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Radiotherapy, osseointegration and hyperbaric oxygen therapy

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Modern therapy of malignant tumors of the head and neck region is effective and more patients survive their cancer. The patients can, however, suffer from defects of the hard and soft tissues from cancer surgery. With the osseointegration concept the possibility to rehabilitate these patients has increased tremendously.

Effects of radiotherapy on oral tissues

The aim of radiotherapy is to eradicate a tumor by exposing it to high doses of ionizing irradiation. Ideally, irradiation will be well tolerated by surrounding structures. In practice, however, some degree of transient or permanent tissue damage will invariably accompany the course of radiotherapy. In curative radiotherapy, the total irradiation dose is high and the treatment is usually prolonged and physically demanding.

The latent irradiation damage to the tissues surrounding the malignant tumor can range in severity from light posttreatment discomfort to life-threatening necrosis. Manifestations of oral complications from head and neck radiotherapy include xerostomia, loss of taste, changes in oral microflora and salivary composition, mucositis, glossitis, increased caries activity, salivary gland dysfunction, dysphagia, muscle fibrosis, temporomandibular joint dysfunction, mucosal and bone necrosis. Osteoradionecrosis, which is a severe complication, is correlated to high irradiation dose, superfractionation, and chemotherapy treatment and to surgical intervention in the irradiated field. This condition is difficult to treat for head and neck cancer patients and initiating trauma should be avoided.

Osseointegration in irradiated tissues

Successful prosthetic restoration for acquired defects subsequent to surgery for cancer of the head and neck is not always possible because of the size, shape and location of the defect and the type of missing structures. Many of these patients have severe problems coping with conventional maxillofacial prostheses.

Osseointegrated implants have been used successfully in selected head and neck cancer patients who have been treated with surgery alone. However, many more of these patients receive combined therapy for eradication of the malignant disease. The combination of radiotherapy with surgery makes successful maxillofacial prosthetic rehabilitation much more difficult. Two major issues need to be addressed in relation to implant surgery in irradiated patients. The first is the possibility that implants may be integrated in the irradiated bone; the second is the risk of severe complications due to implant surgery.

Are implant failures higher in irradiated bones?

There seems to be a general agreement that irradiation induces changes in the bone, soft tissues, oral mucosa and salivary gland function that need special consideration when planning the rehabilitation of cancer patients. There is, however, no general agreement that osseointegrated implants should fail to a higher degree due to irradiation. The disagreement has been focused mainly on osseointegration in the mandible, whereas the incidence of higher

implant failure in other parts of the maxillofacial skeleton seems more accepted. Over the last 10 years, the number of publications concerning osseointegrated implants in irradiated tissues, both from an experimental and a clinical point of view, has increased, being now well over 100. Several scientific groups continue reporting accumulated data of their original patient material, which means that the real number of irradiated patients rehabilitated according to the osseointegration concept is lower than suggested from the number of publications. In two review articles, different views of problems from osseointegration in irradiated patients are discussed (15, 57). Nishimura et al. (57) found a higher implant failure after irradiation. Implant failures seem to be correlated to the anatomic region in which the implants are inserted. In some regions, e.g. the orbit, implant failures are so high that special considerations like preoperative hyperbaric oxygen therapy (HBO) are required. The publication by Esposito and coworkers (15) is an evidence-based review article using meta-analysis. The authors came to the conclusion that irradiation *per se* is no contraindication to implant installation. Implant failure rate in the mandible is only 4.9%, thus not exceedingly high. Doses above 55 Gy, however, seem to be critical for implant survival. It may thus be necessary to give HBO in high irradiation doses, or for reasons other than implant survival, like healing of the soft tissues.

A number of factors responsible for clinical success of oral cancer patients must be taken into account. These include the irradiation source, dose and fractionation, use of chemotherapy, risk for tumor recurrence, anatomic region in which the implants are to be inserted, timing from radiotherapy to implant surgery, preoperative planning, retention systems used, loading factors, handling of the soft tissue and risk of osteoradionecrosis. These factors will be discussed in the following sections.

Experimental studies

Animal studies have shed some light on the possibility of osseointegration in previously irradiated bone. Jacobsson et al. have performed a series of studies in rabbits (30–32). Different implant systems were used to study tissue reactions inside and outside titanium implants. The vital microscopic chamber was developed to be able to follow tissue reactions in a 100-μm-thick slit inside the implant by light microscope. The tissue reactions that followed radiotherapy were decreased bone formation capacity (decreased number of osteoblasts and osteocytes), increased resorption of bone (increased number of osteoclasts) and reduced number of capillaries (31). By using the bone harvest chamber, quantitative parameters could be obtained to follow the tissue reactions after radiation. Radiation was delivered by ^{60}Cobalt gamma rays in single doses varying from 0 to 40 Gy. A single dose of 15 Gy reduced the bone formation capacity by 72%.

Johnsson et al. (36–38) also used the long bones of rabbit as a model system. The animals were given a 15 Gy single dose of ^{60}Cobalt irradiation to one hind leg, the other leg serving as control. Titanium screws were inserted in the tibia and femur after 12 weeks and 52 weeks after irradiation. Evaluation was performed by removal torque measurements and by histomorphometry. A healing period of 1 year significantly increased removal torque necessary to unscrew the implant. The amount of bone around the implants increased after 12 and 52 weeks, showing that irradiated bone has a certain regeneration potential. Cancellous bone recovered faster from irradiation than cortical bone. Schweiger studied the effects of placing titanium implants in the mandibles of previously irradiated dogs (70). This study demonstrated that osseointegration occurred around implants placed in the irradiated sites, although less predictably and completely than in control sites. Asikainen et al. (6) also used irradiated beagle dog mandibles. Sixty titanium implants were inserted in bone irradiated to 40, 50 and 60 Gy by fractionated electron beam irradiation. All implants were lost in the 60 Gy group, a few in the 50 Gy group and none in 40 Gy group. This shows that the irradiation dose is of importance in relation to implant integration. The authors also reported more mucosa dehiscences in the high irradiation dose group (6). Öhrnell et al. (62) studied the effects of single-dose ^{60}Cobalt irradiation to titanium screws in rat femur. It was found that increasing doses of irradiation up to 35 Gy reduced the remodeling capacity of bone surrounding the titanium implants. They also found a dose-correlated reduction in torsion, indicating a reduced mechanical capacity of the bone-implant interface.

Summarizing these studies, it seems that osseointegration is possible to achieve after irradiation in different bones. Blood vessel number and function are affected by radiotherapy and bone formation is reduced, especially after high doses of irradiation There is a regeneration capacity of bone in animal models at least up to 1 year after irradiation.

Clinical outcome

Multicenter studies

Data from multicenter studies of implants placed in irradiated jaws are limited. Albrektsson (1) reported 21 mandibular and 10 maxillary implants placed in previously irradiated jaws with no loss of implants at 1–5 years. Niimi et al. (55) reported from nine Japanese and two American centres. Altogether, 228 implants were installed in 44 patients. Only 3/169 implants were lost in mandibles but 17/59 implants were lost in maxillas. Adjunctive HBO did not improve the very good results in the mandible, but improved implant survival in maxillas from 62.5% to 80%.

Niimi et al. (54) reported from nine Japanese centers. Altogether, 118 implants were inserted in 24 patients. Three implants of 71 were lost in mandibles, 9/39 were lost in maxillas. HBO had a preventive effect on implant failure only in the maxilla.

Reports from 14 centers in the United States and Sweden showed distinctly lower survival rates for osseointegrated implants placed in craniofacial irradiated bone (64). Tolman & Taylor (77) reported on survival rates from 24 treatment centers in the U.S.A: 9/60 implants were lost after irradiation (85% survival rate). Wolfaardt et al. (89) reported from six Canadian centers a 94.4% survival rate, although follow-up time was 5 years shorter than for the other multicenter studies of craniofacial implants.

Implant failures in relation to region

Mandible

There are several clinical reports of implant placement in the irradiated mandible. Some of these present a limited number of patients followed for a short time, whereas others have included many patients and reported statistics over many years. Comparison between different studies is difficult, because it is not always possible to calculate the exact number of implants in relation to the field of irradiation, irradiation dose, exact region of installation, follow-up time, etc. Furthermore, different implant systems were installed, different retention mechanisms and different prosthetic devices were used. Schliephake et al. (69) analyzed the long-term survival rate of implants used for restoration of oral function in patients who had undergone tumor surgery. Eighty-three consecutive patients were enrolled in the study. A life-table analysis was used to determine the survival rate of the implants over 13 years. In all, 145 implants were placed in previously irradiated bone. No statistically significant difference between irradiated and nonirradiated patients was found. Watzinger et al. (83) studied 146 IMZ implants inserted in the mandibles of 26 patients. Life-table analysis demonstrated a 3-year survival rate of 58.3–87.8% depending on whether bone was resected or grafted. Werkmeister et al. (88) reported on implant survival in 29 patients with oral cancer. After 36 months of follow-up, 85% of implants in nonirradiated mandibles were still functioning compared to 73% in irradiated mandibles. Granström et al. (26) reported a 67% implant survival for 15 implants placed in irradiated mandibles and a 100% implant survival rate for 30 implants placed in irradiated mandibles after preoperative HBO treatment. Taylor & Worthington (76) reported an implant success rate of 100% for 21 implants placed in mandibles irradiated at 59.5–65 Gy. Three of four patients were treated with HBO and followed up to 7 years. Arcuri et al. (5) reported an implant survival rate of 94% for 18 implants placed in mandibles irradiated at 55.8-64.8 Gy. All patients of this study were treated in conjunction with HBO and followed up to 5 years. Ali et al. (2) presented 10 patients with 32 mandibular implants placed in irradiated bone with irradiation doses of 25–57.5 Gy. Following an observation period of 52 months, no implants were lost. Marker et al. (47) installed 38 implants in 12 patients, half of which were irradiated. After a mean follow-up of 14 months, all implants remained stable. Four of the implants were placed in grafted bone from rib or iliac crest. Andersson et al. (4) followed 15 patients who had 90 Brånemark system® implants installed in irradiated mandibles and 12 implants installed in the maxilla. Follow-up time was up to 8 years, and only two implants were removed, giving a survival rate of 97.8%. Franzén et al. (18) reported the rehabilitation of five patients irradiated with a mean dose of 40.3 Gy in which 20 implants were inserted. One implant was lost during a 3–6-year follow-up. Using different implant types, different bone grafting techniques and changing the therapy protocol in the study, a mean of 75% implants survived for 7 years in irradiated tissue compared to 86% among nonirradiated controls (86). Wagner et al. (81) reported on 275 Brånemark system® implants placed in mandibles of 63 cancer patients. Five-year implant survival was 97.9%; there was therefore no increased implant failure for irradiation to 60 Gy.

Following tumor surgery and radiotherapy, 71 IMZ and 150 Brånemark system® implants were inserted in mandibles (16). The 5-year survival for IMZ implants was 77.5% and for Brånemark system® implants 83.6%. The control group showed a 5.6% loss during the same time period. Eight percent of the implants were lost early, and another 7% were lost during the following 30 months. Brogniez et al. (10, 11) reported their first 17 and then 19 patients who had implants installed early after irradiation. Two of 53 implants in mandibles were lost after 38 months of follow-up. Eckert et al. (14) reported the experience from the Mayo Clinic. Twenty irradiated patients had 89 implants inserted in the mandible. Only 1/89 implants were lost during follow-up.

Figure 1(a) presents in graph form all the pooled data available from these studies and differentiates irradiated from nonirradiated patients. Data collection is difficult, because all authors do not report the exact number of implants inserted/lost but rather the percentage. There are also difficulties in interpreting follow-up time, irradiate dose to each implant, etc., which makes comparisons difficult. As can be seen, however, implant survival is high up to 5 years of follow-up, whereafter failures are seen in both irradiated and nonirradiated patients. Implant failure seems to accelerate in the irradiated group from 10 years and on. The use of HBO seems justified, as it increases implant survival compared to both nonirradiated and irradiated patients.

Implants in grafted mandibles

Many patients have defects of the mandible as part of cancer surgery. Reconstruction of masticatory function therefore needs involvement of bone grafting to the defect. Due to different cancer treatment traditions, the patient could be irradiated either before or after mandibular reconstruction. Riediger (65) performed 41 microvascularized grafts from iliac crest, half of which were irradiated before grafting. Thirty-eight Tübingen implants were inserted, all of which were functioning after 30 months. Urken et al. (80) presented nine patients with mandibular reconstruction, half of whom were irradiated. Twenty-four titanium implants were installed, all of which were clinically stable upon follow-up. Marker et al. (47) installed four implants in grafted bone in a group of 12 patients. Three of the patients had grafted bone from the iliac crest and one was a rib graft. All implants remained stable after a mean follow-up of 14 months. Watzinger et al. (84), on the other hand, reported an implant survival rate of only 58.3% after 3 years of follow-up in grafted bone. The high implant failures were related to total implant losses in only a few patients.

Grafts that were irradiated after mandibular reconstruction are presented by Sclaroff et al. (72). Twenty-two patients underwent microvascular reconstruction without combined HBO treatment. Of 114 implants placed, only two failed. Implant survival was equally high in fibula and iliac crest grafts. Barber et al. (8) used fibular microvascularized grafts, with adjunctive HBO treatment. All patients were irradiated at 50 Gy postoperatively. During a 6-month follow-up, no failures occurred among the 20 implants inserted. Marx & Morales (50) have used particulate cancellous bone grafts and present data showing increased bone–metal contact when implants are placed in bone grafts. McGhee et al. (51) reconstructed six patients with microvascularized graft from fibula or radius. Implant survival was 100% in the grafts (14/14) and 83% in native mandibles (10/12).

Seven patients were grafted, two by microvascular anastomosed iliac bone grafts and five by open iliac bone grafts (87). Oral cancers in the patients were irradiated with doses of 36–75 Gy. Twenty-one implants were inserted in the grafted bone and 36 in the original bone. Implant failures were similar to those in 48 implants inserted in nonirradiated control bone (3/48 for control, and 4/57 for reconstructed irradiated mandible). Werkmeister et al. (88) reported on implant survival in 29 patients with oral cancer. After 36 months of follow-up, 85% of implants in nonirradiated mandibles were still functioning, compared to 73% in irradiated mandibles. When non-vascularized iliac bone grafts were used to reconstruct the mandibular defects, implant survival in the graft during the same time frame was 68%. Similar data were reported by Watzinger et al. (84). In that study, early implant failures were especially noted. Judging from these studies, it seems that vascularized bone grafts show a higher implant survival and fewer grafting problems and thus are to be preferred.

Figure 1(b) presents a graph of all the pooled data available from the studies above and a comparison of patients that have been grafted without HBO and those grafted with adjunctive HBO. The combined use of HBO to support graft and implant incorporation seems justified.

Maxilla

There are a limited number of reports examining implants in irradiated maxilla. Implant survival rates

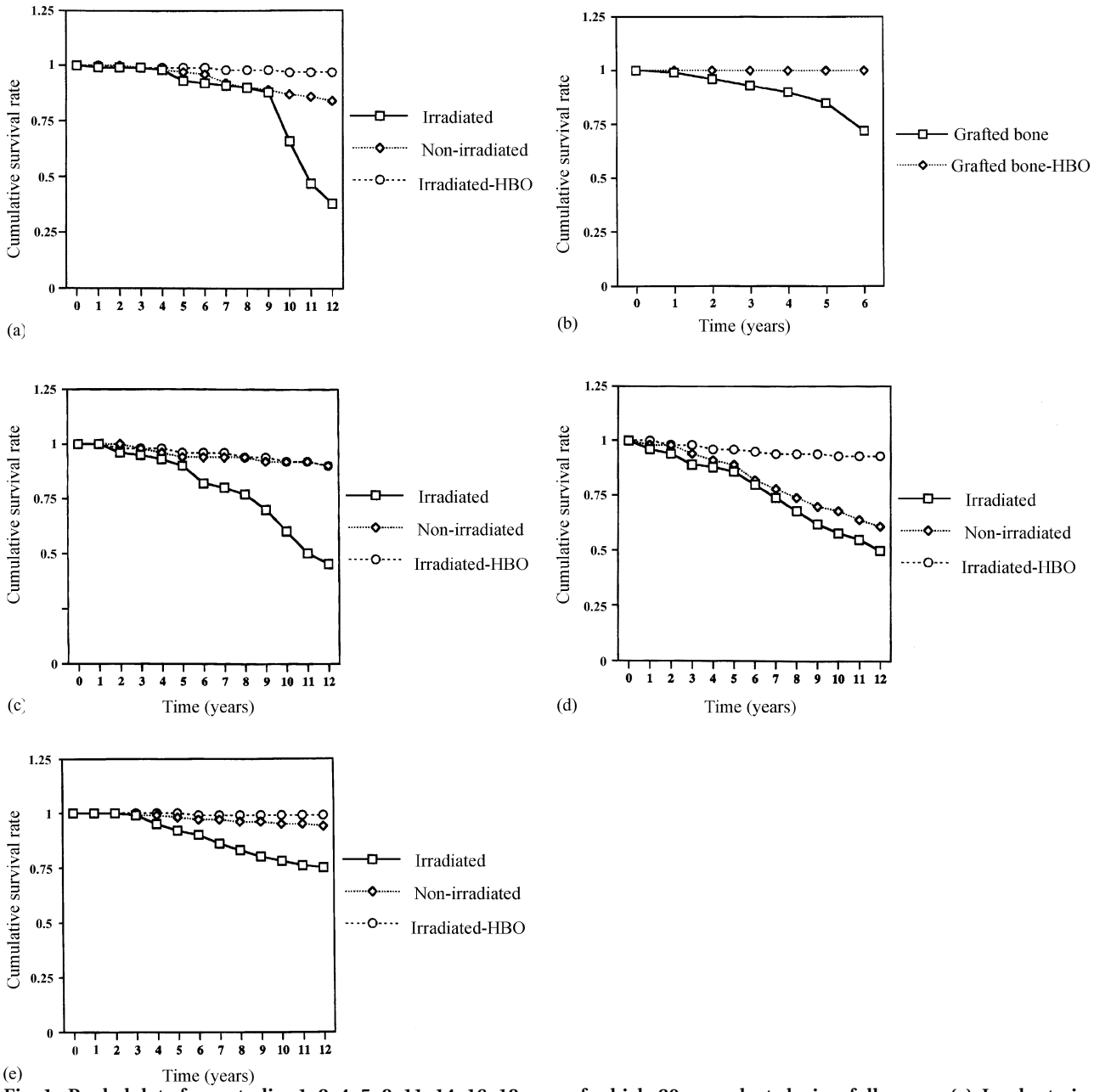

Fig. 1. Pooled data from studies 1, 2, 4, 5, 8, 11, 14, 16, 18, 20, 23, 28, 35, 41, 43, 44, 46, 47, 51– 53, 55, 57–63, 65, 69, 72, 74– 80, 83–89. Data expressed as cumulative implant survival per year. (a) Implants in mandibles. A total of 1609 fixtures were inserted into native mandibular bone, of which 146 were lost during follow-up. (b) Implants in grafted mandibles. A total of 184 implants were inserted, of which 20 were lost during follow-up. (c) Implants in maxilla. A total of 344 fixtures were inserted in maxillary bone of which 57 were lost during follow-up. (d) Implants in orbit. A total of 919 implants were inserted, of which 150 were lost during follow-up. (e) Implants in temporal bone. A total of 1336 implants were inserted, of which 29 were lost during follow-up.

in the irradiated maxillas have ranged from 58 to 95%. Granström et al. (26) reported 86% implant survival for 21 implants placed in the irradiated maxilla. When HBO was administered, the implant survival rate increased to 95% (18/19). Niimi et al. (53) reported on three cases with an 83% implant survival after 2 years. Niimi et al. (55) reported 58% implant survival in U.S. patients and 62.5% survival in Japanese patients. After HBO pretreatment, implant survival was 80%. Niimi et al. (54) reported nine of 39 implants lost in maxillas. In that study, HBO was shown to have a preventive effect on implant failure. Ali et al. (2) presented 10 patients with 10 maxillary implants placed in irradiated bone with irradiation

doses of 25–57.5 Gy. Following an observation period of 52 months, six of 10 implants were lost.

Roumanas et al. (68) studied the use of implants in the restoration of edentulous patients with maxillectomy defects and reported an implant success rat of 83% (19/23) in nonirradiated maxilla, and 69% (27/39) in irradiated maxilla. The radiation dose delivered to the tumor in these patients ranged from 50 to 74 Gy. Implants placed in the posterior maxilla showed a higher failure rate than in the anterior part. Twelve Brånemark system® implants installed in irradiated maxillas were all functioning after 4 years (4). Following tumor surgery and radiotherapy, 28 Brånemark system® implants were inserted in the maxillas of six patients (16). Five-year survival was 85.5%. Eckert et al. (14) reported experience from the Mayo Clinic. Six patients had 22 implants inserted into irradiated maxillas. During follow-up, there was a 36% loss (8/22) of implant integration.

Figure 1(c) presents a graph of all the pooled data available from these studies and differentiates irradiated from nonirradiated patients. Almost half of installed implants have failed after 10 years. Implant placement in nonirradiated and HBO-treated irradiated maxillas show a much higher predictability.

Frontal bone/orbit

Implants placed in irradiated frontal bone for restoration of orbit defects appear to demonstrate a decreased survival rate as the length of the study increases. A 4% implant failure was reported in a multicenter study spanning 1–4 years (89). A 5% implant failure was reported from the University of California at Los Angeles in a study spanning 3 years (46). After 2.5 years, 90.5% of implants survived; 2/6 patients had received HBO (43). In a study spanning up to 5 years, 57% of implants survived, and in a study spanning up to 12 years, 45% survived (64). Tolman & Taylor (77) reported a survival rate of 79% in 14 patients with 43 implants. None of their patients was followed longer than 30 months. Jacobsson et al. (34) reported that 27/43 implants survived in irradiated orbital defects in comparison with 35/38 for nonirradiated sites. Nishimura et al. (60) reported low implant survival rate in irradiated (4/12) as well as nonirradiated (3/8) orbit bone. Granström et al. (26) reported that 32/64 orbit implants were successfully placed in irradiated sites. Tveten et al. (78) placed 17 implants in irradiated orbit patients, all of which were stable after 35 months of follow-up. All eight implants (three after HBO) placed in a multicenter study survived (54). In all, 31/61 implants placed in irradiated frontal bone were lost during a follow-up of 5 years (27). In comparison, 8/20 were lost in nonirradiated frontal bone and 0/20 in HBO-treated irradiated frontal bone (27). Eckert et al. (14) reported experience from the Mayo Clinic. Two irradiated patients received 13 implants. Implant failures were high – 7/13, or 54%.

Figure 1(d) presents a graph of all the pooled data available from these studies and differentiates irradiated from nonirradiated patients a graph. As can be seen, implant failure is high in both irradiated and nonirradiated patients. Adjunctive HBO given to the irradiated patients seems to give a much higher implant survival.

Zygoma

The zygomatic bone has many advantages over the frontal bone in that it lacks sinus spaces and the bone quality is often superior to both frontal bone and maxilla. From the literature it is difficult to differentiate which orbit implants were placed in the frontal bone and which were actually located in the zygoma. However, in the study of Granström (27) it can be seen that 12/28 implants were lost in irradiated zygomatic bone, compared to 1/8 in nonirradiated and 0/13 when the patients were prepared by HBO (27). Most of these implants were, however, of the short flange-type (3–5 mm) and it was thus not possible to use long fixtures.

Perinasal implants

The evaluation of implants placed for restoration of nasal defects is limited by the low number of patients and implants studied. Eight of 10 implants were reported stable (64), 5/5 by Tolman & Taylor (77) and 1/2 by Nishimura (58). As comparison 9/9 irradiated patients with perinasal implants placed after HBO treatment were stable (27). In a matched control group (nonirradiated patients) of the same study, 2/16 implants lost integration.

Temporal bone

The highest survival rates for implants in irradiated, extraoral applications have been in the temporal bone. An implant survival rate exceeding 95% for the nonirradiated temporal bone has been replicated in many centers worldwide (27, 34, 57, 64, 76, 77, 89). There are, however, few data available for implants placed in the irradiated temporal bone. Parel & Tjellström (64) reported 100% survival of 10 implants, and Tolman & Taylor (77) reported 100% survival of six

implants. Granström, on the other hand (26), reported two failing implants of 21 (9%) placed in the temporal bone. In a follow-up study (27), 5/36 implants placed in irradiated temporal bone lost integration compared to a matched control group where 4/40 lost integration; after preoperative HBO treatment, none of six placed implants failed.

Figure 1(e) presents a graph of all the pooled data available from these studies and differentiates irradiated from nonirradiated patients a graph. As can be seen, implant survival in irradiated patients is high up to 5 years of follow-up, after which time failures are common. Implant survival in nonirradiated patients is high, as is implant survival when placed in irradiated bone after HBO treatment.

Human histology studies

Human histologic data concerning irradiated bone that supports osseointegrated implants are sparse. Two Brånemark system® implants were placed one in irradiated native mandible and one in calvarial bone used to reconstruct the mandible (61). Histologic evidence of osseointegration was present for both implants. Jacobsson et al. (33) reported on stable implants in irradiated bone from post-mortem 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 (26). Even though the patient had been irradiated to 92 Gy, the implants were histologically integrated with a high bone–metal contact without surrounding inflammatory reactions in the bone. However, three temporal bone implants removed because of tumor recurrence showed minimum bone–metal contact despite irradiation to only 48 Gy (57). Nakai et al. (52) 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 ratio of bone-to-metal contact was 61.3% and 69%, respectively. The authors concluded that bone–metal contact was not much lower than that seen in nonirradiated bone. Three Brånemark system® implants in the supraorbit rim were removed 3 years after placement in 50 Gy irradiated bone (63). Bone–metal contact 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 (22). It was found that bone–metal contact was reduced (27–35.6%) compared to nonirradiated implants of the same region, which showed 44–46.6% bone–metal contact. As a comparison, average bone–metal contact for extraoral implants was estimated by Bolind et al. (9) to be 62.4%.

Radiotherapy related risk factors

Irradiation dose

Esposito et al. (15) evaluated the relation between totally delivered irradiation dose and implant survival and found the highest failure rate among patients irradiated with more than 55 Gy. Jisander et al. (35) found no correlation between implant failure and irradiation dose. Schliephake et al. (69), on the other hand, found a higher implant survival in patients that had received 60 Gy (84.6%) compared to those who had received 32 Gy (43%). A similar peculiar finding was reported by Granström et al. (27); patients receiving low-dose irradiation showed a higher failure rate. An explanation for this finding was that these patients had been irradiated many years earlier (15–35 years) when low-energy irradiation sources were used, which are known to be tissue-damaging. In contrast, implant survival has been reported in patients irradiated with doses as high as 120 Gy (26). Increasing the irradiated dose further (165 Gy), however, resulted in high failure rates (23). Extrapolating from these studies, it seems reasonable to assume that full-course radiotherapy (50–65 Gy) is no contraindication to implant surgery, but implant surgery in patients irradiated with even higher doses must be performed with the utmost care and the patient must be informed of the possible consequences.

Time from radiotherapy to implant surgery

Based on the studies performed by Jacobsson (30) many investigators have recommended a waiting period of 12 months after radiotherapy before starting the implant rehabilitation. Other investigators have proposed a delay of 2 years (75). Factors that can affect the choice of rehabilitation period are risk of tumor recurrence, risk of osteoradionecrosis, implant survival and patient acceptance. From basic studies by Marx & Johnson (48) it is known that the risk of surgical complications is increased in the time-span between 1 month before and 6 months after radiotherapy. From 6 months to 1.5 years after radiotherapy the risk is low and then increases again (48). Niimi et al. (55) had the lowest implant failure

in the time period from 13–24 months after radiotherapy. Granström et al. (27) showed that implant failure increased with increasing time after radiotherapy, the highest failures occurring in the time period above 20 years from radiotherapy. From a practical point of view, early rehabilitation is recommended. This is in accordance with patient expectations. Although it is well known that a few patients will have a tumor recurrence after implant placement, the improvement of life quality for the patient is so high that early implant rehabilitation is justified.

Time between first and second stage implant surgery

Extrapolating from basic experimental studies on implant integration in irradiated bone, it appears that the integration process in this tissue takes place at a reduced speed. We have therefore previously recommended that the time period from stage-1 to stage-2 surgery be extended from 4 to 8 months (27). Clinical confirmation of this hypothesis has come from Wagner et al. (81) who found a significantly higher implant failure when the time from first to second stage surgery was shorter than 4 months. Another aspect in relation to an extended healing time is the loading of the mucosa by a removable denture. In the study of Taylor & Worthington (75) no loading was allowed during healing between stage-1 and stage-2 surgery. In contrast, Jisander et al. (35) allowed such loading. It was interpreted that more cover-screw perforations resulted as a consequence of early loading. There were no implant failures, however, as a consequence of such a practice.

Fixture length

From an analysis of reasons for implant failures in irradiated tissues it was concluded that a higher proportion of short fixtures than long fixtures were lost (27). This has been confirmed in other studies in which implants 7 and 10 mm in length were removed more often than longer implants (55), especially in the maxilla (54). Similar findings were reported by Ali et al. (2). This is in accordance with studies in non-irradiated jaws (73). It therefore seems justified to insert as long fixtures as possible, and to strive for bicortical anchorage.

Prosthetic retention

Overdentures showed a higher failure rate in irradiated patients than fixed bridges (54). Brogniez et al. (11) observed that the intermaxillary space available did not allow the placement of a resin base and artificial teeth, but only the placement of teeth. Due to high irradiation dose in some patients, tissue fibrosis may result in a smaller oral opening and reduced facial vertical dimensions. Fixed reconstructions may therefore be necessary in certain patients. From an analysis of reasons for implant failures in irradiated patients it was shown that the prosthetic retention affected implant survival (27). Prostheses anchored by magnets, and especially by magnets on extended arms, lost implant anchorage to a higher proportion. It was considered that cantilever effects on implants could be the reason for loss of integration.

Soft tissue condition

Eckert et al. (14) noted that the most significant problem for irradiated implant patients was related to the soft tissues. Gingivitis was more common in these patients than was normally observed. Cover-screw mucosal perforations were observed over the areas of 17% of implants during the healing period between stage-1 and stage-2 surgery (35). August et al. (7), using the fixed mandibular implant system in 18 patients irradiated before or after implant installation, reported increased problems with the soft tissues. Early soft tissue complications included soft tissue overgrowth, tongue ulceration and intraoral wound dehiscence. Late complications included fistula formation. Watzinger et al. (84) reported increased degree of gingivitis in irradiated patients. This was related mainly to poor oral hygiene. Necrosis of soft tissues in the floor of the mouth was observed in 5.2% of patients (16). Up to 9% of patients with orbit epistheses showed granulation tissue reactions around abutments (13). These skin reactions were more common if the patients had been irradiated. Using a clinical scoring for skin reactions where 0 = normal skin; 1 = red skin around the abutment; 2 = red and moist; 3 = granulation tissue; 4 = skin reaction leading to removal of abutment; more grade 1–2 reactions were seen in irradiated patients (21).

Marginal bone loss

Increased marginal bone loss in irradiated patients has been reported by several authors. Watzinger et al. (84) reported 2–9 mm bone loss during a 3-year follow-up period. Weischer & Mohr (85) showed that peri-implant bone resorption increased in irradiated

patients before implant failure. Irradiated maxillectomy patients showed an increased bone resorption, especially in the anterior maxilla (68).

Risk for osteoradionecrosis in relation to implant surgery

The risk of osteoradionecrosis (ORN) is the primary reason that implant therapy is not commonly pursued in previously irradiated patients. This severe complication may be underreported in the international literature. Some authors refuse to employ implant placement, considering the risk of ORN to overshadow the possible benefits of prosthetic restoration (17). Several groups report incidental cases developing ORN (16, 26, 81, 84). In their report from 1998, Wagner et al. (81) reported one case (1.6%) of osteoradionecrosis with contemporary failure of five implants. The authors are of the opinion that this is below an estimated risk of 5% in other studies. Esser et al. (16) reported two cases (3.4%) of ORN development related to implant surgery. Minimum surgical trauma to the mandible is known to cause ORN in the time period close to radiotherapy (49). Such trauma could comprise a tooth extraction or surgery for an osseointegrated implant. To minimise the risk for ORN, HBO is strongly advised.

The interface zone after irradiation

Using new techniques for noninvasive interpretation of osseointegration (29), interesting data can be obtained. A transducer was attached to the abutment, and vibrations from the implant-bone zone were registered. Recordings from 15 irradiated patients registered during 8 years of clinical follow-up are presented in Fig. 2. As can be seen from this figure, the resonance frequency is lowered with time, and in some, implants reach zero value when the implants fail. This is contrary to nonirradiated patients where resonance frequency generally increases with time (29).

Patient selection

Patient selection is always important, and especially so when the patient has previously been irradiated. The patient must fully understand the advantages and disadvantages of implant treatment and the significant risks involved. Informed consent must include discussion of alternative treatments. Risks that must be discussed include osteoradionecrosis, fracture of the jaw, the development of new or recurrent tumor with unknown treatment risks, nonintegration of implants, early or delayed, and soft tissue problems.

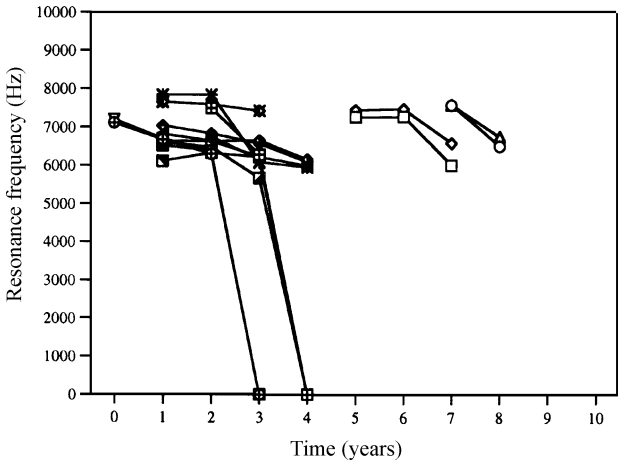

Fig. 2. Changes in resonance frequency values from 15 irradiated patients from implant placement and during annual check-up. Irradiation doses varied from 55 to 64 Gy. Implants were placed in the frontal bone, maxilla, zygoma and temporal bone. Zero-values means implants were loose and were removed.

Preoperative clinical examination and radiographic evaluation follow standard procedures. Obviously, the patient must be free of any evidence of residual or recurrent tumor prior to implant placement. Discontinuation of tobacco use is of the utmost importance, as discussed in another chapter in this publication. Available bone in the jaw for implant placement is critical. Esser & Wagner (16) recommend that at least 15 mm of vertical bone be available.

The Gothenburg experience

Cancer patients have been rehabilitated with the osseointegration concept since 1979 at our clinic. The idea has been to supply patients with prostheses covering defects of the face and skull due to cancer treatment. These prostheses have accordingly been anchored on titanium implants integrated in various craniofacial bones. With modern prosthetic materials, the prosthesis can be made naturally looking and the patients can easily remove and put on the prosthesis. Another advantage is that the cancer surgeon will have access to the tumor cavity for inspection of possible tumor recurrences. A third advantage is the simplicity of the technique. Only a minor surgical procedure is needed to install the implants, which can be done immediately following removal of the tumor. Planning for rehabilitation can thus be performed as a part of cancer treatment.

Table 1. Irradiated oral cancer patients treated in Gothenburg. Irradiation dose was given to the implant sites and varied from 48 to 120 Gy, the highest doses given to a patient irradiated twice for two different cancers in the same region

Implant location	Patients	Implants placed	Implants lost	Percent
Mandible	7	32	7	21.8
Mandible HBO	13	65	1	1.5
Maxilla	8	41	10	24.3
Maxilla HBO	17	68	4	5.8
Total	45	206	22	10.6

Table 2. Data from 28 irradiated oral cancer patients with implants placed in grafted bone. Half of the patients were preoperatively treated with HBO

Patients	Native bone	Grafted bone	Implants lost	Percent
14	8	22	2*	25
14 (HBO)	6	18	0	0

*Implants lost in native bone.

Altogether, 418 cancer patients were supplied with prostheses anchored on osseointegrated implants between 1979 and 2001. One hundred and thirty five patients were irradiated prior to implant surgery, 19 were irradiated after implant installation and four were irradiated both before and after implant installation. Mean follow-up time was 9.8 years (range 2.2–22 years). Results of osseointegration for oral cancer patients are shown in Tables 1 and 2.

Figure 3 shows a 56-year-old man with a T2N0M0 cancer of the anterior part of the tongue. He had preoperatively been irradiated with ^{60}Cobalt, hyperfractionated to 26.4 Gy (Cumulative Radiation effect, CRE 13). The tumor was surgically removed combined with dissection of lymph nodes in the submandibular area and a neck node dissection. Five years later, five fixtures were installed in the edentulous mandible. At stage-2 surgery, 5 months later, all implants were found to be loose and were removed. Fistulation had at that time occurred intraorally. This case shows the risk of performing surgery in previously irradiated as well as bilaterally operated mandibles. At cancer surgery, the lingual and facial arteries are clamped and the blood supply to the mandible is exclusively by the inferior alveolar artery. It is necessary to be aware of the problems that could arise prior to implant surgery despite a relatively low irradiation dose.

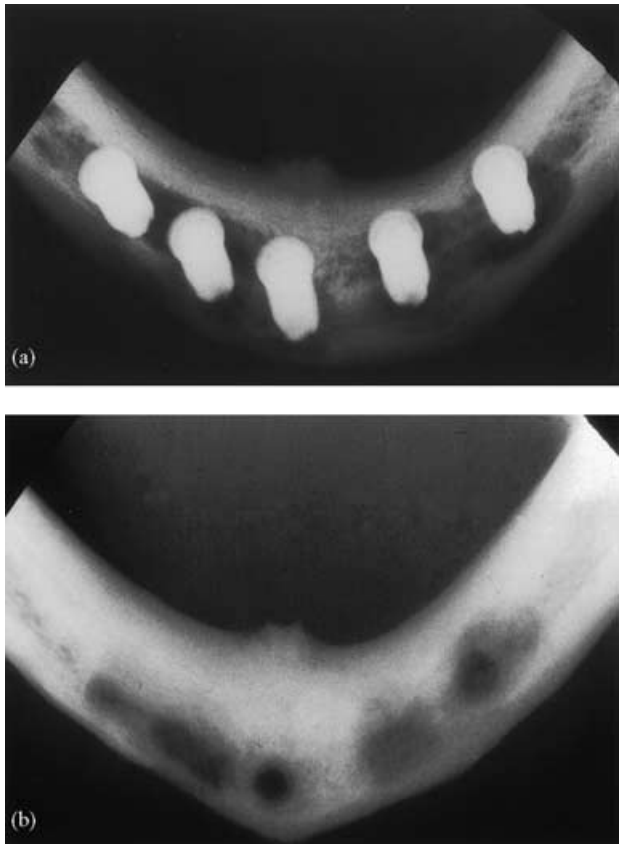

Fig. 3. A 56-year-old man with an oral cancer who received 26.4 Gy irradiation to the mandible. Five years later, five fixtures were installed in the edentulous mandible. At stage-2 surgery, 5 months later, all implants were found to be loose and were removed (a, b).

Figure 4 shows a 60-year-old man with a floor of the mouth carcinoma T1N1M0 that was treated with external ^{60}Cobalt irradiation to 50 Gy and internal ^{192}Irridium irradiation to 30 Gy. A neck dissection was also performed. He had a recurrence in the anterior part of the mouth 14 months later. This was surgically removed, including the lingual cortical plate of the mandible. Postoperatively, the patient developed osteoradionecrosis that was healed by conventional methods. Three years later, four fixtures were installed in the anterior part of the mandible and a fixed bridge prepared. This initially worked fine, but 2 years after installation, the implants in the right side of the mandible failed. This case shows the problems of performing implant surgery in a high-dose irradiation area with bilateral surgery, and earlier osteoradionecrosis. The patient quit smoking after cancer treatment but had insulin–depending diabetes as concomitant disease. The blood flow and bone metabolism of the mandible is probably very low, which negatively affects osseointegration.

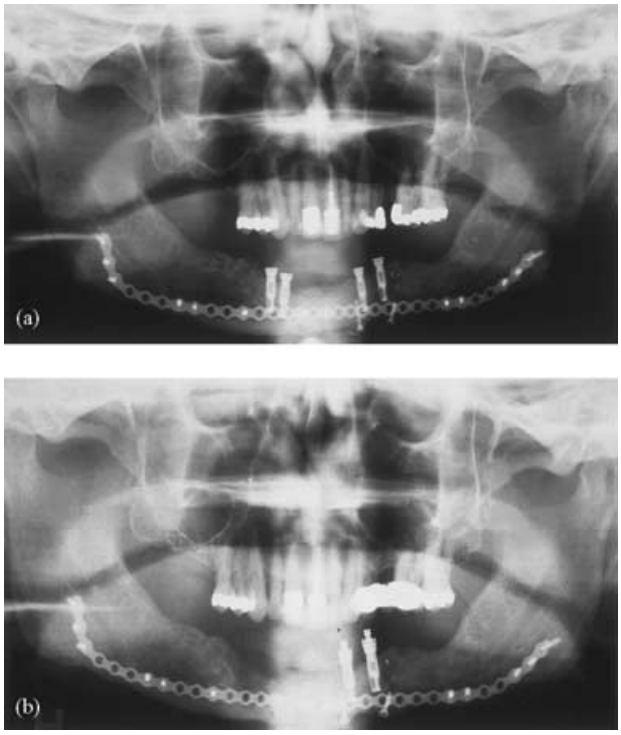

Fig. 4. A 60-year-old man with a floor of the mouth carcinoma that was treated with external and internal irradiation to 80 Gy. Postoperatively, he developed an osteoradionecrosis that was healed by conventional methods. Three years later, four fixtures were installed in the anterior part of the mandible to be used by a fixed bridge (a). This initially worked fine, but 2 years after installation, the implants in the right side of the mandible failed (b).

Figure 5 shows a 55-year-old man who was treated for a right-sided tonsil carcinoma. Treatment was performed by external beam ^{60}Cobalt radiotherapy to 64 Gy. He developed an osteoradionecrosis in the left premolar area of the mandible. Complete planning of the osteoradionecrosis included 30 preoperative HBO treatments followed by sequesterectomy and simultaneous installation of fixtures in the mandible and maxilla. No implants were installed in the vicinity of the necrosis (arrow). Postoperatively, a further 30 HBO treatments were given. Soft tissue healing was slower than usual and a few dehiscences occurred, but at stage-2 surgery all implants were clinically and radiographically integrated. Six years after treatment, the patient is free from tumor, without necrosis and all implants are still functioning.

Fig. 5. A 55-year-old man with tonsil carcinoma who developed an osteoradionecrosis in the left premolar area of the mandible. Treatment planning combined treatment for the ORN with implant installation using HBO. No implants were installed in the vicinity of the necrosis (arrow). Thirty HBO treatments were given before and 30 after implant surgery.

Figure 6 shows a 63-year-old man with a gingival carcinoma $T_4N_0M_0$ that was preoperatively irradiated by ^{60}Cobalt external irradiation to 48 Gy, followed by tumor removal, including a segment of the mandible. The patient was recurrence free for 3 years, after which time reconstruction was performed. After 20 preoperative HBO treatments, a sternomastoid clavicle graft was interposed. Ten postoperative HBO treatments were given. Implant installation was performed at a second stage after soft tissue healing. No further HBO was given. Implant integration was without complications and the patient is still alive without implant failures after 10 years.

Hyperbaric oxygen therapy (HBO)

Basic effects in tissues

The therapeutic effect of HBO is related to an elevated partial pressure of oxygen in the tissues. The pressure itself enhances oxygen solubility in the tissue fluids. For a detailed description of the mechanisms of HBO, the reader is referred to a review article by Kindwall et al. (42). A detailed discussion of HBO effects in relation to osseointegration has also been published earlier (19, 36). Principally, HBO has been shown to affect angiogenesis (49, 74), bone metabolism and bone turnover (20, 37). In relation to radiotherapy, HBO can thus counteract some of the negative effects from irradiation and actually act as a stimulator of osseointegration (20).

The exact mechanisms at the cellular level where HBO acts remain obscure. It has recently been shown that HBO and basic Fibroblast Growth Factor (bFGF) act synergistically in irradiated bone (83). Factors that could be involved in bone protection by bFGF and HBO are bone marrow radioprotection, induction of oxygen radical scavengers and production of different cytokines. HBO and bFGF can also enhance the level of insulin-like growth factor, which is known to promote proliferation and differentiation of bone.

Fig. 6. A 63-year-old man with a gingival carcinoma that was preoperatively irradiated with ^{60}Cobalt external irradiation to 48 Gy, followed by tumor removal including a segment of the mandible. The patient was recurrence free for 3 years, after which time reconstruction was performed. After adjunctive HBO treatment, a sternomastoid clavicle graft was interposed (a). Implant installation was performed at a second stage after soft tissue healing (b, c). Implant integration was without complications and the patient is still alive without implant failures after 10 years (d, e).

They could also affect bone progenitor cells by promoting DNA synthesis, stimulating enzymes involved in bone formation or affect membrane receptors. HBO has furthermore been shown to affect the interface between the titanium implant and bone, which could be different from a cellular effect (39).

Oxygen under hyperbaric conditions could thus play a role in osseointegration by affecting bone cell metabolism, implant interface and the capillary network in the implant bed.

Clinical performance

To perform HBO, a pressure chamber is needed. To the author's knowledge, pressure chambers are available in all countries where osseointegration surgery is undertaken. Treatment can be performed in multiplace chambers, where several patients are treated simultaneously, or in monoplace chambers, for individual treatment. Oxygen is delivered by face-masks, hoods, or in the atmosphere of the chamber. The recommended protocol for osseointegration surgery

is 20 preoperative treatments at 240 kPa, 90 min daily and 10 postoperative treatments (19). Pre-HBO investigations, contraindications and details of the clinical performance can be obtained from Granström (19). Cost for the treatment is related to the osseointegration procedure. For an ear reconstruction, the cost of HBO is approximately 50% of the total cost, for an orbit reconstruction 30%, for a midface reconstruction 20% and for a mandibular reconstruction 10% (21). The price must also be related to avoidance of complications in the compromised patient. For example, the cost in year 2002 prices for 30 HBO treatments is equivalent to 1 day at an intensive care unit at the Sahlgrenska University Hospital.

HBO, radiotherapy and osseointegration

Experimental studies

The Bone Harvest Chamber (BHC) was used to elaborate possible effects of HBO on bone formation capacity in relation to titanium implants. In a study where the animals served as their own controls, 3 weeks of HBO (2.8 ATA, 2 h daily) was compared to 3 weeks of normobaric air (56). Using densitometric recordings, it could be shown that HBO significantly stimulated the bone formation capacity.

In rabbits, studies were conducted to investigate possible HBO effects in relation to the bone–implant interface. Standardized titanium screws were used to measure the removal torque necessary to unscrew the implants (39). The force necessary to unscrew the implants after irradiation with 15 Gy ^{60}Cobalt was decreased by 60%. HBO increased the force necessary to unscrew implants in the control group by 25% and in the experimental group by 40%. It thus seems that HBO affects bone formation in the implant–bone contact area – the *interface zone*.

In a study using hydroxyapatite implants in the long bones of rat, a 15 Gy single dose irradiation was given (12). Implants were inserted 3 months after irradiation. The healing process was evaluated by histology and by histomorphometry. HBO improved trabecular bone formation in the irradiated bone, accelerated bone remodeling in the nonirradiated bone and improved HBO/bone contact in both irradiated and nonirradiated bones.

In another study, the long bones of rabbits were used. The animals were irradiated with a single dose of 15 Gy and titanium screws placed directly after irradiation (37). Half of the animals received HBO for 4 weeks and histologic preparations were taken after 8 weeks. The bone–metal contact and bone in threads was evaluated morphologically. It was found that irradiation reduced the capacity for osseointegration, HBO improved bone formation and bone maturation. Larsen et al. (45) studied the potential for osseointegration of cylindrical implants in irradiated rabbit tibias. Irradiation was given to a total dose of 45 by ^{137}Cesium fractionated 10 times. Osseointegration was successful with both titanium and hydroxyapatite-coated implants in irradiated bone and controls. All groups were similar with the exception of those in which irradiated animals were not treated preoperatively with HBO. A significant decrease in the percentage of histologic bone–metal contact was noted in these animals. HBO pretreatment allowed bone–metal contact in irradiated animals approaching that seen in nonirradiated controls.

Clinical studies showing a stimulating osseointegration effect by HBO

In a case-controlled study, data from 26 nonirradiated patients, 32 irradiated patients and 20 irradiated patients who had undergone HBO treatment before implant installation were compared (28). Mean observation time was 7.4 years. In irradiated patients, 53.7% implant failures were observed, compared to 13.5% for the control group and 8.1% for irradiated HBO-treated patients. There was a significant difference between the irradiated compared to the HBO-treated and control groups.

Ueda et al. (79) reported placement of 21 implants in the maxillofacial region in four patients irradiated with between 40 and 101.5 Gy. All patients were preoperatively treated with HBO. Twenty of the 21 implants (92.3%) were stable during the follow-up time. Arcuri et al. (5) reported on 18 implants in previously irradiated mandibles of four patients. Each patient underwent HBO before and after implant placement. At the abutment connection, 94% of implants were judged to be integrated. Ali et al. (2) discussed the use of HBO to prevent fixture losses, especially in the maxilla. Marx & Morales (50) reported a 5-year survival in 622 out of 748 osseointegrated implants after HBO treatment.

In a debate article, Larsen (44) defended the use of HBO for implant integration in the mandible. Twenty-eight implants were installed in five patients who had all received irradiation above 50 Gy. No failures were observed during a 1–5-year follow-up.

Table 3. Blood flow in drilled holes for implant insertion in different regions of human maxillofacial area. A total of 540 recordings were performed according to Granström et al. (72)

Region	Control	Irradiated	Irradiated/HBO
Temporal	5.2 ± 0.3	3.0 ± 0.2	11.4 ± 0.5
Frontal	4.8 ± 0.3	2.5 ± 0.2	7.9 ± 0.8
Zygoma	6.0 ± 0.8	3.6 ± 0.2	8.7 ± 0.8
Maxilla	10.8 ± 1.4	3.2 ± 0.3	12.5 ± 1.1
Mandible	4.8 ± 0.4	2.5 ± 0.5	6.8 ± 0.5
Bone graft to mandible	10.2 ± 1.2	6.5 ± 0.8	12.9 ± 0.5

Values (mean ± SEM) expressed as ml/min × mg bone

Jisander et al. (35) reported on 103 implants, most of these Brånemark system® implants. Cumulative implant survival after 1 year was 97% in the mandible and 92% in maxilla. HBO was used in patients irradiated above 60 Gy. This study recommended using HBO above a radiation dose of 50 Gy.

Taylor & Worthington (75) reported that when implants were placed in conjunction with HBO therapy healing was more reliable, although still slow. They recommended HBO for patients treated with more than 50 Gy. Esser & Wagner (16) noted 5.2% soft tissue necrosis after implant surgery in the mandible and came to the conclusion that HBO might be used to prevent such necrosis.

It is possible to measure clinically some of the effects induced by HBO in the tissue. Measuring blood flow by Laser-Doppler during implant preparation (24), it can be seen that blood flow in irradiated patients is decreased compared to nonirradiated patients (Table 3). Irradiated patients who were preoperatively treated with HBO showed higher blood flow values compared to irradiated patients. The highest blood flow values were recorded from patients with bone grafts in the mandible.

Clinical studies proving HBO is not necessary for osseointegration

Eckert et al. (14) recommends that multicenter studies be performed to prove the necessity of using HBO in irradiated patients. As judged from their very good results of integration in the mandible, not all patients will need HBO. Keller et al. (41) reported 19 patients in whom implants were installed in irradiated mandibles without HBO. These patients were thus earlier reported in the study of Eckert (14). The authors presented a 99% implant survival without HBO. Eight of the patients performed a mandibular reconstruction with a mixture of free vascularized grafts and autogenous grafts. It is important to note that by a strict selection procedure in this study, complicated and expected problem patients were excluded from implantation already from the beginning. In our own studies we have aimed to allow *all* patients to be part of the implant rehabilitation program irrespective of possible drawbacks.

Keller (40) in his debate article against the use of HBO gathered arguments against the use of HBO and summarizes the dangers of using HBO treatment. His argument is that HBO has no advantages other than prolonged wound healing. In his view, a number of risk factors are controllable by using selection criteria. Wagner et al. (81) concludes that as the risk for ORN after implant surgery is below 5%, there is no indication for HBO.

Irradiation after osseointegration

There is a general concern among oncologists to irradiate with metal implants close to a tumor in the field of irradiation. The implantologist may therefore be faced with the question of whether to remove osseointegrated implants before cancer treatment continues. There is limited information in the scientific literature as to the best way to handle these patients.

Experimental studies

In vitro studies

Dose enhancement on titanium/tissue surfaces caused by backscatter irradiation has been reported. This effect has been reported to be limited to a distance closer than 1 mm and to be negligible at 1–2 mm from the titanium surface (3, 66, 82). The dose can, however, nearly double in the angle at the thread bottoms because of electron contribution from two sides (67).

In vivo studies

Titanium alloy screws and hydroxyapatite cylinders were placed in rabbit mandibles and irradiated by a single 15 Gy ^{60}Cobalt dose on the fifth postoperative day (71). It was found that mature bone was relatively radioresistant, but newly formed bone was damaged. Bone–metal contact was less in the irradiated group.

Table 4. Site and number of implants inserted and lost after postoperative irradiation

Site	Patients	Implants inserted	Implants lost	Percent
Mandible	2	12	0	0
Maxilla	2	8	0	0
Zygoma	2	4	0	0
Orbit	3	9	3	33.3
Mastoid	14	30	7	23.3
Total	23	61	10	16.3

Table 5. Regions of implant placement and implant losses among patients that were irradiated both before and after implant placement

Region	Placed	Lost	Percent
Frontal bone	9	5	55.5
Zygoma	4	2	50
Maxilla	6	4	66.6
Temporal	2	2	100
Total	21	13	61.9

Irradiation doses varied from 80 to 195 Gy.

Clinical studies

In 1993, we reported our experience with postoperative irradiation on 32 implants in 11 patients (25). Implant failure was not exceedingly high (12.5%) during the follow-up. Soft tissue dehiscences were, however, more common than in corresponding non-irradiated patients. This led us to recommend that all superstructures should be removed prior to radiotherapy except the fixtures covered with skin or mucosa. We have since included a further eight patients in this group. The present follow-up results are presented in Table 4.

As can be seen from this table, with increasing follow-up time, implant losses increase. The question of one needs to remove the implants before irradiation must be discussed together with the oncologist and cancer surgeon in relation to the individual case. It must then remembered that there is a certain risk that osteoradionecrosis might develop if implants are removed.

Irradiation before and after implant placement

Occasionally one meets patients who have undergone preoperative irradiation, followed by surgical removal of the tumor. Upon evaluation of the pathologic specimens, tumor surgery might not have been radical. It may not always be possible to perform extended cancer surgery because of intracranial growth of the tumor, or tumor growth near vital blood vessels or other structures, and hence postoperative irradiation will be recommended (23). We have four such patients on our files. The tissue in which osseointegrated implants are placed will thus receive very high doses of irradiation. Implant failures have been high (Table 5), and slow wound healing a prominent feature, and three of the patients have developed osteoradionecrosis. It may nevertheless be worthwhile to rehabilitate patients like these with prostheses based on osseointegrated implants because the quality of life was much improved while these patients were alive.

Chemotherapy and osseointegration

Chemotherapy as a contributing factor for implant failures has been discussed by Andersson et al. (4). Wolfaardt et al. (90) carried out a multicenter investigation to elucidate the rate of osseointegration failure after chemotherapy. Many cancer patients receive combined chemotherapy/radiotherapy for the malignant tumor. Both these groups showed higher failure rates compared to controls. In particular, chemotherapy given close to implant surgery provided the highest failure score.

Conclusions

Rehabilitation of oral cancer patients who have been irradiated as part of cancer therapy can be performed according to the osseointegration concept. It is recommended that patients should be treated at osseointegration centers with the capacity and skill to treat radiologic and surgical problems in cancer patients. A number of factors responsible for clinical success of these patients must be taken into account. These factors include the irradiation source, dose and fractionation, use of chemotherapy, risk for tumor recurrence, anatomic region in which the implants are to be inserted, timing from radiotherapy to implant surgery, preoperative planning, retention systems used, loading factors, handling of the soft tissue and risk for osteoradionecrosis. The adjunctive

use of hyperbaric oxygen treatment with implant installation is strongly recommended.

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