Oral Implants in Radiated Patients: A Systematic Review

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Purpose: *Oral malignancy is often treated with a combination of surgery and radiation therapy (RT). The aim of this systematic review was to examine the effects of pre- and postimplantation RT on dental implant failure.* ***Materials and Methods:*** *The literature published from 1990 through 2006 was reviewed for studies assessing pre- and postimplantation RT. Potential studies were identified by searches of PubMed, SCIRUS, and the Cochrane Central Register of Controlled Trials (CENTRAL). The incidence of implant failure has been linked to the following variables: post- versus preimplantation RT, site of implant placement, RT dose, delay from RT to implant placement, and timing of implant failure after placement.* ***Results:*** *Similar failure rates were found for implants placed post-RT compared to those placed pre-RT (3.2% and 5.4%). In preimplantation RT, the implant failure rate was lower for the mandible (4.4%) in comparison to the maxilla (17.5%; OR = 4.63; 95% CI: 2.25 to 9.49). Other results did not reach statistical significance. No failures were observed in association with an RT dose lower than 45 Gy. All implant failures observed occurred within 36 months after RT, and most occurred between 1 and 12 months after placement.* ***Conclusion:*** *Notwithstanding the low number of implants evaluated, this review showed similar failure rate for implants placed post-RT and those placed pre-RT (3.2% and 5.4%, respectively).* (Systematic Review) INT J ORAL MAXILLOFAC IMPLANTS 2007;22:616–622

Key words: *dental implants, oral cancer, radiation therapy*

Surgical treatment of malignancies involving the oral cavity often results in an altered anatomic situation, which may severely hamper oral functions. Reconstruction of complex soft tissue and bone defects often requires a free vascularized tissue transplant.[1] With developments in surgical techniques, including the use of endosseous implants, dental prosthetic rehabilitation has been considered the final goal of treatment. Osseointegrated implants have been used successfully in selected head- and neck-cancer patients with surgical defects that cannot be adequately reconstructed with a removable prosthesis.[2]

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Radiation therapy (RT) is often applied preceding or following cancer surgery to improve the therapeutic outcome. In these cases, implants may be placed before or after RT; however, some degree of transient and/or permanent tissue damage invariably follows the course of RT, and this may interfere with the success of endosseous implants.[3]

The aim of this systematic review was to evaluate and compare the effects of pre- and postimplantation RT. Incidence of implant failure linked to the following variables was assessed: site of implant placement (mandible, maxilla, and vascularized free flap), RT dose, delay from RT to implant placement, and timing of implant failure after placement (within a month, within a year, after 1 year).

MATERIALS AND METHODS

A thorough review of the relevant literature linking implant placement with RT of the oral region was performed. The literature search was carried out using PubMed, SCIRUS, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms used were "oral cancer AND dental implants," "dental implants AND radiation therapy," "dental implants AND radiated bone," and "dental implants

AND vascularized free flaps." The "related articles" tool was used to improve the PubMed searches, and references of included studies were checked.

Studies were selected on the basis of the following inclusion criteria. They had to be original studies based on humans (randomized and nonrandomized clinical trials, cohort studies, case-control studies, and case reports), with a publication date from 1990 to 2006. The use of RT before or after implant placement, the use of vascularized grafts in the case of bone reconstruction, and a minimum follow-up of 6 months from abutment placement were required. A criterion of exclusion was lack of information about the timing of abutment placement, the number of radiated patients treated, the number of placed implants, or the length of the follow-up of each implant.

Two independent observers made a quality assessment of the study protocol, data analysis, and presentation of the articles according to fixed criteria of inclusion. The title and abstract of each record resulting from the different search strategies were examined separately. If at least 1 reviewer considered the article relevant, it progressed in the review process.

The full-text versions of relevant articles were obtained, and the methods and results sections of each article were read and scored by 2 independent blind readers. If both considered the article relevant, it was included in the study. The readers discussed their evaluation, and when disagreement occurred, it was resolved through discussion and rereading. The main outcome considered was implant failure, defined as implant mobility, implant removal necessitated by progressive marginal bone loss or infection (biologic failure implying failure to establish or to maintain osseointegration). Implant fracture or other events causing implant removal not related to osseointegration were not considered implant failure. Neither the presence of peri-implantitis nor the outcome of prosthetic rehabilitation were considered determinant of success: for example, a sleeping (not loaded) implant was considered a positive outcome.

The overall implant failure rate was compared for preimplantation RT versus postimplantation RT. Four variables were compared: site of implant placement (maxilla versus mandible), dose of RT, delay from RT to implant placement, and timing of implant failure.

Statistical Analysis

To evaluate dichotomous variables (preimplantation RT versus postimplantation RT, maxilla versus mandible), the estimates of effect were expressed as odds ratios (ORs) together with 95% confidence intervals (CIs). Conversely, to evaluate the importance of the radiation dose, delay from radiation therapy to implant placement, and timing of implant failure after placement, the χ^2 test for trend was performed. The statistical unit was the implant rather than the patient. The significance level was set at .05.

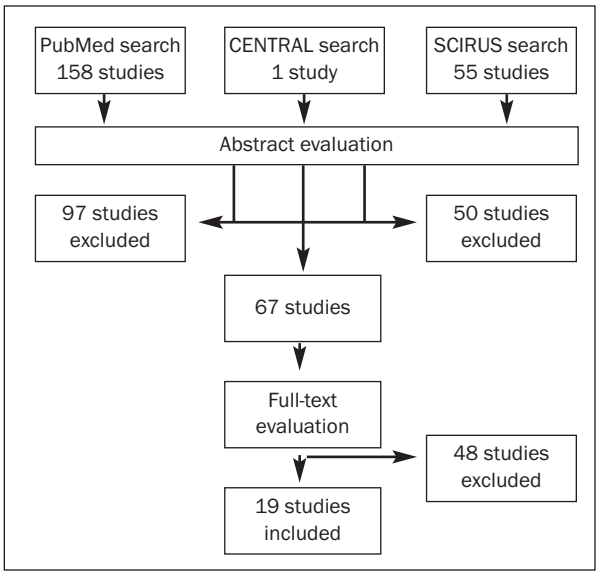

Fig 1 Flowchart of the selection process of studies for systematic review on dental implants in the radiated patient.

RESULTS

The PubMed search identified 158 potentially relevant studies: 36 were selected on the basis of the abstract information (11 of 69 for the "oral cancer AND dental implants" search, 22 of 70 for "dental implants AND radiation therapy," 2 of 8 for "dental implants AND radiated bone," and 1 of 11 for "dental implants AND vascularized free flaps"). Another 25 items were selected on the basis of the references of these 36 papers; thus, 61 full-text articles were selected for further evaluation. Forty-three of 61 papers were excluded, as they did not completely meet the inclusion criteria, while 18 were considered eligible for inclusion in the review.

The SCIRUS search identified 55 items (19 Web results and 36 journal results). Five full-text articles were selected on the basis of the abstract review. Four were excluded, as they did not completely meet the inclusion criteria, and 1 was included in the review.

Cochrane Central Register of Controlled Trials (CENTRAL) gave 1 result, which was not included in the review. The review process (Fig 1) resulted in the selection of 19 studies, as reported in Table 1.

Table 1 Reviewed Studies

Author	Search strategy	Publication date	Preimplantation RT: No. of patients	Preimplantation RT: No. of implants	Preimplantation RT: Implant failure n	Preimplantation RT: Implant failure %	Postimplantation RT: No. of patients	Postimplantation RT: No. of implants	Postimplantation RT: Implant failure n	Postimplantation RT: Implant failure %	Follow-up
Taylor and Worthington[4]	a,b	1993	4	15	0	0					0 to 6 y
Granström et al[5]	b	1993					1	5	0	0	39 mo
Barber et al[6]	b	1995	5	20	0	0					13 to 15 mo
Franzén et al[7]	a,b	1995	5	20	1	5					3 y
Watzinger et al[2]	b	1996	26	103	13	12.6					3 y
Eckert et al[8]	b,c	1996	21	111	9	8.1					12 y
Weischer et al[9]	a	1996	13	42	1	2.4					26 mo
McGhee et al[10]	b	1997	6	26	2	7.7					6 to 12 mo
Arcuri et al[11]	b	1997	4	15	1	6.7					12 to 61 mo
Keller et al[12]	b	1997	15	85	1	1.2	1	8	0	0	10 y
Niimi et al[13]	b	1997	24	110	12	10.9					> 1 y
Andersson et al[14]	b	1998	15	90	2	2.2					1 to 8 y
Brogniez et al[15]	a,b	1998	19	53	2	3.8					6 to 68 mo
Mericske-Stern et al[16]	b	1999	4	16			7	17	2	11.8	Up to 7 y
Schultes et al[17]	b	2002	38	143	2	1.4					29 mo
Schoen et al[18]	b	2003					5	20	0	0	12 to 40 mo
Fukuda et al[19]	d	2004	5	24	0	0					22 to 72 mo
Iizuka et al[1]	b	2005	12	24			7	13	0	0	> 2 years
Schepers et al[20]	a	2006					21	61	2	3.3	

a = PubMed, Oral cancer AND dental implants; b = PubMed, Dental implants AND radiation therapy; c = PubMed, Dental implants AND radiated bone; d = SCIRUS, Dental implants AND radiated bone.

Implant Failure in Postimplantation RT

Data are reported in Table 1. Six studies overall reported on 124 implants, with 4 failures (3.2%): 2 reported by Mericske-Stern et al[16] and 2 reported by Schepers et al.[20] Because of lack of data, no comparisons were performed with regard to the 4 variables to test.

Implant Failure in Preimplantation RT

The reported data showed an overall failure rate of 5.4% (43/789), which was not significantly different from the rate found in association with postimplantation RT (3.2%). The reason for failure was reported in 22 of 46 cases: 9 of 459 were deemed failures because of lack of osseointegration, 12 were deemed failures because of marginal bone loss, and 1 failure was due to biting trauma (Table 2).

Placement Site. Information about the site of placement was found in 12 studies (Table 3). The reported rate of implant failure in the maxilla was 17.5% (17/97). Half of these were reported by Eckert et al.[8] In their study, 8 implants placed in 2 patients were lost; 1 patient lost all 6 implants placed. The other 9 failures were reported by Niimi et al[13] in a Japanese multicenter study.

The reported rate of implant failure in the mandible was 4.4% (23/524). The implant failure rate was significantly higher in the maxilla than in the mandible ($P < .001$; OR = 4.63; 95% CI: 2.25–9.49). Vascularized free flaps (performed before RT) were associated with the lowest rate of implant failure (3 of 168, or 1.8%), although this rate was not significantly different from the failure rate in the mandible.

Radiation Dose. Data on radiation dose and implant failure are reported in 6 studies (Table 4). In cases where the radiation dose was lower than 45 Gy, no failures have been observed. Conversely, failure rates of about 5% were reported in association with radiation doses greater than 45 Gy: 5.4% (4/74) for doses between 46 and 55 Gy, 5.2% (9/172) for doses between 56 and 66 Gy, and 5.1% (2/39) for doses greater than 66 Gy. Although no failures have been observed in association with radiation doses under 45 Gy, it has not been possible to find a significant cutoff value linked with implant failure nor an increasing trend of failures linked to RT dose.

Delay from RT to Implant Placement. The link between this variable and implant failure has been reported in 4 studies. The delay has been divided into 7 groups in order to compare the studies (Table 5). All implant failures occurred within 36 months after RT. It has not been possible to find a significant cutoff value linked with implant failure nor an increasing trend of failures.

Timing of Implant Failure. The period between implant placement and implant failure was divided into 3 groups: within 1 month after placement, between 1 month and 1 year after placement, and

Table 2 Implant Failure in Preimplantation RT

Author	Lack of osseointegration			Marginal bone failure			Traumatic occlusion		
	Failures (n)	Implants (n)	%	Failures (n)	Implants (n)	%	Failures (n)	Implants (n)	%
Franzén et al[7]	1	20	5	0	20	0	0	20	0
McGhee et al[10]	2	26	7.6	0	26	0	0	26	0
Watzinger et al[2]	0	103	0	12	103	11.6	0	103	0
Weischer et al[9]	1	42	2.3	0	42	0	0	42	0
Keller et al[12]	1	85	1.1	0	85	0	0	85	0
Andersson et al[14]	1	90	1.1	0	90	0	1	90	1.1
Brogniez et al[15]	2	53	3.7	0	53	0	0	53	0
Schultes et al[17]	1	143	0.6	0	143	0	0	143	0
Total	9	459	1.9	12	459	2.6	1	459	0.2

Table 3 Evaluation of Implant Site in Preimplantation RT

Author	Maxilla		Mandible		Free flaps	
	n	%	n	%	n	%
Taylor and Worthington[4]			0/15	0		
Barber et al[6]					0/20	0
Franzén et al[7]			1/20	5		
McGhee et al[10]			2/12	16.6	0/14	0
Watzinger et al[2]			12/84	14.2	1/19	5.2
Eckert et al[8]	8/22	36.3	1/89	1.1		
Weischer et al[9]			1/36	2.7	0/6	0
Keller et al[12]			0/72	0	1/13	7.6
Niimi et al[13]	9/39	23	3/71	4.2		
Andersson et al[14]	0/12	0	2/78	2.5		
Schultes et al[17]			1/47	2.1	1/96	1
Fukuda et al[19]	0/24	0				
Total	17/97	17.5	23/524	4.4	3/168	1.8

Table 4 RT Dose and Implant Failure in Preimplantation RT

	≤ 25 Gy		26–35 Gy		36–45 Gy		46–55 Gy		56–65 Gy		≥ 66 Gy	
	n	%	n	%	n	%	n	%	n	%	n	%
Taylor and Worthington[4]									0/19	0		
Franzén et al[7]					0/4	0	0/13	0	1/5	20		
Eckert et al[8]	0/5	0	0/5	0			2/3	66.7	7/54	12.9	0/5	0
Keller et al[12]			0/10	0			0/10	0	1/55	1.8	0/5	0
Andersson et al[14]					0/22	0	1/40	2.5	0/6	0	1/23	4.3
Brogniez et al[15]					0/5	0	1/8	12.5	0/33	0	1/6	16.7
Total	0/5	0	0/15	0	0/31	0	4/74	5.4	9/172	5.2	2/39	5.1

Table 5 Time Delay (mo) from RT to Implant Surgery in Preimplantation RT

	1–12		13–24		25–36		37–60		61–120		121–180		≥ 181	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Taylor and Worthington[4]			0/4	0	0/9	0			0/6	0				
Keller et al[12]			0/18	0	1/5	20	0/17	0	0/30	0/10	0/10	0	0/5	0
Andersson et al[14]	0/18	0	1/30	3.3	1/17	5.9			0/4	0				
Brogniez et al[15]	1/30	3.3	1/19	5.3			0/3	0					0/1	0
Total	1/48	2.1	2/71	2.8	1/31	3.2	0/20	0	0/40	0	0/10	0	0/6	0

Table 6 Timing of Implant Failure in Preimplantation RT

Author	< 1 mo from surgery		1 to 12 mo from surgery		> 12 mo from surgery	
	n	%	n	%	n	%
Taylor and Worthington[4]	0/15	0	0/15	0	0/15	0
Barber et al[6]	0/20	0	0/20	0	0/20	0
Franzén et al[7]	0/20	0	1/20	5	0/20	0
McGhee et al[10]	0/26	0	2/26	7.7	0/26	0
Watzinger et al[2]	0/103	0	0/103	0	4/103	3.9
Weischer et al[9]	0/42	0	1/42	2.4	0/42	0
Arcuri et al[11]	0/15	0	1/15	6.7	0/15	0
Keller et al[12]	0/85	0	1/85	1.2	0/85	0
Niimi et al[13]	0/110	0	11/110	10	1/110	0.9
Schultes et al[17]	0/143	0	2/143	1.4	0/143	0
Fukuda[19]	0/24	0	0/24	0	0/24	0
Total	0/603	0	19/603	3.1	5/603	0.8

more than 1 year after placement (Table 6). The implant failure reported by Franzén et al[7] (1/20; 5%) occurred at the time of abutment surgery 5 months after the implant placement. McGhee et al[10] reported the failure of 2 implants in the same patient (2/26; 7.6%). Even without evidence of osteoradionecrosis, at the time of placement of the healing abutments (4 to 8 months from placement), the implants were found to be exposed and mobile. The patient failed to keep regular follow-up appointments and continued to use smokeless tobacco, which probably contributed to the implant failure.

Conversely, Watzinger et al[2] reported the failure of 4 primarily osseointegrated implants because of postradiation-osteonecrosis (PRON; 4/103; 4.2%). The patient had had a marginal resection of the anterior mandible and soft tissue reconstruction with a microvascular jejunal flap. One was lost 18 months after placement after progressive failure of osseointegration. Two months later, the patient suffered from a mandibular fracture passing through the empty implant socket. The remaining implants had to be removed, and a mandibular resection was carried out. The histologic evaluation confirmed that PRON had occurred.

In a study by Weischer et al,[9] 1 implant (1/42; 2.3%) failed; the implant, which was placed in radiated bone, did not osseointegrate and was removed at the time of abutment surgery 6 months after placement. In a study by Arcuri et al,[11] 1 implant was judged nonosseointegrated at abutment connection 7 months after placement and was removed (1/15; 6.6%). In a study by Keller et al,[12] 1 nonintegrated implant (1/85; 1.1%) was removed 7 months after placement and 1 month after abutment connection in a free vascularized (and irradiated) scapular bone grafting. In the multicentric study of Niimi et al,[13] of implants placed in the maxilla, 5 of 39 (12.8%) implants were removed 7 to 9 months after placement, 3of 39 (7.6%) were removed 10 to 12 months after placement, and 1 of 39 was removed more than 12 months after placement. For the mandible, no implant was removed after 10 or more months of healing, while 2 implants were removed 4 to 6 months after placement, and 1 was removed 7 to 9 months after placement. In a study by Schultes et al,[17] 2 of 143 implants (1.3%) were lost after a healing period of 4 months. On exposure, they were found to be loose and required removal.

Thus, no failures were registered within 1 month after surgery (0/603; 0%), 19 of 603 (3.1%) were encountered between 1 and 12 months, and 5 of 603 (0.8%) were registered more than 12 months after surgery.

DISCUSSION

Implant failures in radiated patients are due to radiation-induced changes in both hard and soft tissues. Blood vessels of the haversian canals may become obliterated, and the periosteum loses cellularity, vascularity, and osteoid formation. Hemopoietic proliferation becomes sparse in the bone marrow, and the sinusoids become irregular in configuration and distribution.[21] The late effects of RT may result in the catabolic processes of bone exceeding the anabolic processes, which eventually leads to a net reduction in the mineral content of radiated bone.[22] These changes in the radiated bone increase the risk of

developing PRON from implant placement. The long-term function of osseointegrated implants is dependent on the presence of viable bone capable of remodeling as the implants are subjected to stresses associated with supporting, stabilizing, and retaining prosthetic restorations.[23]

There is controversy in the literature about the timing of implant placement in patients who need RT. Especially when it is likely that postoperative RT is indicated, some authors advise that implants be placed immediately following the ablative procedure (ie, in the same surgical session). This procedure should allow better initial implant healing (osseointegration) before irradiation, eliminate the need for further surgical intervention or adjunctive hyperbaric oxygen therapy (HBO), and benefit speaking and swallowing rehabilitation.

A major disadvantage of immediate implant insertion is the risk of improper placement in the case of gross alterations in the anatomic situation and impairment of the prosthodontic treatment. Moreover, other factors must be considered: the risk of interference with or delay of the oncologic therapy, including RT; the development of post-treatment complications; and the risk that an early tumor recurrence could make implants useless.

Reconstruction and oral rehabilitation may be divided into primary and secondary reconstruction. Patients who underwent a partial mandibulectomy without bone reconstruction might need a secondary reconstruction before implant placement in the defect site. Due to the frequency of recurrences and metastases within 2 years after primary treatment, it seems reasonable to apply more sophisticated treatment methods only after this high-risk period.[24]

Some problems arose with respect to the review process of this study. It was hard to compare studies because of difficulty in determining the exact implant location (anatomic site and relations with the site of RT), differences between studies with respect to the length of the follow-up period, and differences between implant systems, retention mechanisms, and prostheses. Moreover, other variables, such as systemic diseases, smoking, advanced age, short implants, acentric loading, inadequate number of implants, and parafunctional habits have been cited in the literature as linked to implant success. These variables could not be included in this systematic review. Although the methods of investigations are of value, they would have reduced even more the number of implants to be considered for comparison.

As the results of this review showed similar failure rates for preimplantation RT versus postimplantation RT, factors other than implant failure rate should be used to determine which sequence is preferable. Regarding the site of implant placement, the present results are in keeping with Goto et al,[25] who reported a higher cumulative survival rate for grafted bone. The advantage of vascularized free flaps is significant only if compared to maxillary sites. In case of residual bone, better results were obtained in the mandible than in the maxilla. The differences in the bone structure of maxilla and mandible are reportedly responsible for the better results typically obtained in the mandible.[26–30]

With respect to the dose, implant failures have been reported only in association with doses greater than 45 Gy. However, no significant links have been found between RT dose and implant failure rate. It is possible that the lack of implant failures at doses less than 45 Gy is due to the low incidence of such small doses. Similarly a significant inverse link between implant failure and delay between RT and implant placement has not been established.

Only failures observed in the period between 1 month from the surgery until 12 months can be considered linked to lack of osseointegration due to RT. In the studies considered in this review, no failures were registered within 1 month of surgery, and 5 of 603 failures were registered after 12 months from surgery (0.3%). The majority of failures occurred between 1 and 12 months from surgery (19/603; 3.1%).

In the literature, some protocols to maximize implant success in post-RT implant have been described.[31,32] A delay in implant placement surgery ranging from 6 to 12 months[31,32] and an increased integration time of 5 to 6 months before stage-2 surgery and loading have been recommended.[32–34] This review did not find significant data to support those protocols.

Watzinger reported that PRON occurs most frequently within the first years following RT but may also present many years later; in this period, the incidence of trauma-induced osteoradionecrosis after radiotherapy is higher.[2]

The use of HBO therapy was not evaluated in this review but was the subject of a review by Coulthard et al.[35] It is thought that oxygen may improve bone and tissue healing; however, the review found no trials to show the effects on dental implants post-RT.

Based on the available results, the timing of implant placement (pre- or post-RT) is not linked to a significant difference in implant failure rate. However, significantly better outcomes were observed in the mandible than in the maxilla. These conclusions are based on a relatively small number of studies evaluating few patients and few implants; therefore, the possibility that clinical differences exist cannot be excluded. Further studies involving higher numbers of patients are needed to better investigate these issues.

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