Time Interval after Radiotherapy and Dental Implant Failure: Systematic Review of Observational Studies and Meta-Analysis

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ABSTRACT

Background: Typically, dental implants are placed in irradiated bone after a delay that exceeds 6 months, but it is not known whether longer delays are beneficial.

Purpose: The purpose of the study is to review the literature comparing the failure rate of dental implants placed in irradiated bone between 6 and 12 months and after 12 months from the cessation of radiotherapy.

Materials and Methods: Four electronic databases were searched for articles published until February 2013 without language restriction: Lilacs, Medline, Scopus, and the Cochrane Central Register of Controlled Trials. Two reviewers independently assessed the eligibility criteria and extracted data. Fixed effect meta-analysis was performed.

Results: Overall, 3,749 observational studies were identified. After the screening of titles and abstracts, 236 publications were selected, and 10 were included in the final analysis. The pooled relative risk (RR) of failure was $RR_{pooled} = 1.34$ (95% confidence interval [CI]: 1.01–1.79), higher in individuals who had dental implants installed between 6 and 12 months after receiving radiotherapy. I^2 indicated nearly 21% heterogeneity ($p = .25$). Egger's test indicated no evidence of publication bias ($p = .62$); however, the removal of one study significantly affected the overall RR ($RR_{pooled} = 1.08$, 95% CI: 0.77–1.52).

Conclusions: Placing implants in bone within a period shorter than 12 months after radiotherapy may result in a higher risk of failure; however, additional evidence from clinical trials is needed to verify this risk.

KEY WORDS: dental implants, meta-analysis, osseointegration, osteoradionecrosis, radiotherapy

INTRODUCTION

Radiotherapy is common among patients with head and neck neoplasms as a primary therapy or as an adjuvant to surgery or chemotherapy. Several complications can occur as a result of irradiation. Osteoradionecrosis is the most serious complication because its treatment requires large resections of the bone involved, including dental extractions,[1] and its incidence has been estimated to be 7.4%,[2] although it has been reported to vary from 0.4% to 56%.[1]

Treatment with dental implants is considered to be relatively contraindicated in such cases, but there can be a significant benefit even if implants are installed in irradiated sites or in bone graft areas.[3–5] Evidence indicates that the failure rate of dental implants is higher in irradiated patients.[6,7] Therefore, clinicians should wait for a partial recovery of vascularization and the emergence of a new bone formation, which usually

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occurs within 3 to 6 months after radiotherapy, prior to implantion.[8,9] However, there is a controversy regarding the appropriate period for rehabilitation and placement timing,[10,11] and the optimal period may be as long as 9 months after the end of radiotherapy.[12]

Typically, studies of dental implants in irradiated bone tissue have examined an installation delay that exceeds 6 months.[12–16] However, no clinical studies have evaluated whether a delay longer than 6 months could be beneficial. Many observational studies report on the placement of implants after different delay periods, and many of these studies provide data on implants placed before and after 1 year following radiotherapy.[12–16] One systematic review described the success rates of dental implants among cancer patients but did not specifically evaluate the time delay or perform a meta-analysis.[17] Therefore, the objective of the present systematic review was to compare the risk of failure of dental implants placed within 6 and 12 months after the end of radiotherapy with the risk of those implants placed after 12 months from the end of radiotherapy.

METHODS

This study followed the meta-analysis of observational studies in epidemiology guidelines (MOOSE Statement) for reporting systematic reviews and meta-analyses of observational studies, which was also taken into consideration during the development of the study protocol.

Type of Study, Participants, Interventions, and Outcome

Preliminary database searches (including of the Cochrane Central Register of Controlled Trials) did not reveal any clinical trial. Therefore, we included any type of observational study (cross-sectional, case-control, or cohort) and case series conducted in humans. Editorials, narrative reviews, letters, in vitro studies, and animal studies were disregarded. Using the Population, Intervention, Control and Outcome (PICO) strategy, we defined our target population as any patient rehabilitated with dental implants who received irradiation in regions of the head and/or neck as a result of any type of malignant tumor. The *exposed group* (EG) was defined as individuals who received dental implants between 6 and 12 months after the end of radiotherapy, whereas the *control group* (CG) comprised individuals who received dental implants at least 12 months after the end of radiotherapy. We considered radiotherapy used to treat any type of malignant tumor. The outcome of interest was failure (success or failure) of the dental implants caused by any reason and measured by a clinical (implant mobility, peri-implantitis, lack of osseointegration, pain, osteoradionecrosis, or infection) or radiographic (radiolucent area) exam.

Studies were excluded if they contained no data that could be categorized in the aforementioned groups (within/after 12 months from the end of radiotherapy) or if the follow-up period was less than 6 months. Studies with short follow-up times were considered to be unable to assess the possibility of success and failure of dental implants.

Data Sources and Search Strategies

The search strategy included the following databases: Lilacs, Medline, Scopus, and the Cochrane Central Register of Controlled Trials without language restriction. We also checked the references cited in the included articles and tracked cited articles using SCOPUS citation tools. In addition, we identified five reviews regarding implants in irradiated patients and checked their references.[6,7,11,17,18] The authors of included studies (and other six potentially included) were contacted by e-mail and asked if they had knowledge of any other study that could be included and also to provide some extra information when needed (overall, five authors answered but no extra study could be added). Searching for grey literature (e.g., theses) and hand-searching of specific journals were not conducted. Publications up to February 2013 were initially included.

The descriptors used in the search strategy combined the following fields: (1) outcome descriptors, (2) dental implants, and (3) type of intervention (radiotherapy). Preliminary searches indicated that specific terms would result in very few publications retrieved. In contrast, nonspecific words (e.g., "failure") resulted in too many irrelevant publications being returned. After evaluating the results of particular search strategies, we adopted a combination of terms that was deemed to be sufficiently specific without losing sensitivity. For databases such as Medline, we used controlled vocabulary in the search strategy combined with free words in the title or abstract. For all other databases, the search strategy described was adapted. The full search was as follows:

1. "osteonecrosis"[Title/Abstract] OR "Osteonecrosis" [Mesh] OR ("necrosis" [Title/Abstract] AND

("mandible" [Title/Abstract] OR "maxilla"[Title/Abstract] OR bone [Title/Abstract])) OR ("Necrosis"[Mesh] AND ("Bone and Bones" [Mesh] OR "Mandible"[Mesh] OR "Maxilla"[Mesh])) OR "Peri – Implantitis"[Mesh] OR "Tooth Mobility"[Mesh]
2. Dental implant*[Title/Abstract] OR "osseointegration"[Title/Abstract] OR "osseointegration" [Title/Abstract] OR "Dental Implants"[Mesh] OR "Dental Implantation"[Mesh] OR "Osseointegration"[Mesh]
3. Radiotherapy[Title/Abstract] OR "Radiotherapy" [Mesh] OR ("Radiation, Ionizing"[Mesh]) AND "Neoplasms"[Mesh])
4. #1 **AND** #2.
5. #1 **AND** #3.
6. #2 **AND** #3.
7. #4 **OR** #5 **OR** #6.

The combination of strategies 1, 2, and 3 resulted in only five publications. Therefore, we opted to implement a dual combination as described above.

Data Extraction

The title and abstract of each article identified were screened by two reviewers (M.P.C. and S.A.M.J.) to determine whether the article should be further considered for inclusion. After the screening, the included articles were read in entirety for extraction of relevant data. Data extraction was independently performed by two reviewers (M.P.C. and either R.K.C. or S.A.M.J.) who were not blinded to the publication authors. Disagreements were resolved by discussion to reach a consensus.

Data were extracted using a standardized form with four parts. One part concerned the bibliometric characteristics of the articles. The second part contained the methodological features. The third part contained data on the outcome results. Finally, we extracted data on the potential factors that could explain data heterogeneity from the methodological, clinical, or contextual aspects of the articles, for example, country where the study was conducted, follow-up time, type and dose of radiation, use or nonuse of bone grafts, and any type of adjunct therapy, such as hyperbaric oxygenation.

Heterogeneity and Quality Assessment

Heterogeneity can occur as a result of differences in the clinical and methodological characteristics of studies. Therefore, key aspects of the research design as mentioned above were collected for future investigation. Heterogeneity was evaluated using the chi-square Q-test and the I-squared measure, which describes the fraction of the total variation across studies arising from heterogeneity rather than chance.[19,20] A preliminary analysis of the included studies verified that no significant statistical heterogeneity in pooled risk difference (RD) or in relative risk (RR) existed. Therefore, a fixed effects meta-analysis was performed.

Methodological quality was assessed based on a checklist of six common aspects assessed in observational studies:[21] (a) Were exposed and nonexposed individual selected from the same population? (b) Were prognostic factors (graft bone, radiation dose, sex, smoking, age, previous periodontal disease, hyperbaric oxygen [HBO] therapy) balanced among the groups? (c) What was the lost of follow-up if longitudinal? (d) Was the outcome measured in the same way for both groups by trained examiners? (e) Were examiners blinded to the exposure or study hypothesis? and (f) Were exposure or outcome measurement prone to memory bias?

Statistical Analysis

Data from each included study were described for both groups and summarized by a meta-analysis of fixed effects of the RR and the RD. In addition, the number needed to harm (NNH) was calculated. The presence of publication bias was assessed using a funnel plot and an analysis of the influence of each individual study to the overall effect.[20] All analyses were performed using Stata® version 11.2 (StataCorp, College Station, TX, USA).

RESULTS

Initially, the following number of articles were identified in the databases consulted: 76 in Lilacs (via the website of the Virtual Health Library: www.bireme.br), 1,451 in Medline (via PubMed), and 2,765 in Scopus. Of these articles, many were present in more than one database. After consolidation of the results, removing duplicates from different databases, using the program EndNote 9.01 (Thompson Reuters, Philadelphia, PA, USA), there were 3,746 distinct articles. Examination of the references of the included articles identified another 223, and 161 publications were identified from articles citing the included articles. After the application of selection criteria, 236 studies were selected for analysis of their full text. Preliminary research titles and abstracts are shown in the flowchart in Figure 1. Of the 236 articles selected for full-text reading, 1% was written in 1979, 4% in the 1980s, 36% in the 1990s, 45% from 2001 to 2010, and 14% in 2011 until 2013. The countries that contributed >5% of these 236 publications were as follows: the USA (28.2%), Germany (11.2%), Sweden (10.2%), the Netherlands (7.3%), and UK (5%). No article was excluded because it had a follow-up time of less than 6 months. Two articles were excluded[22,23] because they had an overlap of patients, and we kept the article with a larger sample size, which was also more recent. One article had only data with <17 months or more.[24] The most common reason for exclusion was a lack of time-delay data (108 studies), but we also excluded nine publications that were animal studies, or in vitro studies, one letter to the editor, 38 that were facial or nondental implant related, 26 that were narrative literature reviews, and 36 that were case reports (Figure 1). In the end, only 10 studies were included: nine in English and one in French.

Among the included studies (Table 1), 588 implants were placed between 6 and 12 months post-irradiation (EG), of which 80 failed (13.6%). One study reported a 25% failure rate,[12] whereas another study reported no failure.[25] In the CGs, 920 implants were placed, 92 failed (10.0%), and the failure percentage varied from 1.5%[26] to 17.7%.[27] Methodologically, the 10 included studies were fairly heterogeneous; five studies[12,16,25,26,28] included implants placed in mandibular and maxillary bone unbalanced between groups, four studies[26,28–30] included patients with implants in grafted bone, two studies[25,31] included implants placed before 6 months after radiotherapy, two studies included patients who received hyperbaric oxygen therapy (HBO), and one study[29] included all or almost all patients who received radiotherapy doses ≥50 Gy.

The methodological quality of the studies (Table 2) was difficult to assess because of a lack of information. Overall, most studies presented at least some possibility of selection bias and measurement bias. The more recent publications presented better descriptions of their critical study characteristics, and they tended to present better quality as well. When contacted through e-mail, only two of the authors answered, and one reported a lack of further information because the study was old. Therefore, some information could not be found for our tables.

The meta-analysis of the 10 included studies (Table 3 and Figure 2) indicated an overall effect RR = 1.34 (95% confidence interval [CI]: 1.01–1.79), that is, implants placed before 12 months postradiotherapy were 34% more likely to fail. In absolute terms, this represents a positive 3.6 percentage points (95% CI: -0.0–7.3), which indicates that the incidence of failure was higher in the EG that received implants before

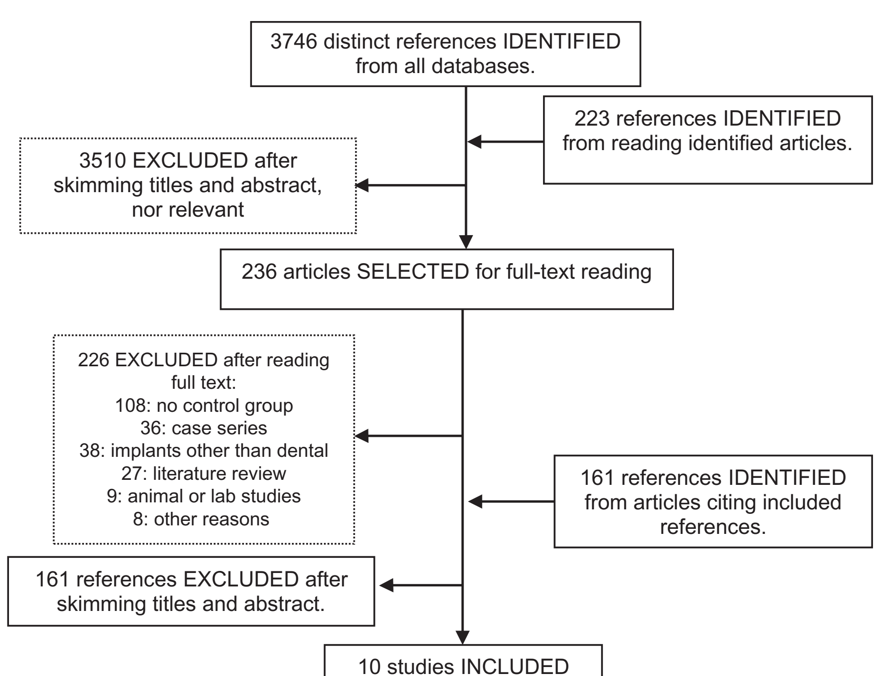

Figure 1 Flowchart of reviewed studies.

TABLE 1 Data Extracted from the Studies Included in the Systematic Review according to the Timing of Implant Placement after Radiotherapy

		Exposed Group (<12 months)					Control Group (>12 months)				
Study	Country	Patients (*n*)	Implants (*n*)	Failures (*n*)	Follow-Up (Months)	Risk of Failure (%)	Patients (*n*)	Implants (*n*)	Failures (*n*)	Follow-Up (Months)	Risk of Failure (%)
Jacobson (1988)[12]	Sweden	2	8	2	up to 30	25.0	7	27	4	up to 40	14.8
Ueda (1993)[25]	Japan	1	6	0	up to 11	0.0	3	12	1	>10	8.3
Lambert (1993)[30]	Belgium	5	28	1	up to 30	3.6	7	18	1	up to 40	5.6
Andersson (1998)[26]	Sweden	4	25	1	up to 40	4.0	11	66	1	up to 90	1.5
Niimi (1998)[10]	Japan–USA	11	25	4	up to 50	16.0	33	203	16	up to 50	7.9
Brogniez (1998)[28]	Belgium	10	30	1	up to 70	3.3	9	23	1	up to 70	4.3
Visch (2002)[16]	Holland	NI	175	29	up to 170	16.6	NI	271	35	up to 170	12.9
Yerit (2006)[29]	Austria	NI	143	29	up to 160	20.3	NI	173	15	up to 160	8.7
Schoen (2007)[31]	Holland	6	21	1	>12	4.8	20	82	10	>12	12.2
SamMartino (2011)[27]	Italy	NI	127	12	up to 70	9.4	NI	45	8	up to 170	17.7
Total		>29	588	80		13.6	>77	920	92		10.0

12 months after radiotherapy. Based on the RD (Table 3), the NNH was calculated as 28, which indicates that 28 dental implants needed to be placed in the exposed for one additional failure to occur in that group compared with the CG.

For the meta-analysis RR and RD, the heterogeneity was reasonable ($I^2 = 21.5\%$ and $I^2 = 36.1\%$, respectively) but not significant (heterogeneity tests, $p = .25$ and $.12$). A funnel plot (Figure 3) indicated a lack of publication bias, as all studies were inside the acceptable limits and were rather symmetrical. Publication bias was assessed using Begg's tests ($p = .79$) and Egger's test of bias ($p = .63$), and the results of both tests rejected the hypothesis of publication bias. However, an influence analysis (Table 4) indicated that one study was responsible for significant influence on the RR,[29] and the removal of that study from the meta-analysis reduced the RR to 1.08 (95% CI: 0.77–1.52).

DISCUSSION

The main finding of this systematic review was that placement of dental implants between 6 and 12 months postradiotherapy was associated with a 34% higher risk of failure. Such a result challenges the current understanding that 6 months, or perhaps 1 year, are sufficient for complete bone healing. Such risk is not only statistically significant but also clinically relevant. Furthermore, the absolute difference between the two groups was 3.6 percentage points, which indicates that for every 28 exposed implants, there would be one additional failure in this group. This absolute difference is likely to increase when the overall risk of failure increases. Among the included studies, the absolute risk of failure varied from 0% to 25% among the exposed patients. Furthermore, the follow-up time of CG was longer than the EG; had it been the same, the risk of failure among exposed would have been higher. Our RR could be higher because one study[24] that was excluded presented a RR of 2.3 (EG had 21% failures and nonexposed had 9%); however, the definition of exposed/not exposed did not fit fully our criteria.

This review covered the main journal databases in the field using a comprehensive search strategy that had no time or language restrictions. Although grey literature was not actively searched, there was no evidence of publication bias. In addition, abstract reading and data extraction were performed by two different researchers, and the original authors of the identified articles

TABLE 2 Quality Assessment of Included Studies

		Selection Bias			Measurement Bias		
Study: Author (Year)	Study Design	Exposed and Nonexposed Patients from the Same Population	Prognostic Factors* Balanced among the Groups	Losses during Follow-Up	Outcome Measured in the Same Way for Both Groups	Examiners Aware of Study Hypothesis	Measurement Prone to Memory Bias
Jacobson (1988)[12]	Retrospective	No information provided	No information provided	No information provided	No information provided	No information provided	Yes
Ueda (1993)[25]	Pilot study	All patients from the same hospital	Balanced only for age	No losses reported	No information provided	No information provided	Yes
Lambert (1993)[30]	Retrospective	No information provided	Not balanced for sex, age, radiation dose	No information provided	No information provided	No information provided	Yes
Andersson (1998)[26]	Retrospective	All patients from the same hospital	Balanced only for HBO	Informed	Yes	No information provided	Yes
Niimi (1998)[10]	Survey	Nine centers in Japan and two in the USA	No information provided	No information provided	No information provided	No information provided	Yes
Brogniez (1998)[28]	Retrospective	No information provided	Balanced only for HBO	Informed	Yes	No information provided	Yes
Visch (2002)[16]	Historical cohort	All patients from the same hospital	Balanced only for HBO	Informed	Yes	No information provided	Yes
Yerit (2006)[29]	Historical cohort	No information provided	Balanced only for HBO	Informed	Yes	No information provided	Yes
Schoen (2007)[31]	Longitudinal	All patients from the same university medical center	Yes	Informed	Yes	No	No
SamMartino (2011)[27]	Longitudinal	Three centers in Italy	Not balanced for sex and age	Informed	Yes	Conducted by three clinical examiners blinded to the interview results	No

*Factors: bone graft, radiation dose, sex, smoking, age, previous periodontal disease, and hyperbaric oxygen (HBO).

TABLE 3 Fixed-Effects Meta-Analysis of the RR among Observational Studies Examining the Failure of Dental Implants Placed between 6 and 12 Months (Exposure) and after (Controls) 12 Months from the Cessation of Head and Neck Radiotherapy

Study	Relative Risk	(95% CI)	Weight	Risk Difference†	(95% CI)	Weight
Jacobson (1988)[12]	1.69	(0.38 : 7.58)	2.8%	10.2	(−22.7: 43.0)	2.0%
Ueda (1993)[25]	0.62	(0.03 : 13.28)	1.6%	−8.3	(−34.1: 17.5)	1.3%
Lambert (1993)[30]	0.64	(0.04 : 9.64)	1.8%	−2.0	(−14.6: 10.6)	3.5%
Andersson (1998)[26]	2.64	(0.17 : 40.61)	0.8%	2.5	(−5.7: 10.7)	5.9%
Niimi (1998)[10]	2.03	(0.74 : 5.60)	5.3%	8.1	(−6.7: 23.0)	7.2%
Brogniez (1998)[28]	0.77	(0.05 : 11.62)	1.7%	−1.0	(−11.5: 9.5)	4.2%
Visch (2002)[16]	1.28	(1.82 : 2.02)	41.5%	3.7	(−3.1: 10.5)	34.4%
Yerit (2006)[29]	2.34	(1.31 : 4.19)	20.5%	11.6	(3.8: 19.4)	25.3%
Schoen (2007)[31]	0.39	(0.05 : 2.88)	6.2%	−7.4	(−19.0: 4.1)	5.4%
SamMartino (2011)[27]	0.53	(0.23 : 1.22)	17.8%	−8.3	(−20.6: 3.9)	10.8%
Mantel-Haenszel pooled	**1.34***	(1.01 : 1.79)	100.0%	**3.6****	(−0.0: 7.3)	100.0%

*Heterogeneity Test (chi-square) $p = .25$; $I^2 = 21.5\%$.
**Heterogeneity Test (chi-square) $p = .12$; $I^2 = 36.1\%$.
†Percentage points.
CI, confidence interval; RR, relative risk.

were contacted. Furthermore, MOOSE[32] guidelines were followed to ensure critical quality points. Despite the use of MOOSE guidelines, some limitations of the meta-analysis should be highlighted. First, the validity of results for any systematic review depends largely on the quality and quantity of the included studies. In our analysis, there were no randomized clinical trials, and even the best observational study may be equivocal because of selection or measurement bias and lack of control for confounding variables. Among the 10 included studies, the quality was rather low, and some methodological characteristics were reported. We acknowledge that publication bias is better detected with more than 10 studies,[33] and our analysis may have

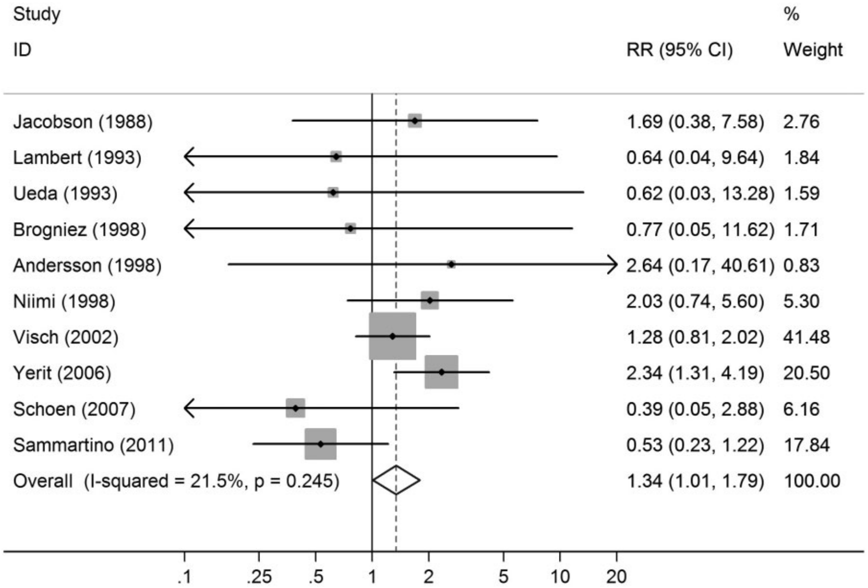

Figure 2 Forest plot of meta-analysis of the risk of failure of dental implants placed between 6 and 12 months (exposure) and after (controls) 12 months from the cessation of radiotherapy.

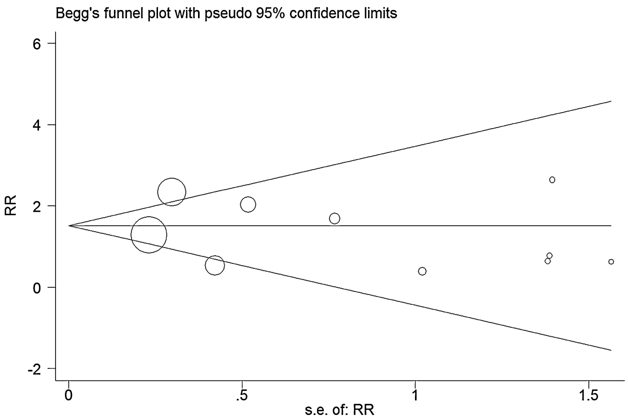

Figure 3 Begg's Funnel plot of the risk of failure of dental implants and timing of placement in the 10 included studies to evaluate potential publication bias.

suffered from a lack of power. Finally, the number of implants per patient may be an issue because of autocorrelation in cases where one patient received more than one implant, and different patients received different numbers of implants.

A fixed-effect meta-analysis was performed, as there was no evidence of heterogeneity, which suggests that the results are robust and that the variability is caused by chance. The methodological characteristics and the presence of prognostic factors differed considerably. Nonetheless, the characteristic and prognostic factor differences did not explain the differences in RR among the studies. If any bias existed, it equally affected all studies. For example, patients with a worse prognosis may be the first ones to be considered for implants in all studies, and thus, those with implants placed before 1 year postradiotherapy may have a higher rate of failure. Importantly, caution is warranted, as only one study had a statistically significant association with the RR of failure, and the overall meta-analysis depended to some extend on that study.[29] Although the removal of that study did not change the direction of the association, the study[31] with the best methodological quality pointed in the opposite direction (RR = 0.39).

TABLE 4 Analysis of the Influence of Removing Individual Studies on the Overall Relative Risk Obtained from a Fixed-Effects Meta-Analysis

Study Removed	Overall Relative Risk	(95% Confidence Interval)
Jacobson (1988)[12]	1.33	(0.99–1.79)
Ueda (1993)[25]	1.35	(1.01–1.81)
Lambert (1993)[30]	1.35	(1.01–1.81)
Andersson (1998)[26]	1.33	(0.99–1.78)
Niimi (1998)[10]	1.30	(0.96–1.76)
Brogniez (1998)[28]	1.35	(1.01–1.80)
Visch (2002)[16]	1.38	(0.95–2.00)
Yerit (2006)[29]	1.08	(0.77–1.52)
Schoen (2007)[31]	1.40	(1.05–1.88)
SamMartino (2011)[27]	1.51	(1.11–2.07)
Combined (overall)	1.34	(1.01–1.79)

The literature suggests that patients treated with radiation doses exceeding 50 Gy are at an increased risk of failure of osseointegration of dental implants because of the loss of the ability to repair and neovascularize the irradiated bone.[16,29,34–36] However, in this review, the radiation dose did not modify the association of the RR of failure. The literature also indicates that adjuvant HBO therapy reduces the risk of failure of the implant in the irradiated head and/or neck of patients because the exposure of irradiated bone to HBO increases the number of capillaries and fibroblasts.[3,4,8,10,22] However, such an effect was not observed in this review, as the additional use of HBO therapy did not alter the RR of failure, which agrees with the results of Esposito and colleagues,[5] who found that HBO is not an essential therapy for implants being placed in irradiated patients.

In most of the studies included, but not in all, failure could be attributed to the effect of radiation. Radiation induces hypocellularity in bone tissue, combined with vascular and cellular effects, which disrupts the dynamic balance of the process of bone resorption and overhaul.[37] In addition to delayed bone healing, another important result of radiotherapy is reduced bone neovascularization.[38] A new hypothesis proposes that osteoradionecrosis occurs as a result of a radiation-induced fibro-atrophic mechanism that includes free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling, and finally, bone and tissue necrosis.[39] Therefore, the key event in the progression of osteoradionecrosis is the activation and deregulation of fibroblastic activity that lead to atrophic tissue within the previously irradiated area.[40–42] Finally, it has been reported that the risk of development of osteoradionecrosis depends on the radiation dose as well as the fractioning and volume of the irradiated tissue.[16,29,34–36]

In conclusion, a minimum waiting period of 6 months postradiotherapy prior to dental implantation is unlikely to be the most suitable, and healing periods with duration over 1 year may be beneficial. However, the evidence is not strong, and specific clinical trials are needed. Furthermore, differences in the reasons for failure should be considered, as they may vary over time. Clinicians should use the best evidence available and wait, if possible, longer than 12 months after completion of radiotherapy to install dental implants.

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