

Crestal bone loss around dental implants placed in head and neck cancer patients treated with different radiotherapy techniques: a prospective cohort study

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Abstract. The aim of this prospective cohort study was to evaluate how the radiation technique can affect crestal bone loss and the implant survival rate in head and neck cancer patients treated with radiotherapy. In this study, the type of radiotherapy treatment, i.e. three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiation therapy (IMRT), was the predictor variable. The primary outcome variable was crestal bone loss, recorded at implant placement and after 3, 6, 12, and 24 months. A descriptive analysis and ANOVA test were performed; significance was set at $P < 0.05$. Thirty-two patients were enrolled and a total of 113 dental implants placed in irradiated residual bone. There was no statistically significant difference in crestal bone loss levels between the groups at any of the intervals ($P > 0.05$), except after 6 months ($P = 0.028$). The cumulative dental implant survival rate was 94.7%. After 24 months, the mean marginal bone loss was 0.83 ± 0.12 mm in the 3D-CRT group and 0.74 ± 0.15 mm in the IMRT group ($P = 0.179$). The data suggest that the different radiation techniques did not affect the outcomes of implant-supported prosthetic rehabilitation, as related to crestal bone loss and implant survival. However, long-term follow-up studies are necessary to evaluate the real influence of the radiotherapy technique on dental implants.

Key words: dental implants; radiotherapy; crestal bone loss; osseointegration.

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According to the World Health Organization, head and neck cancer is the eleventh most common cancer worldwide¹. The management of these oncological patients requires the cooperation of different specialists, who follow the patient through the phases of diagnosis, therapy, and rehabilitation²⁻⁴. Two different types of radiation therapy may be performed as definitive treatment or after radical surgical treatment: external beam radiotherapy (EBRT) and brachytherapy⁵. EBRT can be done either with three-dimensional conformal radiotherapy (3D-CRT) or with intensity modulated radiation therapy (IMRT).

In recent years, IMRT has become widely used among institutions, due to its ability to modulate the conformal dose distribution over standard 3D-CRT, allowing a better sparing of normal structures and organs at risk (OARs), such as the mandible, temporomandibular joint, salivary glands, and swallowing structures. This results in fewer long-term side effects (xerostomia, osteoradionecrosis) and an improved quality of life^{6,7}. The therapeutic radiation protocols consist of 50–70 Gy. The radiation dose may be delivered in mean fractions of 2 Gy (range 1.8–2.2 Gy) either once a day (standard fractionation therapy) or twice a day (hyperfractionated therapy) for a defined time period, which is usually 6 weeks^{8,9}. In postoperative radiotherapy, a dosage of 60–66 Gy is given to patients^{8,9}.

Following the therapeutic phase, patients then undergo prosthetic rehabilitation, which includes either a tooth-supported or implant-supported prosthesis^{10,11}. Dental implants can potentially result in a more effective oral rehabilitation in terms of mastication, aesthetics, and speech function¹²⁻¹⁴. However, increased implant failure rates for implants placed in irradiated bone are reported in the literature, as radiotherapy may result in progressive fibrosis of the soft tissues and vessels, reducing bone vascularity; furthermore, data on implant survival rates remain controversial¹⁵⁻¹⁹.

The purpose of this study was to evaluate how different radiation techniques may affect the amount of crestal bone loss around dental implants in post-oncological patients. The specific aims were to compare the mean crestal bone loss and the implant survival rate between IMRT and 3D-CRT patients. It was hypothesized that dental implants placed in patients treated with IMRT would show lower crestal bone loss levels compared to those placed in patients treated with 3D-CRT.

Materials and methods

Study design

To address the research purpose, the authors designed and implemented a prospective cohort study, conducted at the Department of Oral and Maxillofacial Sciences, at Sapienza University of Rome. The study was approved by the institutional review board.

The study sample was composed of a population derived from patients presenting at the university department for oral cancer management, who were treated by IMRT or 3D-CRT and later underwent prosthetic rehabilitation with dental implants over a time interval of between 12 and 24 months.

In order to be included in the study sample, patients had to meet specific eligibility criteria. Inclusion criteria were a diagnosis of head and neck cancer, age ≥ 18 years, underwent ablative surgery and adjuvant radiotherapy or definitive radiotherapy followed by implant-prosthetic rehabilitation, and provided signed informed consent, in accordance with the World Medical Association Declaration of Helsinki. Patients were excluded from enrolment into the study if they were aged < 18 years, had any uncontrolled systemic disease or a history of mental disorders, had missing or incomplete medical records, or refused to participate in the study.

The paper was written according to the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines/checklist.

Study variables

The binary predictor variable was radiotherapy treatment, which included 3D-CRT or IMRT. The primary outcome variable was the level of crestal bone loss, which was recorded at implant placement and after 3, 6, 12, and 24 months. Other variables included radiation dosage, implant survival rate, age, sex, type of treatment, dental implant type, implant site, and the development of osteoradionecrosis.

For the assessment of marginal bone loss, standardized peri-apical radiographs (Rinn, Dentsply, York, PA, USA) were obtained for each implant placed, and mesial and distal implant crestal bone levels were measured on the peri-apical radiographs. The radiographs were evaluated by an independent investigator and expert in the field. The reference point for the bone level measurement was the implant shoulder. The bone level was evalu-

ated digitally by measuring the distance between the implant shoulder and the first visible bone contact on the implant. The bone level measurements were recorded for the mesial and distal aspects of each implant.

The following secondary variables were recorded at every follow-up visit: (1) implant survival (an implant in place at the respective follow-up visit was considered a surviving implant). (2) Plaque index (PI), which was determined on the mesial, buccal, distal, and palatal surfaces of the implant, according to Mombelli et al.²⁰ as follows: score 0, no plaque detected; score 1, plaque only recognized by running a probe across the smooth marginal surface of the implant; score 2, plaque can be seen with the naked eye; score 3, abundance of soft matter. (3) Sulcus bleeding index, which was determined on the mesial, buccal, distal, and palatal surfaces of the implant according to Mombelli et al.²⁰ as follows: score 0, no bleeding when a periodontal probe is passed along the gingival margin adjacent to the implant; score 1, isolated bleeding spot visible; score 2, blood forms a confluent red line on the margin; score 3, heavy or profuse bleeding. The full mouth plaque score (FMPS) and full mouth bleeding score (FMBS) were also obtained at baseline (prior to implant placement) and at every follow-up visit.

Surgical and prosthetic phases

Subjects were treated with multiple implants based on their clinical needs and the volume and quality of available bone remaining, assessed according to the Lekholm and Zarb classification²¹. The time interval between radical oral cancer surgery, radiation therapy and implant placement, respectively, ranged from 12 to 24 months.

A complete medical and dental history check was performed, and a radiological examination, which included a panoramic radiograph and cone beam computed tomography, was conducted. Furthermore, conventional impressions were taken to produce the diagnostic wax-ups. The preparation of the locations for the implants was performed according to the defined sequence provided by the implant manufacturers. All patients were required to provide written consent for implant treatment, and prophylactic antibiotics (2 g of amoxicillin and clavulanic acid (Augmentin); Roche S.p.A., Milan, Italy) were administered to the patients 1 hour prior to surgery.

Medical examinations were scheduled for 7, 14, and 28 days after surgery and then once a month. The definitive prosthetic restorations were delivered between 3 and 6 months after implant placement.

Data collection

Of the patients who attended the university's oral cancer department and needed a prosthetic rehabilitation between January 2014 and April 2015, 32 fitted the inclusion criteria and agreed to participate in the study. Sixteen of these patients underwent IMRT, while 16 were treated with 3D-CRT. The allocation of patients to the two different radiotherapy treatment groups was not randomized: subjects were treated with IMRT or 3D-CRT based on the hospital waiting list.

Statistical analysis

Descriptive statistics (mean, range, standard deviation) were computed for each study variable. Fisher's exact test and the χ^2 test were computed to determine the bivariate association between radiotherapy treatment and the relevant study variables collected (age, sex, type of treatment, dental implant type, treatment

site, radiation dosage). Analysis of variance (ANOVA) was performed to examine differences by group and time for the primary outcome variable. A P -value of <0.05 was considered significant. Specific statistical software was used to analyze the data (IBM SPSS V10 Statistics, IBM, Armonk, USA).

Results

Thirty-two patients were enrolled in the study: 20 female and 12 male, with a mean age of 53 ± 29.7 years (range 32–74 years). The subjects were all post-oncological patients treated by definitive or adjuvant radiotherapy for malignant oral cavity neoplasia (23 in the mandible/floor of the mouth and nine in the maxilla) (Table 1).

Squamous cell carcinoma was the most prevalent tumour diagnosed. Other cancer types were malignant ameloblastoma, osteosarcoma of the jaw, and carcinoma ex pleomorphic adenoma. Ablative surgery was performed in 23 patients: a segmental mandibulectomy was performed in 11 cases, while seven patients underwent a marginal mandibulectomy; five patients were treated by total ($n=2$) or partial ($n=3$) maxillectomy. The patients were

then reconstructed microsurgically using a range of vascularized flap techniques: fibula free flaps in 12 patients, anterolateral thigh flaps in eight patients, and iliac crest flaps in three patients (Table 1). All subjects underwent adjuvant radiotherapy only after a mean interval of 6 weeks. Nine patients who presented squamous cell carcinoma of the oral cavity of stage I/II (T1–2, N0) were treated by definitive radiotherapy without primary surgery.

A total of 113 dental implants were placed in irradiated residual bone, with a minimum interval of 12 months between irradiation and implant placement. Seventy-eight implants were placed in the mandible and 35 in the maxilla. All dental implants were inserted inside the irradiation field, as confirmed by the radiotherapy protocols provided by the radiotherapists. The quality of available bone in the implant area was classified as follows: type I ($n=8$), type II ($n=27$), type III ($n=53$), and type IV ($n=25$).

At baseline, mean FMPS was 43% in IMRT patients and 38% in 3D-CRT patients, and mean FMBS was 27% and 29%, respectively ($P=0.102$). After 24 months, FMPS was 24% in the IMRT group and 26% in the 3D-CRT, and mean FMBS was 18% and 15%, respectively, with no statistically significant difference ($P=0.176$).

In the primary outcome variable analysis, there was no statistically significant difference in crestal bone loss levels between the groups at any of the intervals ($P > 0.05$), except after 6 months ($P=0.028$) (Fig. 1). After 24 months, mean marginal bone loss was 0.83 ± 0.12 mm in the 3D-CRT group and 0.74 ± 0.15 mm in the IMRT group ($P=0.179$). In both groups, dental implants placed in the maxilla showed lower values of crestal bone loss than those placed in the mandible (0.68 ± 0.11 mm vs. 0.81 ± 0.08 mm for IMRT; 0.72 ± 0.22 mm vs. 0.93 ± 0.17 mm for 3D-CRT, respectively); however, the difference was not statistically significant ($P > 0.05$).

With regard to the type of prosthetic rehabilitation, implants placed in fixed prostheses showed higher values of marginal bone loss than those placed in removable prostheses in both groups ($P=0.251$).

Osteoradionecrosis occurred in just one patient (6.25%), who was treated with 3D-CRT in the parasymphysis region of the mandible. However, this was not considered statistically significant ($P=0.264$).

The mean radiation dosage in IMRT and 3D-CRT patients was 64 ± 2.84 Gy

Table 1. Descriptive statistics.

Study variable	Descriptive statistics
Sample size, n	32 patients
Sex, n (%)	
Male	12 (37.5%)
Female	20 (62.5%)
Age (years), mean \pm SD (range)	53 ± 29.7 (32–74)
Follow-up (months), mean \pm SD (range)	25.5 ± 3.4 (24–30)
Type of treatment, n (%)	
Ablative surgery and adjuvant radiotherapy	23 (71.9%)
Definitive radiotherapy	9 (28.13%)
Type of radiotherapy, n (%)	
3D-CRT	16 (50%)
IMRT	16 (50%)
Type of oral cancer	
Squamous cell carcinoma	19 (59.4%)
Ameloblastoma	6 (18.7%)
Osteosarcoma of the jaw	3 (9.4%)
Pleomorphic adenoma	4 (12.5%)
Dental implants	113
Types of dental implant	
PTTM enhanced titanium dental implants ^a	34
BioHorizons Laser-Lok tapered internal implants ^b	42
Osseotite implants ^c	37
Type of prosthetic rehabilitation	
Removable overdenture	8
Cement-retained implant-supported prosthesis	17
Screw-retained implant-supported prosthesis	7
Implant survival	94.7%

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy; SD, standard deviation.

^a Trabecular Metal Dental Implant, Zimmer Dental Inc., Carlsbad, CA, USA.

^b BioHorizons, Birmingham, AL, USA.

^c 3i Biomet, Palm Beach Gardens, FL, USA.

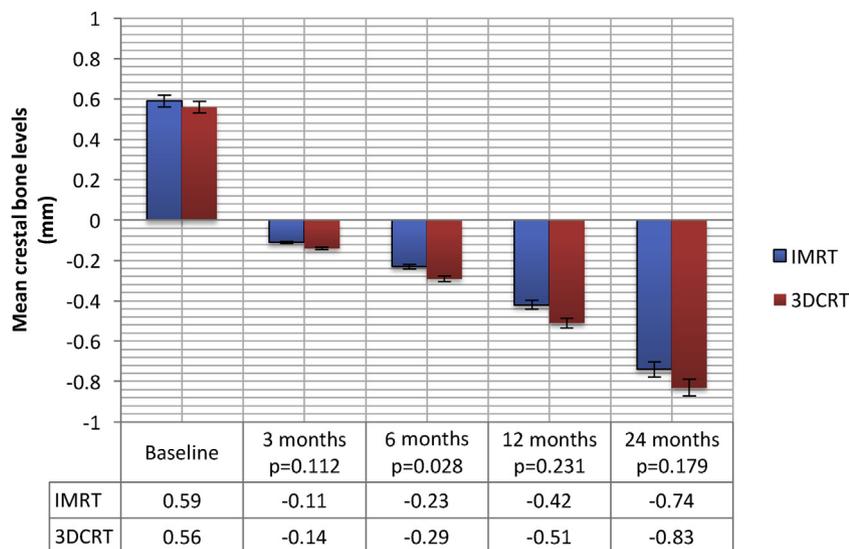


Fig. 1. Mean crestal bone loss values.

(range 60–70 Gy). The mean dose/radiation exposure values at implant treatment sites were calculated using the radiation isodose mapping associated to every single patient, as 41 ± 1.32 Gy (range 12–51 Gy) and 43 ± 1.87 Gy (range 21–50 Gy), respectively. The mean irradiated bone dose (mandible and jaw) was 44 ± 0.87 Gy (range 4–71 Gy) for IMRT patients and 43 ± 0.57 Gy (range 23–70 Gy) for 3D-CRT patients (Table 2).

Prosthetic rehabilitation included implant-supported fixed prostheses and removable overdentures (Table 1).

The cumulative dental implant survival rate was 94.7%. Just six implants failed, all due to early biological complications. Four implants were lost in the first 3 months, while two failed in the interval 3–6 months. Three implants failed in the mandible and three in the maxilla, with no statistically significant difference between groups ($P = 0.371$) or implant sites ($P = 0.45$). The implant survival rate did not differ significantly between the two groups according to Kaplan–Meier survival analysis adjusted for correlation among implant observations from the same sub-

ject ($P = 0.111$). The mean observation period after prosthetic rehabilitation was 25.5 ± 3.4 months (range 24–30 months).

No statistically significant association was found between the primary outcome variable and the other relevant variables recorded (Table 2).

Discussion

The purpose of this study was to evaluate how different radiation techniques can affect crestal bone loss around dental implants and implant survival in post-on-

Table 2. Bivariate analysis between the primary outcome variable (type of radiotherapy) and relevant variables collected.

Variable	IMRT	3D-CRT	P-value
Sample size, <i>n</i>	16 (50%)	16 (50%)	NA
Age (years), mean \pm SD	49 ± 21.6	57 ± 13.5	0.35
Sex			0.441
Male	7 (43.75%)	5 (31.25%)	
Female	9 (56.25%)	11 (68.75%)	
Type of treatment			0.241
Ablative surgery and adjuvant radiotherapy	13 (81.25%)	10 (62.5%)	
Definitive radiotherapy	3 (18.75%)	6 (37.5%)	
Type of oral cancer			NA
Squamous cell carcinoma	9 (56.25%)	10 (62.5%)	
Ameloblastoma	2 (12.5%)	4 (25%)	
Osteosarcoma of the jaw	3 (18.75%)	0	
Pleomorphic adenoma	2 (12.5%)	2 (12.5%)	
Dose/radiation exposure at implant treatment sites (Gy), mean \pm SD (range)	41 ± 1.32 (12–51)	43 ± 1.87 (21–50)	0.141
Irradiated bone dose (mandible and jaw) (Gy), mean \pm SD (range)	44 ± 0.87 (4–71)	43 ± 0.57 (23–70)	0.326
Treatment site			0.45
Mandible	12	11	
Maxilla	4	5	
Dental implants	52	61	NA
Type of dental implants			0.123
PTTM enhanced titanium dental implants	24	10	
BioHorizons Laser-Lok tapered internal implants	18	24	
Osseotite implants	15	22	
Osteoradionecrosis	0	1 (6.25%)	NA

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy; NA, not applicable; SD, standard deviation.

cological patients. There is a lack of information in the current literature, with no study directly addressing this topic. It was hypothesized that dental implants placed in patients treated with IMRT would show lower crestal bone loss levels compared to those placed in subjects treated with 3D-CRT. This assumption was based on the premise that IMRT, by sparing OARs and preserving treatment site areas from an excessive radiation/dose exposure, would restrict the high-risk region to the jawbone adjacent to the tumour, in contrast to 3D-CRT in which both jaws are exposed bilaterally^{22,23}.

The survival of implants placed in irradiated bone depends on the dose received, but in oral cancer patients it is not always possible to spare the mandibular or jaw bone, irrespective of the technique used^{24,25}. IMRT is considered more able than 3D-CRT to reduce the dose in particular areas of affected bone prior to treatment, because sites useful for implant placement are outlined as areas of interest^{24,25}.

With regard to crestal bone loss, there are only a few studies available in the literature. In 2016, Ernst et al.²⁶ investigated peri-implant bone loss in irradiated and non-irradiated post-oncological patients and reported mean values of 1.4 mm mesially and 1.3 mm distally after 3 years. Landes and Kovács described mean crestal bone changes of 1.4 ± 0.9 mm after 2 years in irradiated patients, with considerably higher values compared to non-irradiated patients (0.9 ± 0.4 mm, $P < 0.01$)²⁷. In the present study, crestal bone loss levels in irradiated patients after 2 years were not affected by the type of radiotherapy (0.74 mm vs. 0.83 mm) and are quite similar to data reported in the literature after the same interval of time for non-irradiated subjects^{28–30}. According to the authors, as can be seen by our results, there is no difference between the two techniques in the radiation dose received from the bone.

The implant survival rate in irradiated patients remains a controversial issue among clinicians. Over the years, several authors have reported a significantly greater risk of implant failure in irradiated bone compared to non-irradiated bone^{31–33}. In a recent systematic review, Smith Nobrega et al.³⁴ reported a lower survival rate for implants installed in irradiated bone tissue compared to implants installed in non-irradiated bone, with a mean value of 84.3%. On the other hand, De la Plata et al.¹⁹ reported a survival rate of 92.6% after 5 years of follow-up, while Linsen et al.¹⁸ recorded an implant survival rate of 89% after the same interval and a meta-analysis by Schiegnitz et al.³⁵ indicated an implant survival rate of 83%, describing

comparable implant survival in non-irradiated and irradiated native bone, with no statistically significant difference (odds ratio 1.44).

It appears that there is just one study in the current literature comparing implant survival in IMRT vs. 3D-CRT patients. Curi et al.³⁶ reported an overall 5-year survival rate of 92.9% in irradiated patients, with dental implants placed in patients treated with IMRT presenting a significantly higher probability of implant success ($P < 0.01$).

The preliminary results in the present study indicate that osseointegration was achieved in irradiated bone and that the dental implants remained functionally stable during the observation period.

The development of osteoradionecrosis of the jaw (ORN) is a severe adverse effect of radiotherapy treatment. It is more frequent in the mandible, although the prevalence is still controversial, and patients exposed to a therapeutic radiation dose >60 Gy are considered at risk^{37,38}. ORN can lead to the loss of a considerable amount of bone, with a reduction in chewing, speaking, and swallowing function, severely influencing and very often compromising the possibility of future prosthetic rehabilitation^{37,38}. Schweyen et al.³⁹ reported a prevalence of ORN of 6.6% in a cohort of 776 patients who underwent radiation therapy, with 82% of cases occurring in subjects treated with 3D-CRT. Several authors have reported that a combination of IMRT and strict oral hygiene follow-up resulted in very few cases of ORN^{40,41}. Data from the present study appear to be in agreement with this, with just one patient treated with 3D-CRT developing ORN (in the parasymphysis region of the mandible).

Radiation therapy may compromise future prosthetic rehabilitation. However, several other factors, such as oral hygiene and periodontal status or the type of prosthesis, need to be carefully taken into account and may influence implant survival and crestal bone loss levels.

The main limitations of this study are represented by the small sample size and the limited follow-up available, together with the absence of a control group (non-irradiated patients) and randomization process for allocation of the patients to the two different radiotherapy techniques. Furthermore, other variables, such as oral hygiene status and the patient's compliance to a regular maintenance programme, may severely influence implant outcomes.

Taking into account the limitations of this study, the following conclusions can be drawn with caution: the data suggest

that the different radiation techniques do not affect the outcomes of implant-supported prosthetic rehabilitation, as related to crestal bone loss and implant survival. However, long-term follow-up studies with larger samples are necessary to evaluate the real influence of the radiotherapy technique on dental implants.

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Nothing to disclose.

Competing interests

The authors declare that they have no conflict of interest. The study was self-funded by the authors and their institution.

Ethical approval

The study was approved by the Ethics Committee of Sapienza University of Rome (Ref. 3452).

Patient consent

Not required.

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