Bone-anchored reconstruction of the irradiated head and neck cancer patient

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Titanium implants in facial bones for retention of epitheses or dental bridges were used for reconstruction in cancer patients after tumor surgery. Even heavily irradiated bones could integrate the implants and bear the load from the epithesis. No major complications, such as wound infection, fistulation, or osteoradionecrosis, occurred after implant surgery. There was, however, an increased loss of implants with time after irradiation, especially in the orbital region. When hyperbaric oxygen was used as adjunctive treatment, implant losses were reduced. (OTOLARYNGOL HEAD NECK SURG 1993;108:334-43.)

The recommended treatment for cancer in the head and neck region is a combination of radiotherapy and surgery. After ablative surgery, the patient might be left with large soft tissue and skeletal defects. The need for reconstruction of the operative defect arises after curative cancer treatment. Surgical reconstruction in irradiated patients is fraught with complications. No doubt the most challenging reconstructive problems arise in patients who have tissue defects and have been irradiated with more than 50 Gy (5000 rad).

In an effort to improve the cosmetic and functional outcome in these patients, an alternative system was developed in which facial epitheses (prostheses) were anchored by titanium implants in the facial bones.[1] Because this technique induces a much smaller surgical trauma to the irradiated tissue compared to conventional surgical techniques, it could be an alternative in the rehabilitation of cancer patients to avoid complications.

The aim of the present study was to investigate the capacity for osseointegration of titanium implants in the irradiated bone tissue, which is known to have a reduced healing capacity.[2] Secondly, it aimed to investigate if hyperbaric oxygen (HBO) could improve the osseointegration of implants in the irradiated patients.

SUBJECTS AND METHODS

All patients intended for rehabilitation with bone-anchored facial epistheses or dental bridges after tumor surgery at the ENT clinic, Sahlgrenska Hospital and at the Brånemark Osseointegration Centre between 1979 and 1992 were reinvestigated. Specifically, those patients who had been irradiated in conjunction with implant surgery were studied. Age, type and location of tumor, type of irradiation source, and fractionation schedules were reevaluated from the patients' files.

To determine the healing rate and bone quality of the implanted skeleton, the patients were preoperatively and postoperatively investigated with plain x-ray films, x-ray tomography, computed tomography, or magnetic resonance imaging, ^{99}technetium scintigraphy, and selective angiography of the common carotid artery. Transcutaneous O_2 and blood flow was measured in the operation field with an EOS pulse-oxymeter (Engström AB, Sweden) and an ALF 21 laser Doppler (Transonic Systems Inc., New York, N.Y.). Bacteriologic samples were taken from the skin, mucous membranes, and from tissue biopsies.

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Selective biopsies were taken from the irradiated tissue during operation, and morphological methods used to determine the condition of the irradiated tissue were routine histology of serially sectioned soft tissue and decalcified bone, ground sections of bone, and microradiography of ground sections of bone, as described earlier.[3] Twelve of the patients were treated in combination with hyperbaric oxygen, given at 20 preoperative and 10 postoperative sessions at 2.5 ATA, 90 minutes per session.

Implantation of titanium fixtures and evaluation of osseointegration were performed according to Albrektsson et al.[4] Appropriate areas for implants were the superior and inferior orbital rims, the anterior part of the zygoma, the medial and lateral aspects of the maxilla, and the mastoid process. The concept of osseointegration[5] is based on a two-stage operation procedure. During the first stage procedure, the skin and periosteum are elevated in appropriate implant areas. During intensive cooling, drilling and threading are performed and the titanium fixture is inserted. The fixture is made of commercially pure titanium and supplied with a flange for not moving too deep during insertion. The periosteum and skin are closed and healing is awaited.

The second stage operation is performed after 4 to 6 months, when osseointegration has occurred. The skin over the implant is reduced in thickness, and the periosteum is incised. An abutment is applied on top of the fixture and this part is penetrating the skin. After a healing period of 3 to 4 weeks, the prosthetic construction (episthesis) can be applied to the abutment with metal clips or magnets. The number of implants is balanced against the weight of the epithesis and is connected with a titanium bar. Skin reactions around the abutments were registered at each patient visit and graded from *0* to *4*, according to Holgers et al.[6]: *0* = reaction, *1* = reddish, *2* = moist, *3* = granulation, and *4* = removed.

RESULTS

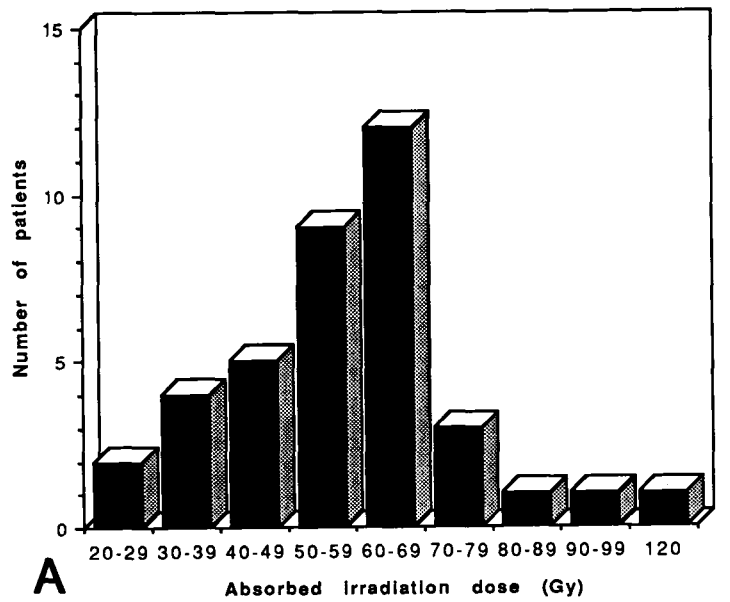
One hundred seventy-eight patients had titanium implants installed in the head and neck region for rehabilitation after tumor surgery between 1979 and 1992. Of these patients, 40 had undergone irradiation as part of tumor treatment. The age range for these patients at time of followup was 15 to 89 years, with a mean of 62.8 ± 15.9 (SD).

The type of tumors treated are presented in Table 1. As can be seen, the majority of patients were treated for tumors that affected the maxilla, orbit, and external ear. In one patient treated with irradiation in childhood for a rhabdomyosarcoma of the base of tongue, an adenocarcinoma of the submandibular gland developed 20 years later. She was again treated with a full course of irradiation and hence had received very high absorbed doses of irradiation before implant surgery.

Table 1. Type and frequency of malignant tumors of the patients in the study

Tumor type and location	No. of patients
Carcinoma	
Maxilla	10
Gingival	4
Auricle	3
Floor of mouth	2
External ear canal	2
Ethmoid	1
Hypopharynx	1
Palate	1
Rhabdomyosarcoma	
Base of tongue	1
Auricle	1
Orbita	1
Malignant glioma	
Temporal lobe	1
Sarcoma	
Orbita	2
Adenocarcinoma	
Lacrimal gland	2
Parotid gland	2
Submandibular	2
Malignant lymphoma	
Maxilla	2
Malignant melanoma	
Auricle	1
Basal cell carcinoma	
Nose	1

The patients were between 4 and 72 years old at the time of tumor surgery and irradiation. In all cases, the irradiation field comprised the implantation field. Irradiation against the tumors had been performed either with electrons or ^{60}cobalt with absorbed doses ranging from 25 to 120 Gy (cumulative radiation effect, 16 to 40; see Fig. 1). From this Figure it can be seen that 27 of 40 patients received irradiation of more than 50 Gy. For those patients who received doses lower than 50 Gy, hyperfractionation was generally administered. For two of the patients, the absorbed doses could not be calculated because the patient files had not been saved long enough (more than 30 years). Normal fractionation had been given to 25 patients and hyperfractionation to 13 patients. ^{60}cobalt had been used as irradiation source, except in two cases in which electrons were used. External irradiation had in one case been



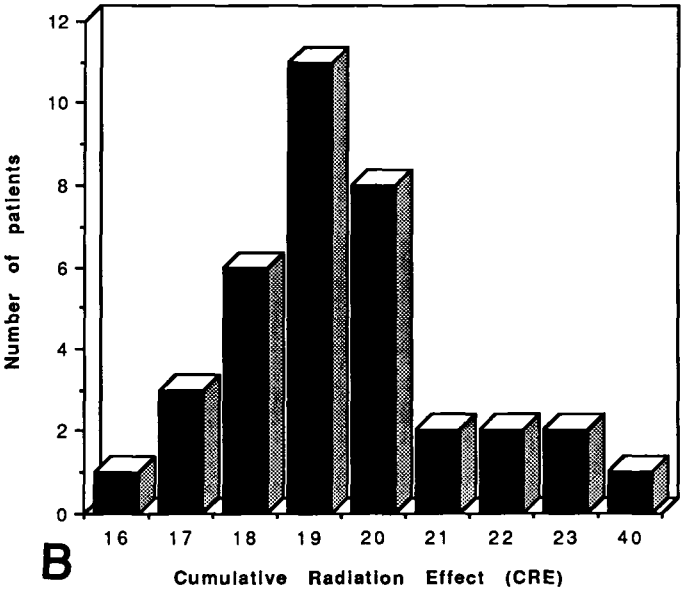


Fig. 1. A, Absorbed irradiation doses of the patients intended for implant surgery; **B,** Cumulative radiation effect values.

added with ^{192}iridium and in one case with ^{226}radium. Irradiation had in nine cases been preceeded by chemotherapy, the number and type of which are shown in Table 2.

Eighteen of the patients had undergone maxillectomy, 10 had ethmoidectomy, and 10 had spenotomy (opening of sphenoid sinus and removal of mucosa) as a result of a malignant tumor of the maxillary sinus or gingiva (Table 3). Twenty patients had evisceration of the orbit as a result of a malignant tumor of the eye or lacrimal gland or as a result of tumor spread from the maxillary sinus. Seven patients had their external ears removed because of cutaneous ear or ear canal neoplasms; two of these operations were combined with mastoidectomy. Two patients underwent parotidectomy and another

Table 2. Number and type of chemotherapy given in conjunction with irradiation for tumor therapy

Chemotherapeutic agent	No. of patients
Bleomycine	7
Vincristine	4
Methotrexate	3
Cyclofosfamide	2
Dactinomycine	2
Melphalane	2
Doxorubicine	1
Fluorouracile	1
Cisplatinum	1
Etoposide	1

Table 3. Overview of patients with respect to tumor surgery

Type of surgery	No. of patients
Evisceration of orbit	20
Maxillectomy	18
Ethmodectomy	10
Sphenotomy	10
Ablation of the external ear	7
Radical neck resection	6
Ligation of the internal carotid artery	4
Parotidectomy	2
Submandibular resection	2
Mastoidectomy	2
Local resection	2
Nose resection	1
Hemimandibelectomy	1

two underwent resection of the submandibular gland. One patient each underwent hemimandibelectomy and nose resection. Four patients underwent ligation of the internal carotid artery and six had radical neck surgery performed as part of tumor treatment (Table 3).

The time interval between irradiation and implant surgery varied from 1 month to 37 years (Fig. 2). Eight of the patients received irradiation after implant surgery. Two of the patients were also irradiated against laryngeal carcinomas; the therapy of these, however, did not add further irradiation to the implant area. A pulmonary carcinoma developed in one patient after treatment of his original auricular carcinoma. The treatment of this did not interfere with implant surgery.

The age of the patient at tumor surgery varied from 12 to 80 years, with a mean of 58.7 ± 15.6 years (SD). Six of the patients died during the investigation time: three of these died of tumor recurrences and the others died of cerebrovascular diseases or heart failure.

A total of 200 fixtures were installed in the craniofacial skeleton of the tumor patients (Fig. 3). Follow-up time after implant surgery varied from 0.5 to 11 years, with a mean of 4.4 ± 3.5 years (SD). The material has been divided into two groups: group A underwent no further treatment and group B was treated preoperatively and postoperatively with hyperbaric oxygen. Of the 134 fixtures installed in group A, 86 were stable after an average follow-up time of 56 months (Fig. 3, *A*). Forty-eight of the fixtures were removed, mainly for not having osseointegrated or because of loss of integration. This gives a total fixture loss with time of 35% in irradiated bone. Fixture loss was highest in the frontal bone (50%), followed by zygoma (46%), mandible (33%), maxilla (14%), and temporal bone (9%).

In the HBO-treated group B, 66 fixtures were installed—65 of which were stable after an average follow-up time of 28 months (Fig. 3, *B*). This gives a total fixture loss with time of 1.5% in the HBO group. The only fixture lost was in the maxilla.

Implant loss with time is shown in Fig. 4. As can be seen, most implants were lost during the first 3 years after implantation and there seems to be a plateau after 6 years, when most implants are retained. After HBO treatment, there is a significant difference already after 1 year of observation time. After 4 years, the difference is significant at the $p < 0.001$ level using the Student's *t*-test or the Wilcoxon Signed Rank test.

Around four of the implants, soft tissue infection was observed within 4 months after abutment surgery, bacteriologic culturing showing *Staphylococcus aureus*. This was handled with topical application of topical ointment with antibiotics and antimycotics (Terracortril with polymyxin B sulfate; Pfizer, New York, N.Y.), after which the soft tissue reaction healed. No implants had to be removed for reasons of bone infection and in no case did an osteoradionecrosis develop, as recorded clinically and radiographically. Skin reactions in the whole group of implants were grade 0, 88.5%; grade 1, 7.5%; grade 2, 3.1%; grade 3, 0.9%; and grade 4, 0%.

We were able to remove four fixtures in the temporal bone from a patient who died of intracranial tumor growth with the fixtures still in place (Fig. 5). As can be seen from these histologic specimens, even in heavily irradiated bone (92 Gy), the bone-forming capacity was sufficient to be able to integrate titanium implants in the bone. No inflammatory reaction was seen in the implant contact area.

Figure 6 shows an example of a patient treated for

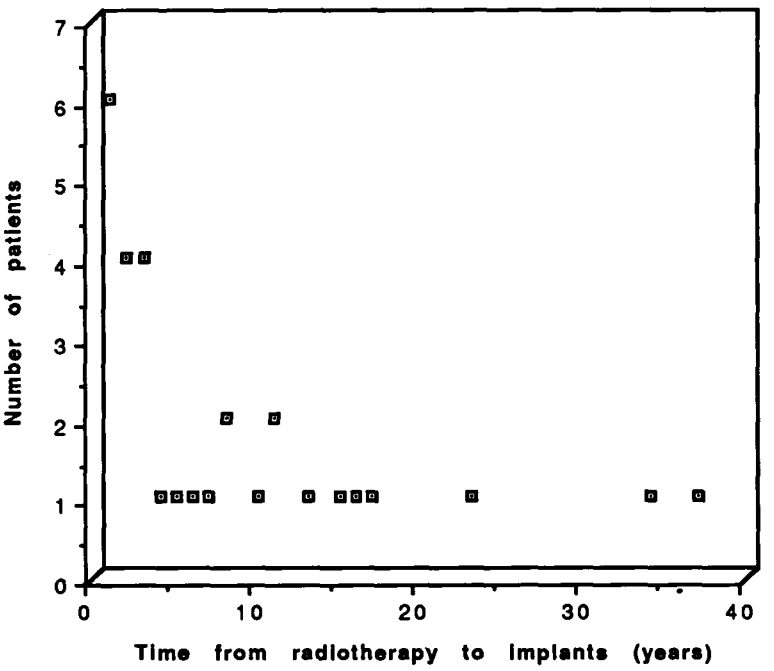


Fig. 2. Time from irradiation to implant surgery.

a basal cell carcinoma of the infiltrative type, located on the nasal alae. It was treated with extensive surgery and postoperative irradiation to 62.4 Gy. After $2\frac{1}{2}$ years he still had no recurrences. The patient was originally supplied with an acrylic prosthesis fastened on the spectacles. This was too heavy and caused mucosistis of the nasal and sinus mucosa (Fig. 6, *A*). Before fixture installation he was treated with HBO. While the patient was under general anesthesia, 13 titanium fixtures were implanted in the frontal bone, zygoma, and maxilla (Fig. 6, *B*).

A framework of titanium was prepared for anchorage of the facial epithesis. Bone marrow from the hip was transplanted to build up the contour of the maxilla and to provide enough bone to put the implants in. One fixture was lost in the maxilla. After fixture installation, the patient received postoperative HBO treatment (Fig. 6, *C*). This epithesis is much lighter than the first and is easily removed for inspection of the tumor cavity. It is still functioning well 4 years after surgery (Fig. 6, *D*).

DISCUSSION

A dental implant system, the Brånemark osseointegration system, was developed at the University of Gothenburg in 1965.[7] Since then, more than 600,000 titanium implants have been inserted in more than 200,000 patients and the 25-year clinical success rate has been more than 90 per cent.

In 1975 it was postulated that it ought to be possible to base a skin-penetrating implant system on the same principles as the osseointegrated dental implant. The clinical program with percutaneous titanium implants was started at the ENT clinic, Sahlgrenska Hospital in 1977.[8] There have been two main indications for surgery: the first is a stable anchorage of an external bone-conduction hearing aid in certain cases of hearing disorders, and the second is a stable anchorage of a facial epithesis in the case of missing ear, eye, nose, or face as a result of congenital malformations or status after cancer surgery or traumatic disorders.[1]

Between 1979 and 1992, 377 patients have been supplied with the bone-anchored hearing aid, 147 patients have been supplied with external ear epitheses, 41 with eye epitheses, and 21 with midface or nose epitheses. The number of extraoral implants totals more than 1000 in more than 600 patients. Implant survival until today is 98%, which means the clinical success rate is almost 100%.

Maintenance of a permanent skin penetration has been considered a crucial point for the implant concept. With the right implant material and surgical technique, however, a permanent skin penetration can be achieved. Of great importance, however, is proper patient care for and cleansing of the area. The skin reactions recorded in this study are of the same magnitude as reported earlier[6] and led in no

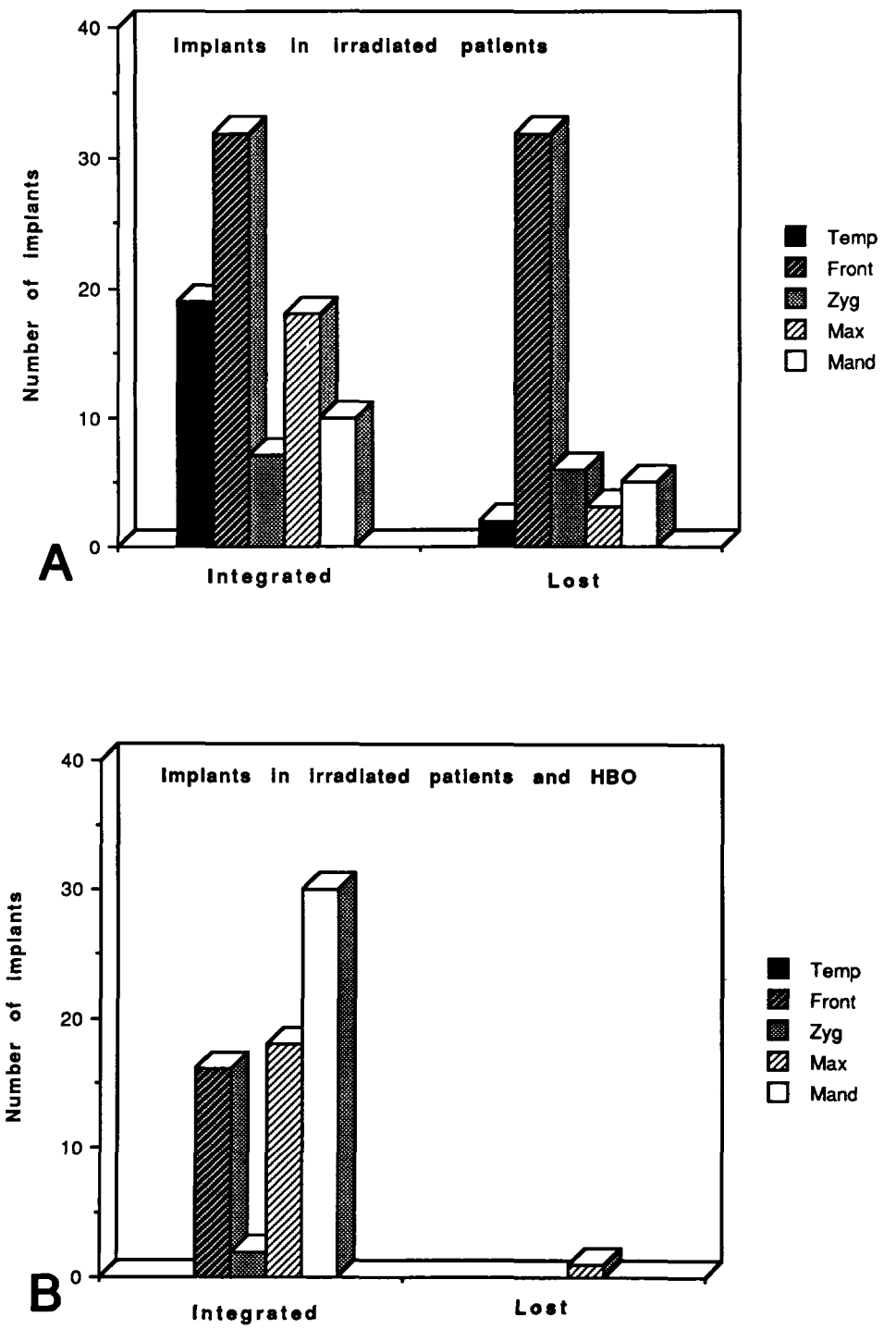


Fig. 3. A, Implant losses in different localities. *To the left* are integrated implants and *to the right* are implants lost during followup. **B,** Implant losses among patients treated with HBO. *To the left* are integrated implants and *to the right* are implants lost during followup.

case to removal of an implant. Thus it seems the irradiated skin and nonirradiated skin can be handled similarly.

It was considered originally a contraindication to perform implant surgery in irradiated patients because of the risk of inducing osteoradionecrosis. However, as the need for reconstruction increased in cancer patients after ablative surgery, attempts were

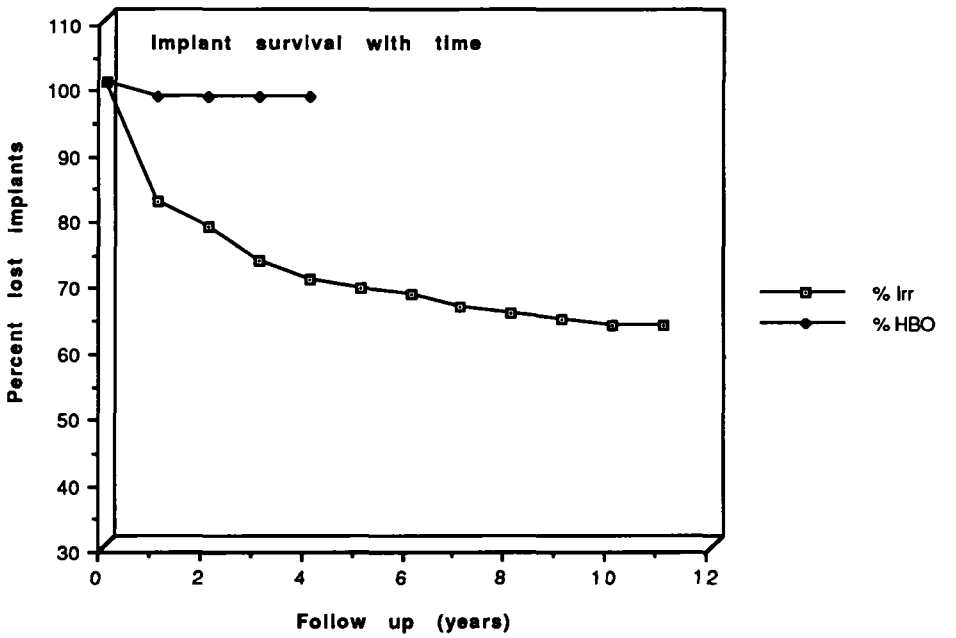


Fig. 4. Cumulative implant loss with time among group A patients and group B (treated with HBO).

made to use the osseointegration system also in these patients. There are two major advantages to this technique: the first is that surgery is performed in a biologically sound way, with small incisions, extensive cooling, and low-speed drilling in the bone and thus the risk of bone damage is reduced. The second advantage is that the tumor cavity is left open for inspection and tumor recurrences can thus be detected earlier than if the cavity had been covered with, for example, tissue transfer. The rehabilitation of the patient can thus start earlier after tumor surgery, which is of benefit to the patient.

The majority of patients in the study were treated for orbital and external ear defects, both of which are difficult to reconstruct in an acceptable way by plastic surgery. In five of the patients, however, implant surgery was combined with conventional plastic surgery techniques to obtain enough bone in which to insert the implants.

No major surgical complication occurred after implant surgery; nevertheless, since the start of implantation in irradiated patients it was soon realized that implant losses were higher than in other patients. Implant losses in the irradiated patients seems to continue with time, at least during the first 6 years after surgery. This is in accordance with the hypothesis that irradiation damage to the tissue is a continuous process, mainly depending on a gradual endarteritis with succeedingly fewer vessels per tissue area with time.[9]

Though the total number of irradiated patients treated with implants is still low, the tendency in northern Europe and North America seems to be the same (i.e., increased loss of implants with time, especially in the frontal bone and zygoma).*

In an earlier report we noted an increased loss of implants in irradiated patients.[10] This occurred predominantly in the orbital region, whereas the temporal bone seemed to be relatively radioresistant. Also in this study, HBO could be seen to reduce implant losses. Ehrenfeld[11] studied 46 oral implants in patients irradiated with 10 to 70 Gy. An average of 28 months between irradiation and implant surgery was noticed. There were seven losses, all of which appeared with the Tübinger implants (7 of 12), whereas 15 Brånemark implants, 10 Bonefit, seven IMZ-implants, and two HaTi-implants could be clinically integrated. None of these patients was treated with HBO.

In earlier experimental studies we have found that bone formation in titanium-based harvest chambers increased after HBO in the nonirradiated rabbit tibia.[12] HBO stimulated lamellar bone formation as studied by densitometry and microradiography. These findings could later be shown to occur also in irradiated animals.[13] In this study we noted that bone

*Allen, Bodin, Deadman, Ehrenfeldt, Melén, Schwartz, and Vesterhauge: personal communications, 1991 and 1992.

formation increased both in the irradiated bone and on the control side. HBO can increase hard tissue formation such as dentin and enamel in continuously growing teeth.[14] It can also increase production of bone-matrix in experimental osteogenesis using the bone harvest titanium chamber.[12] An increased mineralization has been seen in experimental systems such as mandibular fracture repair, in which an enhanced bony trabecular production is accompanied by increased mineralization after HBO therapy.[15] The basic mechanisms of action, whereby HBO exerts its beneficial effects on osteogenesis, are based on factors secondary to the elevation of pO_2 (e.g., effects on the differentiation of mesenchymal cells).[12,16]

Our findings in this study support earlier findings that HBO has a stimulating effect on the healing and remodelling process of bone tissue. It also supports clinical studies that show a prolonged titanium implant survival after HBO in irradiated patients.[10,17] HBO therapy for radiation-damaged tissues was introduced in 1973 by two principal studies.[18,19] Today, several well-defined protocols based on human trials have been developed.[20,21] The daily elevation of oxygen tension in hypoxic bone and soft tissues results in the ingrowth of capillaries,[22] fibroblastic proliferation and collagen synthesis,[23] and capillary angiogenesis.[24]

Numerous studies have attested to the usefulness of HBO for the treatment of osteoradionecrosis of different bones.[25] Using a standardized protocol including surgery, antibiotics, and HBO, Marx[21] showed the efficacy of HBO. In addition to HBO's usefulness in the treatment of osteoradionecrosis, it may also prevent this condition.[26]

In the study by Marx et al.[26] it was shown that HBO-induced angiogenesis became measurable after eight sessions, rapidly progressed to a plateau at 80% to 85% of nonirradiated tissue vascularity by 20 sessions and remained at that level without further improvement with additional HBO. Patients who were restudied up to 3 years after the original HBO therapy had tissue O_2 levels at or within 90% of their values recorded just after treatment. This study therefore indicates that the induced angiogenesis after HBO therapy does not undergo regression with time. Several studies have suggested that maximum stimulation of neovascularization and fibroplasia occur between 20 and 30 hours of exposure of oxygen at pO_2 200 to 250 kPa using 100% oxygen at 2.0 to 2.5 atmospheres absolute pressure.[22,24] It is therefore believed that more than 30 hours of preoperative HBO exposure will not improve the recipient tissues any further. The rationale for the ten postoperative

Fig. 5. Light photomicrograph from postmortem specimen of patient who had received 92 Gy before titanium fixture implantation. Bone tissue adjacent to titanium fixture with normal appearance of osteocytes, bone lamellae, and blood vessels. (Original magnification ×40.)

treatments (15 treatment hours) is reduction of the potential for wound dehiscence by promotion of collagen production at incision lines, fixture surface, and assistance for graft cell survival and early revascularization by intermittent reversal of the hypoxia inherent in all surgical wounds.

The results thus far point to a good possibility for HBO to actually increase fixture survival in the irradiated patient.[27,28]

CONCLUSION

It is concluded that the bone-anchored epithesis system is a good alternative to conventional reconstructive surgery in the rehabilitation of cancer patients. Titanium implants can be integrated in bone tissue in patients who have undergone previous radiotherapy, even at high-dose levels. No major complications such as wound infection, fistulation,

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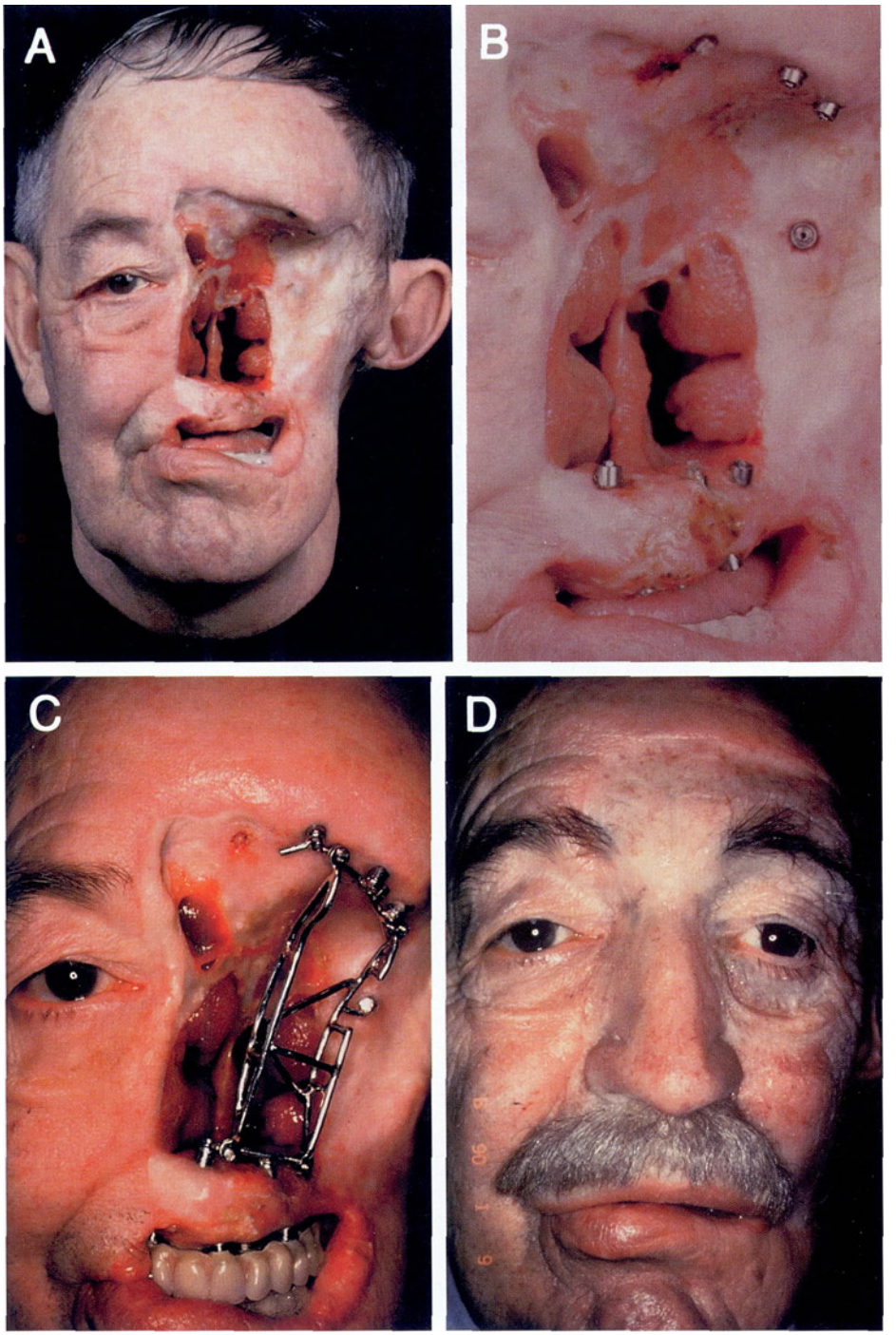

Fig. 6. Clinical documentation from patient with extensive surgery as a result of a basal cell carcinoma of the left nasal ala. After multiple operations, he received 62.4 Gy external irradiation. **A,** Status before treatment. Note full denture in upper jaw. **B,** Status after 20 HBO treatments; 13 fixtures were inserted in the maxilla, zygoma, and frontal bones. Abutments were attached to the fixtures. The contour of the maxilla was extended by transferral of marrow bone from the hip. **C,** A framework of titanium was connected to the abutments; a fixed, bone-anchored dental bridge replaces the denture. **D,** A silicone epithesis was attached to the framework with clips and was thus removable for inspection of the tumor cavity.

or osteoradionecrosis occurred after implant surgery. There was, however, an increased loss of implants with time after irradiation—especially in the orbital region. The combined treatment with hyperbaric oxygen reduced implant losses with time.

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