Retrieved Implants from Irradiated Sites in Humans: A Histologic/Histomorphometric Investigation of Oral and Craniofacial Implants

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ABSTRACT

Purpose: The aim of this report was to quantitatively and qualitatively evaluate the tissue response to bone-anchored implants retrieved from irradiated sites in patients.

Materials and Methods: The material consists of 23 consecutively received Brånemark® implants (Nobel Biocare AB, Göteborg, Sweden) placed in pre- or postoperatively irradiated sites. Twenty-two of the 23 implants were suitable for histologic evaluation of undecalcified sections in the light microscope.

Results: The oral implants with shorter time in situ demonstrated sparse bone to implant contact with mainly dense connective tissue in the interface. However, for implants with longer time in situ, high amounts of bone-implant contact and bone fill of threads were noted. The mean values of bone-implant contact and bone area within the thread were calculated to 40% (16–94) and 70% (13–96), respectively. The craniofacial implants, with the exception of two implants lined with a capsular formation, demonstrated mature and newly formed bone at the bone-implant interface. The mean value for bone-metal contact was calculated to 45 and 53% for two specimens. The mean value for bone area within the thread ranged from 65 to 88% for three specimens.

Conclusion: The possibility to achieve bone anchorage of implants in irradiated tissue was supported by the findings in this study. However, due to limited material, conclusions with regard to radiation dose and bone tissue response to implants cannot be stated.

KEY WORDS: dental implants, histology

Radiotherapy in combination with surgery is a common treatment form for patients suffering from malignant tumors in the oral and maxillofacial regions. As a result of tumor resection, the patient might be left with large soft tissue and skeletal defects and a need for rehabilitation of oral function and aesthetic appearance.

The introduction of bone-anchored oral implants ad modum Brånemark® (Nobel Biocare AB, Göteborg, Sweden) in the 1960s and the further extension of the concept, by Tjellström and colleagues,[1,2] for retention of craniofacial prostheses have given a valuable option for rehabilitation of these patients.

Published follow-up data for the Brånemark implants, both with an oral and craniofacial application, have demonstrated considerable clinical success in long-term evaluations.[3–5] However, high-dose radiotherapy is known to alter the predictability of the bone-anchored implants with a decreased implant success rate.[6]

The morphologic examination of osseointegrated implants retrieved from humans is important to establish the causal determinants of implant failure and to

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TABLE 1 Description of Brånemark System Intraoral Implants and Results of Morphometric Analyses

Age (years)	Gender	Reason for Removal	Time in Place (months)	Loading Time (months)	Location	Bone-Metal Contact (%) Three Best Consecutive Threads		Bone Area (%) Three Best Consecutive Threads	
						Number of Threads	Mean	Number of Threads	Mean
75	—	Postmortem	2	0	Md	3	20	3	28
		Postmortem	2	0	Md	3	49	3	92
		Postmortem	2	0	Md	3	49	3	91
		Postmortem	2	0	Md	3	29	3	80
		Postmortem	2	0	Md	3	22	3	75
		Postmortem	2	0	Md	3	27	3	61
61	M	Postmortem	16	9	Mx	—	—	2	13
		Postmortem	16	9	Mx	2	30	—	—
		Postmortem	16	9	Mx	—	—	3	76
		Postmortem	16	9	Mx	—	—	3	84
		Postmortem	16	9	Md	3	38	3	91
		Postmortem	16	9	Md	3	39	3	55
		Postmortem	16	9	Md	3	41	3	59
		Postmortem	16	9	Md	3	16	3	68
—	—	Postmortem	>36	36	Md	2	66	2	86
55	M	Occlusion follow resection	74	71	Md	3	94	3	96

Md = mandible; Mx = maxilla.

compare and validate results obtained from animal studies. There are a number of morphological studies of osseointegrated implants retrieved from the oral cavity, but relatively few from extraoral sites. Likewise, only case reports are available from irradiated human specimens.

The aim of the present study was to qualitatively and quantitatively evaluate tissue response to bone-anchored implants retrieved from irradiated sites in patients gathered over a 15-year period.

MATERIALS AND METHODS

Data of Retrieved Implants

The material consists of 23 consecutively received Brånemark implants (Nobel Biocare AB) placed in pre- or postoperatively irradiated sites and related patient data provided by the clinicians. One sample of a retrieved implant that had supported an orbital epithesis was lacking tissue remnants, and thus, was not suitable for a histologic evaluation.

Sixteen of the 22 histologically evaluated implants were intended for a dental application and retrieved from the oral cavity. The implants were turned and made of commercially pure (c.p.) titanium with the standard or self-tapping design of 3.75-mm diameter. Eleven of the implants were retrieved from the mandible and four implants were retrieved from the maxilla. The position for one implant was not disclosed. At the time of retrieval, the implants had been in place from 2 to 74 months. Ten of the implants were reported loaded with a loading time ranging from 9 to 71 months.

The 16 implants were retrieved from four patients. Patient age at the time of retrieval of the implants is known for three of the four patients, range 55–75 years. Two patients' gender was stated as male. Radiation therapy had in all four patients been performed prior to implant placement (Table 1).

Patient death was the reason for retrieval of 14 implants. One implant was removed due to incongruity of the occlusion following a partial resection of the

mandible. For one implant, there was no stated reason for removal by the clinician.

Six of the 22 histologically evaluated implants were intended for support of auricular or orbital epithesis. The implants were turned and made of c.p. titanium, 3 or 4 mm in length, 3.75 mm in outer diameter, with a top flange of 5.5 mm. Five of the implants were retrieved from the temporal bone and one implant was retrieved from the frontal bone. At the time of retrieval, the implants had been in place from 4 to 35 months. Loading of the implants was reported for four of the six implants, three implants supporting an auricular epithesis and one implant supporting an orbital epithesis.

The six implants were retrieved from three patients: 1 female and 2 males. Patient age at the time of retrieval of the implants ranged from 50 to 70 years. Radiation therapy had in two patients been performed prior to implant placement and in one patient with the implants in situ (Table 2).

Three implants in one patient were retrieved postmortem, two implants in one patient were removed at an extended resection of the tumor, and one implant in one patient was removed due to pain.

Histologic Procedures

At the time of removal, the implants were immersed in 4% neutral buffered formaldehyde for fixation and transported to the Department of Biomaterials/Handicap Research (Göteborg University, Göteborg, Sweden) for further preparations. Following fixation, the samples were dehydrated in solutions with increasing concentration of ethanol (70% – absolute) and preinfiltrated in diluted resin and thereafter infiltrated in pure resin by stirring under vacuum conditions. Finally, the samples were embedded in either LR White® resin (London Resin Co., Ltd, Berkshire, UK) or Technovit 7200 VLC®/light-curing resin (Kulzer, Germany). With EXAKT® sawing and grinding equipment (EXAKT Apparatebau GmbH & Co., Norderstedt, Germany), the cured specimens were divided at the midsection along the long axis of the implant. The surfaces were evenly ground, and a Plexiglass of known thickness was glued to the surface of the sample. Initially, a thick section, 150–200 μm, was sawn from the samples. The sections were then ground to a final thickness of about 10 μm.[7] Routinely, the sections were stained in toulidine blue mixed with pyronin G. Preparation and staining techniques followed the recommendations by Donath and Breuner.[8,9] These procedures are routinely carried out for all retrieved human samples at the Department of Biomaterials/Handicap Research.

Evaluation

The histologically stained and undecalcified sections were quantitatively and qualitatively evaluated under a light microscope. The evaluations were performed under a Leitz Aristoplan® light microscope equipped with a Microvid® unit (Ernst Leitz GmbH, Wetzlar, Germany), coupled to a personal computer and a computer mouse. The quantitative analyses were performed directly in the eyepieces of the microscope with an objective of ×10 and zoom (up to ×2.5) when needed.

The entire thread length and then the bone-contacting lengths were outlined; the bone-contacting lengths were divided by the thread length to calculate the percentage of bone-metal contact. Bone area was measured by first outlining the total area bounded by the thread and then marking the total area occupied by the bone inside the thread; the percentage of bone area inside the thread was calculated by dividing the area of the bone inside the thread by the total area bounded by the thread. All threads, with an entire thread length having bone tissue in contact or bone tissue within the thread on both sides of the implant, were measured. A mean value for the three best consecutive threads was calculated per implant for both bone-metal contact and bone area within the thread.

The qualitative analyses were performed with objectives from ×1.2 to ×40 and zooming, giving a magnification range of ×400 to ×800.

RESULTS

Implants with an Oral Application

Six unloaded implants retrieved postmortem from one patient were unloaded and had been in situ for 2 months at the time of removal (Figure 1). The patient had been treated for a gingival carcinoma located in the lower jaw. Twenty months following resection and radiation therapy, 60 Gy, standard fractionated dosage, the implants were placed. In sections from all the implants, traces from the site preparation were visible. Few areas of bone in implant contact had signs of remodeling, indicating a low activity in the bone. Part of the tissue implant interface constituted of dense connective tissue lined by a soft tissue with inflammatory cells and small

TABLE 2 Description of Brånemark System Extraoral Implants and Results of Morphometrical Analyses

Age (years)	Gender	Reason for Removal	Time in Place (months)	Loading Time (months)	Location	Bone-Metal Contact (%) Three Best Consecutive Threads		Bone Area (%) Three Best Consecutive Threads	
						Number of Threads	Mean	Number of Threads	Mean
50	M	Postmortem		24	Temporal	3	45	3	65
		Postmortem		24	Temporal	—	—	—	—
		Postmortem		24	Temporal	3	53	3	88
70	F	Pain	36	31	Orbital	—	—	—	—
66	M	Extended excision of tumor	4		Temporal	—	—	—	—
		Extended excision of tumor	4		Temporal	—	—	3	73

Brånemark System Intraoral

Age	Gender	Reason for Removal	Time in Place (months)	Loading Time (months)	Radiation Therapy	Grafting	Location	BMC (%) Three Best Consecutive		Bone area (%) Three Best Consecutive	
								Number of Threads	Thread Mean Value	Number of Threads	Thread Mean Value
75	—	Postmortem	2	0	Yes		Md	3	20	3	28
		Postmortem	2	0	Yes		Md	3	49	3	92
		Postmortem	2	0	Yes		Md	3	49	3	91
		Postmortem	2	0	Yes		Md	3	29	3	80
		Postmortem	2	0	Yes		Md	3	22	3	75
		Postmortem	2	0	Yes		Md	3	27	3	61
61	M	Postmortem	16	9	Yes		Mx	—	—	2	13
		Postmortem	16	9	Yes		Mx	2	30	—	—
		Postmortem	16	9	Yes		Mx	—	—	3	76
		Postmortem	16	9	Yes		Mx	—	—	3	84
		Postmortem	16	9	Yes		Md	3	38	3	91
		Postmortem	16	9	Yes		Md	3	39	3	55
		Postmortem	16	9	Yes		Md	3	41	3	59
		Postmortem	16	9	Yes		Md	3	16	3	68
—	—		>36	~36	Yes			2	66	2	86
55	M	Occlusion follow resection	74	71	Yes		Md	3	94	3	96

Age	Gender	Reason for Removal	Time in Place (months)	Loading Time (months)	Radiation Therapy	Grafting	Location	BMC (%) Three Best Consecutive		Bone area (%) Three Best Consecutive	
								Number of Threads	Thread Mean Value	Number of Threads	Thread Mean Value
50	M	Postmortem		~24	Yes		Temporal	3	45	3	65
		Postmortem		~24	Yes		Temporal	—	—	—	—
		Postmortem		~24	Yes		Temporal	3	53	3	88
70	F	Pain	36	31	Yes		Orbital	—	—	—	—
66	M	Extended excision of tumor	4		Yes		Temporal	—	—	—	—
		Extended excision of tumor	4		Yes		Temporal	—	—	3	73

BMC = bone-metal contact; Md = mandible; Mx = maxilla.

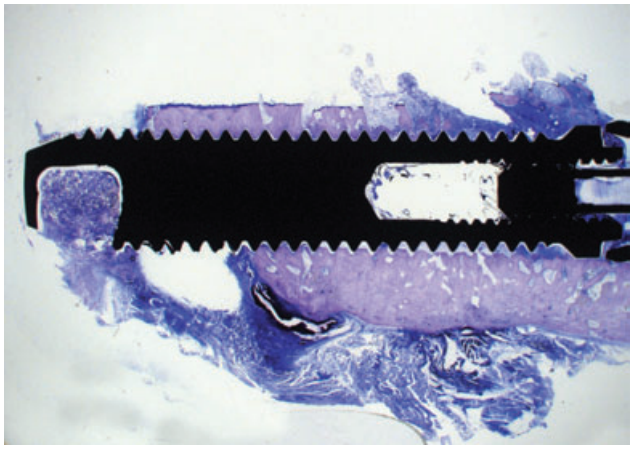

Figure 1 Overview of unloaded implant, retrieved 2 months postplacement. Magnification: implant diameter 3.75 mm.

vessels present in contact with the surrounding bone. At a distance from the implant, bone trabeculae with newly formed bone were visible. In a section from one of the six implants, nerve bundles were found in close proximity to the implant surface.

Eight implants, four maxillary and four mandibular retrieved postmortem from one patient, had been in situ for 16 months, whereof 9 months loaded (Figure 2). The patient had been treated for a squamous cell carcinoma of the throat with metastasis in the mandible and soft palate. Radiation therapy was delivered preoperatively to the maxilla and mandible with 50 Gy, and to the tonsil region with 65 Gy. The last radiation was given approximately 10 years prior to implant placement. In

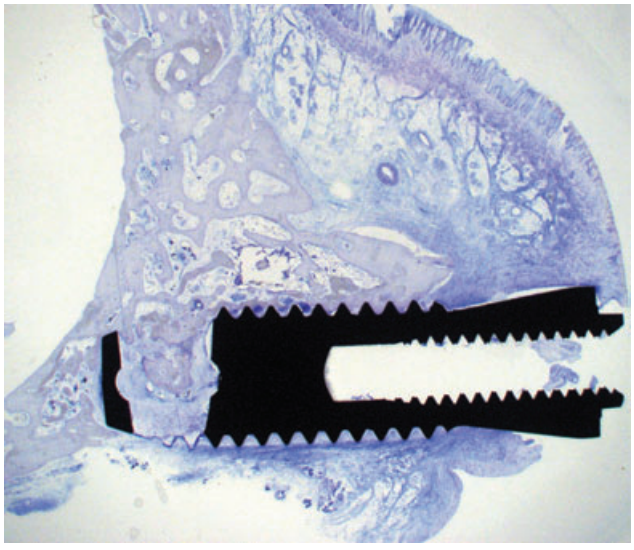

Figure 2 Overview of implant, retrieved 9 months postloading. Time in situ 16 months. Magnification: implant diameter 3.75 mm.

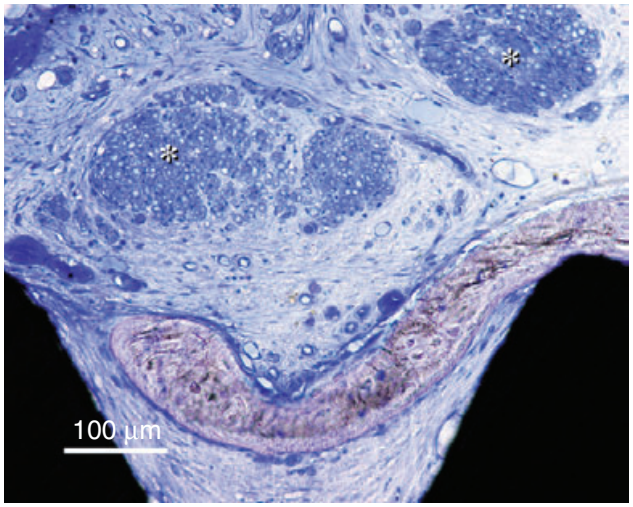

Figure 3 Implant retrieved from a mandible postmortem. Time in situ 16 months. Nerve bundles in close proximity to the implant. Bone trabeculae (purple) can be observed in close relation to the implant and the nerve structure. Bar: 100 µm.

the sections from the maxillary implants, one side of the implants was not positioned within the bone tissue. Instead, the implant surfaces were covered by a dense connective tissue that was partly lined with muscles. The implant surfaces within the bone tissue had a sparse bone-implant contact. Mainly, the interface constituted of dense connective tissue lined by a soft tissue with more cells and vessels present bordering the surrounding bone tissue. In a section from one maxillary implant, islands of bone with a thick osteoid layer and seam of osteoblasts were visible. In yet another section of a maxillary implant, nerve bundles were found in close proximity to the implant surface. In general, in the sections from the mandibular implants, half of one side of the implants was located coronal to the bone tissue. The coronal bone surfaces showed signs of bone resorption with inflammatory cells present in the covering soft tissue. Bone remodeling activities were limited within the threads. However, at a distance from the implants, bone formation was more frequent. In a section from one implant, nerve bundles in close proximity to the implant surface were present. Bone tissue was found interposed between the implant surface and the nerve bundles (Figure 3).

One implant retrieved from an unspecified location in one patient had been loaded for 36 months at the time of removal. The implant site had been subjected to radiation therapy, 90 Gy, 10 years prior to implant placement. Information on the reason for radiation therapy was not disclosed. In the section from this implant, areas

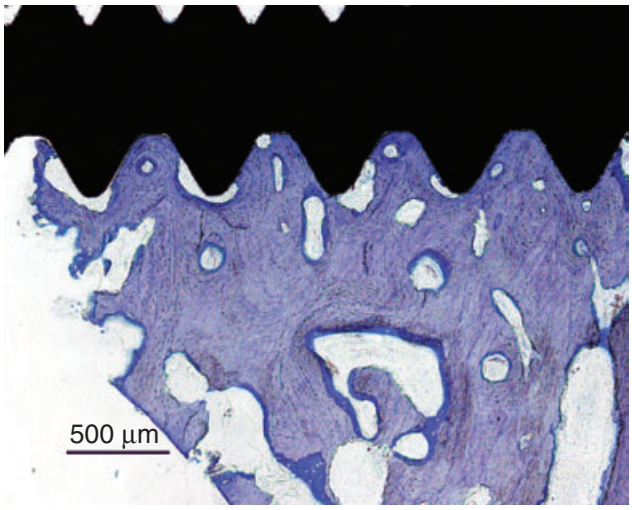

Figure 4 Implant removed due to incongruity of the occlusion following a partial resection of the mandible. Time in situ 74 months. A high amount of bone contact and bone fill of threads. Bar: 500 µm.

with osteoid-like tissue and bone surfaces with signs of resorption were present. The bone tissue inside the threads demonstrated areas of terminated resorption, as indicated by a darker stained surface. On these surfaces, bluish-stained tissue was present that could indicate a less mature bone area or a disturbed mineralization of the tissue. Macrophages and occasionally giant cells could be detected. However, both osteoblasts and osteoclasts were hard to detect.

One loaded mandibular implant retrieved from one patient due to incongruity of the occlusion following a partial resection of the mandible had been in situ 74 months, whereof 71 months loaded. The patient had been treated for a carcinoma of the floor of the mouth. Following resection, radiation therapy, 60 Gy, was delivered. The implant was placed approximately 8 years postradiation. In the section from the implant, the coronal soft tissue was missing. Bone remodeling, as indicated by osteoid formation and bone surfaces with signs of resorption lined with osteoclasts, was detected in the section. A high amount of bone-implant contact as well as bone fill of the threads was noted (Figure 4). An additional finding in this section was distinctly stained bone tissue areas. These areas may indicate less mature bone and/or disturbed mineralization. In the same region, resorption of the bone with osteoclasts present was observed (Figure 5).

Histomorphometric calculations were performed for all samples. However, due to technical reasons, that is, overstained interface and sparse amount of bone tissue at the interface, in the sections from three samples, bone-implant contact could not be measured and due to limited uncertain amount of bone tissue inside one thread in the section from one sample, the bone area within the thread was not calculated. In sections from three samples, only two consecutive threads were possible to measure.

Based on all measurements of 242 individual threads, the mean bone-implant contact for the three best consecutive threads in 13 implants was 40% (16–94%), and the mean bone area within the three best consecutive threads in 15 implants was 70% (13–96%).

Considering only the six unloaded implants in one patient for calculation, the mean bone-implant contact for the three best consecutive threads was 33% (20–49%), and the mean bone area within the three best consecutive threads was 71% (28–92%).

Implants with a Craniofacial Application

The three implants supporting an auricular episthesis and retrieved postmortem had been loaded for 24 months with no clinical complications. The implants were placed 24 months postradiation therapy, 66 Gy fractionated doses. In the sections from the implants, there were signs of resorption at the coronal bone surface below the flange. In the coronal soft tissue, a variation in degree of inflammatory cells was detected. Mature and newly formed bones were present at the interface. In one section, vessels in close proximity to the apical bone implant interface were found.

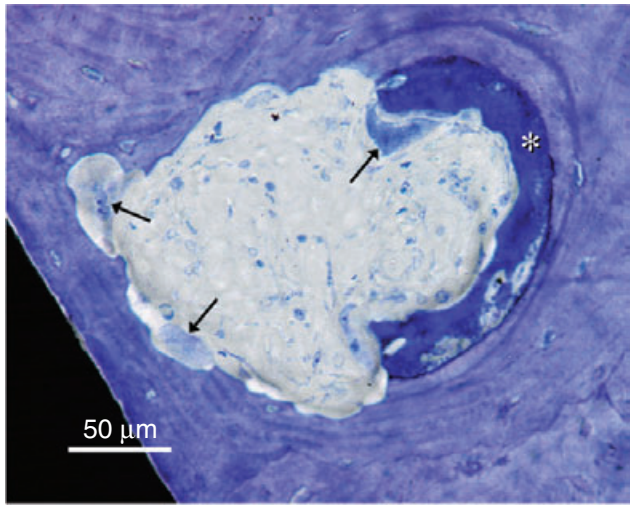

Figure 5 Distinctly dark-stained bone areas (*). A high number of osteoclasts (arrows) could be observed but no osteblasts. Bar: 50 µm.

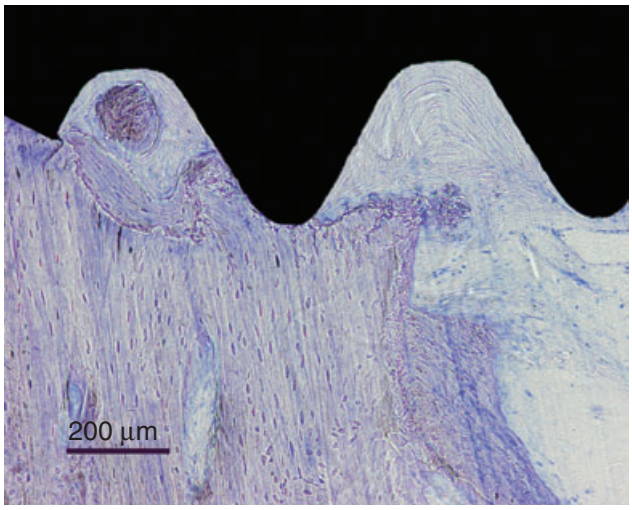

Figure 6 Implant removed from the temporal bone due to an extended resection in the area. Time in situ 4 months. A capsule formation, partly separating the implant from the bone, was observed. Bar: 200 µm.

The implant supporting an orbital episthesis and retrieved due to pain had been loaded for 31 months. The patient had been treated for a carcinoma of the maxilla. Prior to surgery, the patient received radiation therapy, 50 Gy fractionated doses. Nineteen months later, implants were placed for support of an orbital episthesis. In the section from the specimen, the soft tissue cells were not visible. There were no signs of ongoing remodeling activity in the bone. Pycnotic nuclei were present in the osteocytes. However, if this is a result of the fixation or a true picture of the bone tissue in vivo remains uncertain.

The two implants intended for an auricular episthesis and retrieved due to an extended resection of the tumor had been in place for 4 months, but not loaded with an episthesis. Radiation therapy with 50 Gy fractionated doses was given prior to the extended resection with the implants in place. In the sections from the implants, a limited amount of inflammatory cells was found in the soft tissue below the flange. A capsular formation was partly separating the two implants from the surrounding bone tissue (Figure 6). Bone-implant contact was mainly mature and in some instances under resorption. In the apical region, large areas of bone dust, that is, possible remnants from the site preparation, were observed.

Histomorphometric calculations were performed in sections from three of the six implants retrieved from the temporal bone in two patients. However, in sections from one of the implants, bone-implant contact was not measured, as the interpretation of the tissue in the interface was uncertain. The sections from the remaining three implants, one from each patient, were not suitable for histomorphometric calculation due to technical problems, that is, separation of tissue and implant in the section and one section with very limited amount of bone tissue present. The calculated mean values for bone-implant contact in the three best consecutive threads per implant were 45 and 53%, respectively. The calculated mean values for bone within the thread in the three best consecutive threads per implant were 65, 73, and 88%, respectively.

DISCUSSION

Osseointegration in the irradiated patient was originally considered a contraindication.[10] This was due to the expected complications (implant failures, osteoradionecrosis) from installing implants in previously irradiated bone. Nevertheless, implant placement has been done in irradiated patients and the number of publications in the scientific literature on this topic is increasing, being today well over 100.[11] Long-term follow up of patients who have been irradiated shows that osseointegration is possible, although implant failures are higher compared to the nonirradiated patient.[12] Factors that determine the long-term survival of implants are irradiation source, dose, and fractionation; time from radiotherapy to implant surgery; adjunctive chemotherapy; implant length; region of installation; prosthetic retention system; and adjunctive hyperbaric oxygen treatment. Noncontributing factors to implant survival are gender, age, smoking habits, tumor type and size, surgical oncologic treatment, and osseointegration surgery experience.[12]

Principally, irradiation has an effect on the bone-forming cells (osteoblasts and osteocytes) that will reduce their capacity for replication and new bone synthesis. The principal resorptive cells in bone, the osteoclasts, can migrate into the bone after radiotherapy and continue bone resorption. With increasing time after radiotherapy, there is an imbalance where resorption exceeds formation. Radiotherapy will also reduce the number of capillaries in the bone due to a progressive endarteritis. With increasing time, a hypovascular bone bed might occur that is less well adapted to host osseointegrated implants.[13]

Histologic studies of retrieved intraoral implants in humans have been published for different implant systems.[14–18] Most of the articles include a limited number of samples, providing only a qualitative evaluation.[19] The histologic evaluation revealed mainly a close contact between the implant and the bone. In another article presenting data of removal torques for craniofacial implants placed in the mastoid region, a histologic analysis of a 4-mm long flange fixture was also presented. This analysis 4 months after installation verified a direct bone-implant contact in the temporal bone.[20] In the only available report of extraoral craniofacial implants retrieved from humans allowing a quantitative analysis,[21] a mean bone-metal contact (BMC) for all included implants of approximately 61% was found. If compared with the present study, the mean BMC for all implants was 40%, and for bone in threads, 70%. Reports of retrieved nonirradiated osseointegrated implants from the oral cavity show mean BMC of the mandible to be approximately 80% and in the maxilla approximately 60%.[22] In the present study, we found no correlation between high irradiation dose and reduced BMC or bone in threads. Rather, a correlation between time after insertion and BMC/bone in threads. This shows that irradiated bone has also the possibility to regenerate with time after the surgical trauma induced by osseointegration surgery. The limited number of implants in the present study does not allow us to draw any general conclusions.

Human histologic data concerning irradiated bone that supports osseointegrated implants are sparse. Two Brånemark implants were placed: one in irradiated native mandible and one in calvarial bone used to reconstruct the mandible.[23] Histologic evidence of osseointegration was present for both implants. Jacobsson and colleagues[24] reported on stable implants in irradiated bone from postmortem specimens. The implants were surrounded by bone tissue in direct contact with the implant. Four temporal bone implants were retrieved on the expiration of one patient and processed for histology.[25] Despite the fact that the patient had been irradiated to 92 Gy, the implants were histologically integrated with a high BMC without surrounding inflammatory reactions in the bone. Three temporal bone implants removed because of tumor recurrence showed, on the other hand, minimum BMC despite irradiation to only 48 Gy.[26] Nakai and colleagues[27] described the histologic findings in two implants retrieved from irradiated bone. One implant was removed from the frontal bone 24 months after placement in 50 Gy irradiated bone. The other implant was removed from the maxilla irradiated to 60 Gy. The ratios of bone-metal contact were 61.3 and 69%, respectively. The authors concluded that BMC was not much lower than that seen in nonirradiated bone. Three Brånemark implants in the supraorbital rim were removed 3 years after placement in 50 Gy irradiated bone[28]; BMC varied between 30 and 70%. In a study of 18 osseointegrated implants retrieved from 10 patients, three of the implants were from an irradiated patient.[29] It was found that BMC was reduced (27–35.6%) compared to nonirradiated implants of the same region that showed 44–46.6% BMC. As a comparison average, the BMC for loaded extraoral implants was estimated to be 62% by Bolind and colleagues.[21] For 10 intraoral implants in this study with a *time in situ* exceeding 12 months, the reason for removal was not associated with the implant anchorage. Seven of these 10 implants have a BMC calculation. Comparing the mean value in percentage for these implants, 46% (range 16–94, $n = 7$), with corresponding implants in our retrieval bank placed in nonirradiated bone, 82% (range 52–100, $n = 34$), demonstrates a lower percentage of bone-implant contact for implants placed in irradiated bone.

The possibility to achieve bone anchorage of implants in irradiated tissue is supported by this study. However, due to the limited material, conclusions with regard to radiation dose and bone tissue response to implants cannot be stated.

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