fully edentulous patients diagnosed with HNC who underwent prosthetic rehabilitation with dental implants. Irradiation significantly decreases the number and density of blood vessels in this group. In sites with dosages greater than 50 Gy, the proportion of smaller vessels decreased significantly. This indicates that a local radiation dose greater than 50 Gy affects smaller blood vessels to a greater degree than larger blood vessels. Over time after irradiation, the participation of smaller vessels in the mandibular bone marrow decreased. The formation of new vessels can be impaired causing a hypovascularization situation, which is more pronounced in the posterior phase of RT [5].

RT aggravates implant-supported oral rehabilitation in patients with HCN in a dose-dependent manner at the implant site, Wolf et al. evaluated the impact of irradiation at the implant site and parotid gland in a retrospective study with 121 patients with irradiated HNC [6]. Strong predictors of implant failure were correlated with a specific dose at the implant site greater than 50 Gy and a dose in the parotid greater than 30 Gy. Modern radiation techniques of modulated intensity with planning of several modulated fields were associated with less severe xerostomia rates compared to conventional radiotherapy techniques. Thus, the deleterious effects of RT are attributed to the high dose level of irradiation at the implant site and due to irradiation-induced xerostomia.

A prospective cutting study was developed by Papi et al. One group of 16 patients with HNC underwent intensity modulation radiotherapy (IMRT), while another group of 16 participants with HNC were treated with three-dimensional conformed radiotherapy (3D-CRD) [7]. The aim of this study was to evaluate how the irradiation technique can affect the level of the periimplant bone crest and the survival rate of implanted implants. In this study there was no significant difference in bone loss levels between groups.

Based on a review of the scientific literature, the aim of this article is to test the null hypothesis given by "there is no difference in failure rates of dental implants installed in patients submitted to head and neck RT". The null hypothesis is the fact that neck head RT does not interfere with dental implants.

2. MATERIALS AND METHODS

2.1. Database

The electronic search was carried out on August 16, 2021, in the MEDLINE database, to retrieve the articles published in the last five years.

2.2. Search strategies

The keywords used were "radiotherapy", "dental implants" and "head and neck cancer", the following combinations were used: (("radiotherapy" [MeSH terms] OR "radiotherapy" [All fields] OR "radiotherapies" [All fields] OR "radiotherapy" [MeSH Subheading] OR "radiotherapy s" [All Fields]) AND ("dental implants" [MeSH Terms] OR ("dental" [All Fields] AND "implants" [All Fields] OR "dental implants" [All Fields]) AND ("head and neck neoplasms" [MeSH terms] OR ("head" [All fields] AND "neck" [All fields] AND "neoplasms [All fields] Fields]) OR" head and neck neoplasms " [All fields] OR ("head" [All fields] AND "neck" [All fields] AND "cancer" [All fields]) OR "head and neck cancer" [All fields])) AND (y_5[Filter]). The research was carried out using the publication date filter: 05 years.

2.3. Selection and inclusion of studies

The following question structured the present study: is there a change in the survival rate of implants installed in patients undergoing head and neck RT? The search strategies recovered a total of 67 articles, of which, after reading the titles and abstracts, a partial sample of 14 articles was analyzed in full, according to the following eligibility criteria: (1) studies in individuals with head and neck cancer who underwent dental implants and RT as a test group, and individuals not treated with RT as a control group; (2) studies with a minimum follow-up of 12 months. After evaluating the full text, a final sample of four articles was selected, review studies were excluded. In each of the included studies, the following data were extracted and arranged comparatively: (1) author and year of publication; (2) number and average age of the participant; (3) number of implants installed; (4) type of prosthetic rehabilitation; (5) type of tumor; (6) technique and irradiation dose used; (7) follow-up time and implant survival rate. The distribution of the selection of studies is shown in Figure 1.

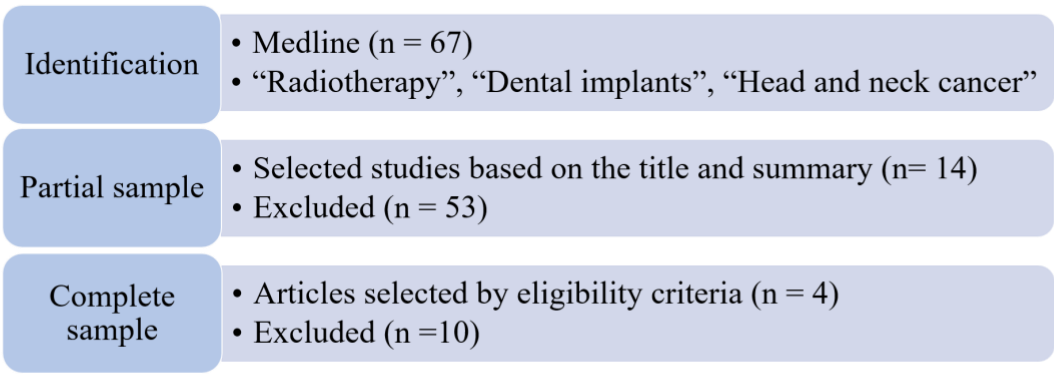

Figure 1: *Flowchart of selection and excluded studies.*

3. RESULTS AND DISCUSSION

Most of the selected studies are retrospective (75%), Ernst et al. [8] and Patel et al. [9] each of them made a retrospective cohort study, Pieralli et al. [11] produced a retrospective case-control study and Alberga et al. [10] conducted a clinical trial. All selected articles evaluated the survival rate of dental implants in irradiated and non-irradiated sites in patients submitted to RT as a treatment modality for HNC, associated or not, with other therapies. The total number of participants included in the final sample was 237, and the mean age was 64.6 years. A total of 950 implants were included in this review, a greater number of implants were installed in the mandible (654) than in the maxilla (295). The implants installed in irradiated bone tissue (375) were in smaller number than those installed in non-irradiated bone (470), in addition 105 implants were installed in a control group (healthy patients). Twenty-two implants failed; overall implant survival was 97.68%. The survival rate of implants installed in the control group was 100%, no implant was lost. Fourteen implants were lost in the group of irradiated patients, the survival rate of implants installed in irradiated sites was 96.26%. Eight implants were lost in the group of non-irradiated patients, the survival rate of the implant installed in non-irradiated bone tissue was 98.29%.

Two studies declared approval by the institutional ethics committee of the University of Charité, Berlin, Ernst et al. [8] and Pieralli et al. [11]. Of the articles included, only half of them, Alberga et al. [10] and Pieralli et al. [11] mentioned that the patients signed the free and informed consent form.

All studies analyzed the survival rate of implants installed through data extracted from clinical and radiographic analyses. The degree of satisfaction of patients in relation to their prostheses was the target of interest in two articles: Alberga et al. [10] and Pieralli et al. [11]. The study by Ernst et al. in patients treated at the Department of Oral and Maxillofacial Surgery of Charité, Berlin, evaluated chances in the marginal bone level of dental implants in irradiated and non-irradiated sites after tumor resection in the mandible [8], and identified possible factors of influence that could impair osseointegration. Patel et al. [9] evaluated data collected from medical records of cancer patients who underwent oral rehabilitation with dental implants at Leeds Dental Institute, United Kingdom, and identified the survival rate of implants installed in irradiated and non-irradiated sites, in addition, they considered the best time to install the implants. The interest in the best moment of implant installation in RT is also present in the study by Alberga et al. [10] who evaluated the results of immediate implant installation after dentition removal in patients with HNC, research conducted at the head and neck center of the University Medical Center Groningen, the Netherlands. In turn, Pieralli et al. [11] evaluated the clinical results and those reported in forms on prosthetic rehabilitation supported by implants in patients treated surgically with HNC with or without adjuvant RT, compared to a healthy control group, and the treatments were performed in the Department of Maxillofacial Surgery of Charité, Berlin, the same institution of the study by Ernst et al. [8].

The relationship and detail of the location and number of implants installed in the studies were varied. One study evaluated implants installed only in the mandible [10], while the other studies evaluated implants installed in the maxilla and mandible [8,9,11]. In the study by Ernst et al. [8] of the 36 participants (7 women and 29 men), 17 patients were irradiated and received surgical therapy and adjuvant RT (n = 5) or radiochemotherapy (n = 12); and 19 non-irradiated patients received surgical resection followed by bone reconstruction, all bone grafts were performed in patients in the non-irradiated group; the number of implants installed in the mandible was higher than those installed in the maxilla, respectively, 121 and 73. The study by Patel et al. [9] evaluated a total of 115 participants, 376 implants were evaluated, of which 277 were installed in the mandible (108 in irradiated bone, and 169 in non-irradiated bone), and 99 were installed in the maxilla (24 in irradiated bone, and 75 in non-irradiated bone). Alberga et al. [10] evaluated implants installed only in the mandible, and of the 29 participants (15 men and 14 women) 8 patients were treated only with resection surgery for HNC and 21 patients were treated with RT (8 patients underwent primary RT and 13 patients treated with postoperative RT); probably because is the only clinical trial in the sample evaluated a smaller number of implants (n = 58). In the study by Pieralli et al. [11], the 57 participants (28 women and 29 men) received 322 implants (124 in the maxilla and 198 in the mandible) and 79 prosthetic reconstructions. Data with the number of participants, mean age, number of implants, type of prosthetic structure, type of tumor, irradiation technique and dose, follow-up time and percentage of survival of the implants are described in table 1.

All studies implemented clinical and radiographic evaluation to monitor bone loss. In the study by Ernst et al. [8] all patients were clinically evaluated every six months through a standard protocol and evaluated with panoramic radiographic examinations at three specific times: group after implant installation, group after 12 months and group after 36 months. Patel et al. [9] collected data from the medical records of patients undergoing cancer treatment at Leeds Dental Institute, including clinical notes, radiographs, radiographic reports, registration of component applications, and letters. Alberga et al. [10] evaluated periimplant clinical parameters, specifically plaque index, bleeding index, gingiva index, probing pocket depth; all patients were clinically evaluated every six months and at least two panoramic radiographs were performed in each patient: one after implant installation and another during the final evaluation; the evaluation of oral function and the satisfaction of patients with prostheses was also the object of this study and were performed through questionnaires. Pieralli et al. [11] they used standardized protocols for surgical interventions of reconstruction and tissue augmentation, related to flaps, bone tissue graft, lifting of the floor of the maxillary sinus, vestibuloplasty, implant installation and prosthetic rehabilitation, in clinical monitoring included evaluation of periimplant conditions, such as: probing depth, attached peri-implant mucosa, bleeding index and plaque index. In addition, the research on patient satisfaction with implant-retained prostheses was implemented through forms of patient-reported outcome measures (PROMs) or oral health impact form (OHIP).

In the study by Ernst et al. [8] the implants were installed six months after the completion of RT. Panoramic radiographic evaluation was used to quantify bone loss in the mesial and distal site. The statistical analysis showed no significant difference between changes in bone level and age, gender, or reconstruction procedure; however, there was a correlation between bone crest loss and RT (p <0,001). In addition, the mean amount of bone alteration after three years was twice as high in irradiated patients as in non-irradiated patients, and due to the location of the tumor, the maxillary bone was not directly included in the radiation field; however, periimplant bone loss analyses showed a significant difference in the alteration of the level of the maxillary bone crest. Thus, bone loss was higher in irradiated patients than in non-irradiated patients. In view of these observations, the authors assume that factors such as: xerostomia and progressive progressive fibrosis also play a decisive role in bone losses, in addition to the RT dosimetric distribuition at the implant site.

Table 1: Data from selected studies.

Study year	Participants, n / Mean age, y	Implants, n	Prosthetic superstructures	Type of tumor	Tec. / Radiation Dose, Gy	Follow-up, mo/ Survival Rate, %
Ernst et al., 2016	36/65,8	194	bar-retained overdenture, locator, screw-fixed	SCC	IMRT / 55-72	Mean 52.92 / 98.4
Patel et al., 2020	115 / 61	376	overdenture (31%)	SCC (n=55)	ND / 61	Mean 46.92 / 97
Alberga et al., 2020	29 / 63,4	58	overdenture bar-clip	HNC	IMRT / 46-70	Median 18.5 / 93.10
Pieralli et al., 2021	57 / 68.3	322	overdenture bar and locator, fixed prostheses	SCC (n=34)	2D-RT, 3D-RT, IMRT, VMAT, / ≤78.2	Mean 81.2 / 98.1

Abbreviations: 2D-RT: conventional radiotherapy, 3D-RT: three-dimensional conformal radiotherapy, HNC: head and neck cancer, IMRT: radiotherapy with modulation of beam intensity, ND: nothing declared, RT: radiotherapy, SCC: squamous cell carcinoma, SR: survival rate, VMAT: volumetric modulated arc therapy.

In the study by Patel et al. [9] most implants were installed after resection of the primary tumor. This fact increases the time prescribed from diagnosis to implant placement. However, it was not possible to determine statistically whether the time of implant installation in relation to resective surgery of the tumor influenced the survival of the implants. The authors considered that there is an increasing trend of implant placement during primary resection, significantly reducing the time of prosthetic rehabilitation in this patient population. However, this management increases the complications that may impair the rehabilitation of oral health through implants, such as obtaining well-positioned implants and risk of implant failure associated with backscattering during RT. According to the study, the placement of the implant in the maxilla or grafted area in patients exposed to RT negatively influenced the survival of the implants, but did not represent significant results ($p > 0.05$).

Alberga et al. [10] they used periimplant clinical parameters as methods of analysis. There was no significant difference between irradiated and non-irradiated patients, except for the bleeding index that was higher in the non-irradiated group ($p = 0.004$). Radiographic analyses revealed greater bone loss around the implants in the irradiated group, but without statistical difference ($p = 0.17$). These results are comparable to the findings in the study by Patel et al. [9], showing that RT had a negative effect on implant survival, since all implant losses occurred in irradiated patients. However, due to the small sample size, no conclusion can be reliable about the survival rate of the implants. One factor that may have influenced the loss of these implants was the process of osseointegration not being complete when RT was initiated. The result of the investigation on oral function and patient satisfaction when the prosthesis was in operation, for a minimum period of six months, validated the findings of: " reasonably satisfied" patients, there was no significant difference between irradiated and non-irradiated groups.

Pieralli et al. [11] concluded that irradiated and non-irradiated patients have similar survival rates at the implant and prosthesis level, and there was no significant difference in masticatory capacity and satisfaction rates between groups. The possible explanation is due to special care, with minimally invasive surgical procedures in nonsmokers, through the proper management of soft tissues and the rigorous maintenance of oral hygiene. Data on implants installed in irradiated and non-irradiated sites, control group, failed implants and survival rate are shown in table 2.

The results of this review indicate that the percentage of failures tended to increase in irradiated patients, except in the study by Pieralli et al, [11] that of the four implants that failed two were lost in patients in the HNC-TR/RT group (head and neck cancer – treated with surgical resection and radiotherapy) and the other two were lost in patients in the HNC-TR group (head and neck cancer treated with surgical resection). The only study that showed a statistically significant difference between bone loss and RT was the study by Ernst et al. [8].

Table 2: Data of implants installed in irradiated site, in non-irradiated site, control group, failure implant and survival rate

Study year	Irradiated implants sites, n	Non irradiated implants sites, n	Implants control group, n	Failure implant, n	SR irradiated implants, %	SR non irradiated implants, %
Ernst et al., 2016	88	106	0	4	96.59	99.05
Patel et al., 2020	132	244	0	10	96.06	97.90
Alberga et al., 2020	42	16	0	4	90.50	100
Pieralli et al., 2021	113	104	105	4	98.20	98.10

Abbreviation: SR: survival rate.

In the study by Ernst et al. [8] all tumors diagnosed were squamous cell carcinoma localized on the floor of the mouth or tongue and were surgically removed. Due to tumor resection and when the mucosa was not adequately able to ensure periimplant soft tissue stability, vestibuloplasty procedures were performed. In Patel et al. [9] not all tumors were identified as squamous cell carcinoma, although 47.82% were diagnosed as squamous cell carcinoma (n = 55), and a total of 56 participants had tumor resection involving dental alveolus. There was a significant association between the need for soft tissue revision and the installation of dental implants in areas associated with some type of reconstructive flap.

Alberga et al. [10] considered as a disadvantage the risk of recurrence of the neoplasm when the installation of implants occurs immediately after extraction of the remaining teeth during tumor resection, a fact that occurred in five patients in the study. In the study by Pieralli et al. [11] 91.89% of participants in the HNC group were diagnosed with squamous cell carcinoma. The implants were installed at least six months after RT; while, in cases where enhanced procedures of autogenous bone graft, xenografts or free flaps were performed, a minimum period of six months after RT was respected. In cases of insufficient adhered mucosa around the implants, partial-thickness skin grafts were performed from the thigh.

Condezo et al. [12] conducted a systematic review with meta-analysis to evaluate the influence of hyperbaric oxygen therapy (OHB) on the survival rate of dental implants installed in patients who underwent RT for HNC. There was no evidence that the risk for implant failure was different between patients who received OHB and those who did not receive therapy.

Modern RT techniques can vary widely the dose for organs and tissues of interest. Consequently, the dose for tumor volume does not reflect the irradiation dose in the specific area for implant installation. Neckel et al. [13] in an observational study, in 15 patients with irradiated HNC, investigated the influence of the current dose of specific irradiation at the site of implants installed after RT. The results revealed in the maxilla a correlation with the specific dose at the implant site and can be observed after 1 to 3 years, in the mandible a significant correlation was found after three years. In addition, another result found was the influence of gender on bone level changes in relation to the specific radiation dose at the implant site, and women showed higher rates of bone loss than men after one year, but these results stabilized after a period of three years.

Wolf et al [6] determined that the risk for the development of periimplant osteoradionecrosis with average doses of 60 Gy is rapidly increased, particularly for mandible implants. RT prevents the successful implantation in a manner dependent on the irradiated dose at the implant site. RT with a general average dose of more than 50 or 60 Gy was not decisive for implant failure; however, specific average doses in the implant bed exceeding 50 or 60 Gy are predictors of implant failure.

Nobrega et al. [14] conducted a systematic review and meta-analysis and indicated a statistically significant difference between the success rates of implants installed in irradiated bone tissue and those of implants installed in non-irradiated tissue. The survival rate of implants installed in irradiated area was lower than that of implants installed in non-irradiated areas. In another study, Panchal et al [15], through a systematic review and meta-analysis, determined the survival rate of dental implants installed in patients undergoing maxillary reconstruction or vascularized mandibular. Dental implants without exposure to RT had better survival than those implants exposed to radiation ($p < 0.01$) in an average follow-up of 36 months. Among the irradiated group, implant survival tended to be higher among patients who received RT after implant placement than those who received RT before implant placement, although this was not statistically significant.

The ideal time for the installation of the implant is controversial, it can be installed before RT, immediately after extraction during the removal of the tumor, or after the termination of RT at a later stage. Some studies recommend the installation of implants at the time of tumor removal. Veld et al. [16] conducted a systematic review to identify and evaluate the outcome of immediate installation treatment and loading of dental implants in edentulous jaws in patients with HCN prior to RT. The meta-analysis demonstrated a slightly higher survival of implants installed immediately compared to those of delayed installation. However, there was no significant difference between the groups characterized by patients who installed the implants immediately and received their prostheses earlier compared to delayed-on patients. The other meta-analysis comparing the number of implants that received RT after surgery and the number of implants that did not receive RT postoperatively showed that irradiation did not significantly affect the survival rate or functionality of implants installed immediately.

Two studies included in the present study evaluated the ideal time for implant installation, Alberga et al. [11] concluded that the placement of implants in the mandible during the removal of the remaining teeth and prior to the treatment of head and neck cancer is a favorable option, considering the potential benefits such as reduced rehabilitation time, decreased surgical procedures and increased quality of life. The other study that evaluated the best time was Patel et al. [10], which suggest a tendency to install implants earlier so that patients with HNC treatment can benefit from rehabilitation as soon as possible. However, contrary results are reported by Di Carlo et al. [17] in a retrospective study collected data from 17 individuals with oral cancer treated with RT and evaluated the best time for implant installation and loading. Statistical analysis showed significantly better results when the implant was installed at least 14 months after RT and implant loading up to at least 6 months after installation, and concluded that delay in implant installation and a delayed loading protocol will give better chances of osseointegration for implants, therefore the safest protocol [17].

4. CONCLUSION

Dental implants installed in the irradiated area have a high survival rate, provided that rigorous clinical and dosage monitoring is established as a treatment protocol to avoid complications. Since the late effects of RT may be present years after treatment, observational studies and controlled clinical trials in humans with long follow-up periods are necessary to confirm potential clinical changes and limitations in dental implant installations in this specific situation.

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