Implants Placed in an Irradiated Dog Mandible: A Morphometric Analysis

Véronique Brogniez, MD[1]/William D'Hoore, MD, PhD[2]/Vincent Grégoire, MD, PhD[3]/
Everard Munting, MD, PhD[4]/Hervé Reychler, MD, DDS[5]

The objective of this research was to evaluate the influence of radiotherapy on the osseointegration of oral implants in a canine model. After the extraction of all mandibular premolars and first and second molars, 11 male beagles were divided into 3 groups. The control group (3 dogs) received no radiation. The second group (4 dogs) was irradiated 4 weeks after implantation. The third group (4 dogs) was irradiated 8 weeks before implantation. Eight implants were placed in each dog, in an alternating pattern: 4 non-submerged ITI Bonefit titanium plasma spray-coated and 4 submerged Steri-Oss hydroxyapatite-coated. The irradiated dogs received 4.3 Gy daily for 10 days. After 6 months of osseointegration, the dogs were sacrificed and each hemimandible was dissected to isolate the implants. Quantification of the extent of the direct bone-implant contact was carried out by scanning electron microscopy backscattered electron images that reproduced each implant in its entirety, using a digitizing table connected to a computer. The results were expressed as a percentage of direct bone-implant contact versus total perimeter accessible to bone. The bone contact percentage for the control group was 87% for Steri-Oss implants and 69% for the ITI Bonefit implants; for the animals irradiated after implantation, the percentages were 82 for Steri-Oss implants and 58 for ITI Bonefit implants; and for the animals irradiated before implantation, the percentages were 62 for Steri-Oss implants and 28 for ITI Bonefit implants. A statistically significant difference appeared between the 2 types of implants ($P < .001$). A statistically significant difference was also seen between the 3 groups for both types of implants, except between the control group and the group irradiated after implantation ($P = .14$). This indicates that, overall, the timing of irradiation influences osseointegration. Osseointegration is possible before and after radiotherapy; however, the direct bone-implant contact increased when the implants were placed before irradiation. (Int J Oral Maxillofac Implants 2000;15:511–518)

Key words: *dental implants, dogs, endosseous dental implantation, irradiation*

Patients treated by surgery and postoperative radiotherapy for maxillofacial malignant tumors should be restored functionally and esthetically, and oral implants are a viable option for restoration. Encouraging results of implant osseointegration in irradiated patients have been published.[1–11] In clinical studies, success rates of implants placed after radiotherapy vary from 83 to 99%, depending partly on the delay between radiotherapy and implantation; the longer the delay, the better the outcomes.[1–3] To avoid delays between treatment and rehabilitation, a strategy of implantation before radiotherapy has been developed.[12] Several factors influence implant failure: irradiation dosage, time interval between radiotherapy and implant surgery, material and shape of implant, and sequence of procedures.

Ten years ago, the first experimental studies on the osseointegration of oral implants after irradiation were published[13–17] (Table 1). Schweiger[13] published results on Brånemark implants (Nobel Biocare, Göteborg, Sweden) placed in the hemimandibles of

[1]Assistant Professor, Prosthodontics Department, Catholic University of Louvain, St. Luc University Hospital, Brussels, Belgium.
[2]Professor, School of Public Health, Catholic University of Louvain, St. Luc University Hospital, Brussels, Belgium.
[3]Professor, Radiation Oncology Department, Catholic University of Louvain, St. Luc University Hospital, Brussels, Belgium.
[4]Professor, Orthopedic Surgery Department, Catholic University of Louvain, St. Luc University Hospital, Brussels, Belgium.
[5]Professor and Head, Oral and Maxillofacial Surgery Department, Catholic University of Louvain, St. Luc University Hospital, Brussels, Belgium.

Reprint requests: Véronique Brogniez, Catholic University of Louvain, Avenue Hippocrate 15/5732, B-1200 Brussels, Belgium. Fax: +32-27648983. E-mail: Brogniez@prdt.ucl.ac.be

Table 1 Comparison of 5 Animal Experiments Involving Radiation and Implantation

	Animal model				Implants				
Study	Species	Implant location	Control	Radiation dosage	No.	Type	Placement timing	Integration time	Difference in osseointegration (%)*
Schweiger[13]	Beagle	½ mandible	½ mandible	30 × 2 Gy	10	Titanium	9 mo after irradiation	5.5 mo	50
Larsen et al[14]	Rabbit	Tibia	Tibia	10 × 4.5 Gy	10	TPS, HA-coated	4 mo after irradiation	4 mo	13.5
Matsui et al[15]	Rabbit	Mandible	Mandible	1 × 15 Gy	10	HA-coated	3 mo after irradiation	3 mo	7
Schön et al[16]	Rabbit	Mandible	Mandible	1 × 15 Gy	8	Titanium alloy HA-coated	5 days before irradiation	1.8 mo	15 12
Asikainem et al[17]	Beagle	½ mandible	½ mandible	10 × 4 Gy	20		2 mo after irradiation	4 mo + 6 mo loaded	0
				10 × 5 Gy	20	Titanium		4 mo + 6 mo loaded	25
				15 × 4 Gy	20			4 mo	100

*Percent difference between irradiated and non-irradiated samples.

dogs 9 months after irradiation up to a cumulative dose of 60 Gy (30 fractions) and analyzed 5.5 months after implantation. Histologic observation showed that osseointegration was 50% less in irradiated bone. Larsen et al[14] studied the effects of irradiation and hyperbaric oxygen therapy on osseointegration of 2 different types of implants (titanium plasma-sprayed [TPS] and hydroxyapatite- [HA] coated) in rabbit tibiae. A total of 45 Gy irradiation was administered. After 4 months osseointegration, a 13.9% difference was observed between the irradiated (79.6%) and control specimens (93.5%). No comparison was available between the 2 implant types.

Matsui et al[15] studied osseointegration of 80 implants placed in rabbit mandibles, with varying intervals between radiotherapy and implantation (3 to 12 months), and varying intervals between implantation and sacrifice (7 to 90 days). A single dose of 15 Gy was administered. After 3 months of osseointegration, the difference between control and irradiated groups was 7%. Schön et al[16] published morphometric results with 2 implant types (titanium alloy and HA-coated titanium) placed in rabbit mandibles 5 days before a single 15-Gy dose of irradiation. After 5 days osseointegration, non-irradiated HA-coated implants performed better than HA-coated irradiated implants (92% versus 80%). Titanium alloy implants did not perform as well as HA-coated implants; non-irradiated implants had 85% osseointegration and irradiated implants had 70% osseointegration. Recently, Asikainem et al[17] tested the influence of irradiation (40, 50, and 60 Gy administered between 1.5 and 3 months) on osseointegration of titanium implants placed in the mandibles of beagle dogs 2 months after irradiation.[17] After 4 months of osseointegration, implants were loaded for 6 months. All implants submitted to 60 Gy irradiation failed before loading, 25% of the 50-Gy group were mobile, and 100% of the 40-Gy group were satisfactory.

In these studies, key experimental conditions, ie, animal model, site of implantation, reference site, irradiation dose and schedule, implanted material, and integration time, differed from each other. The objectives of the present study were the following:

1. To evaluate which sequence of procedures produces higher rates of success: irradiate and then place implants, or place implants first, and then irradiate.
2. To evaluate the survival rate of 2 different implants, characterized by their coating and placement method (submerged or not), in combination with the sequence of procedures.

MATERIAL AND METHODS

Eleven male 1-year-old beagle dogs, with similar weight (about 12 kg) and size, were randomly divided into 3 groups: a control group of 3 non-irradiated dogs (C), a group of 4 dogs that were irradiated after implantation (AI), and a group of 4 dogs that were irradiated before implantation (BI). In each dog, 2 mandibular premolars and 2 mandibular molars were extracted from each side to create 2 edentulous areas.

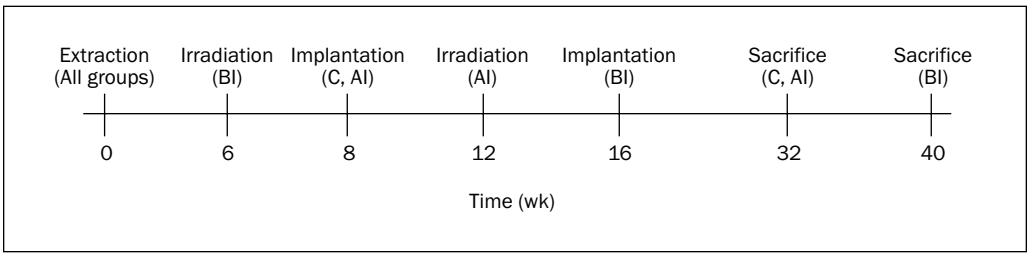

Fig 1 Sequence of events during study. C = controls (no irradiation); AI = irradiated after implantation; BI = irradiated before implantation.

Two different types of implants were placed: Steri-Oss submerged HA-coated implants, 3.8 mm in diameter and 8 mm in length (Yorba Linda, CA); and ITI Bonefit non-submerged implants with TPS coating, 4 mm in diameter and 8 mm in length (Straumann, Waldenburg, Switzerland). In each dog, 8 implants were placed in the edentulous area, 4 on each side, alternating between Steri-Oss and ITI Bonefit implants. A total of 88 implants was placed. Surgery was performed under general anesthesia (Nembutal, Abbott Laboratories, Louvain, Belgium) with laryngeal intubation and under sterile conditions. Cefazolin administered intravenously was used for antibiotic prophylaxis.

Figure 1 details the sequence of procedures followed. Groups C and AI received implants 8 weeks after extraction. Group AI was irradiated 4 weeks after implantation. Group BI was irradiated 6 weeks after extraction, and implants were placed 8 weeks after irradiation.

Irradiation was delivered with a telecobalt therapy unit. Irradiated dogs first underwent simulation to accurately localize irradiation fields. Field marks were drawn on the outer cheek to allow reproducibility of positioning across sessions. Daily doses of 4.3 Gy were administered for 10 consecutive days, for a total dose of 43 Gy. According to Arnold et al[18,19] this schedule is equivalent to a total dose of 60 Gy delivered over a 6-week period with 5 sessions a week. During the irradiation period, dogs were given daily intramuscular injections of ketamine hydrochloride for sedation. Mucositis appeared 1 week after the completion of irradiation in all dogs. Antiseptic mouth rinses with chlorhexidine digluconate 0.2% were administered daily for 7 days. No other treatment or intervention was applied.

Intraoral radiographs were taken 3 times: immediately after implantation, at the time of irradiation or after an equivalent time interval for the control group, and 6 months after implantation. After 6 months of implantation, the dogs were sacrificed with a lethal dose of Nembutal. Each hemimandible was cut in blocks to isolate each implant. The mandibles were fixed for 4 weeks in 10% phosphate-buffered neutral formalin before dehydration in methanol then embedded in methyl methacrylate resin. Serial sections were cut longitudinal to the axis of the implant with a diamond saw (Leitz, Wetzlar, Germany) and polished on a rotating grinding machine (Planapol 2, Struers, Copenhagen, Denmark). All sections were coated with carbon prior to scanning electron microscopy with backscattered electron imaging (Leica, Videoscan 260, Cambridge, United Kingdom).[20,21] This provides high-resolution images, allowing accurate identification of the boundaries between metal, HA, bone, and soft tissue without any projection artifacts related to the thickness of the section.[22] Exact quantification of the extent of direct bone-implant contact was carried out on the electron micrographs, which reproduced entirely 10 or 11 sections of each implant using a digitizing table (Numonics, 2200-056TLA, Kessel, Belgium) connected to a computer with appropriate software.

For the statistical analysis, repeated measures were averaged on a per-subject level. The authors then computed differences between means of groups defined by the experimental factor (irradiated vs. non-irradiated, irradiated before or after implantation) with *t* test for independent samples (degrees of freedom proportional to no. of dogs/group). Differences between implants were tested with the paired *t* test (degrees of freedom proportional to no. of dogs). All tests were 2-tailed, and statistical significance was set at $P \leq .05$.

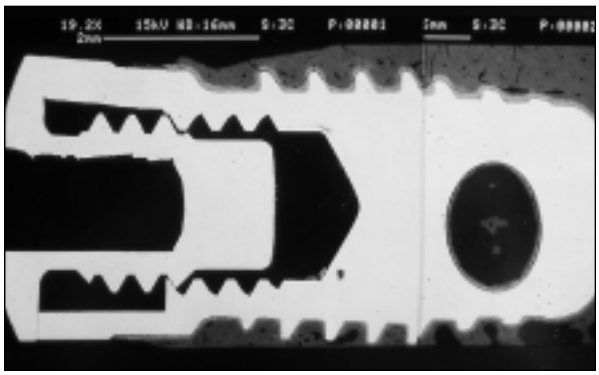

Fig 2a Composite scanning electron micrograph of control (non-irradiated) implant (Steri-Oss) (magnification ×19).

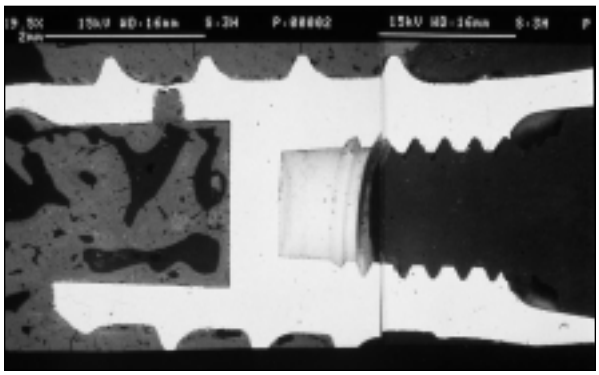

Fig 2b Composite scanning electron micrograph of control (non-irradiated) implant (ITI Bonefit). Bone can be seen around the apical part of the implant (magnification ×19).

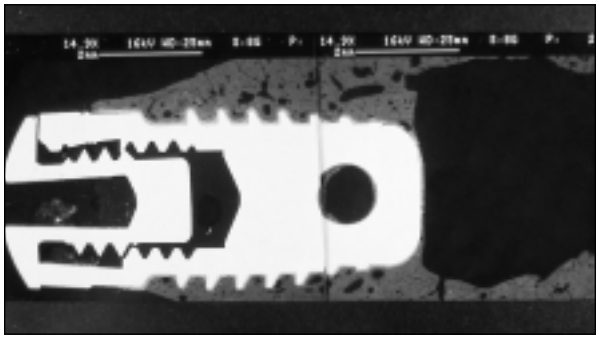

Fig 3a Composite scanning electron micrograph of a Steri-Oss implant in the AI group (magnification ×15).

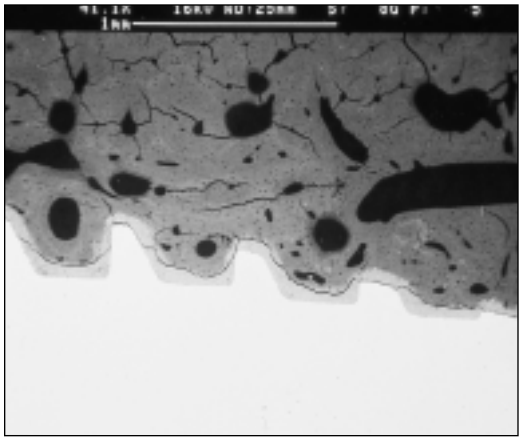

Fig 3b Higher-power view of a Steri-Oss implant in the AI group. The bone appears more porous than the non-irradiated implants (magnification ×41).

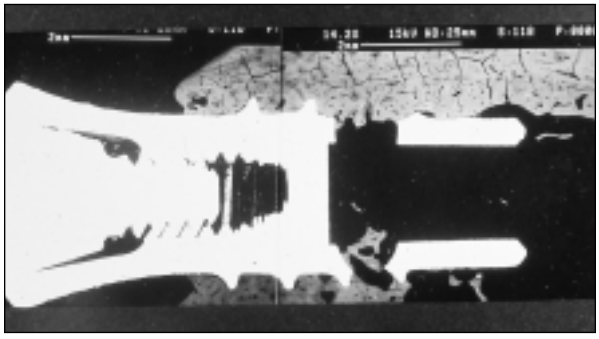

Fig 4a Composite scanning electron micrograph of an ITI Bonefit implant in the BI group. There is no bone in the vent of the implant (magnification ×14).

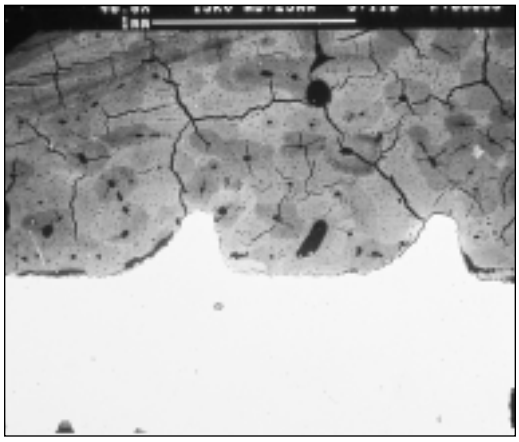

Fig 4b Higher-power view of ITI Bonefit implant in the BI group (magnification ×41).

Table 2 Morphometric Data for Both Types of Implants in All Groups Tested

	Zone A			Zone B			Total		
	Length (mm)	Contact (mm)	% contact	Length (mm)	Contact (mm)	% contact	Length (mm)	Contact (mm)	% contact
Controls									
Steri-Oss (n = 12)	12.08	11.01	91	7.25	5.83	80	19.34	16.84	87
ITI Bonefit (n = 12)	16.66	12.77	76	5.84	2.89	49	22.5	15.66	69
Both (n = 24)	14.37	11.89	82	6.54	4.36	66	20.92	16.25	78
Irradiated after implantation									
Steri-Oss (n = 16)	15.93	14.05	88	6.58	4.31	65	22.51	18.36	82
ITI Bonefit (n = 16)	18.98	11.98	62	3.9	1.36	34	22.88	13.35	58
Both (n = 32)	17.45	13.01	74	5.24	2.83	54	22.69	15.85	70
Irradiated before implantation									
Steri-Oss (n = 16)	13.48	10.2	74	8.08	3.15	39	21.55	13.36	62
ITI Bonefit (n = 16)	17.98	6.8	36	7.11	0.58	8	25.09	7.38	28
Both (n = 32)	15.73	8.5	54	7.59	1.86	24	23.32	10.36	44

Length = interface perimeter; contact = bone-to-implant contact.

RESULTS

The study evaluated osseointegration clinically, radiographically, and morphometrically.

Implant Mobility

No implant failure was observed during the experiment. However, 3 of the 88 implants demonstrated mobility at 6 months. These were ITI Bonefit implants placed in the BI group, and 2 of these were in the same dog.

Radiographic Evaluation

With the exception of the 3 mobile implants, no area of radiolucency between the implants and adjacent cortical bone was detectable.

Morphometric Analysis

Two zones were defined for each section (Figs 2 to 4, Table 2). The area of the implant (in mm) apparently in contact with cortical bone at the time of implantation was designated zone A. The area of the implant (in mm) where no bone was present at the time of implantation was designated zone B. Typically, zone B represents the tip of an implant placed in the dental canal and any perforations present at the apical extremity of the implant. Bone contacting an implant in zone B indicates osteoconduction. Addition of the zone A value to the zone B value gave the total perimeter accessible to bone (Table 2). The amount of measured contact between bone and implant was divided by the total perimeter of the implant accessible to bone to produce the percentage of bone-implant contact. Blind scoring was done for the experimental groups.

Hypotheses were tested as to the influence of timing of irradiation and type of implants on bone-implant contact. For both types of implant, there was a significant difference in bone-implant contact between the control group (mean 78%) and the 2 irradiated groups (mean 57%) (P = .013) (Table 2). A significant difference was also seen between the AI group (mean 70%) and the BI group (mean 44%) for both types of implant (P = .026), and between the control group (mean 78%) and the BI group (mean 44%) (P = .011). There was a difference between the control group (mean 78%) and the AI group (mean 70%), but it was not statistically significant (P = .14).

The timing of irradiation affected the 2 types of implants differently (Table 3). Analyses were also conducted with the t test for independent samples, but caution is required given the small sample size. For Steri-Oss implants, irrespective of the zone (A, B, or total), there were no significant differences between the control group and the AI group or between the AI and BI groups. The difference was also statistically insignificant between the control group and the BI group with regard to zone A and the total, but a significant difference was observed for zone B for controls versus the BI group. For ITI Bonefit implants, no significant differences were present between the control group and the AI group. Statistically significant differences were present in comparisons between the control group and the BI group and between the AI and BI groups.

In this study, the Steri-Oss implants had more bone-implant contact than the ITI Bonefit implants (P < .001, paired t test, n = 11). Regarding the total extent of osseointegration, the difference between

Table 3 Comparison of Means (*t* Test) for Between-Group Differences for Each Implant Type

	Zone A		Zone B		Total	
Implant/group	Contact (%)*	*P* value	Contact (%)*	*P* value	Contact (%)*	*P* value
Steri-Oss						
Control	91 ± 2	.133	80 ± 4	.369	87 ± 2	.174
AI	88 ± 2		68 ± 21		82 ± 5	
Control	91 ± 2	.082	80 ± 4	.041†	87 ± 2	.064
BI	74 ± 13		40 ± 25		62 ± 18	
AI	88 ± 2	.077	68 ± 21	.137	82 ±5	.073
BI	74 ±13		40 ± 24		62 ± 18	
ITI Bonefit						
Control	76 ± 7	.072	45 ± 11	.763	69 ± 8	.200
AI	63 ± 8		42 ± 18		58 ± 10	
Control	76 ± 7	.007†	45 ± 11	.004†	69 ± 8	.003†
BI	36 ± 14		10 ± 8		28 ± 11	
AI	63 ± 8	.017†	41 ± 18	.018†	58 ± 10	.007†
BI	36 ± 14		10 ± 8		28 ± 11	

For each group, the per-animal mean was calculated for each type of implant; then means were computed for each group based on irradiation status.
*Shown as mean ± SD.
†Statistically significant ($P \leq .05$).
AI = irradiated after implantation; BI = irradiated before implantation.

Steri-Oss implants and ITI Bonefit implants was 18% in the control group, 24% in the AI group, and 34% in the BI group (Table 2). No direct comparison between implants was performed here, but the results suggest the possibility of differing osteoconduction rates, which could be tested with other experiments.

Since 2 implants were lost in the same dog, a "dog effect" was tested with the Kruskal-Wallis test so as to compare bone-implant contact between dogs. A significant difference was present between irradiated dogs versus control group dogs ($P < .003$). The dog with lost implants had a 10% mean osseointegration, whereas the mean was 28% to 46% in other dogs.

DISCUSSION

Many factors make comparisons of studies difficult, and the results of studies can be difficult to translate into clinical practice. The choice of animal model, implantation site (mandible or tibia), the choice of an appropriate control group, the choice of implants, irradiation dose, and sequence of procedures are among these factors. Larsen et al,[14] Matsui et al,[15] and Schön et al[16] achieved better results in rabbits than Schweiger[13] and Asikainem et al,[17] who used dog models. Dogs have a bone turnover rate that is closer to that of humans; thus, dogs were selected for this study.[23] However, extrapolation of these results to humans should be made with caution, since no animal model is exactly comparable to humans.[24]

The mandible was selected as the site for implantation to better simulate the clinical reality of maxillofacial surgery. Non-irradiated dogs were chosen as controls because irradiation of a hemimandible could reach the other hemimandible.[25,26] However, distinct subjects may have different sensitivities to surgery and radiotherapy. The "dog effect" was analyzed, and as was shown, 1 dog experienced 2 implant failures. The sample size should be large enough to limit such statistical abnormalities. A fourth factor, the implant type, is at the discretion of the investigator; various systems or special implants can be used, and various implantation techniques (submerged or not) can be used, which makes comparisons impossible.

In the present study, better results were achieved with Steri-Oss implants than ITI Bonefit implants. The difference in bone-implant contact was 18% in the non-irradiated group, and this may be a result of submerged placement as well as coating. Either the coating or the placement method could explain the better results for Steri-Oss implants, but the experimental design did not provide the opportunity to distinguish which factor was responsible for the results. Further experimentation could be conducted to test precisely which factors are responsible for the advantages. Osseointegration is known to be influenced by surgical technique and type of

implant. Levy et al[27] compared 2 surgical techniques (submerged or non-submerged) by placing 24 implants in the mandibles of 4 beagle dogs. After 6 weeks of healing, histomorphometric analysis revealed bone-implant contact to be greater for the submerged implants.[27] Steflik et al[28,29] compared bone-implant contact for the same type of implant placed in either a submerged approach or a non-submerged approach. The non-submerged implants had 14% less bone-implant contact than submerged implants after 5 months of healing. This difference dropped to 5% after a 24-month loading period. Submersion of implants in the tissue may have provided better vascularization and thus also more complete healing.[28,29] Coating also has an impact on bone-implant contact, as demonstrated by Matsui et al's comparison of titanium alloy (Ti-6Al-4V) implants that were HA-coated or left uncoated.[30] After 6 months, it was shown that HA-coated implants had 80% bone-implant contact, whereas uncoated implants had 40% contact. In a more recent experiment by Carr et al in baboons,[31] HA-coated implants achieved 61.5% bone-implant contact, and uncoated implants achieved 40% contact. It may be concluded that HA has higher osteoconductibility than titanium.[20,32] This effect could offset that of submerging.

Irradiation dose and administration schedule vary greatly among reported studies. A single dose does not compare to clinical practice, since it does not take cellular repair capacity into account.[24] The timing from radiotherapy to implantation also plays a role in implant success and failure, and a long healing interval following irradiation has been proposed to improve implant success. Cellular damage is dose-dependent, and it has been shown that complications are rare with doses under 50 Gy, whereas they can be common at doses above 50 to 60 Gy delivered as 2 Gy per fraction.[33,34] Timing of implantation (before or after radiotherapy) also influences implant failure. The concept of overdose around metallic implants has been raised. For instance, a dose increase of 15% at the bone-implant interface has been reported for titanium implants in vitro.[35] Wang et al[36] examined dose enhancement at bone-implant interfaces from scattered radiation during simulated head and neck radiotherapy. Three cylindric implant systems with different compositions (pure titanium, titanium alloy, titanium coated with HA) and a high gold content transmandibular implant system were studied. The high gold content transmandibular implant system experienced a significantly higher dose enhancement than the other groups. Titanium implants coated with HA were statistically indistinguishable from the control group, which had no implants.[36] Clinical results are inconclusive, although complications have been observed in the soft tissues surrounding implants when abutments were left in situ during irradiation therapy.[37,38]

In the present study, clinical symptoms of overdose around non-submerged implants were not detected. The results tend to support the hypothesis that better results are observed when irradiation follows implantation. Indeed, there were no significant differences between the control group and the AI group for the 2 types of implants.

CONCLUSION

The present results suggest that implantation in patients with maxillofacial cancer probably should be performed at the time of surgical tumor resection, or in the time interval that precedes radiotherapy. However, taking into account all prosthetic and gnathologic factors, it is often very difficult to decide perioperatively where implants should be placed. Beyond that, patient survival probability is not known at the time of the surgical treatment, and the routine placement of implants could be seen as unnecessary or even as overtreatment.

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