CLINICAL REVIEW

Dental Implants Installed in Irradiated Jaws: A Systematic Review

L. Chambrone¹, J. Mandia Jr², J.A. Shibli³, G.A. Romito^{1*}, and M. Abrahao²

Abstract: *The aim of this study was to assess the survival rate of titanium implants placed in irradiated jaws. MEDLINE, EMBASE, and CENTRAL were searched for studies assessing implants that had been placed in non-grafted sites of irradiated patients. Random effects meta-analyses assessed implant loss in irradiated versus non-irradiated patients and in irradiated patients treated with hyperbaric oxygen (HBO) therapy. Of 1,051 potentially eligible publications, 15 were included. A total of 10,150 implants were assessed in the included studies, and of these, 1,689 (14.3%) had been placed in irradiated jaws. The mean survival rate in the studies ranged from 46.3% to 98.0%. The pooled estimates indicated a significant increase in the risk of implant failure in irradiated patients (risk ratio: 2.74; 95% confidence interval: 1.86, 4.05; $p < .00001$) and in maxillary sites (risk ratio: 5.96; 95% confidence interval: 2.71, 13.12; $p < .00001$). Conversely, HBO therapy did not reduce the risk of implant failure (risk ratio: 1.28; 95% confidence interval: 0.19, 8.82; $p = .80$). Radiotherapy was linked to higher implant failure in the maxilla, and HBO therapy did not improve implant survival. Most included publications reported data on*

machined implants, and only 3 studies on HBO therapy were included. Overall, implant therapy appears to be a viable treatment option for reestablishing adequate occlusion and masticatory conditions in irradiated patients.

Key Words: radiotherapy, osseointegration, prognosis, cranial irradiation, dental implantation/endosseous, meta-analysis.

Introduction

The success of implant-supported restorations is associated with effective osseointegration of the dental implant, the health of the peri-implant tissue, and the reestablishment of function and aesthetics (Amarante *et al.*, 2008; Faggion *et al.*, 2011; Mangano *et al.*, 2011). Other conditions may be associated with implant failure in specific groups of patients who are systemically compromised, including those suffering from head and neck cancer. Worldwide, head and neck cancers are among the most common types of cancer and are likely to occur more frequently among elderly people (Parkin *et al.*, 2005). Subjects treated with radiation therapy to the head present with decreased saliva

production, local vascularity and cellular production, and an increased risk for osteoradionecrosis and mucositis (Marx and Johnson, 1987; National Institutes of Health, 1989; Meraw and Reeve, 1998; Coulthard *et al.*, 2008). Thus, irradiation may play a key role in the prognosis of patients treated with dental implants.

Previous studies have reported contrasting outcomes regarding implants placed in irradiated jaws. Granstrom *et al.* (1994) found an increased rate of implant loss in irradiated subjects compared with nonirradiated ones. Conversely, Buddula *et al.* (2011) reported high success rates of implants placed in grafted (98.1%) and native (100.0%) mandibular bones over a 3-year period. Moreover, 2 publications using animal models have shown that implant stability during osseointegration may be impaired in irradiated jaws because of the decrease in bone vascularity and vitality (Verdonck *et al.*, 2008b); however, in the short term, the bone mineral density seems to be similar to that of nonirradiated alveolar bone (Verdonck *et al.*, 2008a). Similarly, Brasseur *et al.* (2006) showed higher bone resorption around implants placed in irradiated areas, but they considered osseointegration to be “compatible with bone irradiation, as bone turnover activities were

DOI: 10.1177/0022034513504947. ¹Division of Periodontics, Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, SP, Brazil; ²Department of Otorhinolaryngology and Head and Neck Surgery, Federal University of São Paulo, São Paulo, Brazil; ³Department of Periodontology and Oral Implantology, Dental Research Division, Guarulhos University, SP, Brazil; *corresponding author, garomito@usp.br

A supplemental appendix to this article is published electronically only at <http://jdr.sagepub.com/supplemental>.

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maintained throughout the experiment.” It has been suggested that a six-month period between irradiation and implantation should be implemented to allow improved bone apposition and adequate osseointegration (Brasseur *et al.*, 2006). This finding is in line with data from Brogniez *et al.* (2002), who reported progressive deposition of woven and lamellar bone around implants placed before or after irradiation of the bone, as well as a positive balance between bone resorption and remodeling after 8 weeks of radiotherapy. Histologic data on removed implants from irradiated human jaws suggest that bone anchorage of these implants is feasible (Bolind *et al.*, 2006). It has been shown that within a short time *in situ* (2 mos), implants may develop a dense connective tissue layer near the bone-to-implant interface and sparse bone-to-implant contact (mean, 33%) compared with implants that have been *in situ* longer (> 36 mos) (Bolind *et al.*, 2006).

No systematic review has focused on this topic. Therefore, the aim of this systematic review was to evaluate the survival rate of titanium implants placed in irradiated jaws. The following focused question was answered: “Does radiation therapy to the head decrease the survival rate of titanium dental implants placed in nongrafted jaws?”

Materials & Methods

This review was prepared in accordance with guidelines from PRISMA (Moher *et al.*, 2009), the Cochrane Collaboration (Higgins and Green, 2011), and Check Review (Chambrone *et al.*, 2010b).

Type of Studies and Inclusion Criteria

Observational studies reporting outcomes from irradiated and nonirradiated patients were considered eligible for inclusion, as were randomized controlled trials (RCTs) and controlled clinical trials assessing irradiated patients submitted to different implant-based treatment protocols. The inclusion criteria involved the following: (1) titanium implants were placed in patients who

had undergone radiation therapy to the head to treat cancer, and (2) outcomes from irradiated and nonirradiated patients/implants were reported separately. Studies reporting data from irradiated patients, some of whom had been subject to bone-grafting procedures, were included only when the outcomes from nongrafted areas were reported separately.

Exclusion Criteria

Studies reporting data on implants placed only in grafted areas were excluded from the review.

Outcome Measure

The outcome measure was the number and/or percentage of implants lost as reported by each study (overall number of implants lost and/or the number of implants lost per patient).

Search Strategy

Comprehensive search strategies were established to identify studies for this systematic review. The MEDLINE (via PubMed), EMBASE, and CENTRAL databases were searched for articles published before February 1, 2013, based on the MEDLINE search strategy (Appendix S1). Databases were searched without language restrictions using MeSH terms, key words, and other free terms; Boolean operators (OR, AND) were used to combine searches. Unpublished studies were identified by searching the OpenGRAY database, and reference lists of any potential articles were examined. Four dental implant journals were identified as being important to this review—namely, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *International Journal of Oral and Maxillofacial Implants*, and *Journal of Oral and Maxillofacial Surgery*—and their electronic databases were searched.

Assessment of Validity and Data Extraction

Two independent reviewers (J.M. and G.A.R.) screened the titles, abstracts, and full texts of the articles that were identified. Disagreement between

the reviewers was resolved through discussion, and consensus was reached. When agreement could not be reached, a third reviewer (L.C.) was consulted. When important data for the review were missing, we attempted to contact the authors to resolve ambiguity from the trials. The following data were extracted and recorded in duplicate: citation, publication status, and year of publication; location of the trial; study design; characteristics of the participants; outcome measures; methodological quality of the trials; and conclusions.

Quality Assessment and Risk of Bias in Included Studies

Two methodological quality assessment tools were used on the basis of the type of study. For RCTs and controlled clinical trials, the methodological quality of the trials (Appendix S2) was evaluated per the Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green, 2011), as adapted by Chambrone *et al.* (2010a). Briefly, the randomization and allocation methods were classified as *adequate*, *inadequate*, *unclear*, or *not applicable*, whereas the completeness of the follow-up period and blinding of examiners were coded as *yes/no* responses. Based on these answers, the risk of bias was categorized according to the following classifications: (1) a low risk of bias if all criteria were met (*i.e.*, adequate methods of randomization and allocation concealment and a *yes* answer to all questions about completeness of follow-up questions and masking of examiners), (2) an unclear risk of bias if one or more criteria were partly met (*i.e.*, unclear criteria were set), or (3) a high risk of bias if one or more criteria were not met.

For the observational studies, an adapted version (Chambrone *et al.*, 2013a, 2013b, 2013c) of the Newcastle-Ottawa scale (Wells *et al.*, 2001) was used to assess the methodological quality (Appendix S3). The following topics were evaluated:

- selection of study groups (sample size calculation, representativeness of the irradiated patients, and selection of the nonirradiated patients), ascertainment or assessment of peri-implant

Figure 1.

Flow chart of articles screened through the review process.

conditions, clarity in the description of radiotherapy timing, training or calibration of assessors of outcomes, data collection methods, and use of clear inclusion/exclusion criteria;

- comparability (comparability of patients based on study design/analysis and management of confounders);
- outcome (evaluation of results, ascertainment or criteria applied to confirm exposure to radiation, and adequacy of patient follow-up); and
- statistical analysis (appropriateness/validity of statistical analysis and unit of analysis reported).

Additionally, stars/points were given for each methodological quality criterion, and each included study could receive a maximum of 14 points. Studies with 11 to 14 points (approximately 80% or more of the domains satisfactorily fulfilled) were arbitrarily considered to be of high quality; studies with 8 to 10 stars were of medium quality; and studies with fewer

than 8 stars were of low methodological quality.

Data Synthesis

The data were pooled into evidence tables, and a descriptive summary was created to determine the quantity of data and study variations (characteristics and results). If a study did not report raw data on implant loss but did present percentages regarding the outcome of interest, the summary was converted when necessary. Random effects meta-analyses were performed throughout the review using dichotomous data (*i.e.*, number of implants lost per group/total number of implants assessed), and the results were expressed as pooled risk ratios (RR) and associated 95% confidence intervals (CIs). The significance of discrepancies in the estimates of the treatment effects from the different trials was assessed by means of the Cochrane test for heterogeneity and the I^2 statistic (Higgins and Green,

2011). The analyses were performed using Review Manager statistical analysis software (Version 5.0, Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search

The search strategy yielded 1,051 articles. Of these, 1,029 were excluded after review of the title or abstract. Twenty-two full-text articles were examined, but only 15 fulfilled the proposed inclusion criteria for the review (Figure 1).

Included Studies

Thirteen case series were considered eligible for inclusion (Albrektsson *et al.*, 1988; Eckert *et al.*, 1996; Niimi *et al.*, 1997; Andersson *et al.*, 1998; Brogniez *et al.*, 1998; Esser *et al.*, 1999; Granstrom *et al.*, 1999; Werkmeister *et al.*, 1999; Goto *et al.*, 2002; Visch *et al.*, 2002; Landes and Kovacs, 2006; Schepers *et al.*, 2006; Katsoulis *et al.*, 2013),

Table 1.

Characteristics of Included Studies Evaluating Irradiated and Nonirradiated Patients

Study	Methods	Participants	Results	Conclusions	Notes
Albrektsson <i>et al.</i> (1988)	CS, retrospective design, data from 14 centers, up to 8 yrs of follow-up	7996 implants in nonirradiated jaws and 49 in irradiated jaws Number of smokers not reported Branemark-type implants	Implants placed in irradiated jaws = 33 mand/16 max Implants placed in nonirradiated jaw = 4907 mand/3089 max 3 implants lost in irradiated jaws (6.1%)—all in the maxilla 270 implants lost in nonirradiated jaws (3.4%)—52 in the mandible and 218 in the maxilla	“In the case of irradiation, however, the outcomes may definitely depend on the given dose and the time since the exposure”	University hospital and practice based (Sweden) Data derived from 14 practices
Esser <i>et al.</i> (1999)	CS, retrospective design, mean follow-up of 58.2 mos	62 patients (34 irradiated and 28 nonirradiated) and 276 implants Number of smokers not reported Branemark-type implants	Implants placed in irradiated mandible = 148 Implants placed in nonirradiated jaw = 128 9 implants lost in irradiated jaws (6.1%) ^a 4 implants lost in nonirradiated jaws (3.1%) ^a	“The available results and clinical studies support a positive assessment of the regenerative potential of the irradiated mandible with regard to osteointegration of endosseous implants”	University hospital based (Germany)
Granstrom <i>et al.</i> (1999)	CS, retrospective design, up to 15.1 yrs of follow-up	Data on 78 patients (52 irradiated and 28 nonirradiated) and 335 implants Number of smokers not reported Branemark-type implants	Implants placed in irradiated jaws = 147 Implants placed in irradiated jaws + hyperbaric oxygen therapy = 99 Implants placed in nonirradiated jaw = 89 79 implants lost in irradiated jaws (53.7%) 8 implants lost in irradiated jaws + hyperbaric oxygen therapy (8.1%) 12 implants lost in nonirradiated jaws (13.5%)	“Irradiation causes significant changes in the host bone bed that reduce the potential for osseointegration, thus increasing implant loss; and that adjunctive hyperbaric oxygen treatment can improve osseointegration”	University hospital based (Sweden)
Katsoulis <i>et al.</i>, (2013)^b	CS, retrospective design, up to > 24 mos of follow-up	Data on 46 patients (19 died after the treatment) and 104 implants (58 placed in native bone) Number of smokers not reported Type of implant not reported Irradiation before implant placement	Implants placed in irradiated jaws = 42 Implants placed in nonirradiated jaws = 16 8 implants lost in irradiated jaws (19.0%) 2 implants lost in nonirradiated jaws (12.5%)	“In spite of disease-related local and general restrictions, most patients gave a positive assessment of quality of life”	University hospital based (Switzerland)
Landes and Kovacs (2006)	CS, prospective design, up to 46 mos of follow-up	Data on 30 patients (5 dropped out of the 12 month recall) and 114 implants Number of smokers not reported TPS and SLA implants Irradiation before implant placement	Implants placed in irradiated jaws = 72 mand (11 TPS and 61 SLA) Implants placed in nonirradiated jaws = 42 mand (4 TPS and 38 SLA) 1 implant lost in irradiated jaws (2.0%) No implants were lost in nonirradiated jaws	“Non-submerged healing and early loading have been shown to be reliable in irradiated and non-irradiated cases in a 2-year follow-up”	University hospital based (Germany)

(continued)

Table 1.
(continued)

Study	Methods	Participants	Results	Conclusions	Notes
Niimi <i>et al.</i> (1997)	CS, retrospective design, up to 73 mos of follow-up	Data on 24 irradiated patients and 118 implants Number of smokers not reported Branemark-type implants Irradiation before implant placement	Implants placed in irradiated jaws = 22 max/57 mand Implants placed in irradiated jaws + hyperbaric oxygen therapy = 17 max/14 mand 6 max/2 mand implants lost in irradiated jaws (10.1%) 3 max/1 mand implants lost in irradiated jaws + hyperbaric oxygen therapy (12.9%)	"The mandible provides a high degree of predictability. However, for the maxilla, predictability is fairly low, even when adjunctive HBO is used"	University hospital based (Japan) Data derived from 9 practices
Schepers <i>et al.</i> (2006)	CS, retrospective design, up to 73 mos of follow-up	Data on 48 patients (21 irradiated and 27 nonirradiated) and 139 implants 11 smokers Branemark-type implants Irradiation after implant placement	Implants placed in irradiated mandible = 61 Implants placed in nonirradiated mandible = 78 2 implants lost in irradiated mandible (3.3%) No implants loss in nonirradiated mandible	"Postoperative radiotherapy does not affect the osseointegration of dental implants placed during tumor ablation and the ultimate number of functional dentures"	University hospital based (Netherlands)
Werkmeister <i>et al.</i> (1999)	CS, retrospective design, up to 15.1 yrs of follow-up	Data on 29 patients (12 irradiated and 17 nonirradiated) and 64 implants ^b Number of smokers not reported Branemark-type implants	Implants placed in irradiated jaws = 30 Implants placed in nonirradiated jaws = 34 8 implants lost in irradiated jaws (53.7%) 5 implants lost in nonirradiated jaws (26.6%)	"Unfavorable results in non-irradiated and irradiated patients in this study were probably due to soft tissue conditions, persisting heavy alcohol consumption and smoking by the majority of the patients."	Hospital based (Germany)

CS, case series; mand, mandibular; max, maxillary; NR, not reported; SLA, sandblasted and acid etched; TPS, titanium plasma sprayed.

^aRaw data calculated from the percentages of implants lost reported by the original study.

^bAn approximate number of implants was calculated based on the survival rate (%), as well only data from implants placed in residual bone were extracted from the study.

as were 2 RCTs (Schoen *et al.*, 2007; Heberer *et al.*, 2011) (Tables 1-3). A total of 10,150 implants were assessed in the included studies, and of these, 1,689 (14.3%) were installed in irradiated jaws.

Risk of Bias in the Included Trials

Among the observational studies that were included, 3 were of medium quality (Esser *et al.*, 1999; Visch *et al.*, 2002; Landes and Kovacs, 2006), whereas the remaining were of low quality (Figure 2). The findings regarding the domains of the modified Newcastle-Ottawa scale were as follows:

1: none of the studies reported sample size calculations;

2 and 3: in all of the studies, the representativeness of the irradiated and nonirradiated (when described) patients was considered to be adequately addressed;

4: assessment of peri-implant conditions was considered adequate in 8 studies (Albrektsson *et al.*, 1988; Andersson *et al.*, 1998; Brogniez *et al.*, 1998; Esser *et al.*, 1999; Granstrom *et al.*, 1999; Goto *et al.*, 2002; Visch *et al.*, 2002; Landes and Kovacs, 2006) and unclear for the remaining articles;

5: only Albrektsson *et al.* (1988) and Granstrom *et al.* (1999) did not describe whether radiotherapy was performed before or after implant placement;

6: none of the studies reported training or calibration of the examiners of clinical outcome;

7: 2 studies had a prospective design (Visch *et al.*, 2002; Landes and Kovacs, 2006);

8: 2 studies reported that all patients received similar implant therapy (Esser *et al.*, 1999; Schepers *et al.*, 2006);

9: 1 publication described statistical assessment performed with control for confounders (Visch *et al.*, 2002);

10: none of the authors described whether independent blind assessment of peri-implant conditions was used;

Table 2.
Characteristics of Included Case Series Evaluating Only Irradiated Patients

Study	Methods	Participants	Results	Conclusions	Notes
Andersson <i>et al.</i> (1998)	CS, retrospective design, 1 to 8 yrs of follow-up	Data on 15 patients and 90 implants in irradiated jaws were available for analysis	Implants placed in irradiated jaws = 78 mand/12 max 2 implants lost in irradiated jaws (2.2%)—all in the mandible	"Implant treatment for oral rehabilitation can be carried out as a safe procedure in patients irradiated for cancer in the head and neck region without adjunctive hyperbaric oxygen"	University hospital based (Sweden)
Brogniez <i>et al.</i> (1998)	CS, retrospective design, mean follow-up of 38 mos	Data on 19 patients and 53 implants in irradiated jaws were available for analysis	Implants placed in irradiated jaws = 50 mand/3 max 2 implants lost in irradiated jaws (4%)—all lost in the mandible	"Based on the clinical results of this investigation, bone irradiation is no longer a contraindication for prosthetic reconstruction"	University hospital based (Belgium)
Eckert <i>et al.</i> (1996)	CS, retrospective design	Data on 111 implants in irradiated jaws were available for analysis	Implants placed in irradiated jaws = 89 mand/22 max 9 implants lost in irradiated jaws (8.1%)—1 in the mandible and 8 in the maxilla	"Implant survival in the maxilla demonstrated less encouraging results with only a 64% survival rate"	University hospital based (US)
Goto <i>et al.</i> (2002) ^a	CS, retrospective design, up to 12 yrs of follow-up	Data on 36 patients and 112 implants in irradiated jaws were available for analysis	Implants placed in irradiated jaws = 65 mand/47 max 11 implants lost in irradiated jaws (9.8%)—1 in the mandible and 10 in the maxilla	"The clinical results obtained in the present study compare favorably with those obtained in other institutions"	University hospital based (Japan)
Visch <i>et al.</i> (2002)	CS, prospective design, up to 14 yrs of follow-up	Data on 130 patients and 446 implants in irradiated jaws were available for analysis	Implants placed in irradiated jaws = 338 mand/108 max 64 implants lost in irradiated jaws (14.3%)—31 in the mandible and 33 in the maxilla	"Implant survival is significantly influenced by the location (maxilla or mandible, 59% and 85%, respectively; $p = 0.001$)"	University hospital based (Netherlands)

CS, case series; mand, mandibular; max, maxillary; NR, not reported.

^aRaw data calculated from the percentages of implants lost reported by the original study.

- 11: all of the studies described the radiation doses used for oncologic treatment, except for Albrektsson *et al.* (1988);
- 12: in 2 publications, > 70% of the treated patients were followed during the entire study period (Landes and Kovacs, 2006; Katsoulis *et al.*, 2013);
- 13: Esser *et al.* (1999), Granstrom *et al.* (1999), Schepers *et al.* (2006), Werkmeister *et al.* (1999), Goto *et al.* (2002) and Visch *et al.* (2002) compared their outcomes using statistical analyses; and
- 14: all authors defined the number of patients and/or implants per group as the unit of analysis.

Both RCTs were considered to have an unclear risk of bias because the methods

of randomization (Heberer *et al.*, 2011), allocation concealment (Schoen *et al.*, 2007; Heberer *et al.*, 2011), and blinding (Heberer *et al.*, 2011) were not described or could not be identified.

Individual Outcomes and Pooled Estimates of Studies

Most of the studies reported that implant survival was adversely affected by radiotherapy, but they also found that implant survival rates in irradiated patients may have been > 80% (Tables 1-3). Overall, the mean survival rate ranged from 46.3% to 98.0% among the studies, and some studies reported that implants placed in irradiated mandible showed better survival rates.

Similarly, the pooled estimates (Figure 3) revealed a significantly increased

risk of implant loss in irradiated patients when the outcomes of 7 publications were included in the meta-analysis (RR: 2.74; 95% CI: 1.86, 4.05; $p < .00001$, $I^2 = 0\%$). The meta-analysis determined the impact of implant loss in irradiated patients according to implant location (maxilla or mandible), with maxillary implants exhibiting 496% greater losses (RR: 5.96; 95% CI: 2.71, 13.12; $p < .00001$, $I^2 = 33\%$). Conversely, analyses that included only data from studies comparing implant loss in irradiated patients who received hyperbaric oxygen (HBO) therapy with implant loss in those who did not showed no significant differences between these groups (RR: 1.28; 95% CI: 0.19, 8.82; $p = .80$, $I^2 = 91\%$).

Table 3.

Characteristics of Randomized Trials Evaluating Irradiated and Nonirradiated Patients

Study	Methods	Participants	Results	Conclusions	Notes
Heberer <i>et al.</i> (2011)	RCT, split-mouth design, data from 14 centers, mean follow-up period of 14.4 mos	20 irradiated patients and 102 implants Only nonsmokers were included Control group: SLA implants Test group: SLActive implants	SLA implants placed = 23 mand/27 max SLActive implants placed = 24 mand/28 max 5 maxillary implants were excluded from the analysis (2 SLA and 3 SLActive) 2 SLA implants lost (4.0%)—all in the mandible No SLActive implants were lost	“Sandblasted, acid-etched implants with or without a chemically modified surface can be loaded early in irradiated patients with a high predictability of success within 1 year after loading”	University hospital based (Germany) This study was partially funded by Straumann AG, Waldenburg, Switzerland
Schoen <i>et al.</i> (2007)	RCT, parallel design, up to 73 mos of follow-up	Data on 26 irradiated patients and 103 implants Number of smokers not reported Branemark-type implants Irradiation before implant placement	Implants placed in irradiated mandible = 54 Implants placed in irradiated mandible + hyperbaric oxygen therapy = 49 3 implants lost in irradiated mandible (5.5%) 8 implants lost in irradiated mandible + hyperbaric oxygen therapy (16.3%)	“HBO therapy does not influence the failure rate of implants inserted in mandibles when compared to patients treated without HBO therapy”	University hospital based (Netherlands)

mand, mandibular; max, maxillary; NR, not reported; RCT, randomized controlled trial; SLA, sandblasted and acid etched; SLActive, modified sandblasted and acid etched.

Discussion

Summary of the Main Findings

The negative effect of radiotherapy on implant survival at residual/native bone sites was confirmed. Most studies reported greater implant loss rate in irradiated maxilla (Tables 1-3), and the pooled estimates (Figure 3) derived from the number of failed implants as a percentage of the total number of implants placed revealed a 174% increase in the risk of loss when the implants were placed in irradiated bone. Maxillary implants placed within irradiated jaws exhibited a 496% increase in the risk of loss compared with mandibular implants. The pooled estimates also indicated that HBO therapy in irradiated patients did not affect implant loss, and there was significant heterogeneity between the individual study estimates.

Quality of the Evidence and Potential Biases in the Review Process

None of the RCTs included in this review were considered to have a

low risk of bias, and none of the observational studies were classified as being of high methodological quality. Case series have noteworthy methodological weaknesses, and their inclusion in a systematic review may lead to inaccurate suppositions in relation to the review's focused question (Chambrone *et al.*, 2010b). Even in meta-analyses in which no significant heterogeneity was identified, additional forms of bias, such as selection and publication bias, may influence outcomes, as may differences in the timing of radiotherapy (whether it occurred before or after implant placement), radiation dose, the type of implant placed, differences between patients' systemic conditions (smoking status), occlusal factors, and follow-up period. Because of the lack of information regarding these issues, they were not considered in the meta-analyses. Because the aim of the review was to evaluate prognosis, in cases where there is a lack of studies with high levels of evidence, other prospective or

retrospective studies (*i.e.*, case series) can serve the purposes of a review as well.

It should be noted that the data reported in the included case series differed as a result of differences in inclusion/exclusion criteria and in treatment protocols and because they were derived from retrospective data collection (Tables 1 and 2). In addition, although implant survival/loss was the outcome of interest reported by these studies, this measure should not be the key and/or unique factor determining implant success (Needleman *et al.*, 2012). Alternatively, implant loss/success should be determined after a broad assessment of clinical/radiographic outcomes, including attachment level, probing depth, bleeding on probing, suppuration, and mobility (Needleman *et al.*, 2012). All the included studies described the results from subjects treated with more than 1 implant. Individual patient data or individual studies' adjusted odds/risk ratios are needed to calculate more accurate pooled estimates (Chinn, 2000; O'Keefe

Figure 2.

Methodological quality of included observational studies (stars assigned to respective study).

and Hale, 2001; Chambrone *et al.*, 2012, 2013a,c) by taking into account the implant weakness or susceptibility to failure. Instead, we opted to use the reported number of failed implants and the number of total implants installed because neither individual patient data nor adjusted estimates were available for the estimation of the exact denominator based on implant years or person years. This meta-analysis model is also representative but less precise for the purposes of answering the research question. Additionally, details on radiation dose and timing could not be included in the statistical models.

In addition, other potential limitations of this review should be highlighted. Based on the meta-analysis of HBO therapy data, it can be argued that the inclusion of a subgroup containing a single RCT may not be logical. Indeed, the outcomes of this trial showed that HBO therapy did not affect implant loss (Schoen *et al.*, 2007); however, the overall analysis included data from 3 studies, which allowed for a general estimate and an illustration of the heterogeneity between study types and designs ($I^2 = 91\%$). Likewise, implant type and surface are potential confounding factors

to be considered, as a few articles indicated that a key variable that could substantially affect the analysis is the use of textured versus machined implants. Most of the included studies evaluated Brånemark machined implants. The use of these implants may be a critical issue, as the results of this systematic review may not represent the current clinical practices (*i.e.*, this implant is no longer used because of its higher failure rate, particularly in the maxilla). For example, Jaffin and Berman (1991) correlated implant loss to type IV bone (*i.e.*, very thin cortical bone with low-density trabecular bone of poor strength) in patients who were treated at a private periodontal practice. Of 444 Brånemark implants placed in the maxilla (52 of them in type IV bone), 37 (8.3%) did not integrate; however, of the total number of implants lost in the maxilla, 23 (44%) were installed in type IV bone.

Rough implants have led to higher success rates compared with smooth implants when placed in patients who were not systemically compromised (Albrektsson and Wennerberg, 2004; Bornstein *et al.*, 2005; De la Rosa *et al.*, 2013). For example, Heberer *et al.* (2011) and Landes and Kovacs (2006)

reported high survival rates for SLA, SLActive, and TPS implants. It would be interesting to group the machined versus textured implants and analyze the differences between them (the results and conclusions might be different from those reported herein). Few studies on textured implants were available for analysis; thus, definitive conclusions regarding the effects of radiotherapy on the survival rate of rough surfaces cannot be effectively reached at this time.

We detected a large discrepancy between the number of implants placed in nonirradiated jaws ($n = 8,461$) and the number placed in irradiated jaws ($n = 1,689$). Moreover, none of the included studies reported sample size calculations or a balanced distribution of irradiated and nonirradiated areas. Similarly, the “weight” of each study in one of the meta-analyses should be noted. The overall RR of the effect of radiotherapy on implant survival might have been overestimated. For example, the study by Granstrom *et al.* (1999), which had a higher weight (50.6%) in the meta-analysis (Figure 3), reported a higher failure rate (53.7%) in the irradiated group than did the other studies: 6.1% (Albrektsson *et al.*, 1988; Esser *et al.*,

Figure 3.

Forest plot of random effects meta-analysis evaluating the risk of implant loss (irradiated vs. nonirradiated patients; irradiated maxilla vs. irradiated mandible; irradiated patients receiving hyperbaric oxygen therapy or not).

M-H, Mantel-Haenszel; CI, confidence interval; τ , Kendall tau; z , z test.

*Type of implant not reported.

3.1 Irradiated vs. non-irradiated patients

3.2 Irradiated maxilla vs. irradiated mandible

3.3 Irradiated patients receiving hyperbaric oxygen therapy or not

1999), 26.6% (Werkmeister *et al.*, 1999), 20% (Katsoulis *et al.*, 2006), 1.4% (Landes and Kovács, 2006), and 3.3% (Schepers *et al.*, 2006). Consequently, the overall RR may not be representative despite the lack of significant heterogeneity ($p = .21$, $I^2 = 28\%$). Consequently, these issues may be the main limitation of this review and need to be considered when interpreting the findings.

Comparison with Other Studies or Reviews

Despite the detrimental impact of radiotherapy described in this review, the data also demonstrated that implants placed in irradiated bone may osseointegrate and reestablish occlusal function. These outcomes are similar to those from previous nonsystematic reviews (Ihde *et al.*, 2009; Javed *et al.*, 2010; Dholam and Gurav 2012; Pace-Balzan and Rogers, 2012). For instance, Ihde *et al.* (2009) concluded that “radiotherapy affects the mineralized bony substrate,” and Ihde *et al.* (2009) and Javed *et al.* (2010) agree that it may increase the risk of implant failure, especially in the maxilla, by up to 300%. Javed *et al.* (2012) concluded that implants may remain clinically stable, but they also suggested that radiation dosages ≥ 50 and ≤ 65 Gy do not have detrimental effects on osseointegration. Similar to Dholam and Gurav (2012), we observed that the outcomes from studies that assessed HBO therapy are controversial (as reflected by the individual studies and pooled outcomes and the degree of heterogeneity related to the pooled estimates). In addition, only studies including outcomes from nongrafted sites were included to evaluate the potential detrimental impact of irradiation on the patients’ bones and to minimize the potential heterogeneity that might have been incorporated by combining outcomes from grafted jaws. However, this inclusion criterion did not allow the assessment of several other studies that reported the effect of radiotherapy on implant healing, osseointegration, and long-term outcomes in grafted jaws.

It has been demonstrated that accumulation of dental biofilm, peri-implant soft tissue inflammation, smoking, and occlusal overload can affect long-term results (Lindquist *et al.*, 1996; Lang *et al.*, 2004; Chambrone *et al.*, 2010a; De la Rosa *et al.*, 2013). In this review, the lower mean values of implant success in irradiated subjects were probably due to the interaction between radiation dose and host response (Werkmeister *et al.*, 1999; Gramstrom, 2003; Schoen *et al.*, 2007). Schoen *et al.* (2007) reported that radiation doses > 40 Gy may jeopardize the regenerative capacity of the osseous tissue. Ihde *et al.* (2009) concluded that doses > 50 Gy appeared to decrease the survival rate of dental implants, whereas Werkmeister *et al.* (1999) and Coulthard *et al.* (2008) suggested that the decreased bone-healing potential is associated with radiation doses > 55 Gy. The most appropriate time for implant installation also remains controversial. Some studies have suggested that implants should be placed at least 6 mos after tumor resection (Brognez *et al.*, 1998; Granstrom *et al.*, 1999), while others have recommended a minimum of 12 mos (Schliephake *et al.*, 1999) or 24 mos (Werkmeister *et al.*, 1999) to avoid detrimental effects on the osseointegration of the implants. It has been reported that osseointegration of previously installed implants does not appear to be affected by radiotherapy (Schepers *et al.*, 2006).

The process of peri-implant bone apposition is a coordinated mechanism involving the expression of different growth factors and humoral angiogenesis factors that regulate bone homeostasis and different aspects of bone development, including chondrocyte differentiation and osteoblast and osteoclast recruitment (Chiapasco, 1999; Dholam and Gurav, 2012). Conversely, irradiation affects angiogenesis (Nemeth *et al.*, 2000; Chiapasco, 1999; Dholam and Gurav, 2012; Klein *et al.*, 2009), several aspects of leukocyte development and function, as well as host cytokine levels (Nemeth *et al.*, 2000; Granstrom, 2003; Dholam and Gurav, 2012; Klein *et al.*, 2009), which could partially explain the lower

success rates observed in the aforementioned studies.

Conclusions

Radiotherapy was associated with higher rates of implant loss in the majority of individual studies and in the overall meta-analysis, especially for implants placed in the maxilla. Most of the included studies assessed machined implants (smooth surfaces). Surface texture may be a key variable in the success of implants placed in irradiated bone, as the failure rate indicated by the limited data on textured implants was not different from the failure rate for normal cases (nonirradiated patients). Regarding the effects of HBO therapy, there is not enough evidence to support or refute the hypothesis that HBO may improve the survival rate of implants installed in irradiated jaws. Consequently, definitive conclusions regarding the effects of HBO therapy cannot be made at this time. Moreover, there was insufficient data regarding the timing of implant placement after radiation therapy. In addition, few prospective studies were available for analysis; therefore, the retrospective nature of the majority of included studies, as well as the difference in the type of implants used in current daily practice (textured implants), should be considered when interpreting the results of this review.

Implications for Practice and Research

Implant therapy appears to be a viable treatment option for reestablishing adequate masticatory conditions and a better quality of life for patients. Prospective cohort studies and RCTs evaluating different implant surfaces are necessary to confirm the present findings.

Acknowledgment

The authors received no financial support and declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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