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Placement of Dental Implants in Irradiated Bone: The Case for Using Hyperbaric Oxygen

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Radiation therapy was originally considered a contraindication for installation of dental implants.[1] Nevertheless, the need to optimally rehabilitate cancer patients has challenged this position. To answer whether the irradiated cancer patient who is scheduled for rehabilitation with osseointegrated implants (OI) would need hyperbaric oxygen therapy (HBO) before surgery, one fundamental question must be asked: Will the patient be subjected to any risk related to OI surgery in relation to having been treated with radiation therapy, or will the implant procedure be performed smoothly without side effects? If the clinician can predict, based on best evidence that there will be no anticipated problems, then HBO is not necessary. The following discussion, however, relates to those patients for whom the experienced OI clinician can anticipate problems in the course of the rehabilitation process of a patient exposed to radiation therapy.

The accurate prediction of problems that would challenge OI intervention is of primary importance in the management of the irradiated patient. A series of important questions that the clinician should ask before planning rehabilitation are therefore discussed below, and the author makes an attempt to answer them in a scientifically valid way, based on today's existing knowledge. The reader will then be aware of the pitfalls that might reduce the benefits of OI in the irradiated patient and how some potential challenges and complications can be prevented with HBO.

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Is There a Reason to Use the OI Concept in the Irradiated Patient?

The answer is definitely yes. Several publications addressing this question have been published during the last 2 decades.[2-9] The reported benefits the patient can anticipate are related to better masticatory ability from an implant-supported prosthesis, and less damage to the oral mucosa from a denture, particularly if xerostomia is present. Factors such as facilitated swallowing and speech function are also improved. Some cancer patients suffer combined defects from surgery in adjacent tissues such as cheeks, maxillary sinuses, nose, and orbits. These defects usually require cosmetic and functional coverage so that the patient can speak and be a fully social person. A better quality of life is thus expected in patients who have received OI for the treatment of cancer and have persistent side effects from their tumor treatment. However, based on our knowledge of the problems that can arise during the OI procedure, it is the author's strong recommendation that the rehabilitation of irradiated patients should be performed at clinics and institutions that are experienced in treating cancer patients. It should not be part of the general dentist's practice.

Are There Any General Drawbacks From Rehabilitating Cancer Patients According to the OI Concept?

RECURRENCE

When rehabilitating a cancer patient, the risk for tumor recurrence or distant metastases exists. Therefore, many clinicians wait a certain time after cancer treatment to detect possible recurrences. The appropriate surveillance time interval between resection and placement of implants is still controversial. In our clinical material, representing more than 100 cancer patients followed since 1979, a high number of cancer patients have survived their disease and are alive and successfully rehabilitated with the OI concept.[10] Mean survival time for those cancer patients still alive today is 16 years, compared with 10 years mean survival time for those who have died. Because of the long expected survival of cancer patients, we are therefore committed to rehabilitating them according to the OI concept. On the other hand, we must plan for a rehabilitation that will last for at least 10 to 20 years. Therefore, implant survival is of great importance in this respect.

TUMOR TYPE AND TUMOR SURGERY

A vast variety of cancers can occur in the head and neck region. The size and location of tumor might differ, so each patient would need quite different rehabilitation procedures including bone grafts, bone containing flaps and soft tissue flaps in conjunction with OI surgery. The rehabilitation must therefore be individualized for the specific patient. The management of these patients is complex and should occur within a team setting. In our implant unit at the Department of Otolaryngology, Head and Neck Surgery (Göteborg University, Gothenburg, Sweden), we have been working very closely in a team consisting of an oral radiologist, oral surgeon, prosthodontist, maxillofacial surgeon, ear nose and throat surgeon, plastic surgeon, and anaplastologist to plan and perform the variety of required procedures. When needed, other specialists such as speech therapists, dieticians, and physiotherapists have been consulted before treatment.

In our files of patients treated during the last 25 years, we have found no factor related to specific drawbacks for the OI-concept regarding tumor type, size, stage, local nodes, or metastasis. Likewise, no specific tumor surgery factor, such as local resections or neck dissection, was related to specific problems encountered with the OI concept.[10] When the implant team and cancer team work closely together, optimal planning for the rehabilitation is achieved. For example, questions such as: can bone necessary for OI implants in the tumor cavity be saved, and can implants be installed at the time of tumor surgery, can be answered before surgery. One must also be aware that there are specific cancer patients with such complicated defects, with such poor tissue quality and other negative contributing factors, that using osseointegration might be impossible. Other solutions must be sought for those patients.

GENDER, AGE

We have found no evidence in our files that implant survival or complications differ between female and male cancer patients. This holds true even in those cases where osteoporosis may exist.[10] Likewise, we have found that advanced age is not a contraindication. In our active patient files we have 2 irradiated patients who are both 100 years old and are still satisfied implant wearers after more than 20 years.

SMOKING, ALCOHOL

Several studies have shown that implant failures are higher among smokers.[11] Because a high percentage of patients with cancers of the head and neck region are heavy smokers and alcohol abusers, restriction of these drugs in the planning procedure is recommended. Whether this statement is also valid for irradiated patients is unclear at present.[10]

What Factors From Radiotherapy Might Affect OI?

RADIOTHERAPY BEFORE/AFTER TUMOR SURGERY

There are different cancer therapy approaches throughout the world. In Sweden there is a long tradition of irradiating most cancer patients before tumor surgery. However, from the surgical point of view, it is advantageous to perform tumor surgery before irradiation. Healing of the surgical wound then proceeds more rapidly with fewer complications such as reduced soft tissue healing time, denuded bone, fistula formation, and infections.[12] If osseointegration is taking place at the same time as tumor surgery, the benefit of installing OI implants in nonirradiated bone is then achieved.

RADIOTHERAPY BEFORE/AFTER OI SURGERY

As a consequence of the practice standards in Sweden, the majority of our cancer patients have been irradiated before osseointegration surgery. Most of the discussion in this article is therefore related to our experience in the irradiated patient. The reverse situation (irradiation with implants already placed in the radiation field), however, may be encountered clinically. There are relatively few studies addressing outcomes of irradiating already-placed implants, but from our previous studies it appears that implant failures during a short-term follow-up were not particularly high.[13] However, according to newer data, implant failures have increased during a longer follow-up.[10] This phenomenon, that implant failures in irradiated bone increase with longer follow-up time, makes it important to define the follow-up time of each study when discussing benefits and drawbacks from OI in irradiated bone. Reporting success with only 2 to 3 years follow-up may give a false impression that OI surgery in irradiated bone is simple and straightforward.

IRRADIATION DOSE

From the available literature, it seems some authors have recommended that OI surgery is safe in patients who have been irradiated at doses below 50 to 55 Gy.[14-16] By defining this selection criterium, no protective measures were found necessary. On the other hand, patients irradiated above 55 Gy would not be rehabilitated with OI implants. That would exclude the majority of cancer patients at our institution from rehabilitation. From an ethical standpoint, it is questionable to leave such a large portion of cancer patients without rehabilitation. We have therefore set out to rehabilitate all patients despite the dose of radiotherapy. Consequently, some patients have been rehabilitated at extremely high doses (>120 Gy). Implant survival at this high dosage has been very low, and the risk for osteoradionecrosis (ORN) is high. Nevertheless, it is important to define the limitations for the OI concept.

The dose Gy (previously termed rad) is furthermore misleading because this denomination does not account for the number of fractions given. If the term "cumulative radiation effect" is applied and calculated as (Total time of treatment/Number of treatments)$^{-0.11}$ × Dose per treatment × Number of treatments$^{0.65}$ [17], a more reliable estimation of irradiation dose can be obtained. Data then show that below a cumulative radiation effect of 18 to 20, relatively few implants will fail (corresponding to 48 to 65 Gy given as standard fractionation radiotherapy), whereas implant failures increase at higher doses. In our experience, at doses above cumulative radiation effect 40 (120 Gy, standard fractionation), all implants have failed.[3,10,18,19]

Implants in the same jaw might have been exposed to different irradiation doses. For example, a patient treated for a tonsillar carcinoma will have a higher irradiation dose in the posterior mandible than in the anterior portion. It is therefore necessary to calculate irradiation dose at each implant site before surgery to determine the optimum installation site for implants. Newer forms of focused radiation (such as intensity modulated radiation therapy) produce reverse planned non-homogenous 3-dimensional treatment volumes that delivered increased dose. The consequence is that implants installed in the same region might fall into highly differing radiation dose gradients. Patients that have received irradiation to other parts of the body, not including the craniofacial region, would have an expected implant survival in the craniofacial region comparable to nonirradiated patients. No specific precautions would be needed in these patients.

TYPE OF IRRADIATION SOURCE: FRACTIONATION

Most studies published on osseointegration in irradiated tissues have used ^{60}Co as the source for radiotherapy since it is still the most commonly used type of radiation. Thus, the data discussed in this section are mainly related to the effects from ^{60}Co therapy. Other radiation sources are available, and have been used, the effects of which remain uncertain at present. Other fractionation schemes, such as twice per day treatment, have been used and calculated as cumulative radiation effect.[10] With the development of higher energy radiotherapy protocols and superfractionation, it is likely that in time other effects on osseointegration will be identified. Brachytherapy is also a part of modern oncologic treatment, and its effect on bone tissues is different than external beam radiotherapy. Again, too little is known about the effect on osseointegration today. Further studies will have to be performed addressing these questions.

TIME FROM RADIOTHERAPY TO OI SURGERY

This factor has been shown to affect osseointegration.[3,12,18] Contrary to what one would believe, irradiation from decades ago seems to have a more negative effect on implant survival than recently administered radiotherapy. This may be attributed to earlier forms of radiation therapy being of lower energy; whereas today, higher energy forms of radiation are typically delivered. A further explanation could be the progressive endarteritis taking place in the irradiated bone, which is known to increase with time.[20]

Patients and their dentists seem to forget about irradiation a long time ago. Sometimes it is argued that no specific precautions need to be undertaken just because radiotherapy took place such a long time ago. Contrary to this, these patients need to be handled with the utmost care. In relation to the discussion in this article, these patients should be handled at institutions/clinics in the practice of treating cancer patients. Thorough planning, careful surgery, and HBO are required.

ADJUVANT CHEMOTHERAPY

Many oncologic treatments use chemotherapy as part of cancer treatment, which is most commonly a combination of radiation therapy and chemotherapy. Whether chemotherapy (in most cases a combination of 5-fluorouracil/cisplatin/methotrexate/bleomycine/vincristine) affects osseointegration is less well documented. In a retrospective investigation, it was shown that chemotherapy given near the time of OI surgery had a negative effect on implant survival.[21] Implant survival was affected less when chemotherapy was administered some time before or within 1 month after OI surgery. In later studies that included a higher number of implants, and followed patients for a longer period of time, it seemed as if chemotherapy in longer-term perspective has a negative effect on osseointegration, comparable to irradiation.[10]

BONE BED, GRAFTED BONE

The quality of the bone bed appears to be of utmost importance for a successful result of OI surgery. If the bone has a reduced capacity for healing after irradiation it is expected that it will integrate the implants less effectively. Grafted bone that will replace bone in an irradiation field will act more like the nonirradiated bone.[16,22-24] Therefore, the discussion in this article is restricted to bone that has been irradiated and not replaced by grafts.

Implant Factors

LENGTH

Several reports have shown a higher incidence of implant failures when using short implants.[25] Failure rates for short implants are increased when they are placed into irradiated bone.[10,18,26] Very short (3 to 7 mm) implants were particularly prone to failure.[10] One would thus recommend using the longest possible implants to optimize bicortical anchorage.

IMPLANT DESIGN AND SURFACE

The author's experience is limited to screw-shaped implants with machined surfaces that have been used consecutively and consequently where chosen for our studies. It is difficult to judge from the literature if other implant designs would perform better in the irradiated tissue. There is recent data showing that a relatively rougher surface might improve osseointegration.[25] Whether this is also a benefit for the irradiated patient is not known.

ABUTMENTS

Loading in the long axis of implants has been shown to distribute forces optimally. In tumor cavities, however, this has not always been possible to obtain. So-called console abutments are used in areas of limited space for facial prosthetics. Their distribution of load often leads to cantilever effects that might be negative for long-term survival of the implants (see below).

PROSTHESIS

Cancer patients may have defects from tumor surgery that extend well beyond loss of teeth. The implant-supported prosthesis must therefore be planned, designed, and constructed for each patient. At our institution, in several cases, parts of the jawbone and soft tissues needed to be replaced by alloplastic material. In these situations, defects of the lips, cheeks, or maxilla are replaced as part of the treatment. Such combined intraoral and extraoral cases are not common at our institution.

RETENTION

Implant survival in irradiated bone has been shown to depend on retention of the prosthesis to a high degree.[10,12,18] The highest implant survival was noted for fixed-retention prostheses. The lowest implant survival was seen for facial prostheses anchored on the combination of clips and magnets on cantilever extensions.[18] In the oral cavity, overdentures have been shown to be associated with higher implant failures.[26,27]

SOFT TISSUE

Eckert et al[28] noted that significant problems in patients with irradiated implants were related to the soft tissues. Gingivitis was more common in these patients than 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.[29] August et al,[30] 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[31] reported an increased degree of the gingivitis in irradiated patients. This was mainly related to poor oral hygiene. Necrosis of soft tissues in the floor of the mouth was observed in 5.2% of patients.[2]

RISK FOR ORN IN RELATION TO IMPLANT SURGERY

It appears that the risk of ORN is the primary reason that implant therapy is not commonly pursued in previously irradiated patients. The incidence of this severe complication may be underreported in the international literature. Some authors refuse to use implant placement, considering the risk for ORN as overshadowing the possible benefit of providing prosthetic restoration.[32] Several groups report incidental cases developing ORN.[2,3,31,33] In their report from 1998, Wagner et al[33] described 1 (1.6%) case of ORN with related failure of 5 implants. The authors were of the opinion that this rate of incidence is below an estimated risk of 5% reported in other studies. Esser and Wagner[2] reported 2 cases (3.4%) of ORN development related to implant surgery. In our material, ORN has appeared in those patients irradiated with extremely high doses after combined pre- and postoperative radiotherapy.[10] Minimum surgical trauma to the mandible is known to cause ORN in the time period close to radiotherapy.[20] Such trauma may typically be associated with extraction or surgery for an OI.

So, Why Use HBO?

Based on the discussion above, in 1988, we made the choice to use HBO as part of the treatment protocol for irradiated implant patients. The reason for choosing this modality was that it was at that time the only known treatment available that could be used clinically and that was known to counteract the negative effects of irradiation. As we were beginning to treat patients at higher risk, such as those who had been exposed to high-dose radiation therapy, our main goal was to reduce implant failure rates that were considered by our group to be unacceptably high. Our choice was based on the scientific knowledge of HBO's effects on irradiated tissues. The exact mechanism that oxygen exerts at the subcellular level remains to be explored. Recent data shows that oxygen under hyperbaric conditions acts synergistically with several growth factors, which stimulate bone growth and turnover, and other studies show that oxygen can act as a growth factor by itself.[34]

For a detailed description of the mechanisms and performance of HBO, the reader is referred to a review article by Kindwall et al.[35] A detailed discussion of HBO effects in relation to osseointegration has also been published.[36,37] Principally, HBO has been shown to improve angiogenesis,[38,39] and bone metabolism and bone turnover.[40,41] In relation to radiotherapy, HBO can thus counteract some of the negative effects from irradiation and actually act as a stimulator of osseointegration.[40]

EXPERIMENTAL STUDIES

Several studies have been performed to analyze the effects from radiotherapy in the bone surrounding OI implants, and the effects from HBO. For a detailed description of the experimental data and discussion, the reader is referred to references 34, 40, and 42. Principally, irradiation will have an effect on the bone-forming cells (osteoblasts and osteocytes) that will reduce their capacity for new bone synthesis. The principal resorptive cells in bone, the osteoclasts, can migrate into the bone after radiotherapy and continue bone resorption. With time, there might be an imbalance where resorption exceeds formation. Radiotherapy will also reduce the number of capillaries in the bone because of a progressive endarteritis. With increasing time, a hypovascular bone bed might occur that is less well adapted to host OI implants.

In the above-cited studies, HBO has been shown to increase formation of new formed bone, increase the bone turnover, and increase the vascular supply to the irradiated bone. Further, the force necessary to unscrew the implants (removal torque) has been shown to be reduced by irradiation, but increased with HBO.[43] Interestingly, the recorded effects are measurable not only in experimental animals but also clinically in patients.[42] Thus, there is comprehensive experimental evidence that supports the use of HBO to reduce irradiation-induced effects and to increase osseointegration.

CLINICAL STUDIES

Today, there are more than 100 scientific publications dealing with OIs in irradiated tissues. In an attempt to summarize the results on implant survival, an analysis of the data available in 2001 was performed.[42] The material comprised reports from 4,392 OIs. Implant survival was calculated from the different studies and plotted as a Kaplan-Meier function. Different regions of insertion were separated from each other, as was material from irradiated, nonirradiated, and HBO-treated patients.[42] With increasing follow-up time, all regions showed an increasing implant failure after irradiation that was higher when compared with nonirradiated patients. HBO improved implant survival in all regions that were subjected to radiation therapy. It should also be appreciated that because of its compact structure, the mandible is a relatively radioresistant bone. In the irradiated mandible, implant survival will remain high for many years, but with longer follow-up times, implant failures appear and after 10 years, failures are high (more than 50%). Compared to the mandible, the maxilla is less radioresistant and failures appear after 5 years. By 10 years, as in the mandible, implant failures are high.[42]

A multivariate analysis was performed on 107 irradiated patients who altogether had 631 OI implants installed in different regions. Irradiation increased the failure of implants in all regions compared with nonirradiated controls. HBO improved implant survival in all regions (except temporal-parietal) with significance at the $P < .001$ level, using the Wilcoxon-Rank test.[10] Implants in the oral maxilla performed better than the average implant site. The implant sites that performed poorest were the frontal bone, zygoma, mandible, and nasal maxilla.[10]

Advocates against the use of adjunctive HBO for irradiated implant patients usually argue that there are no double-blind, controlled clinical studies proving its efficacy.[44] If one considers such a study to be level 1B evidence according to the American Heart Association (AHA), similar to the National Cancer Institute's (NCI) level 1ii,[45] as the ideal study, then that is true. However, today there is 1 AHA level 1C study discussed above.[42] Furthermore, there are 4 AHA level 3 NCI 2 studies conducted on the topic.[3,18,29,46] Additionally, there are 38 clinical studies published at levels AHA 5 and NCI 3ii that show an increased risk for implant failure in irradiated patients compared with nonirradiated controls. There are also 9 clinical studies evaluating the possibility that HBO prevents implant failure at AHA levels 3 to 5 and NCI levels 2 to 3ii. These show a lower risk for implant failure after adjuvant HBO, equal to nonirradiated tissues. If one correlates these studies to each other, the risk for implant failure without HBO prevention would be 734 implants out of 3,431 (21.4%; variance 0 to 100%); and with HBO prevention 147 out of 1,085 implants (13.5%; variance 0 to 16.8%). However, encouraging results are already reported in the scientific literature; the present author strongly supports randomized, controlled studies. Currently, there is a single-blinded, controlled multicenter study being conducted and the goal of the study is to evaluate OI implant failures in irradiated bone. The study further aims to evaluate the effects of HBO on implant survival. Colleagues with an interest in the study are hereby invited to participate. Information and enrollment can be obtained at http://www.oxynet.org/ProtocolsIndex.htm.

In 2 articles published in 1997 by Larsen[47] (as protagonist) and Keller[48] (as antagonist) in the *Journal of Oral and Maxillofacial Surgery*, these authors debated the use of HBO for OI implants in irradiated mandibles. At that time, there were only 19 publications available addressing this question. Despite the authors referring to essentially the same publications, they came to different conclusions regarding the actual failure rate in irradiated mandibles. The same problem can also be revealed in the above-cited studies that report failures of implants from 0% to 100%. These differences in reported treatment outcomes may be attributed mainly to the difference in the number of implants installed and length of time the implants had been followed. The higher the number of implants included in a study and the longer time they are followed, the more valid the statistics will be.

COST FOR PROCEDURE - WHO PAYS?

Another argument for not using HBO is the high cost of the procedure. If the patient has to pay for the whole procedure without support from the health care system, this will of course be of substantial importance in the decision. The cost for HBO in relation to the OI procedure varies greatly in different countries. In Sweden, the cost for HBO would be approximately 10% of a complete fixed implant-supported prosthesis in the upper and lower jaw. The cost for HBO and for the OI procedure is fully covered by the Swedish health care system when rehabilitation involves cancer patients. In nonirradiated non-cancer cases, patients pay most of the OI procedure (no HBO necessary).

The cost for HBO must also be placed in relation to avoidance of complications. For example, the cost for 30 HBO treatments (implant protocol) is equivalent to just 1 day at an intensive care unit at the Sahlgrenska University Hospital (Gothenberg, Sweden). The cost for the treatment of just 1 patient with ORN is equivalent to the treatment of the HBO protocol for 40 implant patients at the same hospital.

SAFETY AND SIDE EFFECTS

HBO is regulated by strict standards in each country. Side effects from HBO are mostly related to difficulties in equalizing the pressure in the middle ears. This can be overcome by transmyringeal grommets. Transitional myopia is described by 30% of patients on long-term treatment. Vision invariably returns to normal within weeks after completion of therapy. In centers where HBO is practiced, long-term evaluations show the procedure to be safe and comfortable for the patients with very few side effects. There are hyperbaric chambers available in all countries where OI surgery is performed. A list of chamber availability can be obtained from http://uhms.org (in the US) and http://www.oxynet.org (Europe).

In conclusion, there is sufficient scientific evidence to show a higher failure rate of OI implants in irradiated patients. This high failure rate can be reduced by adjunctive HBO. Important aspects to consider when comparing outcomes with or without HBO are: region of installation, irradiation dose and timing, adjuvant chemotherapy, quality of the bone bed, implant surgery, implant length and design, prosthetic retention, soft tissue, and risk for ORN. It is important that irradiated cancer patients who require OI implants be treated at institutions/clinics that have experience in the treatment of such patients.[7]

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