THE JOURNAL OF PROSTHETIC DENTISTRY

SYSTEMATIC REVIEW

Irradiated patients and survival rate of dental implants: A systematic review and meta-analysis

Adhara Smith Nobrega, DDS,[a] Joel Ferreira Santiago, Jr, DDS,[b] Daniel Augusto de Faria Almeida, DDS,[c]
Daniela Micheline dos Santos, DDS,[d] Eduardo Piza Pellizzer, DDS,[e] and Marcelo Coelho Goiato, DDS[f]

ABSTRACT

Statement of problem. Radiotherapy has been considered a contraindication for rehabilitation with dental implants because it can change the survival rate of implants. Nevertheless, the installation of implants in irradiated patients has been used with varying success.

Purpose. The purpose of this systematic review was to compare the success rate of implants placed in irradiated human bone tissue with that of implants placed in nonirradiated areas.

Material and methods. Searches were performed in the EMBASE, Cochrane, and PubMed/Medline databases up to December 2013 to identify clinical trials addressing the subject. This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The relative risks of implant failure and survival curves were calculated considering a confidence interval of 95%. Heterogeneity was analyzed by using a funnel chart.

Results. A total of 40 studies involving 2220 participants and 9231 dental implants were selected. The survival curve of the studies indicated a survival rate of 84.3% for implants installed in irradiated bone tissue. The meta-analysis indicated statistically significant differences ($P<.001$) between item success rates of implants placed in irradiated areas and those of implants placed in nonirradiated areas.

Conclusions. Dental implants installed in the irradiated area of an oral cavity have a high survival rate, but strict monitoring is needed to prevent complications, thereby reducing possible failures. (J Prosthet Dent 2016;116:858-866)

The most common treatment for patients with head and neck cancer is surgery, which may be applied with or without radiotherapy and/or chemotherapy.[1-3] Resections from surgical treatment most often result in changes in speech, mastication, and swallowing,[4] as well as anatomic changes and deformities[5] such as tissue loss. These changes eventually hinder conventional prosthetic rehabilitation.[5,6] Thus, individuals with such surgical resections are potential candidates for oral rehabilitation with osseointegrated implants, which improve prosthesis retention and stability and, consequently, function, comfort, esthetics, and quality of life.[7]

However, radiotherapy can change the survival rate (SR) of dental implants, because it reduces the vascularity and regenerative ability of bone tissue. Hypovascularization occurs because increased bone mineral density leads to bone sclerosis,[8] whereas regenerative ability is affected because osteoblasts and osteocytes, bone-forming cells, decrease replicative capacity and bone formation, and osteoclasts, cells responsible for bone resorption, are attracted to the irradiated site. Over time, such events generate an imbalance between bone formation and resorption[9,10] and a decrease in vascularity associated with a decrease in regenerative ability,

---

Presented at the Brazilian Society of Dental Research Annual Meeting, São Paulo, Brazil, September 2014.

[a] Doctoral student, Department of Dental Materials and Prosthodontics, Aracatuba Dental School, Paulista State University, São Paulo, Brazil.

[b] Assistant Professor and Dean of Research and Graduate Studies (PRPPG), Sacred Heart University, Bauru, Brazil.

[c] Assistant Professor, Department of Restorative Dentistry, Dental School, Federal University of Alfenas, Minas Gerais, Brazil.

[d] Assistant Professor, Aracatuba Dental School, Department of Dental Materials and Prosthodontics, Paulista State University, São Paulo, Brazil.

[e] Professor, Department of Dental Materials and Prosthodontics, Aracatuba Dental School, Paulista State University, São Paulo, Brazil.

[f] Professor, Department of Dental Materials and Prosthodontics, Aracatuba Dental School, Paulista State University, São Paulo, Brazil.

Clinical Implications

Many clinicians consider head and neck radiotherapy to be a risk factor for dental implant placement. However, as many irradiated patients are rehabilitated with implant-supported prostheses, the evaluation of clinical risk is important.

which then affect osseointegration and the longevity of the implants.[7,9,10]

For such reasons, radiotherapy has been considered a risk factor for this type of rehabilitation.[11] Nevertheless, implants with variable SRs have been placed in irradiated patients[12,13] This variation can be attributed mainly to the total radiation dose received in the area. Reports[5,14-19] indicate values of total radiation in the range of 50 to 60 Gy are the borderline values for rehabilitation with dental implants, without the need for additional treatments such as hyperbaric oxygen therapy (HBO).

Published studies are not consistent regarding the optimal time interval between irradiation and surgery for implant placement[10] or for how different doses of radiation affect survival.[12] The purpose of this systematic review was to clarify issues regarding this theme.

The null hypothesis presented in this study was that the SR of implants placed in irradiated bone tissue does not differ from the SR of implants placed in nonirradiated tissue.

MATERIAL AND METHODS

Two independent reviewers (A.S.N., J.F.S.) conducted an electronic review of PubMed/Medline, Cochrane, and EMBASE databases for articles published in English from January 1975 to December 2013. The key words used were “radiotherapy” and “dental implants.” The Boolean operators used were (“radiotherapy” [Subheading] OR “radiotherapy”[All Fields] OR “radiotherapy”[MeSH Terms]) AND (“dental implants”[MeSH Terms] OR (“dental”[All Fields] AND “implants”[All Fields]) OR “dental implants”[All Fields] OR (“dental”[All Fields] AND “implant”[All Fields]) OR “dental implant”[All Fields]). A manual search was conducted in review studies addressing the subject. All titles were analyzed, selecting those relevant according to the established criteria.

The initial study selection was directed to the title and abstract analysis. Subsequently, eligible studies were analyzed and included or excluded from the total sample. Randomized controlled trials, prospective, and retrospective studies were included. Thus, the population, intervention, comparison, and outcome (PICO) criteria, as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) topic guidelines,[20] were determined as criteria for questioning to organize a clear clinical question with an appropriate inclusion focus.

The population consisted of patients who required oral rehabilitation with dental implants. The intervention was the installation of implants in irradiated patients, and the comparison was the SR of implants placed in irradiated versus those placed in nonirradiated areas. The outcome was analysis of the SRs and possible indication of implant protocols.

In order to perform the inclusion of studies, the filters selected were human studies in the English language, which contained at least 5 participants who underwent radiotherapy and received dental implants. The studies to be considered also had to report complete data of implant SRs in these regions.

Studies not included were duplicated studies, those describing the surgical technique or focusing on radiotherapy treatment, review, or clinical case studies ($N \leq 5$), studies published more than 20 years ago, articles that did not evaluate the SR of dental implants themselves, and non–peer-reviewed publications. Also excluded were studies considering bone grafting as the most important factor analysis, studies in animals or extraoral implants; studies analyzing mini-implants, periimplantitis, and/or perimucositis; questionnaires about quality of life without considering the longevity of the implants; and studies of participants receiving only chemotherapy or those which focused on histological and histomorphometric analysis. The selection of the 40 studies is presented in Figure 1.

The examiners (A.S.N., J.F.S.) selected the articles in a consensus meeting, and a third examiner (D.A.F.A.) assisted the development of this review. The articles were analyzed and discussed, and possible discrepancies were eliminated by consensus among examiners. The qualities of risk and study limitations were evaluated to eliminate studies that concealed data regarding the SR and possible complications and studies that did not define the success criteria for dental implants.

A Kaplan-Meier test was used to identify the implant survival curve in the analyzed periods and to analyze the SR of the implants installed in the irradiated maxilla or mandible. The risk ratio (RR) with a 95% confidence interval (CI) was used to study only the articles that used the installation of dental implants in the irradiated region and to compare them with those in nonirradiated regions (dichotomous outcome). In all analyses, significant values were considered when the value of P was <.05. Software (Reviewer Manager v5.3; Cochrane Group) was used for the meta-analysis and the elaboration of the forest plot and funnel plot.

The random effects model was used in the comparative analysis of implants placed in irradiated and nonirradiated regions. Heterogeneity was considered significant for $P<.1$ and analyzed using the $Q(x^2)$ method, and the I^2 value was measured. Data were presented qualitatively, allowing

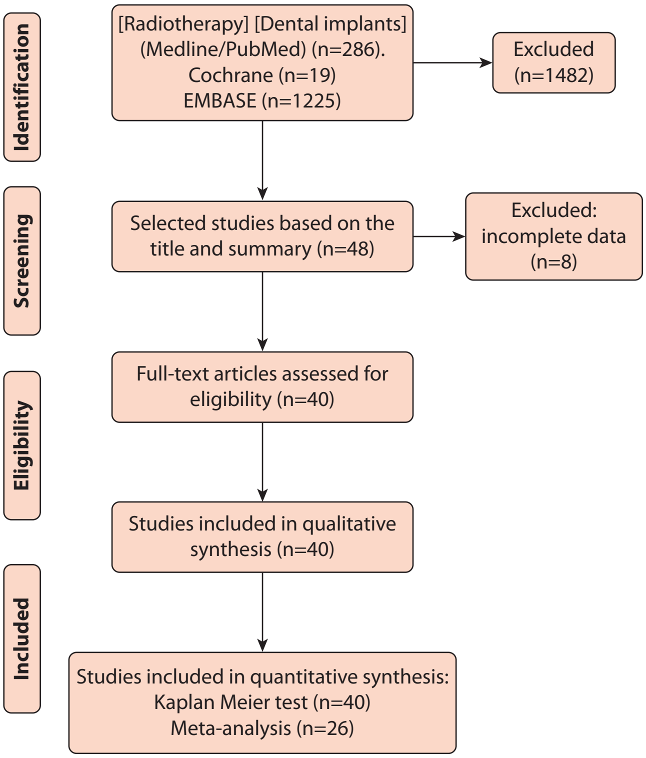


Figure 1. Flowchart of selected and excluded studies for systematic review.

comparison of the studies analyzed (N=40) and quantitatively in order to study the survival of the implants.

RESULTS

According to the inclusion and exclusion criteria established, 40 articles were selected: 1 randomized, 18 prospective, and 21 retrospective. The total number of participants was 2220, with an average 58 years of age.

Regarding implant locations, 13 studies identified the number of installed implants in the maxilla and mandible.[1,3-5,13,15,18,19,21-25] A greater number of implants had been installed in the mandible (2185) than in the maxilla (796). The average SR of implants placed in the mandible was higher than the SR of implants placed in the maxilla (Fig. 2).

Irradiated patients received doses ranging from 10 to 145 Gy, and the interval between radiotherapy and implant installation surgery ranged from 1 to 240 months, with an average minimum timeout of 11.82 months. There were also participants for whom radiotherapy was performed after implant installation.[5,12,24]

A total of 9231 implants were installed in irradiated and nonirradiated participants with variable geometry; the lowest reported diameter was 3.3 mm, and the minimum length was 7.0 mm. The follow-up period from implant placement until the last control of the implant in function ranged from 1 to 276 months.

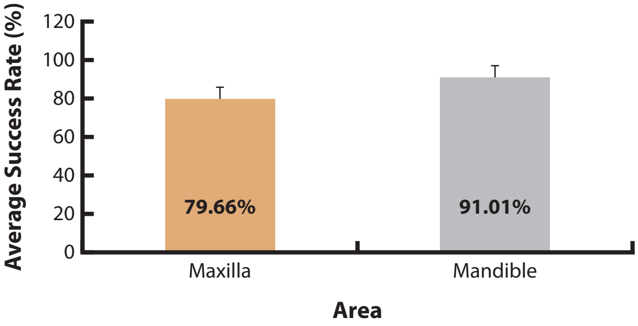


Figure 2. Analysis of success rate of implants placed in maxilla and mandible.[1,5,12,13,15,16,18,19,22,24-26]

Of 5562 implants placed in irradiated participants, 862 (15.49%) were classified as failures, whereas 3669 implants were installed in nonirradiated participants with 191 (5.20%) failures. The brand name most used was Nobel Biocare (Table 1).

In quantitative analysis, a total of 5489 implants were placed in irradiated bone tissue regions, and a total of 862 failures were found in a follow-up period of up to 192 months. The Kaplan-Meier analysis indicated an 84.33% SR during the period from 0 to 192 months (Fig. 3). Moreover, as presented in Table 2, the failures occurred in all analyzed periods, but the highest SR reductions occurred after 60 months. The overall results of this review reveal that the percentage of failures tended to increase in patients undergoing radiotherapy, decreasing the SR of these implants.

In a specific analysis of the number of implants that failed during follow-up, statistically significant differences between irradiated and nonirradiated regions that received dental implants were reported in 26 studies. The sum of implant failures revealed 860 implant failures in the irradiated group and 186 implant failures in the nonirradiated group.

In analysis based on random effects, statistically significant differences were observed in the failure of implants placed in irradiated bone tissue (RR: 2.63; 95% CI: 1.93-3.58; $P<.001$) (Fig. 4).

The heterogeneity observed in studies of implant failure outcome was relevant (chi-square: 56.46; $P<.0003$; I^2: 56%), using the random effects model. The funnel chart indicated a clear symmetry between the differences of the relative risks of the studies analyzed, reducing rates of bias of the study (Fig. 5).

DISCUSSION

This systematic review revealed that the concept of controlled and randomized clinical trials was used only by Schoen et al.[39] High financial costs and detailed planning are involved in controlled and randomized clinical trials that use significant numbers of participants undergoing radiotherapy. For this reason, the sample of included studies basically consisted of retrospective and prospective trials (Table 3), which can be considered biased in this review.

Twelve studies analyzed the SR of implants regarding location.[1,5,12,13,15,16,18,19,22,24-26] In most of the studies, the SR of implants in the mandible was higher than those in the maxilla (Fig. 2). However, Andersson et al,[5] Granstrom et al,[12] and Mericske-Stern et al[24] found higher SRs in the maxilla. The differences between these results is primarily due to bone quality and vascularization capacity.[12] The mandible presents a more cortical bone, and therefore, obtaining primary stability is easier. However, the greater SR observed in 3 studies in the maxilla can be explained because the maxilla has a more trabecular bone, and hence, greater vascularization, thus favoring the secondary stability of implants.[44]

Four studies did not identify significant differences.[3,4,21,23] Although they did not provide data about the SR, they did analyze the statistical correlation (α=.05) between maxillary and mandibular rates. None showed statistically significant differences for the mandible and maxilla SRs.

The results showed a wide variation in total dosage of radiation received, from 10 to 145 Gy (Table 1), and these values changed according to the purpose of the treatment, location, and diagnosis of the lesion.[17] The treatment consisted of radiotherapy dosages applied in daily fractions of up to 2 Gy, carried out 3 to 5 times per week.[3,16,23,25]

Even though no article included in this review approached intensity-modulated radiation therapy (IMRT), it is important to highlight this modality, which is a high-precision radiotherapy. IMRT allows high doses of radiation to be applied to the target but with minimum involvement of adjacent tissues. Because this radiotherapy modality damages healthy tissues less, it is mainly indicated for treatment next to structures and/or vital organs, such as in patients with head and neck tumors.[46,47]

Some studies reached consensus[5,14,16,18] on the risk of the radiotherapy dose, values of 50 to 60 Gy were predominant. In those situations, the use of HBO would be indicated, because this treatment improves bone repair and assists in the osseointegration process[24] by stimulating the irradiated tissues and significantly increasing the oxygen content areas prone to osteoradionecrosis. In the included studies, some authors did not use HBO, explaining that the total radiotherapy dose applied was low.[26] In other studies,[3,29] even with irradiation rates above that range, HBO was not applied as there was no consensus on the need for this treatment.

Some studies[7,12,13,19,24,37,39,45] used HBO as adjuvant treatment to radiotherapy. Although increases in the SR of irradiated implants could not be verified by some authors,[13,19,39] significant biases were found in these studies. Niimi et al[13] claimed that the follow-up period was not enough to assert that HBO was not required because microvascular circulation decreases over time, whereas the effect of HBO continues for many years. In the studies of Shaw et al[19] and Schoen et al,[39] relevant information that could also influence the SR of the implants, such as diameter, length, and surface treatment, was not correlated.

In contrast, other studies[7,12,45] observed significant improvements in regard to the SRs of implants in the irradiated areas subjected to HBO or as an indication of treatment for osteoradionecrosis.[24] The results presented by Granstrom et al[45] deserve attention. In that study, 4 groups of patients were evaluated, with 1 group consisting of irradiated patients who had lost 34 of 43 implants. After losing implants, such patients underwent treatment with HBO, after which 42 new implants were installed; only 5 were considered failures. Therefore, the success rate rose from 21% to 88.1%, confirming the effectiveness of HBO for this group.

In order to analyze the effectiveness of HBO and answer the possible questions regarding this treatment, a search of high scientific evidence studies, specifically for irradiated patients treated with HBO, was performed. The meta-analysis of Bennett et al[48] stated that HBO mitigated the effects caused by radiotherapy in the head and neck. However, because of the inclusion of a single study with dental implants, the study did not conclude anything specific on this topic. In contrast, the systematic review of Chambrone et al[49] addressed implants and stated that HBO did not improve the SR of the implants; in this report, HBO was not the focus of the review, and only 3 studies addressing the issue in question were included. The authors stated that insufficient data were available to support or reject the use of HBO. It appears that there is still no consensus regarding the treatment of irradiated patients also treated with HBO who are rehabilitated with implants. More randomized clinical trials using this treatment to clarify this important issue are suggested.

Another important factor is the waiting period between the last session of radiotherapy and implant surgery. In the present study, this factor varied greatly from 1 to 240 months. However, Table 1 shows that the minimum time adopted by most authors[2,3,18,23,25] was 6 months. Sammartino et al[18] compared 2 groups of participants: the first had implants installed within a waiting period of less than 12 months, and the second group had implants installed after 12 months. The study found that short waiting periods, less than 12 months, do not guarantee a suitable quality of bone and vascularization, which are factors directly related to osseointegration of the implants. Therefore, the largest number of faults found in the group with placement of implants after radiotherapy is explained. The study of Brasseur et al,[50] when evaluating the installation of implants in beagle

Table 1. Data of selected studies

Study year	Study Design	Geographic Region	Participants, n/Mean Age, y	Radiation Dose, Gy	Minimum Waiting Interval, mo	Geometry, mm	Follow-up, mo	Irradiated Bone Implants, n/Failed, n	Nonirradiated bone Implants, n/Failed, n	Brand
Al-Nawas et al[21] 2012	Retrospective	Germany	108/58.8	-	-	3.5	120	87/2	429/7	Astra Tech
Andersson et al[5] 1998	Retrospective	Sweden	15/68	44-68	8	10	96	90/2	-	Nobel Biocare
August et al[14] 1998	Retrospective	U.S.	18/64	65.4	44.5	-	16.4	16/0	-	-
Barrowman et al[4] 2011	Retrospective	Australia	32/50.7	-	-	-	192	48/5	67/0	Nobel Biocare
Bodard et al[32] 2011	Retrospective	France	48/60.2	50.2 - 67.5	17.2	3.3 x 13	60	232/33	-	Nobel Biocare, Serf
Buddula et al[1] 2011	Retrospective	U.S.	23/46	60-65	-	3.3 x 13	27.5	75/6	-	Nobel Biocare
Cao et al[2] 2003	Retrospective	China	27/52.9	36-76	6	-	60	53/9	78/11	Nobel Biocare, Friatec
Cuesta-Gil et al[6] 2009	Prospective	Spain	111/52	50-60	12	-	72 - 108	395/48	311/4	Lifecore Biomedical
Dholam et al[17] 2013	Prospective	India	30/46	20-60	12	-	60	59/10	26/0	-
Esser and Wagner[22] 1997	Retrospective	Germany	221	60	9	13	60	221/33	71/7	Nobel Biocare, Friatec
Fierz et al[31] 2013	Prospective	Switzerland	46/57	56-61	-	-	36 - 72	62/14	42/4	-
Franzén et al[11] 1995	Prospective	Sweden	20	25-64	-	-	36 - 72	20/1	-	Nobel Biocare
Goto et al[26] 2002	Retrospective	Japan	36/52.9	30	-	3.7 x 7	2 - 130	92/19	88/6	-
Granstrom et al[45] 1999	Retrospective	Sweden	78/64.9	25-145	-	-	44.2 - 88.8	331/126	89/12	Nobel Biocare
Granstrom et al[12] 2005	Retrospective	Sweden	207/59.1	21-120	-	-	6 - 275	631/147	614/76	Nobel Biocare
Heberer et al[23] 2011	Prospective	Germany	20/61.1	72	6	4.1 x 8	14.4	102/2	-	Straumann
Jisander et al[15] 1997	Prospective	Sweden	17/67	50	18	-	1 - 62	103/5	-	Nobel Biocare, Astra
Keller et al[35] 1997	Retrospective	U.S.	19/60	60	-	3.75 x 8	120	98/1	-	Nobel Biocare
Korfage et al[36] 2010	Prospective	Netherlands	50/61.5	12-70	-	3.75	60	123/13	72/1	Nobel Biocare
Landés and Kovács[27] 2006	Prospective	Germany	30/63	57	4	4.1 x 12	24 - 46	72/1	42/0	Straumann
Linsen et al[3] 2012	Prospective	Germany	66/55.7	60	6	10	47.99	127/8	135/6	-
Mancha de la Plata et al[7] 2012	Retrospective	Spain	30/55.5	50-70	12	-	60	225/10	130/3	Osseous-Mozograu
McGhee et al[34] 1997	Prospective	U.S.	6	>50	-	3.8 x 10	12	26/4	-	Sterio OS
Mericske-Stern et al[24] 1999	Retrospective	Switzerland	17/59.6	50-74	-	3.4 x 8	12 - 84	33/4	20/0	Straumann
Nelson et al[23] 2007	Retrospective	Germany	93/59	72	6	-	123.6	124/7	311/4	Camlog, Nobel, Biocare, Straumann
Niimi et al[13] 1998	Prospective	Japan/U.S.	44	66	1	7	49	228/20	-	Nobel Biocare
Salinas et al[37] 2010	Retrospective	U.S.	44	60	-	11	144	90/23	116/8	-
Sammartino et al[18] 2011	Prospective	Italy	77/55.8	50	6	8	-	172/56	16/0	-
Schepers et al[38] 2006	Retrospective	Netherlands	61/64.8	10-68	3	-	96	61/2	78/0	Nobel Biocare
Schliephake et al[28] 1999	Retrospective	Germany	83/51.9	32-60	20	-	55.2	145/38	264/0	Nobel Biocare
Schoen et al[39] 2007	Randomized	Netherlands	26/60.1	61.4	-	-	12	103/12	-	Nobel Biocare

(*continued on next page*)

Table 1. Data of selected studies (*continued*)

Study year	Study Design	Geographic Region	Participants, n/Mean Age, y	Radiation Dose, Gy	Minimum Waiting Interval, mo	Geometry, mm	Follow-up, mo	Irradiated Bone Implants, n/Failed, n	Nonirradiated bone Implants, n/Failed, n	Brand
Schoen et al[42] 2008	Prospective	Netherlands	50/61.5	60	-	-	48	76/2	64/2	Nobel Biocare
Shaw et al[19] 2005	Retrospective	United Kingdom	81/58	40-66	12	-	168	172/31	192/25	Friadent, Interpore, International, Nobel Biocare, Imtec
Visch et al[16] 2002	Prospective	Netherlands	130/62	50	-	-	168	446/64	-	Dyna, Screw-vent
Wagner et al[29] 1998	Retrospective	Germany	63/55	60	13.02	-	65	145/5	130/0	Nobel Biocare
Watzinger et al[33] 1996	Prospective	Austria	26/62	50	1	-	36	136/42	-	Friatec
Weischer and Moher[40] 1999	Prospective	Germany	40/55	50	13	-	37	83/10	92/5	-
Weischer et al[30] 1996	Prospective	Germany	27	36-75	13	-	26	57/4	48/3	Nobel Biocare, Friatec
Werkmeister[43] 1999	Retrospective	Germany	29/55	54	24	-	18	49/14	60/5	-
Yerit et al[41] 2006	Prospective	Austria	71/57.8	50	17	-	156	154/29	84/2	Straumann, Friatec
Total			2 220	10-145	11.82		1-276	5 562/862	3 669/191	

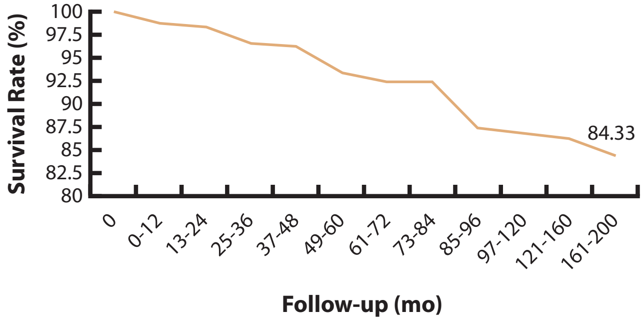


Figure 3. Survival curve analysis of implants installed in irradiated bone tissue. Survival curve of 84.33% in 192 months.[1-7,11-17,19,21-43]

Table 2. Survival curve analysis of implant installed in region with irradiated bone tissue

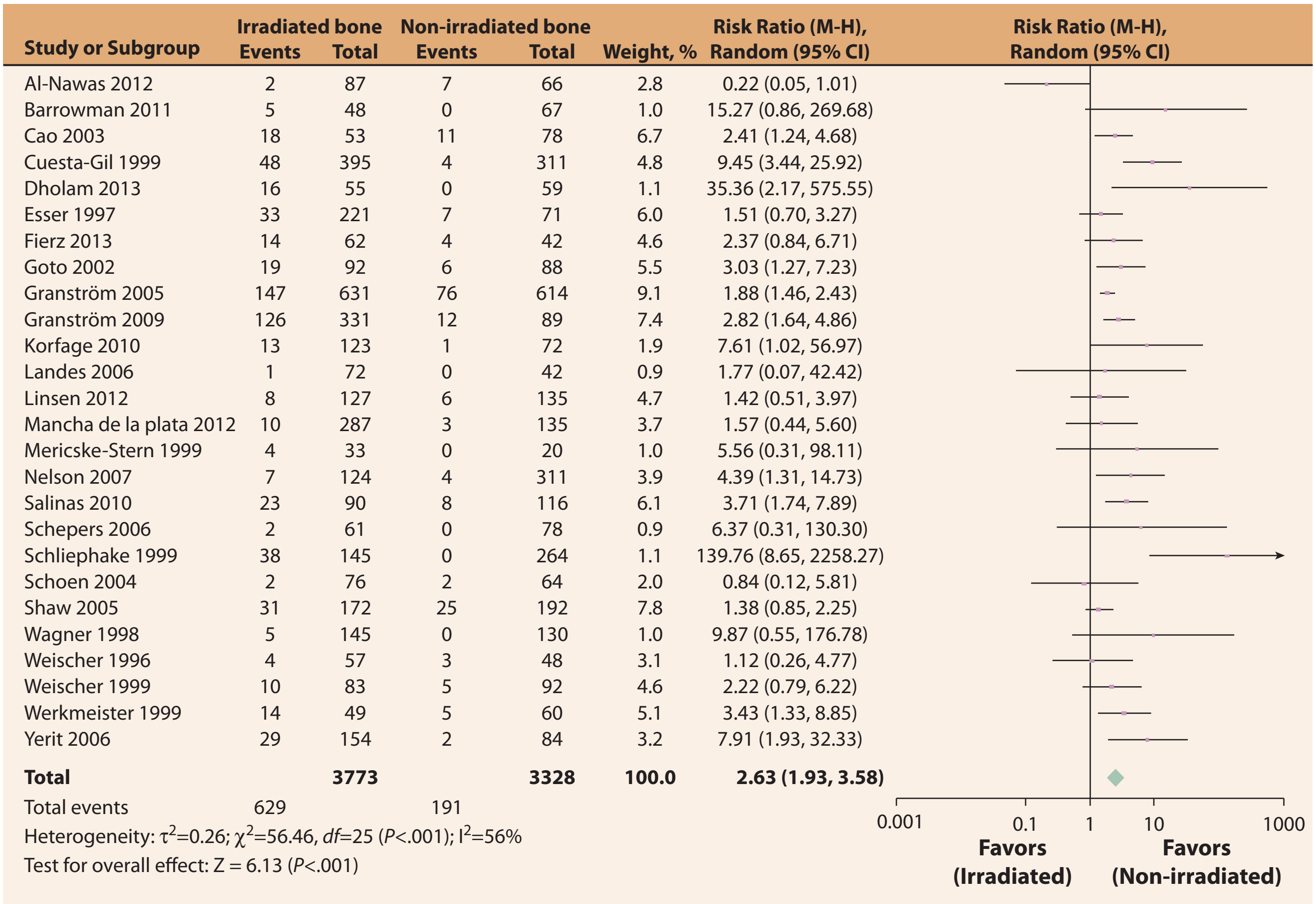
Follow-up Interval, mo	Implants in Each Interval, n*	Failures in Each Interval, n*	Survival Rate Within Each Interval, %*	Cumulative Survival Rate, %
0	5489	0	100	100
0-12	5489	70	98.72	98.72
13-24	5419	21	99.6	98.34
25-36	5398	95	98.29	96.61
37-48	5303	20	99.62	96.24
49-60	5283	158	97	93.36
61-72	5125	53	98.96	92.4
73-84	5072	4	99.92	92.33
85-96	5068	277	94.53	87.28
97-120	4791	26	99.45	86.8
121-160	4765	36	99.24	86.15
161-200	4729	100	97.88	84.33

*Analysis in period.

dogs before and after radiotherapy, found a better osseointegration, very similar to that in the control, in the group that had implants installed first and then underwent radiation doses. The authors attribute the fact that osseointegration in the previously irradiated implant placement group was not similar to that of the control group to the short time between the end of radiotherapy sessions and implant surgery. However, waiting for osseointegration to install implants and only then applying radiotherapy may be contraindicated, because tumor malignancy and the risk of metastasis requires prompt treatment.

Regarding the geometry of the implant, Goto et al[26] observed a greater number of failures in short implants, recommending caution in the use of these implants in irradiated patients. Nevertheless, in the comparative study of Niimi et al,[13] one group exhibited a higher number of failures in implants of 7 to 10 mm in length, whereas in the second group, most failures occurred in implants of 13 to 15 mm in length, suggesting that implant failure can occur regardless of length. However, since this article was published, surface treatments have been developed,[1] and the results may be different. Nevertheless, a current systematic review[51] highlights the view that shorter implants present a greater risk of failure than standard implants, and clinicians must be aware of mechanical and biological care. In this review, a consensus on this issue could not be reached because most of the included studies did not address this information. Future clinical trials should address and analyze such data, as well as the type of implant surface treatment.

Regarding the surface treatment of implants, Buddula et al[1] analyzed a single brand of implants. However,



Study or Subgroup	Irradiated bone Events	Irradiated bone Total	Non-irradiated bone Events	Non-irradiated bone Total	Weight, %	Risk Ratio (M-H), Random (95% CI)
Al-Nawas 2012	2	87	7	66	2.8	0.22 (0.05, 1.01)
Barrowman 2011	5	48	0	67	1.0	15.27 (0.86, 269.68)
Cao 2003	18	53	11	78	6.7	2.41 (1.24, 4.68)
Cuesta-Gil 1999	48	395	4	311	4.8	9.45 (3.44, 25.92)
Dholam 2013	16	55	0	59	1.1	35.36 (2.17, 575.55)
Esser 1997	33	221	7	71	6.0	1.51 (0.70, 3.27)
Fierz 2013	14	62	4	42	4.6	2.37 (0.84, 6.71)
Goto 2002	19	92	6	88	5.5	3.03 (1.27, 7.23)
Granström 2005	147	631	76	614	9.1	1.88 (1.46, 2.43)
Granström 2009	126	331	12	89	7.4	2.82 (1.64, 4.86)
Korfage 2010	13	123	1	72	1.9	7.61 (1.02, 56.97)
Landes 2006	1	72	0	42	0.9	1.77 (0.07, 42.42)
Linsen 2012	8	127	6	135	4.7	1.42 (0.51, 3.97)
Mancha de la plata 2012	10	287	3	135	3.7	1.57 (0.44, 5.60)
Mericske-Stern 1999	4	33	0	20	1.0	5.56 (0.31, 98.11)
Nelson 2007	7	124	4	311	3.9	4.39 (1.31, 14.73)
Salinas 2010	23	90	8	116	6.1	3.71 (1.74, 7.89)
Schepers 2006	2	61	0	78	0.9	6.37 (0.31, 130.30)
Schliephake 1999	38	145	0	264	1.1	139.76 (8.65, 2258.27)
Schoen 2004	2	76	2	64	2.0	0.84 (0.12, 5.81)
Shaw 2005	31	172	25	192	7.8	1.38 (0.85, 2.25)
Wagner 1998	5	145	0	130	1.0	9.87 (0.55, 176.78)
Weischer 1996	4	57	3	48	3.1	1.12 (0.26, 4.77)
Weischer 1999	10	83	5	92	4.6	2.22 (0.79, 6.22)
Werkmeister 1999	14	49	5	60	5.1	3.43 (1.33, 8.85)
Yerit 2006	29	154	2	84	3.2	7.91 (1.93, 32.33)
Total		**3773**		**3328**	**100.0**	**2.63 (1.93, 3.58)**
Total events	629		191			

Heterogeneity: τ^2=0.26; χ^2=56.46, *df*=25 (*P*<.001); I^2=56%

Test for overall effect: Z = 6.13 (*P*<.001)

Figure 4. Comparison of implants installed in irradiated and nonirradiated bone. Outcome, implant failure. CI, confidence interval; *df* = degree of freedom.

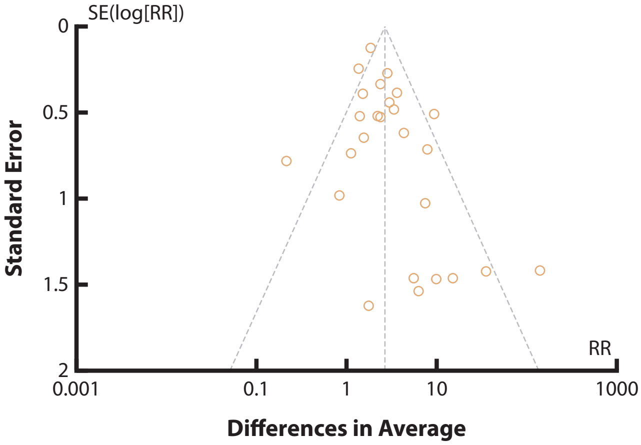


Figure 5. Funnel plot for publication bias assessment. All studies were used.

Table 3. Comparative assessment of methodological quality for 40 studies selected

Studies (ref. number)	Study Design	Mean Sample Size of Patients	Mean No. of Implants	Mean Periods of Follow-up, mo
1,2,4,5,7,12,14,19, 21,22,24-26,28,29, 32,35,37,38,43,45	Retrospective	63	268	105.1
3,6,11,13,15,18,23,27, 30,31,33,34,36,40-42	Prospective	48	192	59.7
39	Randomized	26	103	12

Studies grouped according to resemblances in their methodology.

one group used machined implants and another used surface treatment implants. They verified that the machined implants tended to fail 2.9 times more than the implants with surface treatment. The properties of the implant surfaces, such as topography and chemical treatment,[23] are important factors. In addition to providing greater contact between the bone and the implant, especially in areas of less corticalized bone tissue, which favors biological responses that accelerate the osseointegration process, surface treatments also increase mechanical strength and reduce corrosion.[52,53] The diversity of brands of implants tested is shown in Table 1. However, few studies[7,12,19,21,23,25,36] specified the brand of implants placed, and the authors did not correlate the implant SR when different types were used in the same study, the only exceptions being Buddula et al,[1] Landes and Kovacs,[27] and

Nelson et al.[25] Some of the studies[3,14,17,18,26,31,37,40,43] did not even identify the brand of implants.

The main outcome of the presnt study was that the success rate of implants placed in irradiated tissue was lower than that of implants placed in nonirradiated tissue ($P<.001$); thus, the null hypothesis was rejected. Homogeneity was noted in the included studies, which showed a lower SR in irradiated sites (Fig. 4). The only exception was the retrospective study of Al-Nawas et al,[21] where results showed that the risk of implant loss in nonirradiated patients was higher than in irradiated patients. The authors[21] attributes such results to the use of bone grafts and also to the bias of the study, which presented a small number of participants undergoing radiotherapy compared with the total number of participants.

The lowest SR in irradiated sites is explained in the study of Verdonck et al,[44] where, although the primary stability of implants in irradiated and nonirradiated sites was very similar, the secondary stability of implants in irradiated areas was damaged over time. This difference is because the primary stability depends only on the bone density where the implant was installed, whereas secondary stability, which is related to osseointegration effectiveness, depends on bone remodeling that is directly linked to vascularization. Some studies,[2,4,5,7,9,10,21] despite having cited some complications like periimplantitis and osteonecrosis, did not give due relevance to the question, the exception being Granstrom et al.[45] Complications in such patients can have serious consequences, for which, at times, no possible treatment is available.

Finally, this study supports the predictability of dental implants in irradiated patients, because it can improve the quality of life for patients and can facilitate social rehabilitation. A strict treatment protocol with detailed periodic monitoring by the dentist, including occlusal adjustments, contact points, radiographic follow-up, and cleaning techniques, should be performed. However, to establish a protocol of treatment, the waiting interval, the dose risk, and the most appropriate geometries of implants for irradiated patients, new studies must be conducted as randomized and double-blind trials.

CONCLUSIONS

Although the results of this meta-analysis state that the favorable SR of implants installed in irradiated areas is 85% after 16 years of follow-up, only a few studies performed a lengthy follow-up, which may be a bias of this result. This study concluded that dental implants placed in irradiated areas have a lower SR than those installed in nonirradiated areas, and possible complications are a high-risk threat throughout the life of these patients. Close monitoring is necessary to avoid complications and reduce the chances of failure.

REFERENCES

1. Buddula A, Assad DA, Salinas TJ, Garces YI, Volz JE, Weaver AL. Survival of turned and roughened dental implants in irradiated head and neck cancer patients: a retrospective analysis. J Prosthet Dent 2011;106:290-6.
2. Cao Y, Weischer T. Comparison of maxillary implant-supported prosthesis in irradiated and non-irradiated patients. J Huazhong Univ Sci Technolog Med Sci 2003;23:209-12.
3. Linsen SS, Martini M, Stark H. Long-term results of endosteal implants following radical oral cancer surgery with and without adjuvant radiation therapy. Clin Implant Dent Relat Res 2012;14:250-8.
4. Barrowman RA, Wilson PR, Wiesenfeld D. Oral rehabilitation with dental implants after cancer treatment. Aust Dent J 2011;56:160-5.
5. Andersson G, Andreasson L, Bjelkengren G. Oral implant rehabilitation in irradiated patients without adjunctive hyperbaric oxygen. Int J Oral Maxillofac Implants 1998;13:647-54.
6. Cuesta-Gil M, Ochandiano Caicoya S, Riba-Garcia F, Duarte Ruiz B, Navarro Cuellar C, Navarro Vila C. Oral rehabilitation with osseointegrated implants in oncologic patients. J Oral Maxillofac Surg 2009;67:2485-96.
7. Mancha de la Plata M, Gias LN, Diez PM, Muñoz-Guerra M, González-García R, Lee GY, et al. Osseointegrated implant rehabilitation of irradiated oral cancer patients. J Oral Maxillofac Surg 2012;70:1052-63.
8. Verdonck HW, Meijer GJ, Nieman FH, Stoll C, Riediger D, de Baat C. Quantitative computed tomography bone mineral density measurements in irradiated and non-irradiated minipig alveolar bone: an experimental study. Clin Oral Implants Res 2008;19:465-8.
9. Bolind P, Johansson CB, Johansson P, Granstrom G, Albrektsson T. Retrieved implants from irradiated sites in humans: a histologic/histomorphometric investigation of oral and craniofacial implants. Clin Implant Dent Relat Res 2006;8:142-50.
10. Brogniez V, Lejuste P, Pecheur A, Reychler H. Dental prosthetic reconstruction of osseointegrated implants placed in irradiated bone. Int J Oral Maxillofac Implants 1998;13:506-12.
11. Franzen L, Rosenquist JB, Rosenquist KI, Gustafsson I. Oral implant rehabilitation of patients with oral malignancies treated with radiotherapy and surgery without adjunctive hyperbaric oxygen. Int J Oral Maxillofac Implants 1995;10:183-7.
12. Granstrom G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. J Oral Maxillofac Surg 2005;63:579-85.
13. Niimi A, Ueda M, Keller EE, Worthington P. Experience with osseointegrated implants placed in irradiated tissues in Japan and the United States. Int J Oral Maxillofac Implants 1998;13:407-11.
14. August M, Bast B, Jackson M, Perrott D. Use of the fixed mandibular implant in oral cancer patients: a retrospective study. J Oral Maxillofac Surg 1998;56:297-301.
15. Jisander S, Grenthe B, Alberius P. Dental implant survival in the irradiated jaw: a preliminary report. Int J Oral Maxillofac Implants 1997;12:643-8.
16. Visch LL, van Waas MA, Schmitz PI, Levendag PC. A clinical evaluation of implants in irradiated oral cancer patients. J Dent Res 2002;81:856-9.
17. Dholam KP, Pusalkar HA, Yadav PS, Quazi GA, Somani PP. Implant-retained dental rehabilitation in head and neck cancer patients: an assessment of success and failure. Implant Dent 2013;22:604-9.
18. Sammartino G, Marenzi G, Cioffi I, Tete S, Mortellaro C. Implant therapy in irradiated patients. J Craniofac Surg 2011;22:443-5.
19. Shaw RJ, Sutton AF, Cawood JI, Howell RA, Lowe D, Brown JS, et al. Oral rehabilitation after treatment for head and neck malignancy. Head Neck 2005;27:459-70.
20. Moher D, Liberati A, Tetzlaff J, Altman DG; , PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
21. Al-Nawas B, Kammerer PW, Morbach T, Ladwein C, Wegener J, Wagner W. Ten-year retrospective follow-up study of the TiOblast dental implant. Clin Implant Dent Relat Res 2012;14:127-34.
22. Esser E, Wagner W. Dental implants following radical oral cancer surgery and adjuvant radiotherapy. Int J Oral Maxillofac Implants 1997;12:552-7.
23. Heberer S, Kilic S, Hossamo J, Raguse JD, Nelson K. Rehabilitation of irradiated patients with modified and conventional sandblasted acid-etched implants: preliminary results of a split-mouth study. Clin Oral Implants Res 2011;22:546-51.
24. Mericske-Stern R, Perren R, Raveh J. Life table analysis and clinical evaluation of oral implants supporting prostheses after resection of malignant tumors. Int J Oral Maxillofac Implants 1999;14:673-80.
25. Nelson K, Heberer S, Glatzer C. Survival analysis and clinical evaluation of implant-retained prostheses in oral cancer resection patients over a mean follow-up period of 10 years. J Prosthet Dent 2007;98:405-10.
26. Goto M, Jin-Nouchi S, Ihara K, Katsuki T. Longitudinal follow-up of osseointegrated implants in patients with resected jaws. Int J Oral Maxillofac Implants 2002;17:225-30.
27. Landes CA, Kovacs AF. Comparison of early telescope loading of non-submerged ITI implants in irradiated and non-irradiated oral cancer patients. Clin Oral Implants Res 2006;17:367-74.

28. Schliephake H, Neukam FW, Schmelzeisen R, Wichmann M. Long-term results of endosteal implants used for restoration of oral function after oncologic surgery. Int J Oral Maxillofac Surg 1999;28:260-5.
29. Wagner W, Esser E, Ostkamp K. Osseointegration of dental implants in patients with and without radiotherapy. Acta Oncol 1998;37:693-6.
30. Weischer T, Schettler D, Mohr C. Concept of surgical and implant-supported prostheses in the rehabilitation of patients with oral cancer. Int J Oral Maxillofac Implants 1996;11:775-81.
31. Fierz J, Hallermann W, Mericske-Stern R. Patients with oral tumors. Part 1: Prosthetic rehabilitation following tumor resection. Schweiz Monatsschr Zahnmed 2013;123:91-105.
32. Bodard AG, Bemer J, Gourmet R, Lucas R, Coroller J, Salino S, et al. Dental implants and free fibula flap: 23 patients. Rev Stomatol Chir Maxillofac 2011;112:e1-4.
33. Watzinger F, Ewers R, Henninger A, Sudasch G, Babka A, Woelfl G. Endosteal implants in the irradiated lower jaw. J Craniomaxillofac Surg 1996;24:237-44.
34. McGhee MA, Stern SJ, Callan D, Shewmake K, Smith T. Osseointegrated implants in the head and neck cancer patient. Head Neck 1997;19:659-65.
35. Keller EE, Tolman DE, Zuck SL, Eckert SE. Mandibular endosseous implants and autogenous bone grafting in irradiated tissue: a 10-year retrospective study. Int J Oral Maxillofac Implants 1997;12:800-13.
36. Korfage A, Schoen PJ, Raghoebar GM, Roodenburg JL, Vissink A, Reintsema H. Benefits of dental implants installed during ablative tumour surgery in oral cancer patients: a prospective 5-year clinical trial. Clin Oral Implants Res 2010;21:971-9.
37. Salinas TJ, Desa VP, Katsnelson A, Miloro M. Clinical evaluation of implants in radiated fibula flaps. J Oral Maxillofac Surg 2010;68:524-9.
38. Schepers RH, Slagter AP, Kaanders JH, van den Hoogen FJ, Merkx MA. Effect of postoperative radiotherapy on the functional result of implants placed during ablative surgery for oral cancer. Int J Oral Maxillofac Surg 2006;35:803-8.
39. Schoen PJ, Raghoebar GM, Bouma J, Reintsema H, Vissink A, Sterk W, et al. Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: effects of hyperbaric oxygen therapy. Oral Oncol 2007;43:379-88.
40. Weischer T, Mohr C. Ten-year experience in oral implant rehabilitation of cancer patients: treatment concept and proposed criteria for success. Int J Oral Maxillofac Implants 1999;14:521-8.
41. Yerit KC, Posch M, Seemann M, Hainich S, Dörtbudak O, Turhani D, et al. Implant survival in mandibles of irradiated oral cancer patients. Clin Oral Implants Res 2006;17:337-44.
42. Schoen PJ, Raghoebar GM, Bouma J, Reintsema H, Burlage FR, Roodenburg JL, et al. Prosthodontic rehabilitation of oral function in head-neck cancer patients with dental implants placed simultaneously during ablative tumour surgery: an assessment of treatment outcomes and quality of life. Int J Oral Maxillofac Surg 2008;37:8-16.
43. Werkmeister R, Szulczewski D, Walteros-Benz P, Joos U. Rehabilitation with dental implants of oral cancer patients. J Craniomaxillofac Surg 1999;27:38-41.
44. Verdonck HW, Meijer GJ, Laurin T, Nieman FH, Stoll C, Riediger D, et al. Implant stability during osseointegration in irradiated and non-irradiated minipig alveolar bone: an experimental study. Clin Oral Implants Res 2008;19:201-6.
45. Granstrom G, Tjellstrom A, Branemark PI. Osseointegrated implants in irradiated bone: a case-controlled study using adjunctive hyperbaric oxygen therapy. J Oral Maxillofac Surg 1999;57:493-9.
46. Kaviarasu K, Raj NA, Murthy KK, Babu AA, Prasad BL. Impact of dose rate on accuracy of intensity modulated radiation therapy plan delivery using the pretreatment portal dosimetry quality assurance and setting up the workflow at hospital levels. J Med Phys 2015;40:226-32.
47. Vallard A, Guy JB, Mengue Ndong S, Vial N, Rivoirard R, Auberdiac P, et al. Intensity-modulated radiotherapy or volumetric-modulated arc therapy in patients with head and neck cancer: Focus on salivary glands dosimetry. Head Neck 2016;38:1028-34.
48. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev 2012;5:Cd005005.
49. Chambrone L, Mandia J Jr, Shibli JA, Romito GA, Abrahao M. Dental implants installed in irradiated jaws: a systematic review. J Dent Res 2013;92:119-30.
50. Brasseur M, Brogniez V, Grégoire V, Reychler H, Lengelé B, D'Hoore W, et al. Effects of irradiation on bone remodelling around mandibular implants: an experimental study in dogs. Int J Oral Maxillofac Surg 2006;35:850-5.
51. Lemos CA, Ferro-Alves ML, Okamoto R, Mendonça MR, Pellizzer EP. Short dental implants versus standard dental implants placed in the posterior jaws: a systematic review and meta-analysis. J Dent 2016;47:8-17.
52. Tavares MG, de Oliveira PT, Nanci A, Hawthorne AC, Rosa AL, Xavier SP. Treatment of a commercial, machined surface titanium implant with H2SO4/H2O2 enhances contact osteogenesis. Clin Oral Implants Res 2007;18:452-8.
53. Wennerberg A, Albrektsson T. Effects of titanium surface topography on bone integration: a systematic review. Clin Oral Implants Res 2009;20:172-84.

Corresponding author:
Dr Marcelo Coelho Goiato
Aracatuba Dental School (UNESP)
Department of Dental Materials and Prosthodontics
José Bonifácio, 1193–Vila Mendonça
Araçatuba, SP
BRAZIL
Email: goiato@foa.unesp.br