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Radiotherapy and Dental Implant Applications in Patients with Head and Neck Cancer

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Abstract: Head and neck cancers are aggressive malignancies, with surgery, radiotherapy, and chemoradiotherapy being current therapeutic options. Multiple tooth loss due to rampant caries, ineffective oral hygiene or care, xerostomia, and changes in saliva content are among the common side effects of radiotherapy. Multiple tooth loss will significantly reduce the quality of life by negatively affecting oral activities such as eating, drinking, speaking, chewing, and grinding, as well as social interactions and psychological well-being. Because less saliva is produced after radiotherapy, the use of conventional prostheses

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would be difficult for various reasons. As a result, dental implant-supported prostheses have gained popularity as a reliable oral rehabilitation option for patients who have received radiotherapy. However, the potential risks of dental implant applications and the appropriate scheduling for patients who have undergone or will undergo radiation therapy remain a source of concern. In light of this, the purpose of this chapter is to present a multidisciplinary perspective on dental implant applications, ideal application timing, and considerations in patients with head and neck cancer from the perspectives of radiation oncology and dentistry.

Keywords: dental implant; head and neck cancer; osseointegration; osteoradionecrosis; radiotherapy

INTRODUCTION

The three cornerstones of palliative or curative treatment for head and neck cancers (HNC), which account for 3% of all malignant tumors (1), are surgery, radiation therapy (RT), and chemotherapy. The major salivary glands are situated in the lateral face and submandibular/submental areas and are typically within or close to the target volume of RT for HNC (2). The salivary glands, the composition of the saliva, and the lining of the mouth may undergo significant changes due to RT. Mucosal ulcerations, fissures, mouth sores, dental infections, tooth decay, and tooth loss can result from these pathological changes (3, 4). Furthermore, these individuals may experience incapacitating osteoradionecrosis, jawbone deformities, and related cosmetic issues due to RT and/or ablative surgery (5).

Due to significant advances in treatment modalities and standard medical care in the past 20 years, the survival rate for HNC patients has increased significantly (6). However, with longer life expectancies for HNC patients, it is more important than ever to manage both the short- and long-term side effects of RT and to improve the quality of life of patients (7). One of the most important factors that affect the quality of life of this group of life patients is how well they can manage the oral side effects of oncological therapy, such as chewing, biting, swallowing, speaking, tooth loss, and accompanying facial aesthetic changes (8). Despite some limitations in some patients, oral rehabilitation with removable or fixed prostheses is a common practice used to mitigate these adverse effects and maintain good oral functions.

Implant-supported dentures are contemporary and practical solutions for irradiated HNC patients who cannot wear conventional dentures due to RT side effects, including dry mouth, fragile mucosa, osteoradionecrosis, and damaged anatomy (3, 9, 10). There is no consensus on the safety of dental implant procedures and the associated clinical recommendations. In patients who have received RT for HNC, there is also an ongoing uncertainty regarding dental implant planning, placement procedures, and placement timing relative to RT (11). The purpose of this chapter is to provide a comprehensive review of dental implant procedures, their intricacies, and the ideal timing for the placement of dental implants in HNC patients treated with RT.

THE IMPACT OF RADIOTHERAPY ON OSSEOINTEGRATION AND SURVIVAL OF DENTAL IMPLANTS IN HEAD AND NECK CANCER PATIENTS

Osteoradionecrosis (ORN), which develops when the jaw is exposed to ionizing radiation, is more likely to occur after dental implant implantation, making this restorative option problematic in this population (12–15). Dental implants can be placed for oral rehabilitation before RT, following dental extractions during ablative surgery, or at any time after the completion of RT. There are two distinct study protocols that describe oral rehabilitation with dental implants in patients with HNC in the literature. The first group discusses the impact of immediate versus delayed dental implant placement on implant success or survival rates, while the second group discusses the influence of RT in immediately placed dental implants (12). In addition to concerns with the dental implant implantation method, implant success and function are critical. Albrektsson et al. presented implant success criteria based on successful osseointegration and implant survival (16). Since then, other experts have added new standards to gauge the success of dental implants, including continuous stability of the prosthesis, radiographic bone loss, and absence of peri-implant infection (17, 18).

Anchoring of the implant in the bone, known as osseointegration (19–21), is essential for implant stability and is viewed as a requirement for implant loading and long-term clinical success (22, 23). Local and systemic factors can affect osseointegration and cause early or delayed implant failures (24–27). Local factors include implant design, dental implant diameter and length, surface structure, quantity and quality of bone, history of periodontitis, surgical technique, RT, and timing of implant placement. Systemic factors that can affect osseointegration include osteoporosis, collagen vascular disease, and diabetes mellitus (28).

Before the implant is biologically fixed through ongoing bone apposition and remodeling, the alveolar bone and implant body first lock together during osseointegration processes (29). Any preexisting bone matrix lesion triggers direct bone healing during the osseointegration process. When the matrix comes into contact with extracellular fluid, non-collagenous proteins and growth factors are produced, promoting bone healing (30). On radiographs, evidence of a good link between the implant and the bone shows that osseointegration has occurred and that the implant will be stable and survive a reasonable period of time (22).

RT operates by generating single- or double-strand breaks in the deoxyribonucleic acid (DNA) of irradiated healthy or malignant cells. Understanding the biological impacts of ionizing radiation on the cell cycle will help us better understand how it works (31). Osteocytes become devitalized at high doses (70 Gy), resulting in connective tissue fibrosis, while neoplastic cells, osteoblasts, and bone marrow cells that divide quickly are susceptible to cell death at relatively low doses (50 Gy) of radiation (32). Cellular death occurs at the tissue level at variable rates and for varying periods, with immediate and long-term consequences. Naturally, these consequences hinder the normal healing process after oral surgical operations and must be considered when treating individuals who have undergone RT (31). The primary long-term effect of RT is a vascular change that decreases bone nutrition and causes an osteoporotic-like condition that could shorten the life expectancy of dental implants (33).

Another problem is that the most severe chronic RT complication, ORN, is more likely to affect bones than soft tissues, which are more likely to dehisce (31). Increased endarteritis coupled with decreased microcirculation, which results in hypoxic, hypovascular, and hypocellular bone, is believed to be the root cause of ORN (34). In addition to the periosteum above fibrosing, osteoblasts, osteoblasts, and osteocytes sustain irreparable damage (34). Natural healing processes are inhibited by tissue hypoxia, which exposes necrotic bone (35, 36). Therefore, irradiated bone may jeopardize implant effectiveness and/or result in ORN, which can be disastrous and hamper the patient's ability to maintain oral rehabilitation and function.

In essence, a dental implant requires a defect in the jawbone, which is achieved by drilling a hole into the jawbone during placement. Direct bone healing also occurs in such defects, in addition to primary fracture healing and osseointegration being triggered by any lesion of the pre-existing bone matrix (22). When the bone matrix is exposed to extracellular fluid, growth factors and non-collagenous proteins are released, which stimulate bone repair (30). Osseointegration is a biologically predetermined process that goes through three stages after activation: incorporation through woven bone formation, adaptation of bone mass to load (lamellar and parallel fibered bone deposition), and remodeling of the bone structure. The RT-induced inflammatory response, vascular occlusion by inflammatory mediators, and activation of fibrosis by tissue hypoxia and fibrinolytic agents all preclude the formation of the bone implant anchor around the implant (37, 32). Additionally, non-healing bone necrosis during the ORN development process can trigger a series of unfavorable incidents that cause decreased implant stability and even implant loss (37). In an in vivo study, Soares et al. investigated the biomechanical and morphological changes caused by ionizing radiation in the bone tissue surrounding 20 rabbit dental implants (38). The choice of rabbits was made to provide an excellent short-term analysis of the osseointegration process because of their similar Haversian systems to human beings and a three-fold faster rate of bone turnover. The rabbits were randomized into two groups: those who received RT and those who did not; the RT group received a single dose of 30 Gy of RT two weeks after implant placement. Four weeks after implant surgery, animals were sacrificed and bone were taken. It was decided to mimic the early stages of osseointegration by delaying the sacrifice period by four weeks, which forms the basis for current human treatment protocols. Cortical cortex volume, cortex thickness, and porosity, which define the integrity and quality of cortical bone, were among the microCT data that were analyzed in this study. The authors concluded that impaired vascularization and osteoblast activity may have contributed to the decrease in bone mass found in irradiated groups of bone tissue near and far from the implant (Figure 1).

There is no consensus on the lowest threshold doses that do not alter implant survival rates, despite reports suggesting a detrimental effect of high doses of radiation on osseointegration physiology (39). According to some research, radiation doses greater than 40 Gy or 50 Gy may impede bone repair, putting implant osseointegration at risk (40, 41). The literature review by Javed and colleagues suggested that osseointegration was probably not affected by rates up to doses of up to 65 Gy, as evidenced by 100% implant survival rates (42). According to the findings of this study, some radiation doses between 40 Gy and 65 Gy may be cited as proof that such RT doses have no adverse effects on osseointegration. Contrary to what was assumed, Cao and Weischer reported that after a median follow-up of two years, the implant survival rate was significantly lower in patients with irradiated oral

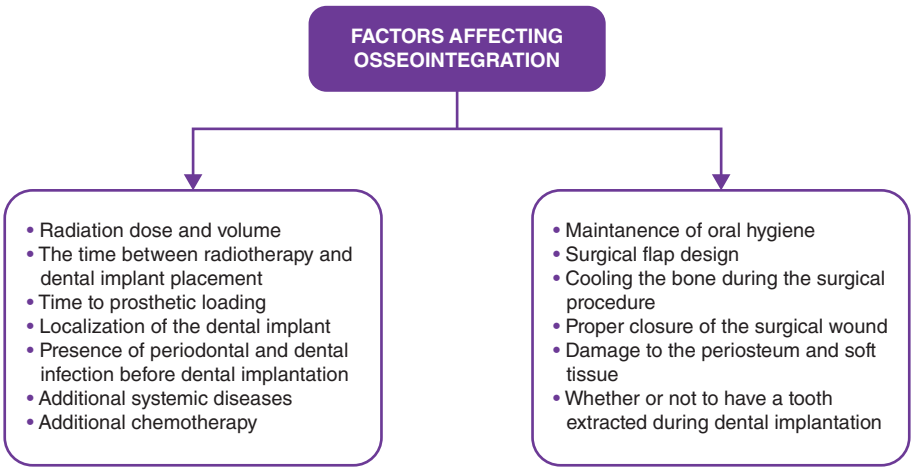

Figure 1. Factors that affect osseointegration.

cavity cancer after a dose range of 36 to 76 Gy than in patients without irradiation (43). In their study of 116 dental implants that were placed on native bones and given 50 to 70 Gy, Klein et al. (44) found that the 5-year implant survival rates were 77.5% and 90.9% for implant zones that received more than 50 Gy and less than 50 Gy, respectively. This outcome can be explained by the decline in blood supply and nutrition caused by the long-lasting and gradually worsening tissue effects of RT over time (36). To support this claim, Nack et al. reported implant survival rates of 92%, 80%, and 75.2% at 1, 3, and 5 years, respectively, after 72 Gy RT in patients with HNC patients who had implants placed approximately 6 months after RT (45). Due to the ongoing debate over the most secure time to place implants, patients who have received RT should always be informed of the potential complications of implant surgery and should formally consent to them.

Researchers generally use the total RT dosage delivered to the primary tumor as a baseline to analyze the prevalence of ORN (46), as well as the survival of dental survival implants (36, 45). However, the key factors that define the real risk of ORN and, consequently, the success of osseointegration are the mean, median and Vx (mandibular volume receiving X Gy or more) (47). Although total RT doses administered to the tumor may indirectly influence ORN development (48), the planning of target volumes and jaw doses may differ dramatically between tumor types. Li et al. (49) evaluated the survival of 151 implants in 58 patients with HNC who received RT using this knowledge and found that the median dose delivered to the tumor was 62.4 Gy, while the average dose delivered to the implant bed was 40 Gy. Despite the absence of volumetric dosimetry data, the authors concluded that the quantity of bone resorption around implants that received > 40 Gy was significantly greater than the amount of bone resorption around implants that received < 40 Gy. These results underscore the importance of volumetric dose exposures and point out that the dose prescribed to the tumor site alone may not be sufficient to assess the risks of ORN or dental implant loss and will not accurately reflect the true prevalence of these complications.

Although exact mechanisms are difficult to describe, the deterministic effects of radiation on irradiated tissues may help to explain the correlation between increased implant failure rates and high radiation doses: the higher the radiation dose, the more frequently and intense tissue damage occurs. Without a doubt, exposure to ionizing radiation damages vascular endothelial cells in a dose-dependent manner, followed by obliteration of blood vessels and restriction of the perfusion of osteogenic cells, especially at sites where bones grow and form (50, 51). Because they are more radiosensitive than other bone cells, osteoblasts are the first to experience apoptotic cell death after direct tissue damage or hypoxic/malnourished conditions caused by ionizing radiation (52). Furthermore, it is suggested RT changes collagen modulation, which in turn slows the mineralization process and contributes to implant failure (38). Ionizing radiation may also have an effect on osteoblast activity by impeding normal deposition and the production of crystals of hydroxyapatite from the inorganic matrix (53, 54). This suggestion is supported by the fact that irradiation generates free radicals through the radiolysis of water molecules, damages collagen molecules, and hinders fibrillary sliding movements, all of which interfere with the molecular configuration for the biomineralization process to occur (53–55).

Based on the interpretation of these pathophysiological processes and the findings of previous investigations, it is plausible to hypothesize that implant lifespan and radiation dose exposed at implant placement site are related. Although the precise dose-response connection is uncertain, doses greater than 40–50 Gy appear to be associated with higher implant failure than their lower dose equivalents. However, it is important to note that additional research is required that examines dose-volume-response correlations to identify the critical RT doses or the volume of the implant placement site that receives doses above a crucial threshold value that can precisely predict implant failures in this patient population. To avoid unnecessary implant losses in these groups of patients, we recommend delineating the actual or potential implant zones separately and keeping radiation doses as low as possible at these sites until the results of the study are available.

THE DILEMMA OF OPTIMAL TIME OF DENTAL IMPLANT PLACEMENT IN HEAD AND NECK CANCER PATIENTS

Although ORN is an infrequent late-onset complication of RT, patients who have undergone dental implant surgery or had wisdom teeth removed may experience this severe complication more frequently (56). Due to the invasive nature of dental implant surgery, jawbone trauma of varying degrees will unavoidably occur in such patients (57). After early (4 months after RT) or late (4 months or more after RT) trauma, if the injury caused by the trauma cannot heal, ORN develops once cell death is apparent (37). This is due to the time-dependent increased vulnerability of bone cells and their soft tissue counterparts to mitotic death and necrosis after RT. Therefore, RT patients are at risk of developing long-term radiation-related complications that could be triggered by infection or surgery (37, 58, 59). Whenever possible, all invasive surgical procedure, including dental extractions and the placement of dental implants, should be avoided with meticulous treatment planning because the risk of ORN persists for the duration of the patient's remaining life (60).

Although 6–12 months after irradiation is suggested in the literature as a relatively safe window for implant placement, the best time to implant placement has not yet been scientifically proven (42, 60). On the contrary, some authors support implant placement after tumor surgery and claim that this schedule is advantageous because initial implant healing (osseointegration) takes place prior to irradiation, increasing the chance of implant sustainability and lowering ORN risk (31, 42, 60, 61). Pitorro et al. evaluated the survival rate of implants placed before and after RT or without it in their insightful systematic review of 16 studies involving 3,445 HNC patients (62). The survival rates for implants placed after RT, before RT, and without RT were reported to be 80% to 100%, 89.4% to 97% and 92.2% to 100%, respectively. These findings led the authors to conclude that the survival rates of dental implants placed before and after RT were high and nearly on par with those of implants placed without RT. In a related systematic review, Collela et al. discovered statistically equivalent failure rates for implants inserted after RT compared to those inserted before RT (3.2% and 5.4%) and noted that implant failures occurred 36 months after RT (63). This result supports Delanian's theory that radiation causes bone tissue to undergo fibrosis, as indicated by the implant failure rate. Reasonably, if the implant is placed in > 8 months after RT, the wound could heal by fibrosis formation due to vascular obliteration and poor blood flow in the affected bone, which could lead to ORN and implant loss (36). Therefore, it is reasonable to assume that the longer the implantation procedure is postponed after RT, the higher the risk of loss of the dental implant.

Kim et al. stated that when they first developed implant-based dental rehabilitation in oral cancer patients, implants were frequently placed after oncological treatment (64). However, it required additional surgery for patients who have been exposed to radiation and receiving antimicrobial prophylaxis. This causes additional therapeutic stress for older patients, many of whom have multiple comorbid conditions. Although they may greatly benefit from an implant-supported prosthesis, patients who receive implant placement in the post-RT phase are much less likely to undergo surgical procedures because they are already burdened by the side effects. In such cases, dental implants could be used as an alternative during tumor surgery (65). This may prevent additional surgery and save a lot of time as the majority of osseointegration occurs during the healing phase before RT. As an alternative, preplanned dental implants can be placed during tumour surgery in such patients (65). Since osseointegration occurs primarily during the waiting period before RT, this treatment sequence may prevent additional surgery and related stress and save time.

Unfortunately, there are no clear guidelines or widely agreed-upon timings for beginning oral rehabilitation with dental implants in HNC patients, and there is controversy about how RT affects the osseointegration process and implant survival rates. Furthermore, making matters worse, the majority of published systematic reviews only looked at the timing of implant placement after RT (66–68). Recent studies have found that the possibility that dental implant placement may become more challenging over time due to the steadily declining bone healing capacity after RT outweighs the evidence currently available regarding the best time to implant placement in HNC patients (69–71). It is time to call for more research on these debilitating issues to find solutions and improve the quality of life of HNC patients, as we anticipate longer survival times soon (Table 1).

TABLE 1 **Select summary of current views on radiotherapy and dental implant placement, and timing of placement in head and neck cancer patients**

Author/year	Type of Study	Conclusion
Anderson et al. (31) 2013	Review article	• The dental health provider must be familiar with the potential risks and complications relevant to implant therapy in the cancer-treated patient to provide safe and predictable treatment. • Guidelines for dental implants are needed
Jawed et al. (42) 2010	Review article	• Dental implants can osseointegrate and remain functionally stable in patients who have undergone radiotherapy • Patients should be informed and consented to in advance about complications associated with implant treatment following irradiation
Pittorro et al. (62) 2022	Review article	• Dental implants placed before and after radiation therapy had high survival rates, similar to those placed without radiation therapy, which helps improve the condition of life of patients with head and neck cancer
Colella et al. (63) 2007	Review article	• There was a similar failure rate for implants placed after RT and those placed before RT (3.2% vs 5.4%, respectively).
Kim et al. (64) 2011	Review article	• Dental implants can positively impact patient quality of life with improved function and cosmetics. • Dental implants could allow patients to minimize the consequences, limitations, and stigma of ablative cancer surgery.
Schoen et al. (65) 2004	Review article	• It is better to refrain from implant placement during ablative surgery when proper implant positioning is doubted.
Petrovic et al. (66) 2018	Review article	• Dental implants provide the best dental rehabilitation for patients who have lost teeth due to tumors or treatment-related factors. • Identifying suitable candidates for immediate or delayed dental implants minimizes postoperative complications. • The implantation time should be determined according to the patient's clinical condition.
Claudy et al. (67) 2015	Review article	• Implant placement in bone less than 12 months after radiation therapy may increase the risk of failure
Nooh (68) 2013	Review article	• The timing of radiation therapy in relation to dental implant placement (before and after implant placement) does not have a significant impact on dental implant survival.
Alberga et al. (70) 2021	Review article	• A combination of tumor surgery and implant placement in the native mandibular bone should be provided as standard care.

CONSIDERATIONS FOR DENTAL IMPLANT SURGERY IN PATIENTS WITH HEAD AND NECK CANCER

Dental implants are a useful tool after oncologic treatment of the head and neck region, according to several studies that have evaluated the indication of implant-supported rehabilitations in irradiated patients. This conclusion is reached despite the fact that there are some risk factors that must be taken into account to prevent complications, such as age, sex, total radiation dose, the amount of time between the end of RT and implant surgery, and the RT technique (73). One of the most severe side effects that physicians encounter in patients who have undergone radiation treatment for HNC is ORN (6). Early research claimed that ORN was caused by high-dose radiation combined with injury and infection (72). Trauma is commonly caused by pre- or post-RT tooth extractions, dental implant placements, other invasive dental surgical interventions, tumor-related surgical manipulations, or mucosal injuries caused by a dental prosthesis (73). Because the alveolar ridge bone is one of the most sensitive bones to systemic changes in bone remodeling metabolism (74), surgical interventions to the jaws in HNC patients who have undergone RT should be performed as minimally traumatically as possible, because trauma is undeniably important in ORN formation (75). Although there have been numerous studies on lowering the risk of ORN after tooth extractions, there have been relatively few studies on the use of dental implants and there are no standards in place.

Because placing dental implants requires an invasive surgical procedure, specific safety precautions must be taken to reduce the risk of ORN by preventing post-procedure infection and promoting wound healing. The flap shape that is created during surgical intervention and dental implantation is crucial when it comes to tooth extractions in patients who have or will have RT. During such surgical procedures, excessive periosteal and vascular damage should be avoided to maintain bone nutrition. Only a flap, large enough to see the surgical wound, will help achieve this objective (76). Furthermore, primary closure of the surgical wound area can speed up the healing process (3). To allow adequate soft tissue healing, the implant procedure should be performed more than 14 days before the beginning of RT (11).

The surgeon must avoid excessive heat when preparing the osteotomy site with a drill or bur. Bone necrosis, which can result in the formation of fibrous tissue and possibly ORN (3, 77), can occur if the temperature of the bone at the implant osteotomy site increases above 43 °C. Delanien's theory (36) states that RT causes bone necrosis by triggering fibrotic activity in the bones and speculates that radiation-induced hypoxia may worsen the condition. Therefore, high heat exposure to bone during implant surgery may result in implant mobility, unsuccessful osseointegration, deterioration of bone healing, ORN, infection, and sequestration due to its additional contribution to the already ongoing fibrotic process. Several factors must be taken into account to avoid excessive heat generation. First, a low-speed motor should not exceed 40–50 rpm, and a high-speed motor should not exceed 2000 rpm. Second, when drilling the bone to prepare the implant site, irrigation with a sterile saline solution is required. Internal irrigation that cools the bur or drill bit is often preferred as part of this irrigation.

Irrigation keeps bone temperature below 43 ° C, reducing the risk of ORN by preventing the onset of a necrotic process (78).

According to Kanatas et al. (79), antibiotic prophylaxis before extraction is the most common attempt to prevent ORN, most likely because it is easy to administer and widely available. Hyperbaric oxygen (HBO), which is believed to induce fibroplasia and angiogenesis in hypoxic, hypocellular, and hypovascular tissue, has been suggested by some authors as a preventative measure for ORN after tooth extraction (37, 80, 81). However, its infrequent availability restricts its use in irradiated patients who require tooth extractions. As an alternative, Lyons et al. recommended the initiation of pentoxifylline and tocopherol a few weeks before extraction to prevent ORN. Although prevention strategies for ORN caused by tooth extraction are strongly urged, specific measures for dental implant applications have not yet been established. However, applying the strategies used for tooth extraction to implant applications may help reduce the risk of ORN, since both dental implant surgery and tooth extraction are invasive surgical procedures that require adequate bone healing.

Finally, another notable contributor to the development of ORN is periodontal health (82). According to Hessling et al. (83), peri-implantitis was caused by inadequately attached gingiva and bone loss in 182 (67%) of the 272 implants placed before RT. Additionally, they listed elements such as RT-induced peri-implantitis, a lack of adequate soft and hard tissue, muscle dysfunction, and xerostomia that are linked to implant failure. The authors added that hypoxia, poor blood supply, and RT-induced obliteration of the minor gingival vessel may all contribute to periimplantitis. This addition makes it clear how crucial it is to treat periodontitis in these patients with care and frequently to lower the risk of ORN caused by periimplantitis.

Although there is no single, widely accepted consensus in the literature regarding dental procedures for HNC patients, many of the same factors that must be taken into account for surgical interventions such as tooth extraction also apply to implant procedures. To provide best practices for these already overburdened patient groups, it is vital to identify preventive and therapeutic methods that apply to each dental application independently, including the installation of dental implants.

CONCLUSION

There is still some disagreement on the use of dental implants in people who have had RT or planning to undergo RT. Multiple tooth loss induced by RT has a significant impact on the quality of life of HNC survivors. In this group of patients, the use of dental implants helps the patient recover functionally, cosmetically, and medically throughout the post-treatment period. Well-designed dental implant placement studies involving a large number of participants are required in order to support patients in terms of dental comfort and medical care with the help of sound recommendations.

Conflicts of Interest: The authors declare that they have no potential conflict of interest with respect to research, authorship, and / or publication of this chapter.

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