Osseointegration in Irradiated Cancer Patients: An Analysis With Respect to Implant Failures

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Purpose: This study retrospectively evaluated implant survival of 631 osseointegrated implants installed in irradiated cancer patients over a 25-year period.

Patients and Methods: The files of 107 patients followed since 1979 were evaluated. Factors influencing implant survival as oncologic treatment, radiotherapy protocols, patient and implant related elements were analyzed.

Results: Compared with a control group of non-irradiated patients, implant failures were higher after previous radiotherapy. High implant failures were seen after high dose radiotherapy and a long time after irradiation. All craniofacial regions were affected, but the highest implant failures were seen in frontal bone, zygoma, mandible, and nasal maxilla. Lowest implant failures were seen in oral maxilla. The use of long fixtures, fixed retention, and adjuvant hyperbaric oxygen therapy decreased implant failures. Noncontributing factors to implant survival were gender, age, smoking habits, tumor type and size, surgical oncologic treatment, and osseointegration (OI) surgery experience.

Conclusion: Survival after cancer therapy is so high, and outcome from OI therapy so favorable that OI in the irradiated patient can be recommended. However, the OI clinician should be aware of the risks and pitfalls of treating such patients.

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Previous radiotherapy was originally considered a contraindication for installation of osseointegrated implants (OI) in cancer patients.[1] Nevertheless, this has been tried in many countries with variable results. In the literature, there is an intense discussion concerning the outcome of OI in cancer patients.[2-10] There seems to be a disagreement whether implant failures or other complications are more common after previous irradiation. There is no general consensus when the ideal time is to rehabilitate cancer patients with OI implants, how irradiation doses affect implant survival, if irradiation after implant installation is possible, whether chemotherapy affects OI, or if hyperbaric oxygen therapy (HBO) is necessary. A number of questions arise concerning what other factors might affect implant survival in the irradiated tissues.

Beginning in 1979, we have used the OI concept for rehabilitation of cancer patients, and in 1981 we operated on the first patient that had been irradiated. Since that time we have gathered experience from more than 100 irradiated cancer patients and more than 1,100 non-irradiated patients (350 of which were cancer patients) treated according to the osseointegration principle. Some clues to the questions above can be related to long-term follow-up of irradiated cancer patients. Because of the Swedish health care system, we have been able to follow each patient from the beginning of treatment. The present investigation was undertaken in an attempt to answer the above questions how OI implants perform in the irradiated tissues.

Patients and Methods

The amount of data gathered during these 25 years required a database to be able to handle it all. Such a database was created using the Microsoft Excel system (Microsoft, Redmond, CA). Approval for the

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study was given by the ethical committee of Göteborg University (Gothenberg, Sweden). All patients that had been irradiated as part of their cancer treatment were included in the database. They were all followed consecutively at the Implant Unit at the ENT-clinic, Sahlgrenska University Hospital from 1979. The end of the study was December 31, 2003. The patient's files were followed until the last follow-up visit at the clinic, or until recordings showed the patient had died. Altogether, data covering 313 different parameters were included and analyzed. Gathering of these data gave more than 26,000 observations. The number of patients investigated, their gender and age were recorded, as well as the reason for rehabilitation. Data included type of rehabilitation, and whether it was intraoral, extraoral, or combined therapy. Smoking habits were recorded, as was concurrent disease. Type of cancer was evaluated including type, size, stage, local nodes, and distant metastasis. Oncologic treatment was investigated. This included all surgical procedures, as well as the timing of the different procedures. Irradiation protocols were evaluated including type of radiotherapy, dose, timing, and sequencing to surgery. Different protocols for chemotherapy were evaluated. This included type of chemotherapy, dose, and timing. Data on osseointegration procedures were registered. This included information of implant type, length, diameter, surface characteristics, and anatomic region of implant placement. Abutment type and other details of prosthetic retention were registered. Implant surgery, timing of surgery, the experience of the surgeon, the tumor cavity, and other surgical data were gathered. HBO was used as a part of the protocol. Number of HBO session, dosage, and timing were registered. Follow-up consisted of registration of implant stability, prosthetic anchorage, soft tissue reactions, possible side effects, and complications from treatment.

Non-irradiated patients treated at the same unit in the same time period served as controls. Age and gender-matched control groups were created for each implant region. They were followed in a similar manner as described above and the data analyzed in a database. The control group consisted of 100 patients, 55 male and 45 female, with age ranging from 15 to 88 years (mean age, 58 years). Preferably non-irradiated cancer patients were selected as comparison, but when this was not achievable, patients rehabilitated for craniofacial malformations, chronic ear disease, and advanced periodontitis were selected.

Implant failure was considered as the primary endpoint of the study. Hence, each individual implant was followed and its fate recorded. Comparisons were made between implant survival and all variables described above. Multivariate statistical analysis was performed using the Wilcoxon-Rank method. Statistical significance was defined to have been reached at $P < .05$.

Table 1. IMPLANT SURVIVAL (WILCOXON RANK TEST, 2-TAILED COMPARISON)

Gender	$P > .30$
Age	$P > .30$
Concurrent disease	$P > .30$
Smoking amount	$P > .30$
Smoking time	$P = .28$

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Results

During this 25-year period, 107 irradiated patients were rehabilitated; 105 of these had cancer or similar tumor as reason for their treatment. Two patients were rehabilitated according to OI for other reasons, but developed malignancies later and were irradiated with the implant in the irradiation field.

Altogether, 631 OI implants were installed in different regions of the craniofacial skeleton, of which 484 were still active and stable at the end of the study period. One hundred forty-seven OI implants had failed during follow-up. Mean follow-up time was 6.3 years and varied from 0.5 to 23 years. Mean age of the patients at the time of OI surgery was 59.1 years (range, 12 to 90 years). There were 67 males and 40 females in the study. Male patients had 391 implants installed (mean, 5.8 implants/male) and female patients had 238 implants (mean, 5.9 implants/female) installed. Of those 71 patients that were still alive at the end of the study, mean survival time was 16 years (range, 0.8 to 37 years). Mean survival time of those 36 patients who died from their cancer or other reason during the study time was 9.8 years (range, 0.9 to 26 years). Concurrent disease was present in 12 patients; 11 had cardiovascular disease and 1 had diabetes mellitus.

In the control group, 614 OI implants were installed of which 538 were active and stable at the end of the study period. Seventy-six OI implants failed during follow-up. Mean follow-up time was 7.2 years (range, 0.8 to 21 years). Mean implant number was 6 per patient (no gender difference). Ninety-four patients were alive at the end of the study. Those that had died had done so because of cardiovascular disease which was not related to the reason for OI surgery.

Fifty-five of the irradiated cancer patients were smokers, 6 were ex-smokers, and 46 were non-smokers. Of the smokers, 26 smoked more than 26 cigarettes per day, 20 smoked between 11 and 20 cigarettes per day, and only 4 smoked less than 10 cigarettes per day. Thirty-two of the patients had been smoking more than 21 years, 19 between 16 and 20 years, and 4 less than 10 years. As can be seen in Table 1, gender, age, concurrent disease, and smoking habits did not influence implant survival.

Table 2. IMPLANT SURVIVAL (WILCOXON RANK TEST, 2-TAILED COMPARISON)

Carcinoma	$P = .15$
Adenoidcystic carcinoma	$P = .28$
Sarcoma	$P > .30$
Adenocarcinoma	$P > .30$
Malignant melanoma	$P > .30$
Malignant lymphoma	$P = .20$
Other cancer	$P > .30$
Orbita	$P = .055$
Maxillary sinus	$P > .30$
Ear	$P > .30$
Skin	$P = .20$
Gingiva	$P = .058$
Floor of mouth	$P > .30$
Other region	$P = .21$
Tumor size	$P = .23$
Node	$P > .30$
Metastasis	$P > .30$

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Of cancer types, carcinoma was the most common, being present in 52 patients. Another 15 had adenoid cystic carcinoma, 9 had a sarcoma, 8 had an adenocarcinoma, 5 had malignant lymphoma, 4 had other carcinoma, and 8 had another type of cancer. Cancers of the orbit were most common (24) followed by maxillary sinus (23), ear (17), skin (8), gingival (6), floor of the mouth (5), tonsil and tongue (4 each), maxilla (3), nasal cavity (2), palate, oropharynx, and bucca (1 each). Ten patients had cancers of other regions.

There were 8 T1 tumors, 40 T2, 17 T3, and 37 T4 tumors in the material. Seventy-seven patients had no signs of local metastasis (N0), 21 had N1, 6 had N2, and 1 had N3 stages. Only 1 patient had a pulmonary metastasis (M1), whereas the other 104 had no detectable distant metastasis (M0). As can be seen in Table 2, there was no correlation between tumor type, size, stage, nodes or metastasis, or region to implant failure. There was a trend, however, that implant failures might be higher in orbit tumors ($P = .055$) and lower in gingival tumors ($P = .058$).

The primary tumor was removed radically, with removal of local surrounding tissues when needed. A unilateral radical neck dissection was performed in 21 patients and 8 patients had unilateral functional neck dissections. One patient had bilateral radical neck dissections performed. No kind of neck dissection was performed on the remaining 77 patients. There was no correlation between tumor surgical procedures and implant failures ($P = .20$ to $>.30$).

Radiotherapy was administered by ^{60}Cobalt irradiation to the tumor and surrounding tissues. Ninety-three patients received radiotherapy before the tumor was resected and 14 had radiotherapy after tumor surgery. The administration of radiotherapy meant

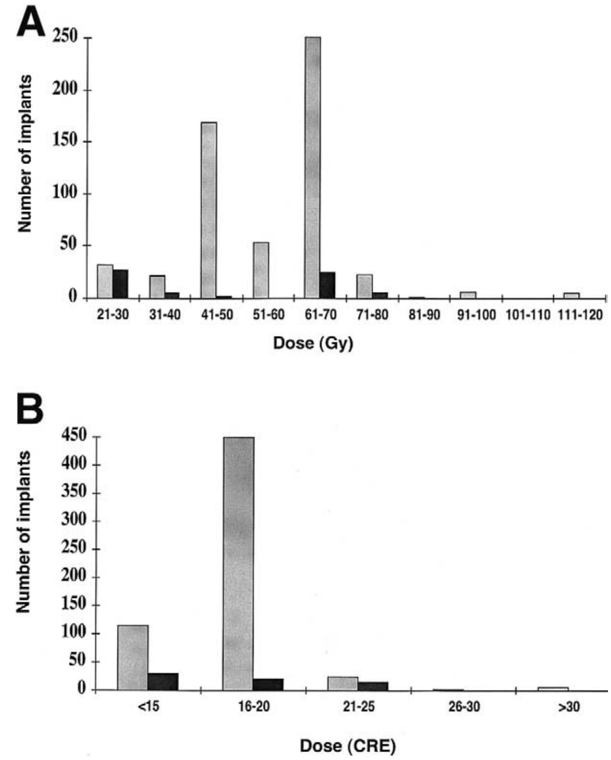

FIGURE 1. Dosage of irradiation given to OI implants. *A*, Expressed as Gy, and *B* expressed as CRE (cumulative radiation effect). Light gray bars, irradiation before implant surgery; dark gray bars, irradiation after implant surgery.

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that 528 OI implants were installed in an irradiation field, 58 OI implants were exposed to radiotherapy after installation, and 14 implants were installed in an irradiation field and were additionally exposed to radiotherapy after installation.

Irradiation dose to each implant was calculated from the patient's files. Two procedures were performed to evaluate the possibility that different fractionation types could affect implant survival. First, the dosage expressed as Gy was evaluated. Then, these data were recalculated according to the formula of Kirk et al[11] as (total time of treatment/number of treatments)$^{-0.11}$ × dose per treatment × number of treatments$^{0.65}$ to obtain the cumulative radiation effect (CRE) values. Both calculations are presented in Figure 1. As can be seen, when expressing irradiation dose in Gy, a 2-peak graph is obtained with the first peak at 41 to 50 Gy. These represent the patients that have received hyperfractionation radiotherapy (twice per day). The other peak (at 61 to 70 Gy) represents the patients that have received standard fractionation therapy (once per day). If one, on the other hand, calculates the CRE, a 1-peak curve appears at CRE 16 to 20. Thus, the majority of patients have obtained full-course radiotherapy and the majority of the implants are either installed in the tumor cavity (maxi-

Table 3. COMPARISON OF THE EFFECT FROM RADIOTHERAPY AND CHEMOTHERAPY ON OI IMPLANTS TO THE CONTROL GROUP (WILCOXON RANK TEST, 2-TAILED COMPARISON)

Radiotherapy before	$P < .001$
Radiotherapy after	$P < .001$
Radiotherapy before + after	$P < .0001$
Hyperfractionation	$P > .30$
Chemotherapy before	$P = .05$
Chemotherapy after	$P = .01$
Chemotherapy before + after	$P < .001$

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mum dosage) or exposed to full course radiotherapy. No implants in grafted or otherwise unexposed bone are included in the material.

Chemotherapy was administered to 29 patients during the course of cancer treatment. Thus, 141 implants were installed after chemotherapy treatment, 32 implants were installed and chemotherapy was given afterwards, and 4 implants were exposed to chemotherapy both before and after installation. Compared with the control group, implant failures were higher after both irradiation and chemotherapy treatment (Table 3). As can be seen from Table 3, comparison between standard fractionation and hyperfractionation turned out to be without significance.

Effect of irradiation dose expressed as CRE on implant survival is presented in Figure 2A. As can be seen in this graph, higher doses increase implant failures. At doses increased above CRE 30, implant failures were statistically significant ($P < .05$). The time from radiotherapy to implant surgery was also found to influence implant failures. Irradiation more than 15 years before implant surgery significantly increased implant failures ($P < .05$; Fig 2B).

Only OI implants with screw shape and machined surface (Nobel Biocare, Gothenburg, Sweden) was used in the study. Eleven regions of implant installation were registered. The different regions in relation to number of implants installed and lost are presented in Figure 3. This graph was divided into 2 parts, part A shows intraoral implants and B showing extraoral implants. In this graph, data from the control group are also included. The anterior and posterior portions of the maxilla and mandible were registered separately. However, there were no significant differences in implant failure between these 2 portions. Comparing implant failures in irradiated with non-irradiated bone, the highest failures were seen in orbita-facial (52%), facial-maxilla-nasal (47%), mandible (44%), orbita-zygoma and facial zygoma (43%), and temporal-parietal (33%), followed by oral maxilla (12.5%). After preoperative HBO, implant failures were reduced in all regions except temporal-parietal. The highest im-

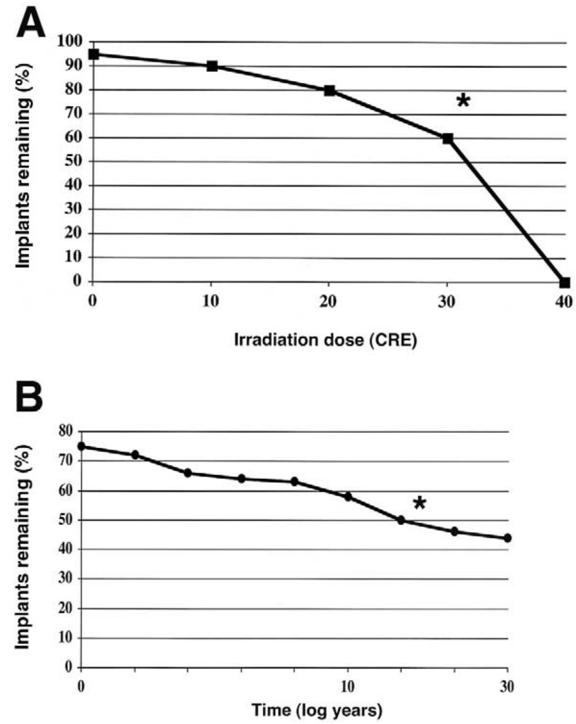

FIGURE 2. Percent of implants remaining in relation to irradiation dose and timing. *A*, Irradiation dose expressed as cumulative radiation effect (CRE; see text for explanation). *, Significance at $P < .05$. *B*, Percent of implants remaining after different times from radiotherapy to OI surgery. *, Significance at $P < .05$.

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plant survival was after HBO noted in oral maxilla and mandible (1% to 2% failures), frontal zygoma (6%), orbita facial/zygoma (14% to 16%), and facial-maxilla-nasal (21%); whereas implant failure in temporal-parietal was still high (30%).

In the non-irradiated control group, implant failures were according to region: mandible (6%), maxilla (6%), orbita frontal (23%), orbita zygoma (18%), facial zygoma (18%), facial-maxilla-nasal (20%), and temporal-parietal (5%). Statistical evaluation is presented in Table 4.

Implant failures in relation to time was also investigated. As can be seen in Figure 4, the majority of implants failed early, after stage 1 surgery or before loading. Another peak was then observed after 2 years, after which time fewer implants were lost. There were, however, failures up to 20 years after installation. Implant length affected survival. It was found that the shortest implants (3 to 7 mm) failed to a higher proportion than longer implants (range, 3 to 45 mm; $P < .001$. Prosthetic retention also affected implant survival. As can be seen in Table 5, a fixed retention is superior to the alternatives. Poorest retention, from the implant survival point of view, was the combination clips plus individual magnets. This is probably related to unfavorable cantilever effects on

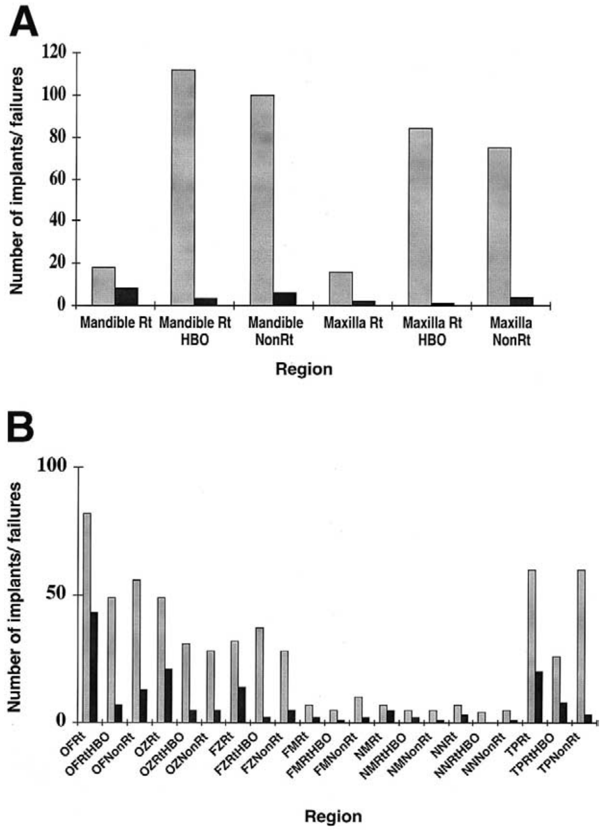

FIGURE 3. Implant failures in relation to region. *A,* Intraoral regions. *B,* Extraoral regions. Rt, radiotherapy; HBO, hyperbaric oxygen therapy; OF, orbita-facial; OZ, orbita-zygoma; FZ, facial-zygoma; FM, facial-maxilla; NM, nasal-maxilla; NN, nasal-nasal; TP, temporal-parietal; light gray bars, installed implants; dark gray bars, failed implants.

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the implants. Further parameters that were evaluated from the implant survival point of view were implant surface, open/closed tumor cavity, and the surgeons experience in years. These were all found to be without significant effect ($P = .20$ to $>.30$).

Skin and mucosa reactions were evaluated during the study period. Using an earlier described classifications system for soft tissue reactions, it was found that there were more grade 1 to 3 tissue reactions ($P < .001$ to $.05$) after radiotherapy compared with the control group. Denuded bone in relation to OI surgery present for more than 6 months was used as definition for osteoradionecrosis. With this definition, 5 patients developed this condition. Four of these were the patients treated with the combined pre- and postoperative radiotherapy, thus receiving extremely high radiation doses. Implant failures were very high in this group of patients. Two of these patients died from their cancer with osteoradionecrosis still present. The other 3 healed after a long time with combined surgery and HBO therapy.

Table 4. DIFFERENCE OF IMPLANT FAILURES IN THE 11 DIFFERENT REGIONS STUDIED (WILCOXON RANK TEST, 2-TAILED COMPARISON)

Region	NonRt-Rt	Rt-RtHBO
Mandible posterior	$P < .001$	$P < .001$
Mandible anterior	$P < .001$	$P < .001$
Maxilla posterior	$P < .02$	$P < .01$
Maxilla anterior	$P < .02$	$P < .01$
Orbita-frontal	$P < .03$	$P < .01$
Orbita-zygoma	$P < .02$	$P < .01$
Facial-zygoma	$P < .02$	$P < .001$
FM + NM + NN	$P < .03$	$P < .02$
Temporal-parietal	$P < .005$	$P > .30$

NOTE. Because of limited number of implants in regions facial-maxilla (FM), nasal-maxilla (NM), and nasal-nasal (NN), these groups were pooled at calculation.

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HBO was included in the program. Three hundred forty implants were installed under HBO protection. Twenty-nine of these were lost during follow-up (8.5%). When comparing with those 291 implants that were installed without HBO, 117 of these failed during follow-up (40.2%). Statistical comparison between these groups (all regions pooled) revealed a statistical significance at $P < .001$ in favor of HBO.

Discussion

Osseointegration has made a tremendous breakthrough in dentistry during the last 3 decades. It has completely changed the foundation of oral rehabilitation. During these 3 decades, a number of factors for successful osseointegration have been determined. These include good material biocompatibility, optimum implant macrostructure and microstructure, skillful surgery, good quality of bone bed and, favorable loading conditions. Despite knowledge of these important factors, over time several changes have been made to the original concept. For example, the originally described 2-stage surgical technique has

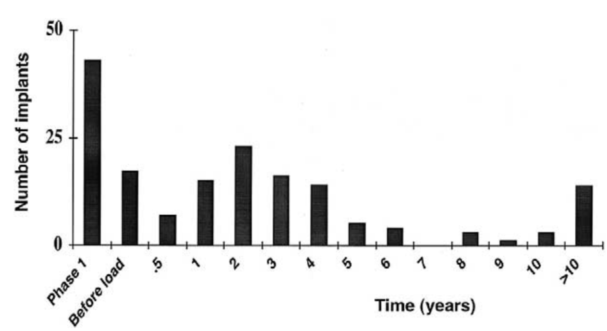

FIGURE 4. Time from OI surgery to implant failure of the 147 implants failing in irradiated bone.

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Table 5. IMPLANT FAILURE IN RELATION TO RETENTION SYSTEM USED (WILCOXON RANK TEST, 2-TAILED COMPARISON)

Bar + clips	$P > .30$
Bar + magnet	$P = .26$
Bar + clips + magnet	$P = .0062$†
Magnet	$P > .30$
Ball	$P = .29$
Fixed	$P < .001$*
Removable	$P = .12$

*Better than average.
†Poorer than average.

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been replaced by 1-stage techniques and has delayed loading to immediate loading. In a similar manner, a number of factors responsible for failure of osseointegration have been described. These include unfavorable implant structure, poor bone quality, traumatic surgical technique, and overloading. A number of patient related factors could be added as concurrent diseases, smoking habits, ingestion of toxic drugs, osteoporosis, and the like. A number of factors obtained during cancer treatment could be added that could threaten osseointegration.

Since 1977, the concept of osseointegration has spread outside the oral cavity, being mainly used for rehabilitation of patients with bone-conduction deafness. The second reason for using OI extraorally has been to rehabilitate patients with craniofacial defects because of cancer surgery or malformations. At our institution, which has handled more than 1,200 patients supplied with OI implants, almost 70% of craniofacial defects have been caused by cancer surgery and of these patients, approximately 35% were irradiated during the course of cancer therapy.

Whenever one rehabilitates cancer patients, the possibility for tumor recurrence is a factor of importance. In this material, which is composed of patients gathered during a 25-year period, the patient survival rate from cancer was high (66%). A mean survival time of 16 years for surviving patients and almost 10 years for deceased patients means that the OI clinician must have a 10 to 20 year perspective on the rehabilitation process. With such a high survival rate and long survival time, an improved quality of life for the patients during this time is expected.

We installed OI implants in a radiated patient for the first time in 1981. The first follow-up report from our institution was published in 1988,[12] and did not show implant failures in irradiated patients to be particularly high, or 14%. However, continuous study of the outcome of the irradiated patients at our institution has shown that implant failures with time have been higher than originally considered.[3,13,14]

The present study sought to analyze the reasons for implant failures in irradiated patients. From the data presented, it can be seen that irradiation per se has a negative effect on OI. If the patient has been irradiated before OI surgery, the higher the dose, the poorer the results. The longer the time from radiotherapy, the poorer the results. This is in accordance with our earlier studies.[15] However, what can also be seen from the study is that patients irradiated after implant placement show higher implant failures than originally believed.[16] The same situation appears for chemotherapy exposure, which was not considered in an earlier study.[17] Thus, it appears that combined oncologic treatment modalities all have a negative effect on the outcome for OI. Particularly high implant failures were seen after the combined pre and post OI radiotherapy.[18] Contrary to oncologic treatment, the surgical oncologic procedure did not seem to affect OI implant survival. Very few small tumors (T1) were relatively rare in the material, whereas larger T2-T4 tumors were common. Thus, a large size of the tumor defect seems to be no contraindication for OI surgery, as long as there is sufficient bone available. Only 1 patient in this material had distant metastasis (treated by partial pulmectomy). Thus, the presence of distant metastases seems to be a contraindication for the OI procedure because of the expected short survival time for the patient.

The regional installation of OI implants affected implant survival in the irradiated tissues. Therefore, the highest failures were seen in the frontal bone, zygoma, mandible, and nasal maxilla. High implant failures in the bone surrounding the orbita are in accordance with ours and other earlier studies.[15,19] High implant failures in the mandible were related to several complete failures in this bone. In other studies, it seems that the mandible is relatively radioresistant and hence can integrate OI implants well.[2,10,20] However, following implant survival during a longer time perspective shows high failures also in this bone with increasing time.[21] Lowest OI implant failures were seen for the oral maxilla, which is in accordance with earlier studies.[22-24]

As in our earlier studies, it could be seen that the shortest implants showed the poorest prognosis.[15] This is probably related to the fact that the shortest implants are those that are exposed to the highest loading forces. The retention mode also affected implant survival. Highest survival was found for fixed retention. Lowest implant survival was for the combination clips and magnets on extended arms. The poor survival for implants loaded with extended arms is probably related to cantilever effects. Contrary to what we found earlier, the experience of the osseointegration surgeon did not affect implant survival.[15] This is further not in accordance with other studies in non-irradiated tissues.[25] Either the surgeons in this study were experienced enough in practicing surgery in cancer patients, or the irradiation factor is more important for implant survival.

Hyperbaric oxygen therapy was introduced as part of the treatment protocol for installation of OI implants at our institution in 1988. This was at the time when we were aware of the increased failure rate of implants installed in previously irradiated bone. Another aspect was that we were also treating patients who had received very high doses (>80 Gy) of irradiation. The reason for choosing HBO was that it was, at that time, the only available clinical method that could be used to counteract the negative effects from radiotherapy. It was also available in all countries using osseointegration. As can be seen from this study, failure of OI implants is reduced by HBO in all regions except the temporal-parietal region. Why implants in the irradiated temporal-parietal region perform less well after HBO is not understood. One reason could be that this region has a limited bone supply, and only the very shortest implants were installed here (3 to 4 mm). For an extended discussion of osseointegration in the irradiated patient, see 2 debate articles in a forthcoming issue of the *Journal of Oral and Maxillofacial Surgery*.[26,27]

Survival after cancer therapy is so high that OI can be used in these patients. Compared with a control group of non-irradiated patients, implant failures are higher after previous radiotherapy. High implant failures were especially seen after high dose radiotherapy and a long time after irradiation. All craniofacial regions were affected, but the highest implant failures were seen in frontal bone, zygoma, mandible, and nasal maxilla. The lowest implant failures were seen in the oral maxilla. The use of long fixtures, fixed retention, and adjuvant HBO decreased implant failures. Non-contributing factors to implant survival were gender, age, smoking habits, tumor type and size, surgical oncologic treatment, and OI surgery experience.

Thorough preoperative planning with a team of specialists is necessary for optimal treatment of these patients. It is therefore the authors' recommendation that rehabilitation of irradiated patients should be performed at clinics and institutions that are experienced in treating cancer patients.

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