Vol. 107 No. 1 January 2009

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

ORAL AND MAXILLOFACIAL IMPLANTS

Effects of radiation therapy on craniofacial and dental implants: a review of the literature

Stefan Ihde, Dr,[a] Sigmar Kopp, Dr,[b] K. Gundlach, ProfDr,[c] and V. S. Konstantinović, ProfDr,[d]
Gommiswald, Switzerland, Guestrow and Rostock, Germany, and Belgrade, Serbia
GOMMISWALD DENTAL CLINIC, UNIVERSITY OF ROSTOCK, AND UNIVERSITY OF BELGRADE

Objectives. The theories of the effects of radiation therapy on craniofacial and dental implants have been challenged by new models. Animal and clinical studies differ on the importance of dose effect and implant location regarding implant survival. Our purpose was to explore the risks of irradiation regarding dose levels, timing of radiation, implant location, and material.

Study design. A systematic search of the literature was performed to identify studies reporting animal and human data on the success of implants in irradiated versus nonirradiated bone.

Results. Eleven animal studies exploring histomorphometric, biomechanical, and histologic features of implants in irradiated bone were summarized. Sixteen human clinical studies evaluating craniofacial (n = 8) and dental (n = 8) implants in irradiated bone were summarized. No meta-analyses of dental implants in irradiated bone were found. Efficacy studies comparing different implant types in irradiated bone were not found.

Conclusion. Studies from both animal subjects and human patients indicate that irradiated bone has a greater risk of implant failure than nonirradiated bone. This increase in risk may be up to 12 times greater; however, studies making these comparisons are of poor to moderate quality, so the magnitude of this difference should be accepted with caution. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:56-65)**

Acquired or genetic maxillofacial defects can result in severe functional, psychologic, and aesthetic difficulties for the patient, as well as ongoing reconstructive challenges to the medical professional.[1] Poor quality or insufficient quantity of hard and soft tissue often limit treatment options, with the leading cause of compromised bone in the craniofacial area being radiotherapy.[2]

The traditional theory of irradiation effects proposes that radiation causes endarteritis leading to tissue hypoxia, hypocellularity, and hypovascularity, which may lead to tissue breakdown and chronic nonhealing wounds. Also, radiotherapy reduces the proliferation of bone marrow, collagen, and periosteal and endothelial cells. New models suggest that damage to osteoclasts occurs earlier than vascular alterations and that the subsequent decrease in bone remodeling is the underlying crux of tissue damage.[3] The extent of changes is dependent upon dose, fields of radiation, and type of radiation treatment (e.g., hyperfractionation vs. standard fractionation). The reduced viability of irradiated bone may not be capable of remodeling, because the implant is subjected to stresses associated with supporting, retaining, and stabilizing prosthetic restorations. Furthermore, there is an increased risk of osteoradionecrosis in irradiated bone. Hyperbaric oxygen (HBO) treatment may help revitalize the bone by stimulating angiogenesis, leading to improved success rates, but long-term clinical follow-up data are still lacking.

Several questions still exist regarding managing craniofacial and dental patients with irradiated bone. No correlation between implant material (e.g., titanium- or hydroxyapatite-coated) and survival has been observed in animal studies, with both types eventually

[a]Gommiswald Dental Clinic, Gommiswald, Switzerland.
[b]Guestrow, Germany.
[c]University of Rostock, Rostock, Germany.
[D]University of Belgrade, Belgrade, Serbia.
Received for publication Mar 11, 2008; returned for revision Jun 6, 2008; accepted for publication Jun 13, 2008.
1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2008.06.014

achieving acceptable osseointegration.[4-6] Furthermore, animal studies have indicated that increasing dose affects may have a negative effect on the histomorphometric and biomechanical characteristics of bone. However, clinical results differ widely on the importance of dose effect, as well as on implant location.

Several questions exist when considering implant therapy in patients with irradiated bone. 1) Are patients with irradiated bone at greater risk of implant failure than patients with nonirradiated bone? 2) Is there a dose response to radiation whereby greater doses lead to higher failure rates? 3) Is implant survival dependent on when a patient receives radiation, i.e., before or after implant placement? 4) Are some anatomic areas at greater risk than others of failure due to radiation? 5) Are some implants more effective than others in treating patients with irradiated bone? 6) Are there adjunctive therapies that may improve the outcome after radiation and implant placement? The purpose of the present review was to critically search the literature to try to answer these questions using a combination of animal and human studies.

Table I. Medline search strategy and results

Terms	*Hits*	*Reviewed*
irradiation AND (orthopedics OR device OR prosthesis OR implant OR nail OR plate")	841,315	
irradiation AND orthopedics AND (device OR prosthesis OR implant)	6	9
"Radiation, Ionizing" [MH] AND "Prostheses and Implants" [MH]	337	
bone AND fixation AND radiotherapy	173	
"Radiation, Ionizing" [MH] AND "Prostheses and Implants" [MH] AND "Comparative Study" [MH]	86	2
"Hyperbaric Oxygenation" [MH] AND "Radiotherapy" [MH] AND "Comparative Study"[MH]	38	7
"Osseointegration/radiation effects" [MAJR]	34	
"Dental Implants" [MH] AND "radiotherapy" [SH]	40	9
"dental implants" AND "radiation" AND "systematic" [SB]		
Studies summarized	(human) 16 (animal) 11	

MATERIALS AND METHODS

Eligibility criteria

A systematic search of the literature was performed with the following eligibility criteria: 1) human studies or meta-analyses comparing the success/failure of craniofacial (CF) and dental implants in irradiated bone and nonirradiated bone; 2) studies describing success/failure of implants in irradiated bone; 3) animal studies of biomechanical, histomorphometric, and histologic measures of CF and dental implants in irradiated and nonirradiated bone; and 4) studies of high methodologic quality (systematic reviews, randomized controlled trials, and cohort studies). Case series with no comparison group, in vitro studies, and studies of diagnostic radiography or radiation and imaging were excluded.

Identification of studies

A Medline search of articles published from 1969 through 2007 was conducted. The search strategy and results are listed in Table I. Additional strategies to identify relevant articles included: 1) use of Medline's "Related Articles" feature for key articles that were identified from the original search strategy; 2) a bibliographic review of retrieved articles; 3) a search for review articles; and 4) a search of the Cochrane database.

Statistical analysis

For human studies that reported rates of outcome but did not calculate effect sizes, relative risks (RRs) with the 95% confidence intervals (CsI) were calculated when possible using Stata software (version 9.0; Stata Corp LP, College Station, TX). The RR is a relative comparison of rates (e.g., failure) between patient groups receiving an implant in irradiated bone to patients receiving an implant in nonirradiated bone. Statistical significance is reached if the 95% CIs do not cross the value of 1.0. Wide CIs around RR estimates indicate a large amount of variability in measurements and/or a small number of subjects. Except where noted, the RR was calculated based on the number of implants, not the number of patients. For animal studies, the authors' findings were reported. It was not appropriate or informative to pool data from these studies.

RESULTS

Literature search

Eleven animal studies evaluating osseointegration in irradiated bone met this paper's objectives and were included in the review. Sixteen human clinical studies that met the objectives were identified evaluating craniofacial (n = 8) and dental (n = 8) implants in irradiated bone. For CF implants, the authors identified 2 cohort studies and 6 case series with historical controls comparing implantation in irradiated versus nonirradiated bone. For dental implants, 6 cohort studies and 2 case series were identifed with a historical control comparing implantation in irradiated versus nonirradiated bone. The subsequent sections are divided as follows: 1) a summary of animal studies on implants in irradiated bone; 2) a summary of human studies on CF implants in irradiated bone; 3) a summary of human

studies on dental implants in irradiated bone; 4) a summary of complications associated with implants in irradiated bone in human studies; and 5) a summary of radiation scattering effects. The studies identified were of poor (e.g., case series) to moderate (e.g., cohort studies) quality, so the conclusions drawn from these comparisons should be accepted with caution.

Animal studies on implants in irradiated bone

Eleven animal studies evaluating osseointegration in irradiated bone met the objectives and were included in the present review. The 3 major parameters most commonly reported were: 1) biomechanical (quantitative measurements of implant stability); 2) histomorphometric (quantitative measurements of bone growth around implants); and 3) histologic (qualitative measurements of bone healing over time).

Irradiated versus nonirradiated bone. Two studies evaluating biomechanical parameters revealed that pull-out load and breakpoint torque were significantly reduced in irradiated rat tibias compared with the opposite tibias (nonirradiated control) with increasing doses.[7,8] However, shear stress and shear moduli were not correlated with radiation dose at 8 weeks after implantation. Another study assessing biomechanical properties reported irradiation in rabbit femurs/tibias resulted in a 54% lower biomechanical force ($P = .005$) required to unscrew the titanium implants in irradiated bone (with HBO treatment) compared with nonirradiated implants, and 69% less force in irradiated bone without HBO treatment compared with the control group.[9]

One study evaluating histomorphometric parameters demonstrated significantly decreased bone thickness measurements in irradiated rat tibias compared with the opposite tibias (control) with increasing doses.[7] Bone contact surface ratio in rabbit mandible was decreased 12-19 days after surgery in both titanium and hydroxyapatite mandibular implants (irradiated at post-implant day 5) compared with nonirradiated controls, and increased after day 9.[6] Specific trabecular bone volume scores were lower in irradiated groups at day 7 but similar to nonirradiated controls by day 61.[6]

Histologic changes in irradiated bone may include both compromised bone remodelling and changes to the vascular architecture. Findings in one study demonstrated that at 5 months after irradiation, bone resorption seemed to exceed osteogenesis, but by 8 months after irradiation the balance appeared to be restored.[4] Bone formation occurred around 97% of implants ($n = 85$ out of 88) with minimal difference in outcome between irradiated (before and after implantation) and nonirradiated bone. No implant failure was observed, but 3 implants showed mobility at the end of the study period. A fibrous appearance of the cartilage and signs of venous blood congestion or arteriolar thrombosis are often noted.[4,7] Inflammation and increased bone resorption is also noted.[10] Thrombosis or hemorrhage attributable to irradiation is not always evident, and vascular architecture may appear unaltered.[10,11] A 30-week study in rabbit tibias showed that immature bone may remain unlamellarized after irradiation.[11]

Dosing of radiation. In rat proximal tibias, increasing doses of radiation were shown to affect osseointegration of pure titanium implants in rats at 8 weeks after implantation. Animals receiving 30 or 35 Gy radiation had noticeably less bone formation around their implants than in their control side and than animals receiving 10 or 20 Gy.[7] Acute dose-dependent skin reactions after radiation were reported in the same study. Most authors did not explicitly report complications. Histomorphometric analyses in the same study indicate that radiation dose may influence bone thickness and implant contact. A significant difference in bone thickness measured at 50 and 550 μm from implant threads was seen with increasing radiation dose (10, 20, 30, or 35 Gy) ($P = .042$; $P = .027$; respectively at 8 weeks after implantation). A significant difference in bone thickness measured at 50, 250, and 550 μm from implant threads was seen between the irradiated and control leg in the 30- and 35-Gy groups ($P = .008$; $P = .020$; $P = .012$; respectively). Biomechanical parameters demonstrated some differences in pull-out force and breakpoint torque between increasing dose groups. No significant difference in pull-out force was seen between rats exposed to 10, 20, or 30 Gy. However, the breakpoint torque and maximal torque decreased significantly compared with the control side ($P = .019$; $P = .006$; respectively) with increasing radiation doses, indicating decreased mechanical capacity.

Timing of radiation. An increase in time interval between irradiation and implant placement appears to improve osseointegration in the animal model. A study in rabbit tibias and femurs comparing implants placed at 12 weeks or 1 year after irradiation showed that the biomechanical force needed to unscrew the implants was significantly increased when placement occurred 1 year after irradiation compared with immediately ($P = .04$). Implants placed both 12 weeks and 1 year after radiation showed improved bone healing compared with direct implant placement.[8] Results of a study in rabbit mandible showed that most implant surfaces were directly covered with new bone within 60 days when implants were placed 6-12 months after irradiation, versus 30 days for the control group and 90 days for implants placed within 3 months of radiation treatment.[12] Bone regeneration was depressed by 70.9% when implants were placed 4 weeks after radiation, compared with 28.9% at 1 year after radiation, a recov-

ery factor of almost 2.5.[13] No improvement in bone formation between immediate drilling or a 12- or 52-week delay from time of irradiation was seen in a study where a biopsy defect in rabbit tibias was created.[10] Large osteoclast foci were observed in postimplant irradiated dog mandible and were significantly greater than the preimplant or nonirradiated group.[4] However, after qualitative histologic analysis, the authors were unable to recommend one sequence over the other, i.e., radiation therapy before implantation, or vice versa.[4] Several animal studies suggest that a delay between irradiation and implant placement is beneficial to implant survival. A delay of even 12 weeks shows a significant increase in success.[8,12,13]

Implant types. Both titanium- and hydroxyapatite-coated (HA) implants were successfully integrated in irradiated bone, with no statistically significant difference in survival rates. At 6 months after implantation, there was no difference in bone-implant interface between the ITI Bonefit titanium plasma spray–coated and Steri-Oss HA implants in dog mandible.[4] However, damage to the surface of both implant types was observed. A study comparing titanium-coated and HA implants in rabbit mandible showed implant failure in 25% of HA implants (n = 2 out of 8) over 56 days, probably due to loss of stability after irradiation of the new bone.[6] Both titanium-coated and HA implants were integrated successfully over a 16-week study of irradiated rabbit tibias.[5]

HBO therapy. Results of HBO therapy were reviewed in several studies of rabbit femurs and/or tibias. Results varied widely. A study of irradiated rabbit femurs demonstrated no statistically significant differences in bone-forming capacity comparing groups that did and did not receive hyperbaric oxygen (HBO) therapy with irradiation.[10] Another study observed a significant reduction of bone in thread areas in irradiated bone without HBO for both the total implant analysis and the 3 best threads (P = .046; P = 0.028; respectively) and in irradiated bone with HBO therapy when calculating the 3 best threads (P = .046).[2] Thus, periosteal bone formation and bone remodeling decreased after irradiation with or without HBO therapy. Hyperbaric oxygen therapy improved bone formation in nonirradiated bone and less in irradiated bone. The authors concluded that HBO may improve bone formation and does improve bone maturation. A study evaluating biomechanical parameters reported that the force required to remove the implants increased 44% (P = .011) in irradiated femurs/tibias after HBO versus 22% (not significant) in nonirradiated bone after HBO.[9] In another study, the biomechanical force needed to unscrew implants was 54% lower in irradiated versus nonirradiated bone without HBO treatment (P = .005). A fourth study showed that rabbits receiving HBO after irradiation and femoral implants differed in bone formation between irradiated and control legs by 9.52% (P = .0008), compared with the non-HBO group who differed by 36.2%.[5]

Human studies on craniofacial implants in irradiated bone

Eight human clinical studies evaluating CF implants in irradiated bone were identified that met the authors' objectives. An attempt was made to address the following categories by relying only on studies that made appropriate comparisons (i.e., cohort studies and case series with historical controls): irradiated versus nonirradiated bone, dosing of radiation, timing of radiation, implant location, implant types, and HBO therapy. Studies were of poor (case series) to moderate (cohort studies) quality, so conclusions should be made with caution (Table II). Rates of failure are reported by implant location in Table II, so a single study may appear more than once in the table.

Irradiated versus nonirradiated bone. Comparing rates of implant failure in irradiated versus nonirradiated bone in CF applications, the risk of implant failure in irradiated bone was as much as 12 times greater than that for nonirradiated bone.[14-18] The increased risk was statistically significant in 7 comparisons; however, only 2 were data from cohort studies (i.e., made the comparison in the same study population).[14,15] Stronger associations were seen in case series compared with historical controls which possess the weakest evidence. Survival rates were based on as little as 1 year and as much as 5 years after implantation.

Dosing of radiation. Few studies were identified evaluating radiation dose in CF applications. One study reported no difference in failure based on dose (<50 Gy vs. ≥50 Gy) in orbital implants; however, the sample size was relatively small.[19] Cumulative radiation effect (CRE) as a measure of dose (≤30) was significantly related to implant failure in a prognostic study.[20] Radiation dose (CRE >30) was the only factor associated with implant failure (P = .05) in that study.

Timing of radiation. Schoen et al.[21] evaluated failure rates based on whether the implants were placed before or after irradiation. The sample sizes were too small to effectively determine the effects of timing or the risks associated with radiation before or after implant placement. No other studies were identified.

Implant location. Location of CF implants may influence the survival rate. Numbers cited in the literature for implant survival in nonirradiated bone by location are as follows: mastoid region >95%, orbital implants 35%-91%, nasal implants 71%-81%.[1] No significant differences were seen for implants in other CF locations. Several studies reported a tendency toward higher failure rate in the orbital area owing to thin bone

Table II. Summary of studies comparing implantation in irradiated versus nonirradiated bone: craniofacial applications

Study	Study design	Implant location	Outcome	Irradiated	Nonirradiated	Effect size, RR (05% CI)
Roumanas[14]	Cohort	All	Implant failure	40% (14/35)	12% (21/172)	3.3 (1.9-5.8)*
Albrekteson[15]	Case series	All	Implant failure	15% (4/34)	1.5% (6/389)	9.5 (3.1-29.6)*
Granstrom[20]	Case series	All	Implant failure	23% (147/631)	12% (76/614)	1.9 (1.5-2.4)*
Granstrom[17]	Case series	All	Implant failure	54% (79/147)	12% (12/101)	4.5 (2.6-7.9)*
Wolfaardt[18]	Case series	All	No osseointegration	30.5% (44/144)	2.5 (31/1221)	12.0 (7.9,18.4)*
Roumanas[14]	Cohort	Various CF	Implant failure	30% (3/10)	27% (9/33)	1.1 (0.37-3.3)
Wolfaardt[18]	Case series	Nasal	No osseointegration	20% (2/10)	17% (9/53)	1.18 (0.29-4.66)
Roumanas[14]	Cohort	Auricular	Implant failure	0% (0/6)	4.5% (5/111)	Incalculable
Wolfaardt[18]	Case series	Mastoid	No osseointegration	0% (0/10)	1.7% (9/516)	Incalculable
Schoen[21]	Cohort	Orbit	Implant failure	11% (4/35)	0% (0/14)	Incalculable
Toljanic[19]	Case series	Orbit	Implant failure	34% (31/92)	24% (21/89)	1.4 (0.89-2.29)
Wolfaardt[18]	Case series	Orbit	No osseointegration	49% (40/81)	6.1% (7/115)	8.1 (3.8-17.2)*
Roumanas[14]	Cohort	Orbit	Implant failure	59% (11/19)	25% (7/28)	2.3 (1.1, 4.9)*
				IR + HBO	*Nonirradiated*	
Granstrom[38]	Case series	All	Implant failure	8.1% (8/99)	13.5% (12/89)	0.60 (0.26-1.4)
				IR + HBO	*Rad. only*	
Granstrom[38]	Case series	All	Implant failure	8.1% (8/99)	54% (79/147)	0.15 (0.7-0.30)*
				IR after implant	*Nonirradiated*	
Schoen[21]	Cohort	Orbit	Implant failure	14% (2/14)	0% (0/14)	Incalculable
				IR before implant	*Nonirradiated*	
Schoen[21]	Cohort	Orbit	Implant failure	9.5% (2/21)	0% (0/14)	Incalculable
				IR after implant	*IR before implant*	
Schoen[21]	Cohort	Orbit	Implant failure	14% (2/14)	9.5% (2/21)	1.5 (0.23-9.4)
				<50 Gy dose	*≥50 Gy dose*	
Toljanic[19]	Case series	Orbit	Implant failure	17% (2/12)	16% (10/61)	1.0 (0.25-4.1)

Cohort studies compared patients in the same treatment population. Case series compared results to historical control subjects.
CF, Craniofacial; *IR*, irradiation; *HBO*, hyperbaric oxygen.
*Statistically significant findings.

in that region,[14,22,23] although others did not find any statistical difference between orbital implant success and other CF implants, whether in irradiated or in nonirradiated bone.[1,18-21] A review of patient data over a 25-year period comparing implant success in irradiated and nonirradiated populations indicated that implant location was not a factor in survival, with the possible exception of orbital implants, which may show a trend toward lower survival rates (P = .055), and gingival implants, which may have a higher survival rate (P = .05).[20]

Implant types. No studies attempting to compare different types of CF implants in irradiated bone were identified, precluding any conclusions regarding superiority of one CF implant type over another.

HBO therapy. One study was identified evaluating the effect of HBO therapy in irradiated bone.[17] Failure was significantly less common (RR 0.15; 95% CI 0.7-0.30) among radiotherapy patients treated with HBO compared with those who had radiotherapy but no HBO. There was no difference in failure rates comparing nonirradiated patients and those who had radiation and HBO.

Human studies on dental implants in irradiated bone

Eight clinical studies on dental implants in irradiated bone were identified that met the objectives. An attempt was made to address the same categories of treatment effects reported in the CF section (Table III).

Irradiated versus nonirradiated bone. The proportion of studies that reported statistically significant differences between irradiated bone and nonirradiated bone in the dental implant studies was far less than reported in the CF studies. Furthermore, the RRs were not nearly as high. Of the 8 studies that compared rates of implant failure in irradiated and nonirradiated bone, only 3 reported statistically significant differences. The risk of implant failure in irradiated bone was 2-3 times greater than that for nonirradiated bone in those studies. In CF studies, the RR was as high as 12. Moy et al.[24] reported nearly a 3 times greater risk of implant failure in irradiated versus nonirradiated bone (RR 2.73, 95% CI 1.10-6.81); however, after adjusting for diabetes and smoking status, the RR was still significant but <2 (RR 1.87; no CI was provided).[24] Raw data were not available, so we did not present them in Table III; however, the author produced

Table III. Summary of studies comparing implantation in irradiated versus nonirradiated bone: dental applications

Study	*Study design*	*Implant location*	*Outcome*	*Irradiation*	*Nonirradiation*	*Effect size, RR (95% CI)*
Weischer[33]	Cohort	Mandible	Implant failure	13.7% (10/73)	5.7% (5/87)	2.4 (0.85-6.6)
			Wound disturbance	4.8% (4/83)	0 (0/92)	Incalculable
			Peri-implant inflammation	22.2% (4/18)	9.0% (2/22)	2.4 (0.50-11.9)
Weischer[34]	Cohort	Mandible	Implant failure	7.0% (4/57)	6.3% (3/48)	1.1 (0.26-4.8)
Landes[39]	Cohort	Mandible	Implant failure	1.4% (1/72)	0% (0/42)	Incalculable
Schepers[40]	Cohort	Mandible	Implant failure	3.3% (2/61)	0% (0/78)	Incalculable
Esser[41]	Case series		Implant failure	16.6% (29/221)	9.9% (7/71)	1.3 (0.81-2.02)
			Osteoradionecrosis	3.4% (2/58)	NR	Incalculable
			Soft tissue necrosis	3.4% (2/58)	NR	Incalculable
Cao[29]	Cohort	Maxilla	Implant failure	51% (27/53)	22% (17/78)	2.3 (1.4-3.8)*
			Osteoradionecrosis	0 (0/53)	0 (0/78)	1.0
Ryu[27]	Case series	Mandible	Implant failure	30.6% (11/36)	9.1% (1/11)	3.4 (1.49-23.2)*
			Osteomyelitis or necrosis	11.1% (4/36)	0 (0/11)	Incalculable
			Chronic pain	2.7% (1/36)	9.1% (1/11)	0.31 (0.02-4.5)
			Complications	30.6% (11/36)	27% (3/11)	1.1 (0.38-3.3)
Landes[39]	Cohort	Mandible	Peri-implant inflammation	3.2% (5/155)	2.2% (3/134)	1.4 (0.35-5.9)
				<1 yr after IR	*≥1 year after IR*	
Visch[25]	Cohort	HA-Titan screw	Implant failure	16.5 % (n = 29/175)	12.9% (n = 35/271)	1.3 (0.81-2.02)
				<50 Gy dose	*≥50 Gy dose*	
			Implant failure	9.2% (19/207)	18.8% (45/239)	0.49 (0.29-0.81)*
				10 yrs after IR		
				Mandible	*Maxilla*	
			Implant failure	9.2% (31/338)	30.6% (33/108)	0.30 (0.19-0.47)*
				IR >10 mos after implant	*IR ≤12 wks after implant*	
			Implant failure	0% (0/10)	42.3% (11/26)	Incalculable
			Osteomyelitis or necrosis	0 (0/10)	15.4% (4/26)	Incalculable
			Chronic pain	0 (0/10)	3.8% (1/26)	Incalculable
			Complications	20% (2/10)	35% (9/26)	0.58 (0.15-2.2)

Cohort studies compared patients in the same treatment population. Case series compared results to historical control subjects.
NR, Not reported; *IR*, irradiation.
*Statistically significant findings.

the RRs and adjusted RRs that we report there. These studies were of moderate quality, and, therefore, risk estimates should be taken with caution.

Dosing of radiation. Visch et al.[25] compared survival rates at 10 years in patients receiving a dose either <50 Gy or ≥50 Gy. Lower radiation dose (<50 Gy) was significantly associated with improved implant survival compared with higher doses (≥50 Gy). This difference was greater than 2-fold (RR 0.49, 95% CI 0.29-0.81). A review article noted that no failures were observed with radiation doses <45 Gy.[26]

Timing of radiation. Several studies compared failure rates for implants placed at varying intervals after irradiation. No differences were seen comparing placement <1 year or >1 year after radiation in one study.[25] Another study found no differences in timing, but the number of subjects and implants was small.[27] One study observed that only the time interval between implant placement and the abutment operation showed significance, with patients receiving implant placement and abutment <4 months apart doing significantly worse than those with the abutment procedure >4 months after the implant (P = .0001).[28] A second study agreed with this finding, noting that significantly more mandibular reconstruction plates were lost when radiation was administered during the perioperative period, defined as within 12 weeks of implant surgery.[27] A third study did not observe a statistically significant difference in survival rates between implants inserted <1 year or >1 year after irradiation.[25] A review article comparing failure rates for implants placed either before or after irradiation showed that failure rates were similar between the 2 groups and not statistically significant (5.4% and 3.2%, respectively).[26]

Implant location. Implant failure in irradiated maxillary bone was twice that of nonirradiated maxillary bone based on 1 study where the comparison could be made.[29] Complications based on radiation status were not well

reported and generally not separated out in those studies reporting complications, making definitive statements about complications, including osteoradionecrosis, difficult. Mandibular implants were significantly less likely to fail compared with maxillary implants.[25] An adjusted RR of 1.79 (P = .001; no CI was provided) for implant failure in the maxilla compared with that in the mandible was reported (all bone). One study showed a survival rate of 59% in the maxilla and 85% in the mandible. (P = .001).[25] In a comparison of total implant locations, high implant failure rates were seen after high-dose radiotherapy and a long time after high-dose irradiation. All CF regions were affected, but the highest rates of implant failures were seen in frontal bone, zygoma, mandible, and nasal maxilla. Lowest implant failure rates were seen in oral maxilla.[20] A review article noted that implant location resulted in significant differences in failure rates, with mandibular implants failing less than maxillary implants (4.4% and 17.5%, respectively; OR 4.63, 95% CI 2.25-9.49).[26]

HBO therapy. Two studies attempting to evaluate the effect of HBO therapy as an adjunct to irradiation for dental implants in irradiated bone were identified.[30,31] Based on the criteria that the patient is expected to experience difficulty during osseointegration, Granstrom[30] proposed the use of HBO therapy as potentially beneficial, reporting from a multivariate analysis of 671 irradiated implants that HBO therapy improved implant survival with significance at the P < .001 level. Conversely, Donoff[31] contends that our understanding of wound healing is incomplete and constantly changing in light of new research, and that our incomplete knowledge precludes any reliable conclusions regarding the necessity for HBO therapy.[31]

Complications associated with implants in irradiated bone in human studies

Complication rates based on radiation status were not well described in any of the comparative studies. Failure to report complications should not be construed as meaning that none were present. Briefly, in the CF studies reviewed, several studies reported no complications,[1,21] 1 study reported a low rate of osteoradionecrosis (4.7% [n = 5 out of 107]),[20] and grade 1-3 tissue reactions were observed in patients receiving radiotherapy ($P < .001$-.05).[20,21]

For the dental implant studies, August et al.[32] reported the following early complications in an oral cancer population: soft tissue overgrowth around pins (22.2% [n = 4 out of 18]), tongue ulcerations (11.1% [n = 2]), and intraoral wound dehiscence (11.1% [n = 2]). Late complications included orocutaneous fistula formation (16.6% [n = 3 out of 18]), submental erythema (11.1% [n = 2]), and persistent tissue overgrowth around pins (5.6% [n = 1]). Soft tissue ulcers also have been noted.[33,34]

Radiation scattering

Implants placed before radiation therapy may cause scattering, resulting in a decreased dose delivered to the tumor and increased exposure to soft tissue and bone adjacent to the implant.[21] Implants of a higher atomic number material cause a greater backscatter dose factor, although the range is small (a few millimeters). Additionally, lower-energy photons, i.e., ^{60}Co, caused greater backscatter than higher-energy photons.[35,36] A study of simulated head and neck radiotherapy showed that highest dose enhancement occurs at a distance of 0 mm from the bone-implant interface in all of the locations and implant materials studied. Transmandibular implants (high gold content, gold-copper-silver alloy) had scatter up to 1 mm from the bone-implant interface. No significant difference was noted in buccal, lingual, mesial, or distal directions. Hydroxyapatite-coated titanium implants demonstrated the best results.[37] An additional study of titanium implants in mandible confirmed that the risk of radionecrosis from backscatter is slightly but not significantly higher with postimplantation radiotherapay.[36]

A dosimetric evaluation of the effect of previously placed dental implants during radiotherapy concluded that the risk of osteoradionecrosis to the mandible is slightly but not significantly affected by the scattered dose in the radiation field exposed to 3 different radiation beams.[36] Granstrom et al.[16] recommended that if irradiation is to be performed after implantation, all prostheses, frameworks, and abutments should be removed before irradiation. Fixtures should be left intact but covered with skin or mucosa, because removal of osseointegrated implants is itself a potentially damaging procedure.

DISCUSSION

In general, the quality of studies comparing implant failure/success and complication rates in irradiated versus nonirradiated bone is moderate at best. For animal studies, no studies evaluated all of the important parameters, such as timing, histomorphometric, biomechanical, and histologic measurements in the same study using irradiated bone with a nonirradiated control leg. Furthermore, few animal studies were designed to compare implant types in irradiated bone.

For human studies, most were of poor (case series) to moderate (cohort studies) quality. No randomized controlled trials or meta-analyses were identified. The majority of comparisons between irradiated bone and nonirradiated bone were with historical controls. Comparisons with historical control groups can be problematic. Data are frequently collected by different methods, and if differences are observed, one cannot

say for sure whether they are due to the exposure itself or to other factors, such as secular time trends, institutional factors, or factors unique to each implantologist's or institution's ability or experience to manage the disease. However, a prospective study comparing patients who do and do not get irradiated in the same consecutive patient population may be difficult to perform. No studies were designed to compare implant types in irradiated bone. This may be the focus for future research.

A review of the animal literature showed numerous changes in irradiated versus nonirradiated bone, including significantly reduced pull-out load and breakpoint torques, and significantly decreased bone thickness measurements. Histologic changes included compromised bone remodeling and changes to the vascular architecture, fibrous appearance of the cartilage, and signs of venous blood congestion or arteriolar thrombosis, inflammation, and increased bone resorption. However, thrombosis or hemorrhage attributable to irradiation was not always apparent, and vascular architecture may remain unaltered. Many changes appeared to be temporary and reversible, with a normal balance of bone resorption and osteogenesis restored over time.

The following is a summary of the findings in human studies addressing the posed questions:

1, *Are patients with irradiated bone at greater risk of implant failure than patients with nonirradiated bone?* Human studies of CF implants suggested that risk of implant failure in irradiated bone was 3 to 12 times greater than that for nonirradiated bone; however, those studies reporting the highest risks were case series compared with historical controls. Human studies of dental implants suggested an increased risk of implant failure in irradiated bone compared with nonirradiated bone; however, the effects were not as large as with CF implants. The risk of implant failure in irradiated bone was between 2-3 times greater than that for nonirradiated bone in those studies that reported a statistically significant difference.
2. *Is there a dose response to radiation whereby greater doses lead to higher failure rates?* In CF applications, the importance of dose was difficult to assess, owing to small patient population sizes. Cumulative radiation effect as a measure of dose was significantly related to implant failure in one prognostic study, whereas a separate review observed no correlation between dose levels or even irradiation versus nonirradiation and implant success. In dental applications, lower radiation dose ($<$50 Gy) was significantly associated with improved implant survival compared with higher doses ($\geq$50 Gy). A review article noted that no failures were observed with radiation doses $<$45 Gy.
3. *Is implant survival dependent on when a patient receives radiation, i.e., before or after implant placement?* In CF applications, no differences in failure were seen comparing implants placed before or after irradiation; however, the small numbers of patients and implants may have precluded the ability to observe a difference. In dental applications, studies comparing implants placed at varying intervals before or after irradiation did not show significant differences in survival rates and could not make a strong recommendation for treatment.
4. *Are some anatomic areas at greater risk of failure due to radiation than others?* In CF applications, implant location may be important to survival rates, with greater risks cited for the mastoid, orbital and nasal regions. As with CF implants, location may be important to survival rates with dental implants. Implant failure in irradiated maxillary bone was twice that of nonirradiated maxillary bone based on 1 study where the comparison could be made. Mandibular implants were significantly less likely to fail compared with maxillary implants.
5. *Are some implants more effective than others in treating patients with irradiated bone?* There was no evidence in either the animal or the human studies that specific implants are superior to others in treating patients with irradiated bone.
6. *Are there adjunctive therapies that may improve the outcome after radiation and implant placement?* In CF applications, adjunctive HBO therapy appeared to significantly decrease failure rates compared with patients receiving radiotherapy only, resulting in failure rates similar to nonirradiated patients. In dental applications, the importance of adjunct HBO therapy for irradiation patients was inconclusive based on the studies found.

Future literature reviews ought to consider if all bone types (e.g., woven vs. plexiform bone) are equally affected by radiation. For example, is woven bone which is created de novo after radiation affected at all? All studies found in the present literature review were in essence related to disturbed osteonal systems and the reduced or impaired bony remodeling leading to clinically observed problems. Those problems can be a result of: 1) spontaneous fractures of devitalized bones in function, as a result of unrepaired functionally derived crack accumulation; or 2) proneness to or promotion of infection (i.e., osteomyelitis) as a result of reduced perfusion of the radiated bone areas. All studies found by the present search were dealing with mature osteonal bone, which is consistent with how

individuals and animals present clinically when seeking dental implants. Some implant designs, however, use new woven bone as opposed to old osteonal bone for their integration,[41,42] which is described as possessing a "dual-integration mechanism."[43,44] Basal implants are primarily anchored in cortical areas. Woven bone is formed de novo from the blood created by the osteotomy, and the formation of bone follows a well known cascade of maturation toward woven bone. The authors have not found any evidence in the literature that this cascade is altered by irradiation. From years of experience in treating fractures in patients with severe osteoporosis, it can be concluded that in this disease the tendency for building new osteonal bone is reduced because more bone is resorbed than formed. This, however, does not affect the woven bone formation in the osteoporotic patient. The clinical problems associated with fractures in osteoporotic patients are associated with the tightening of screws of fracture plates and in reducing the segments adequately with very little bone surface being present in the cortices. Once a fixation of the segments is achieved and infections are absent, the periosteal and endosteal callus formation is a reliable source of new bone formation.

This is mentioned to encourage research regarding the use of basal implants in irradiated patients, because the mechanism of integration uses newly formed woven bone rather than the irradiated bone. This leads to a reduced potential for infection. The partial prophylactic decorticalization which is routinely performed during the insertion of basal implants has proved to eliminate infections in an animal experiment[45] in nonirradiated bone. That experiment has shown that machined implant surfaces and thin mucosal penetration diameters (though partly conflicting with the idea of an "emerging profile"), may reduce the chances of failure in dental implantology. The experimental results were found to be applicable in clinical practice: 2 retrospective studies showed that basal implants were equally successful in healed bone compared with direct placement into even periodontally involved sites.[46,47] A reduction of all potential risks seems vital, especially in patients who are expected to undergo radiation therapy. Future research should include a well designed animal study with adequate sample size that compares different implant types in irradiated and nonirradiated bone (including basal implants). Such a study should assess the following important parameters regarding the implants evaluated: timing of radiation, histomorphometric characteristics, biomechanical characteristics, and histologic characteristics. A well designed human observational cohort study should be performed that follows a group of similar patients during the same time period. Patients exposed to radiation should be compared with patients who are not exposed to radiation. Furthermore, this should be a large enough population with enough implantologists that more than 1 implant type is used in both irradiated and nonirradiated bone. This will allow for the comparison of implants in irradiated and nonirradiated bone regarding the following outcomes: time to loading, implant failure, complications, implant function, and overall quality of life.

CONCLUSION

Radiation affects the mineralized bony substrate and thereby affects the outcomes of dental implant treatment in humans. The risk of implant failure in irradiated bone was 2-3 times greater than that for nonirradiated bone in those studies that reported a statistically significant difference. In dental applications, lower radiation dose ($<$50 Gy) was significantly associated with improved implant survival compared with higher doses ($\geq$50 Gy). A review article noted that no failures were observed with radiation doses $<$45 Gy. Studies comparing implants placed at varying intervals before or after irradiation did not show significant differences in survival rates and could not make a strong recommendation for treatment. In general, mandibular implants were significantly less likely to fail compared with maxillary implants.

REFERENCES

1. Scolozzi P, Jaques B. Treatment of midfacial defects using prostheses supported by ITI dental implants. Plast Reconstr Surg 2004;114:1395-404.
2. Johnsson AA, Sawaii T, Jacobsson M, Granstrom G, Turesson I. A histomorphometric study of bone reactions to titanium implants in irradiated bone and the effect of hyperbaric oxygen treatment. Int J Oral Maxillofac Implants 1999;14:699-706.
3. Teng MS, Futran ND. Osteoradionecrosis of the mandible. Curr Opin Otolaryngol Head Neck Surg 2005;13:217-21.
4. Brogniez V, Nyssen-Behets C, Gregoire V, Reychler H, Lengele B. Implant osseointegration in the irradiated mandible. A comparative study in dogs with a microradiographic and histologic assessment. Clin Oral Implants Res 2002;13:234-42.
5. Larsen PE, Stronczek MJ, Beck FM, Rohrer M. Osteointegration of implants in radiated bone with and without adjunctive hyperbaric oxygen. J Oral Maxillofac Surg 1993;51:280-7.
6. Schon R, Ohno K, Kudo M, Michi K. Peri-implant tissue reaction in bone irradiated the fifth day after implantation in rabbits: histologic and histomorphometric measurements. Int J Oral Maxillofac Implants 1996;11:228-38.
7. Ohrnell LO, Branemark R, Nyman J, Nilsson P, Thomsen P. Effects of irradiation on the biomechanics of osseointegration. An experimental in vivo study in rats. Scand J Plast Reconstr Surg Hand Surg 1997;31:281-93.
8. Johnsson AA, Sawaii T, Jacobsson M, Granstrom G, Turesson I. A histomorphometric and biomechanical study of the effect of delayed titanium implant placement in irradiated rabbit bone. Clin Implant Dent Relat Res 2000;2:42-9.
9. Johnsson K, Hansson A, Granstrom G, Jacobsson M, Turesson I. The effects of hyperbaric oxygenation on bone–titanium implant interface strength with and without preceding irradiation. Int J Oral Maxillofac Implants 1993;8:415-9.

10. Johnsson AA, Jacobsson M, Granstrom G, Johansson CB, Strid K, Turesson I. A microradiographic investigation of cancellous bone healing after irradiation and hyperbaric oxygenation: a rabbit study. Int J Radiat Oncol Biol Phys 2000;48:555-63.
11. Jacobsson M, Albrektsson T, Turesson I. Dynamics of irradiation injury to bone tissue. A vital microscopic investigation. Acta Radiol Oncol 1985;24:343-50.
12. Matsui Y, Ohno K, Michi K, Tachikawa T. Histomorphometric examination of healing around hydroxylapatite implants in 60Co-irradiated bone. J Oral Maxillofac Surg 1994;52:167-72.; discussion 172-3.
13. Jacobsson MG, Jonsson AK, Albrektsson TO, Turesson IE. Short- and long-term effects of irradiation on bone regeneration. Plast Reconstr Surg 1985;76:841-50.
14. Roumanas ED, Freymiller EG, Chang TL, Aghaloo T, Beumer J, third: Implant-retained prostheses for facial defects: an up to 14-year follow-up report on the survival rates of implants at UCLA Int J Prosthodont 2002;15:325-32.
15. Albrektsson T, Branemark PI, Jacobsson M, Tjellstrom A. Present clinical applications of osseointegrated percutaneous implants. Plast Reconstr Surg 1987;79:721-31.
16. Granstrom G, Tjellstrom A, Albrektsson T. Postimplantation irradiation for head and neck cancer treatment. Int J Oral Maxillofac Implants 1993;8:495-501.
17. 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.
18. Wolfaardt JF, Wilkes GH, Parel SM, Tjellstrom A. Craniofacial osseointegration: the Canadian experience. Int J Oral Maxillofac Implants 1993;8:197-204.
19. Toljanic JA, Eckert SE, Roumanas E, Beumer J, Huryn JM, Zlotolow IM, et al. Osseointegrated craniofacial implants in the rehabilitation of orbital defects: an update of a retrospective experience in the United States. J Prosthet Dent 2005;94:177-82.
20. Granstrom G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. J Oral Maxillofac Surg 2005;63:579-585.
21. Schoen PJ, Raghoebar GM, van Oort RP, Reintsema H, van der Laan BF, Burlage FR, et al. Treatment outcome of bone-anchored craniofacial prostheses after tumor surgery. Cancer 2001;92:3045-50.
22. Tolman DE, Taylor PF. Bone-anchored craniofacial prosthesis study: irradiated patients. Int J Oral Maxillofac Implants 1996;11:612-9.
23. Tolman DE, Taylor PF. Bone-anchored craniofacial prosthesis study. Int J Oral Maxillofac Implants 1996;11:159-68.
24. Moy PK, Medina D, Shetty V, Aghaloo TL. Dental implant failure rates and associated risk factors. Int J Oral Maxillofac Implants 2005;20:569-77.
25. 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.
26. Colella G, Cannavale R, Pentenero M, Gandolfo S. Oral implants in radiated patients: a systematic review. Int J Oral Maxillofac Implants 2007;22:616-22.
27. Ryu JK, Stern RL, Robinson MG, Bowers MK, Kubo HD, Donald PJ, Rosenthal SA, Fu KK. Mandibular reconstruction using a titanium plate: the impact of radiation therapy on plate preservation. Int J Radiat Oncol Biol Phys 1995;32:627-34.
28. Wagner W, Esser E, Ostkamp K. Osseointegration of dental implants in patients with and without radiotherapy. Acta Oncol 1998;37:693-6.
29. Cao Y, Weischer T. Comparison of maxillary implant-supported prosthesis in irradiated and nonirradiated patients. J Huazhong Univ Sci Technolog Med Sci 2003;23:209-12.
30. Granstrom G. Placement of dental implants in irradiated bone: the case for using hyperbaric oxygen. J Oral Maxillofac Surg 2006;64:812-8.
31. Donoff RB. Treatment of the irradiated patient with dental implants: the case against hyperbaric oxygen treatment. J Oral Maxillofac Surg 2006;64:819-22.
32. 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.
33. 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.
34. 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.
35. Ravikumar M, Ravichandran R, Sathiyan S, Supe SS. Backscattered dose perturbation effects at metallic interfaces irradiated by high-energy X- and gamma-ray therapeutic beams. Strahlenther Onkol 2004;180:173-8.
36. Ozen J, Dirican B, Oysul K, Beyzadeoglu M, Ucok O, Beydemir B. Dosimetric evaluation of the effect of dental implants in head and neck radiotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:743-7.
37. Wang R, Pillai K, Jones PK. Dosimetric measurement of scattered radiation from dental implants in simulated head and neck radiotherapy. Int J Oral Maxillofac Implants 1998;13:197-203.
38. Granstrom G. Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontol 2000 2003;33:145-62.
39. Landes CA, Kovacs AF. Comparison of early telescope loading of nonsubmerged ITI implants in irradiated and nonirradiated oral cancer patients. Clin Oral Implants Res 2006;17:367-74.
40. Schepers R, 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.
41. Esser E, Wagner W. Dental implants following radical oral cancer surgery and adjuvant radiotherapy. Int J Oral Maxillofac Implants 1997;12:552-7.
42. Ihde S, Goldman T, Himlova L, Aleksic Z. The use of finite element analysis to model bone-implant contact with basal implants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:39-48.
43. Ihde S, Konstantinovic VS. Immediate loading of dental implants. Where is the dip? Craniomaxillofac Implant Dir 2007;3:137-145.
44. Ihde S. Foud-dimensional considerations of bone morphology and mechanics. In: Principles of BOI: Clinical, Scientific, and Practical Guidelines to 4-D Dental Implantology. Heidelberg: Springer: 2005; pp 103-148.
45. Ihde S. Mechanics meets biomechanics. In: Principles of BOI: Clinical, Scientific, and Practical Guidelines to 4-D Dental Implantology. Heidelberg: Springer: 2005; pp 295-302.
46. Kopp S, Kopp W. Comparison of immediate vs delayed basal implants. J Maxillofac Oral Surg 2008;7:116-122.
47. Kopp S. Basal implants: a safe and effective treatment option in dental implantology. Craniomaxillofac Implant Dir 2007;3:110-7.

Reprint requests:

Dr. Stefan Ihde
Gommiswald Dental Clinic
CH-8737 Gommiswald
Switzerland
dr.ihde@bluewin.ch