Dental implants in irradiated versus non-irradiated patients: a meta-analysis

Running Title: Dental implants and irradiation

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KEYWORDS
Dental implants; radiotherapy; infection; marginal bone loss; meta-analysis

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ABSTRACT

Background/Methods. The purpose of the present meta-analysis was to test the null hypothesis of no difference in dental implant failure rates, postoperative infection, and marginal bone loss for patients being rehabilitated by dental implants and being previously irradiated in the head and neck region versus non-irradiated patients, against the alternative hypothesis of a difference.

Results/Conclusion. The study suggests that irradiation negatively affects the survival of implants, as well as the difference in implant location (maxilla vs. mandible), but there is no statistically significant difference in survival when implants are inserted before or after 12 months after radiotherapy. The study failed to support the effectiveness of hyperbaric oxygen therapy in irradiated patients. It was observed a tendency to lower survival rates of implants inserted in the patients submitted to higher irradiation doses. The results should be interpreted with caution due to the presence of uncontrolled confounding factors in the included studies.
INTRODUCTION

In an attempt to decrease implant failure rates, more attention is being placed on understanding the etiologic and risk factors that lead to the failure of dental implants. The question of whether or not irradiated patients in the head and neck region are more at risk of losing dental implants has been receiving increasing attention in the last years, as implants have been increasingly used in oral cancer patients.

Radiotherapy is largely used for treatment of head and neck cancer, as primary therapy, adjuvant to surgery as well as in conjunction with concurrent chemotherapy or as palliative treatment for late stage and untreatable head and neck malignancies. Although the radiotherapy can increase cure rates, the irradiated patient is susceptible to secondary effects and a series of potential orofacial complications. Radiotherapy may result in progressive fibrosis of blood vessels and soft tissues, in xerostomia, in osteoradionecrosis, and in reduction of bone-healing capacity, among others. Because of the cumulative effects of radiation on bone vascularity, the regenerative capacity of these tissues is limited, and this may have a deleterious impact on subsequent implant osseointegration.

The ability to anticipate outcomes is an essential part of risk management in an implant practice. Recognizing conditions that place the patient at a higher risk of failure will allow the surgeon to make informed decisions and refine the treatment plan to optimize the outcomes. The use of implant therapy in special populations requires consideration of potential benefits to be gained from the therapy. To better appreciate this potential, we conducted a systematic review and meta-analysis to compare the survival rate of dental implants, postoperative infection, and marginal bone loss of dental implants inserted in irradiated and non-irradiated patients.
MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines. A review protocol does not exist.

Objective

The purpose of the present review was to test the null hypothesis of no difference in the implant failure rates, postoperative infection, and marginal bone loss for patients being rehabilitated by dental implants and being irradiated or previously irradiated in the head and neck region versus non-irradiated patients, against the alternative hypothesis of a difference.

Search strategies

An electronic search without time or language restrictions was undertaken in April 2014 in the following databases: PubMed, Web of Science, and the Cochrane Oral Health Group Trials Register. The following terms were used in the search strategy on PubMed:

- ((dental implant[Text word]) AND irradiated[Text word])
- ((dental implant[Text word]) AND radiotherapy[Text word])
- ((dental implant[Text word]) AND radiation[Text word])
- ((dental implant[Text word]) AND radiation therapy[Text word])

The following terms were used in the search strategy on Web of Science, in all databases:

- ((dental implant[Topic]) AND irradiated[Topic])
The following terms were used in the search strategy on the Cochrane Oral Health Group Trials Register:

(dental implant OR dental implant failure OR dental implant survival OR dental implant success AND (irradiated OR radiotherapy OR radiation OR radiation therapy))


The reference list of the identified studies and the relevant reviews on the subject were also scanned for possible additional studies. Moreover, online databases providing
information about clinical trials in progress were checked (clinicaltrials.gov; www.centerwatch.com/clinicaltrials; www.clinicalconnection.com).

**Inclusion and Exclusion Criteria**

Eligibility criteria included clinical human studies, either randomized or not, comparing implant failure, postoperative infection, and/or marginal bone loss in patients irradiated for head and neck cancers versus non-irradiated patients. For this review, implant failure represents the complete loss of the implant. Implants that were placed and could not be used because of positional problems (the so-called ‘sleepers’) were here not considered as failures. Exclusion criteria were case reports, technical reports, animal studies, *in vitro* studies, and reviews papers.

**Study selection**

The titles and abstracts of all reports identified through the electronic searches were read independently by the three authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors.

**Quality assessment**

The quality assessment was performed by using the recommended approach for assessing risk of bias in studies included in Cochrane reviews.\(^7\) The classification of the risk of bias potential for each study was based on the four following criteria: sequence generation (random selection in the population), allocation concealment (steps must be taken to secure strict implementation of the schedule of random assignments by preventing foreknowledge of the forthcoming allocations), incomplete outcome data (clear explanation of withdrawals and
exclusions), and blinding (measures to blind study participants and personnel from knowledge of which intervention a participant received). The incomplete outcome data will also be considered addressed when there are no withdrawals and/or exclusions. A study that included all the criteria mentioned above was classified as having a low risk of bias, a study that did not include one of these criteria was classified as having a moderate risk of bias. When two or more criteria were missing, the study was considered to have a high risk of bias.

**Data extraction and meta-analysis**

From the studies included in the final analysis, the following data was extracted (when available): year of publication, study design, unicenter or multicenter study, number of patients, patients’ age, follow-up, days of antibiotic prophylaxis, mouth rinse, implant healing period, failed and placed implants, postoperative infection, marginal bone loss, implant surface modification, radiotherapy, timespan between irradiation and implant surgery, hyperbaric oxygen therapy (HBO), type of prosthetic rehabilitation, jaws receiving implants (maxilla and/or mandible), grafting procedures, observed occurrences of death during the follow-up period, presence of smokers and/or alcohol drinkers among the patients, and adjunctive chemotherapy. Contact with authors for possible missing data was performed.

Implant failure and postoperative infection were the dichotomous outcomes measures evaluated. Weighted mean differences were used to construct forest plots of marginal bone loss, a continuous outcome. The statistical unit for ‘implant failure’ and ‘marginal bone loss’ was the implant, and for ‘postoperative infection’ was the patient. Whenever outcomes of interest were not clearly stated, the data were not used for analysis. The I² statistic was used to express the percentage of the total variation across studies due to heterogeneity, with 25% corresponding to low heterogeneity, 50% to moderate and 75% to high. The inverse variance method was used for random-effects or fixed-effects model. Where statistically significant (P
heterogeneity is detected, a random-effects model was used to assess the significance of treatment effects. Where no statistically significant heterogeneity is found, analysis was performed using a fixed-effects model. The estimates of relative effect for dichotomous outcomes were expressed in risk ratio (RR) and in mean difference (MD) in millimeters for continuous outcomes, both with a 95% confidence interval (CI). Only if there were studies with similar comparisons reporting the same outcome measures was meta-analysis to be attempted. In the case where no events (or all events) are observed in both groups the study provides no information about relative probability of the event and is automatically omitted from the meta-analysis. In this (these) case(s), the term ‘not estimable’ is shown under the column of RR of the forest plot table. The software used here automatically checks for problematic zero counts, and adds a fixed value of 0.5 to all cells of study results tables where the problems occur.

A funnel plot (plot of effect size versus standard error) will be drawn. Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, although the asymmetry may also represent a true relationship between trial size and effect size.

The data were analyzed using the statistical software Review Manager (version 5.2.11, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).
RESULTS

Literature search

The study selection process is summarized in Figure 1. The search strategy resulted in 1683 papers. Four combinations of terms were used for PubMed and Web of Science, which resulted in a number of 686 duplicates. The three reviewers independently screened the abstracts for those articles related to the focus question. The initial screening of titles and abstracts resulted in 78 full-text papers; 919 were excluded for not being related to the topic. The full-text reports of the remaining 78 articles led to the exclusion of 24 because they did not meet the inclusion criteria (9 did not inform of the number of implants per group, 6 evaluated implants only in irradiated mandibles, 3 evaluated implants for craniofacial prostheses, 2 were earlier follow-ups of the same study, 2 were the same study published in another journal, 1 did not insert implants in irradiated bone, and 1 paper was not evaluating implant failures). Additional hand-searching of the reference lists of selected studies did not yield additional papers. Thus, a total of 54 publications were included in the review.

Description of the Studies

Detailed data of the 54 included studies are listed in Tables 1 and 2. Ten controlled clinical trials and forty-four retrospective studies were included in the meta-analysis. When the e-mail of one or more authors of the articles was found, questions were sent to request information about missing data. Authors of three studies replied with the requested information.

Seventeen studies had a maximum follow-up from 5 to 9 years, whereas eighteen studies had a maximum follow-up of at least 10 years. From the studies with available data of patients’ range age, ten included non-adults patients. Eight studies did not inform of the
patients’ age. Only six studies\textsuperscript{22,24,28,47,48,59} provided information about postoperative infection, with 35 occurrences in a total of 158 patients receiving 543 implants. Three\textsuperscript{22,24,47} of the six studies compared postoperative infection between implants inserted in irradiated maxillae and irradiated mandibles, and the other three\textsuperscript{28,48,59} between implants inserted in irradiated and non-irradiated patients. Only four studies\textsuperscript{14,15,17,48} provided information about marginal bone loss. Thirteen studies\textsuperscript{19,23,28,36,37,40,41,43,44,52,55,56,61} did not inform of the healing period of the implants before loading.

Twenty-seven studies\textsuperscript{10,11,13-16,20,25-28,31-33,35,37,44-46,48-51,55,58,59,61} informed of the death occurrences among the patients during the follow-up. Eighteen studies\textsuperscript{5,9,12,17,21,22,32,34,42,44,46-48,50,51,59,61} had patients who were also submitted to adjunctive chemotherapy. In two studies,\textsuperscript{17,50} all patients were submitted to chemotherapy. Part of the patients in nine studies\textsuperscript{5,11,21,35,44,52,58,60,61} were smokers, and two studies excluded smokers.\textsuperscript{17,18} It was informed in five studies\textsuperscript{5,11,58,60,61} that part of the patients was frequent consumers of alcoholic beverages.

Patients were submitted to bone grafting procedures in twenty-nine studies.\textsuperscript{5,9,11,20,22,26-29,31,33,36,38-43,45,50,51,53,57,61} Four studies\textsuperscript{18,37,48,49} evaluated implants in native bone only. Eighteen studies\textsuperscript{5,9,14-16,20,21,29,31,35,36,38,40,48-50,54,58} evaluated implants inserted in the mandible only, of which four studies\textsuperscript{14,15,48,49} assessed the implants in the interforaminal region only, and three\textsuperscript{34,38,42} only in maxilla. HBO was performed in patients of fourteen studies.\textsuperscript{5,10,11,14,30,34,37,43-46,55,56,60}

The most commonly used implants used was the turned Brånemark (Nobel Biocare AB, Göteborg, Sweden), in thirty-five studies,\textsuperscript{5,9,10,12,14-16,19-22,24-27,30-32,34,35,37-39,42,44-47,49,51,52,55,57,59} but not exclusively in twelve studies.\textsuperscript{9,10,20,25,26,39,42,45-47,51,52} Eight studies\textsuperscript{23,36,40,41,43,54,56,61} did not inform of what kind of implants was used. Sixteen studies\textsuperscript{5,12,13,16,18,34,35,39,40,42,45,46,50-52,60} informed whether there was a statistically significant
difference or not between the implant failure rates between the procedures, whereas one study\textsuperscript{28} showed no implant failures. Thirteen studies\textsuperscript{9,10,13,14,17,21,24,28,32,47,48,51,58} provided information about the use of prophylactic antibiotics, and only three\textsuperscript{13,28,48} about mouth rinse by the patients.

The comparisons concerning the outcome ‘implant failure’ are summarized in Table 3.

**Quality Assessment**

Each trial was assessed for risk of bias, and the scores are summarized in Table 4. All studies were judged to be at high risk of bias.

**Meta-analysis**

A summary of the meta-analyses comparisons concerning implant failures is presented in Table 3. The forest plots are presented in Figures 2 to 11.

Six studies\textsuperscript{22,24,28,47,48,59} provided information about postoperative infection. A fixed-effects model was used, due to lack of statistically significant heterogeneity either when comparing implants inserted in irradiated versus in non-irradiated patients (\(P = 0.52; \, I^2 = 0\%\); Figure 12) or when comparing implants inserted in irradiated maxilla versus in irradiated mandible (\(P = 0.86; \, I^2 = 0\%\); Figure 13). The results showed that there was no statistically significant difference in the two comparisons (RR 1.40, 95\% CI 0.73-2.68, \(P = 0.31\) and RR 0.81, 95\% CI 0.09-7.27, \(P = 0.85\), respectively).

Only two studies\textsuperscript{15,48} provided information about the marginal bone loss with standard deviation, necessary for the calculation of comparisons in continuous outcomes, comparing implants inserted in irradiated versus in non-irradiated patients. There was statistically significant difference (MD 0.62, 95\% CI 0.21-1.03, \(P = 0.003\); heterogeneity: \(I^2 = 92\%, \, P < 0.00001\), random-effects model; Figure 14) between the groups concerning the marginal bone
loss, favoring non-irradiated patients. One study\textsuperscript{14} provided information comparing marginal bone loss in implants inserted in irradiated patients being submitted versus not submitted to HBO. A meta-analysis for this comparison was not performed.

**Publication bias**

The funnel plot did not show asymmetry when the studies reporting the outcome ‘implant failure’ in the comparison between irradiated and non-irradiated patients was analyzed, indicating possible absence of publication bias (Figure 15).
DISCUSSION

One relevant question in the present study is whether the lack of a difference between irradiated and non-irradiated patients in some studies concerning implant failure rates is a real finding or is due to the lack of statistical power, given the small number of patients and/or implants per group. However, a statistically and clinically significant difference favoring the non-irradiated patients was found after the meta-analyses, stressing the importance of meta-analyses to increase sample size of individual trials to reach more precise estimates of the effects of interventions. The significantly higher failure rates in irradiated compared to non-irradiated patients might be caused by the long-term effects of reduced vascularization compromising the implantation site. In general, radiation therapy has two antagonistic effects with regard to recovery of irradiated tissue: a short-term positive cellular effect resulting in the improvement of reduced bone-healing capacity, and a long-term negative effect resulting in permanent damage of osteoprogenitor cells and a gradual, progressive endarteritis obliterans, with thrombosis of small blood vessels, fibrosis of the periosteum and mucosa and damage to osteocytes, osteoblasts and fibroblasts. Moreover, irradiation of tissues that contain integrated implants increases the risk of soft tissue dehiscences around the implants, and osteoradionecrosis may lead to loss of the implants. This failure difference after radiation therapy was observed in several studies here included, although the radiation dosage and observation period varied in the majority of these cases.

Another aspect to consider is the use of HBO. There is no strict consensus about the use of adjunctive HBO therapy but many studies stressed the advantages of HBO treatment for wound healing in the irradiated soft and hard tissue. As a result, some authors use HBO as an additive therapy when implant therapy in irradiated bone is planned. It is stated in the literature that HBO results in an increased oxygen tension in the irradiated ischemic bone and provokes capillary neoangiogenesis and bone formation. The exact correlation between
HBO dose and duration of antifibrotic response is not yet settled. It has been convincingly demonstrated that such treatment dramatically decreases the risk of trauma-induced osteoradionecrosis by promoting vascular proliferation, collagen synthesis, bone remodeling activities, and healing of bone wounds in irradiated tissues.\(^\text{67}\) Moreover, HBO therapy increases the amount of force necessary to unscrew integrated titanium implants in irradiated bone\(^\text{68}\) which suggests that promoted integration has occurred. Larsen et al\(^\text{66}\) showed a difference of 13.9% in mean percent of integration after 4 months in irradiated versus non-irradiated animals. This difference dropped to 6.38% when animals received HBO before and after implantation. The difference was shown to be significant, though without establishing whether this reduction is of significance in relation to implant support. As long as the direct bone-implant interface is sufficiently large to support the suprastructure, it can be argued that additional support to the implant surface is unnecessary, particularly in light of patient inconvenience and the cost of HBO treatment.\(^\text{32}\) Moreover, results from animal experiments may only partly be extrapolated to clinically relevant conditions for endosseous implants in irradiated bone. Apart from considerable methodological limitations in the simulation of the therapeutic reality and temporal restrictions, events during the follow-up (induction of neoplasms, loss of implants, osteoradionecrosis, etc), differences related to cell cycles, structural peculiarities of the bone matrix, the periosteal situation, and the enzyme system of the species have to be taken into account.\(^\text{69}\) It is no less important to mention that several studies here included\(^\text{9,10,14,15,17,19,21,23,26-28,30-33,35,47-49,51,59,60}\) demonstrated a high survival rate for the implants placed in irradiated jaws without the use of adjunctive HBO therapy. It might have been expected a significantly higher failure for patients submitted to HBO, since most of the patients selected for HBO could have been at a higher risk for osteoradionecrosis due to a higher irradiation dose, and consequently at a higher risk of implant loss. For example, the difference in implant survival between the HBO and non-HBO treated patients observed in
the study of Schoen et al\textsuperscript{14} was remarkable, but was mainly caused by one HBO treated patient who developed osteoradionecrosis and subsequently lost all four implants. However, the present meta-analysis found no statistically significant difference when comparing implant failures in irradiated patients receiving or not HBO, which is most likely the result of the small sample size in many studies and selection bias. There are still no randomized, controlled, double-blind studies conducted to prove that HBO really has a significant osseointegration stimulating effect in irradiated patients. However, there are certain technical difficulties related to designing such a study, such as blinding a chamber treatment and the design of the placebo treatment.\textsuperscript{37}

The timespan between the irradiation and the implant surgery may influence the survival of the dental implants, but recommendations for an optimal time interval are inconsistent. Dental implants can be inserted during the ablative surgery or after completed radiotherapy. When the implants are inserted during the ablative surgical session, a large part of the integration will occur in the period between surgery and radiotherapy, i.e. within 4-6 weeks\textsuperscript{70} However, a clear majority of studies here reviewed report on implants installed after radiotherapy. The advantage of placement after radiotherapy is that the anatomical situation, residual function and prognosis can be taken into account in the decision of whether to use implants. Moreover, tumor recurrence has been reported to occur most often between 8 and 12 months after surgery according to one study,\textsuperscript{71} or within 2 years according to another one,\textsuperscript{21} thus oral rehabilitation may be delayed until this period of highest risk has passed. The disadvantage is that patients are often psychologically and physically weakened by the therapy, resulting in postponement or even cancellation of prosthetic rehabilitation.\textsuperscript{72}

Moreover, after radiotherapy the vascularization and regenerative ability of the irradiated tissues can be decreased, which may lessen the prospect of successful osseointegration of the dental implants.\textsuperscript{11} The subject is controversial. King et al\textsuperscript{73} indicated that blood vessels that
were destroyed radiologically show partial recovery after 3 to 6 months. Wächter and Stoll\textsuperscript{74} conducted histomorphometric studies, the results of which state that implantation can be performed, at the earliest, 12 to 18 months after the conclusion of irradiation. Jacobsson\textsuperscript{62} reported an improvement in the bone healing capacity by a factor of almost 2.5 during a 12-month period following irradiation. According to the author, functional self-regeneration of the damaged tissue would provide sufficient implant healing and osseointegration capacities of the bone 1 year after radiation therapy. On the other side, Marx and Johnson\textsuperscript{63} stated that after 6 months, fibrosis is expected to start in the irradiated tissues as a result of reduced cell reproducibility and progressive ischemia. This process will increase with time, especially when curative doses of radiotherapy have been given. The present meta-analysis found no statistically significant difference when failure of implants was compared for the implants installed before and after a period of 12 months from the radiotherapy, and this is most likely the fact that only three studies\textsuperscript{13,18,50} performed this comparison. Two other studies did not report defined time point to make the comparison, but did not find any influence of time of implantation on the implant failure rates.\textsuperscript{10,48}

Concerning the radiation dose, the implants inserted into locations irradiated with ≥ 50 Gray in four studies\textsuperscript{13,18,21,54} had a lower survival rate than implants in locations that are irradiated with < 50 Gray. The same happened in another study,\textsuperscript{40} but comparing different dose thresholds (> 54 versus < 54 Gray). Generally, high radiation doses > 50 Gy have been reported to result in chronic complications like radioxerostomia and impaired wound healing.\textsuperscript{75} Also, irradiation doses above 65 Gy may significantly increase the risk of development of osteoradionecrosis,\textsuperscript{76} which may also be a reason for implant failures. Moreover, it was showed that there is a distinct dose-dependent relationship between the duration and extent of irradiation and the resulting reduced osteogenesis.\textsuperscript{77} Bone healing was delayed at lower doses of radiation with the formation of more impaired fibrous tissue and
non-lamellar bone, and bone healing was severely disturbed at radiation doses used to treat head and neck cancer.\textsuperscript{78} However, the present meta-analysis was not able to find a significantly higher risk of losing an implant in patients receiving higher doses of radiotherapy. Once again, this result may have been influenced by the limited number of studies performing this comparison. The comparable survival rates of both groups in the study of Niimi et al\textsuperscript{30} and even a higher survival rate of implants inserted into locations of higher doses in the study of Shaw et al\textsuperscript{45} might be caused by the effects of reduced vascularization that compromises both irradiated and non-irradiated locations.\textsuperscript{63}

Another circumstance that may increase implant failure is the anatomy of the implantation site. Oral anatomy may change after ablative surgery and eventually following reconstruction by grafts and flaps, and the resulting defects and bulky areas or the presence of insufficient soft tissues for coverage may compromise prosthetic rehabilitation\textsuperscript{41,79} One could speculate that the bony section of the graft may have been non-vital from the time of placement or that placement of implants in the grafted block of bone may have compromised the vitality of the block.\textsuperscript{57} Some studies on this topic address the increased implant loss in augmented bone to the reduced primary stability of dental implants due to impaired mechanical bone quality as well as to increased bone resorption kinetics.\textsuperscript{80-82} The lower survival of implants in the grafted bone may be the result of differences in bone quality, bone volume and revascularization compared with the original residual bone. There is also a difference when it comes to the graft type. Vascularized bone flaps maintain their viability even following prolonged periods of ischemia provided that the medullary nutrient blood supply is later restored.\textsuperscript{83} This is unlike nonvascularized bone grafts, where implant placement must await a lengthy delay to allow for ‘creeping substitution’\textsuperscript{84} to occur. Even with all these disadvantages, the present study found no statistically significant difference concerning failures of dental implants when inserted in irradiated grafted bone or in irradiated native
bone. This could be related to the assumption that the clinical courses of implants may not be affected by the presence of grafted bone once the graft has succeeded, even if this is difficult to ascertain, as not every study included in the present review provided detailed information about grafting procedures. On the other side, when the failure rates were compared in irradiated versus non-irradiated patients, there was a statistically significant difference for implants inserted in grafted bone and in native bone. Once again, when the term ‘irradiation’ is inserted into the equation, there are significant differences.

Concerning the different jaws, it was observed in one study that the most dominant variable influencing implant survival in irradiated bone is the implant's location in the maxilla or mandible. The side effects of radiotherapy appear to be more serious in the mandible than in the maxilla because of the inferior blood supply of the former bone. However, according to the results of the present meta-analysis, it appears that implant failure in the maxilla follows a similar course in irradiated and non-irradiated patients. The results comparing implant failures in irradiated and non-irradiated maxilla and in irradiated and non-irradiated mandible must be interpreted with caution, due to the limited number of studies reporting this information (2 and 4, respectively). It is also important to consider whether all implants had been inserted in the field of irradiation, even though this information was rarely provided by the included studies. In the case of the mandible, for example, the external beam radiation therapy for oral malignancies does not always include the whole mandible and, hence, implants inserted anterior to the mental foramina might be inserted in a field of lower radiation dose. This will naturally affect the outcome for the implants.

When it comes to postoperative infection, soft tissue may be affected by irradiation, and the causes might be the post-operative and post-irradiation xerostomia, different saliva quantity and quality and altered microflora as well as the presence of scar tissues after reconstruction and the loss of attached and keratinized gingiva adjacent to the implants. It
may be suggested that stable soft tissue conditions are crucial for the possibility to perform oral hygiene and can influence the clinical performance of the implants in irradiated patients. This could influence the incidence of peri-implantitis and consequently the marginal bone loss. The present meta-analysis showed that there was a statistically significant difference between the irradiated versus non-irradiated patients concerning the marginal bone loss, favoring non-irradiated patients. However, this result must be interpreted with caution, due to the limited number of studies that evaluated the condition. The same can be said about the meta-analysis results for the outcome postoperative infection.

The studies included here have a considerable number of confounding factors, and most of the studies, if not all, did not inform how many implant were inserted and survived/lost in several different conditions.

First, bone resections may result in unfavorable prosthetic circumstances by producing bulky and soft areas. In these situations, (removable) prosthetic appliances are often complicated and may cause overloading of the implants. This negative influence may be responsible for lower survival rate of implants inserted into jaws treated with bone resections, compared with that of implants inserted into jaws that did not undergo bone surgery.13

Second, the percentage of patients who had received postoperative radiotherapy may have decreased over time among the survivors, as it was observed in many studies, which could have contributed to the relatively low failure rate of implants in irradiated bone. Those patients selected to be submitted to radiotherapy may be the patients with cancers of the worst prognosis.

Third, in the analysis of implant survival, it is important to ascertain whether the implants that were placed and considered osseointegrated were, in fact, used for the final implant-supported prosthesis.85 A longer follow-up period can lead to an increase in the failure rate, especially if it extended beyond functional loading, may lead to an increase in the
failure rate, because other prosthetic factors can influence implant failure from that point onward. This might have led to an underestimation of actual failures in some studies. However, it is hard to define what would be considered a short follow-up period to evaluate implant failures when comparing these techniques.

Fourth, most oral cancer patients have a history of poor oral hygiene, smoking and drinking. The local environment is less favorable to dental implants than in healthy subjects. Saliva quantity and quality as well as oral microflora change considerably after salivary gland resection. Landes and Kovács observed that plaque and peri-implant bleeding index remained typically high compared with non-cancer patients. Oral hygiene and compliance were limited although patients received individual oral hygiene instruction. On the other hand, a rapid plaque accumulation and bleeding tendency was concomitant with post-operative and post-irradiation xerostomia, altered microflora, saliva quantity and quality, smoking and drinking. Irradiation leaves a less-viable bone that is prone to infection; furthermore, oral xerostomia post-radiotherapy complicates the situation.

Fifth, as oral cancer represents around 3% of the total cancer incidence, most of the studies were not able to create a homogenous collective for more than factors such as oral squamous cell carcinoma, edentulousness or severely reduced tooth number. By breaking down the study by each variable, the authors of the studies may have had serious doubts regarding the clinical value in a study that is not totally homogenous in tumor staging, precise dose of irradiation, etc. It can be said that in order to have sufficient group sizes and a clinically relevant conclusion, groups in the studies were therefore not supposedly broken down further. Homogenous or matched collectives somewhat have a higher significance but they tend to be inhibited by small case numbers.

Sixth, it is known that the surface properties of dental implants such as topography and chemistry are relevant for the osseointegration process influencing ionic interaction, protein
adsorption and cellular activity at the surface. The studies here included made use of implants with different brands and surface treatments. Titanium with different surface modifications shows a wide range of chemical, physical properties, and surface topographies or morphologies, depending on how they are prepared and handled, and it is not clear whether, in general, one surface modification is better than another.

Seventh, there was a great variation of the implant healing time before the prosthetic loading. In irradiated tissue, the local healing ability is impaired and the vulnerable time period following insertion becomes jeopardized with early loading. Possible overloading of the implants, induced by altered oral anatomy following ablative surgery or reconstruction by grafts and flaps may also increase implant failure in malignant cancer patients compared with healthy patients. The optimal head and neck oncology treatment-related healing time of implants before loading is still in need of further research and probably can be shortened significantly.

Eighth, patients in some studies were subject to adjunctive chemotherapy. The effect of chemotherapy on the osseointegration and survival of endosteal implants is not well established, even though it was shown that the risk of irradiation-induced bone damage is increased by chemotherapy. It is suggestive by animal model studies that chemotherapeutic agents have an adverse effect on normal physiological bone turnover, especially osteoblastic activity, and would also be expected to alter fracture-healing and bone-allograft incorporation by these same mechanisms. However, chemotherapy did not have a detrimental effect on the survival and success of dental implants in some studies, even though implant insertion in these studies was performed after at least 6 months after chemotherapy. Thus, it is unknown whether the time point of chemotherapy might be decisive.

Ninth, it is important that the patients are followed-up long enough before reporting implant success in irradiated bone. However, since the life-span prognosis for most patients
with oral malignant tumors is rather poor and the 5-year survival rate is reached by only approximately 50% of the patients, it is difficult to collect long-term data on implants placed in these patients. Moreover, one study showed that the early dropout after the final prosthetic treatment is high and that some patients were hindered to attend the regular recall sessions due to serious health conditions, which makes even more difficult to collect substantial data on the long-term. It is also important to stress that the patients with better oral and general health conditions are usually the ones who are more willing to pay a recall visit.

Moreover, one study showed that the early dropout after the final prosthetic treatment is high and that some patients were hindered to attend the regular recall sessions due to serious health conditions, which makes even more difficult to collect substantial data on the long-term. It is also important to stress that the patients with better oral and general health conditions are usually the ones who are more willing to pay a recall visit.

Tenth, reports of implants in tumor patients included all types of restorations. Data on the rehabilitation of a well-defined patient collective are rare. This does not allow identifying common characteristic traits and comparing various types of prostheses with regard to function and esthetics.

Thus, the results of the present study have to be interpreted with caution because of its limitations. First of all, all confounding factors may have affected the long-term outcomes and not just the fact that implants were placed in patients who were submitted to radiation therapy or not, and the impact of these variables on the implant survival rate, postoperative infection and marginal bone loss is difficult to estimate if these factors are not identified separately between the two different procedures in order to perform a meta-regression analysis. The lack of control of the confounding factors limited the potential to draw robust conclusions. Second, most of the included studies had a retrospective design, and the nature of a retrospective study inherently results in flaws. These problems were manifested by the gaps in information and incomplete records. Furthermore, all data rely on the accuracy of the original examination and documentation. Items may have been excluded in the initial examination or not recorded in the medical chart. Third, much of the research in the field is limited by small cohort size and short follow-up periods.
The failure of dental implants in irradiated patients is therefore subjected to many considerations and predictability is dependent upon issues like the use of HBO and chemotherapy, the timing of the implant placement in relation to radiation therapy, the radiation dosage, the insertion of implants in native of grafted bone, selection of anatomic site, the patients’ oral hygiene conditions and habits (smoking, drinking), the implant surface treatment, the prosthetic loading conditions, the type of prosthetic restoration, the period of follow-up, and risk of osteoradionecrosis.

CONCLUSION

The results of the present review should be interpreted with caution due to the presence of uncontrolled confounding factors in the included studies, none of them randomized. Within the limitations of the existing investigations, the present study suggests that irradiation negatively affects the survival rates of dental implants, as well as the difference in the implant location, i.e. maxilla or mandible. The study has failed to support the effectiveness of HBO therapy in irradiated patients requiring dental implants. It also suggests that there is no statistically significant difference in survival when implants are inserted before or after 12 months after the radiotherapy. It was observed a tendency to a lower survival rate of implants inserted in the patients submitted to higher irradiation doses.
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32. Andersson G,Andreasson L, Bjelkengren G. Oral implant rehabilitation in irradiated patients


FIGURE LEGENDS

Figure 1. Study screening process.

Figure 2. Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated patients.

Figure 3. Forest plot for the event ‘implant failure’ in the comparison between irradiated patients receiving vs. not receiving HBO.

Figure 4. Forest plot for the event ‘implant failure’ in the comparison between irradiated maxilla vs. irradiated mandible.

Figure 5. Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated maxilla.

Figure 6. Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated mandible.

Figure 7. Forest plot for the event ‘implant failure’ in the comparison between irradiated grafted bone vs. irradiated native bone.

Figure 8. Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated grafted bone.

Figure 9. Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated native bone.

Figure 10. Forest plot for the event ‘implant failure’ in the comparison between higher vs. lower irradiation dose.

Figure 11. Forest plot for the event ‘implant failure’ in the comparison between insertion of implants within 12 months after radiotherapy vs. after 12 months after radiotherapy.

Figure 12. Forest plot for the event ‘postoperative infection’ in the comparison between irradiated vs. non-irradiated patients.
Figure 13. Forest plot for the event ‘postoperative infection’ in the comparison between irradiated maxilla vs. irradiated mandible.

Figure 14. Forest plot for the event ‘marginal bone loss’ in the comparison between irradiated vs. non-irradiated patients.

Figure 15. Funnel plot for the studies reporting the outcome event ‘implant failure’.
Study screening process

1660 records identified through database searching

23 additional records identified through other sources

997 records after duplicates removed

919 records excluded

78 records screened

78 full-text articles assessed for eligibility

24 full-text articles excluded:
- 9 did not inform of the number of implants/group
- 1 not evaluating failures
- 2 earlier follow-up
- 2 same study published in another journal
- 6 evaluating implants in irradiated mandibles only
- 3 implants for craniofacial prostheses
- 1 did not insert implants in irradiated bone

54 studies included in qualitative synthesis

54 studies included in quantitative synthesis (meta-analysis)

John Wiley & Sons, Inc.
Forest plot for the event 'implant failure' in the comparison between irradiated vs. non-irradiated patients

412x359mm (300 x 300 DPI)
Forest plot for the event ‘implant failure’ in the comparison between irradiated patients receiving vs. not receiving HBO.

399x124mm (300 x 300 DPI)
Forest plot for the event ‘implant failure’ in the comparison between irradiated maxilla vs. irradiated mandible

379x198mm (300 x 300 DPI)
Forest plot for the event 'implant failure' in the comparison between irradiated vs. non-irradiated maxilla.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Irradiated Mx</th>
<th>Non-Irradiated Mx</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albrektsson et al.</td>
<td>3 Events</td>
<td>16 Total</td>
<td>3089 Total Weight</td>
<td>90.4%</td>
</tr>
<tr>
<td>Linse et al.</td>
<td>1 Events</td>
<td>17 Total</td>
<td>0 Total Weight</td>
<td>9.6%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>33</strong> Events</td>
<td><strong>3121 Total</strong></td>
<td><strong>100.0%</strong> Weight</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)
Forest plot for the event 'implant failure' in the comparison between irradiated vs. non-irradiated mandible

John Wiley & Sons, Inc.
Forest plot for the event 'implant failure' in the comparison between irradiated grafted bone vs. irradiated native bone.

355x130mm (300 x 300 DPI)
Forest plot for the event 'implant failure' in the comparison between irradiated vs. non-irradiated grafted bone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Irr.Grafted</th>
<th>N-Irr.Grafted</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>McGhee et al.</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Roumanas et al.</td>
<td>0</td>
<td>39</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>Pozen et al.</td>
<td>0</td>
<td>15</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Salinas et al.</td>
<td>14</td>
<td>51</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>Jacobsen et al.</td>
<td>8</td>
<td>13</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>Katsoulis et al.</td>
<td>6</td>
<td>20</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>301</td>
<td>100.0%</td>
<td>3.31 [2.02, 5.41]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>28</td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Forest plot for the event 'implant failure' in the comparison between irradiated vs. non-irradiated grafted bone

374x106mm (300 x 300 DPI)
Forest plot for the event ‘implant failure’ in the comparison between irradiated vs. non-irradiated native bone

360x106mm (300 x 300 DPI)
Forest plot for the event 'implant failure' in the comparison between higher vs. lower irradiation dose.

363x260mm (300 x 300 DPI)
Forest plot for the event ‘implant failure’ in the comparison between insertion of implants within 12 months after radiotherapy vs. after 12 months after radiotherapy

363x83mm (300 x 300 DPI)
Forest plot for the event ‘postoperative infection’ in the comparison between irradiated vs. non-irradiated patients

357x83mm (300 x 300 DPI)
Forest plot for the event ‘postoperative infection’ in the comparison between irradiated maxilla vs. irradiated mandible.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maxilla Events</th>
<th>Mandible Events</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adegheri et al.</td>
<td>0</td>
<td>1</td>
<td>0.67 [0.03, 14.35]</td>
<td>1996</td>
</tr>
<tr>
<td>Ali et al.</td>
<td>10</td>
<td>1</td>
<td>1.00 [0.04, 22.81]</td>
<td>1997</td>
</tr>
<tr>
<td>Bodard et al.</td>
<td>0</td>
<td>62</td>
<td>Not estimable</td>
<td>2006</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22</td>
<td>107</td>
<td><strong>0.81 [0.09, 7.27]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.85)
### Forest plot for the event ‘marginal bone loss’ in the comparison between irradiated vs. non-irradiated patients

409x76mm (300 x 300 DPI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Irradiated</th>
<th>Non-Irradiated</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Landes and Kovacs (1y)</td>
<td>1</td>
<td>0.8</td>
<td>72</td>
<td>0.4</td>
</tr>
<tr>
<td>Landes and Kovacs (2y)</td>
<td>1.4</td>
<td>0.9</td>
<td>72</td>
<td>0.4</td>
</tr>
<tr>
<td>Ghosein et al.</td>
<td>0.6</td>
<td>0.4</td>
<td>76</td>
<td>0.3</td>
</tr>
<tr>
<td>Total (85%)</td>
<td>220</td>
<td></td>
<td>148</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.12; \chi^2 = 23.72, df = 2 (P < 0.00001); I^2 = 92%$

Test for overall effect: $2 = 2.67 (P = 0.003)$
Funnel plot for the studies reporting the outcome event ‘implant failure’

224x140mm (300 x 300 DPI)