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Influence of implant-specific radiation doses on peri-implant hard and soft tissue: An observational pilot study

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Abstract

Objectives: The aim of this study was to investigate the influence of real implant-bed-specific radiation doses on peri-implant tissue health in head and neck cancer (HNC) patients after radiotherapy.

Material and methods: Specific radiation doses in the area of 81 implants, in 15 irradiated HNC patients, were analyzed by matching data from the radiotherapy planning system with those of three-dimensional follow-up scans after implantation. Peri-implant bone resorption was measured radiographically after 1 and 3 years, and peri-implant tissue health was evaluated clinically. Individual parameters, such as age, gender, and localization, regarding the implant-specific radiation dose distribution were analyzed statistically.

Results: The mean implant-bed-specific radiation dose was high, with 45.95 Gy to the mandible and 29.02 Gy to the maxilla, but significantly lower than the mean total dose to the tumor bed. Peri-implant bone resorption correlated with local inflammation and plaque. After 1 year, women temporarily showed significantly more bone loss than men and implant-specific radiation dose had a significant impact on peri-implant bone loss after 3 years.

Conclusions: The presented method is a feasible option to define precise implant-bed-specific radiation doses for research or treatment planning purposes. Implant-based dental restoration after radiotherapy is a relatively safe procedure, but a negative radiation dose-dependent long-term effect on peri-implant bone resorption calls for interdisciplinary cooperation between surgeons and radio-oncologists to define high-risk areas.

KEYWORDS
clinical research, clinical trials, CT Imaging, diagnosis, clinical assessment, patient-centered outcomes, radiology, imaging, soft tissue–implant interactions

1 | INTRODUCTION

The restoration of the stomatognathic system is a major challenge in head and neck cancer (HNC) patients after tumor eradication. Successful cancer treatment can lead to debilitating results with major facial defects and a compromised soft and hard tissue situation. Either the tumor resection itself or the tooth extractions prior to radiation therapy can generate a need for dental rehabilitation (Ernst et al., 2016; Linsen et al., 2012). Especially in locally advanced cases, surgical resection with adjuvant radiotherapy (RT) or chemoradiation (RCT), as well as definitive RT/RCT, is the standard of care (Elkashty et al., 2019). Intensity-modulated radiation therapy (IMRT) is now the standard method, and dose delivery, as well as target selection, results in minimized dose delivery to non-target tissues (Hansen et al., 2012). Yet, these multimodal cancer therapies with surgery and R(C)T often result in changes in the oral anatomy, which do not permit a treatment with mucosa-supported prostheses (Ernst et al., 2016; Korfage et al., 2014; Pace-Balzan & Rogers, 2012). Dental implants in combination with prosthetic restorations are an effective way to rehabilitate the stomatognathic system and alleviate social reintegration in HNC patients (Gómez-de Diego et al., 2014; Moore et al., 2019; Schiegnitz et al., 2014). Even if current and limited data are inconsistent, substantial changes within the alveolar bone, as well as the surrounding tissues, during and after RT might cause relevant impairment of the affected tissue and require proper tissue management and professional care (Costa & Reagan, 2019; Moore et al., 2019). It is known that recovery from RT can induce a short-term positive cellular effect that results in an improvement in bone-healing capacity and a long-term effect resulting in the permanent damage of bone cells, fibrotic conversion and involution of affected tissues, xerostomia, and progressive endarteritis obliterans (Chrcanovic et al., 2016; Scully & Epstein, 1996). Consequently, the compromised bone vascularity seems to limit the regenerative capacity of hard and soft tissues after irradiation, which are vital characteristics for successful implant rehabilitation (Chrcanovic et al., 2016). Total RT doses above 65 Gy are known to increase the risk of osteonecrosis and therefore the possibility of implant failure (Cooper et al., 1995; Jacobsson et al., 1986, 1988; Nguyen et al., 1988). Implant survival rates in irradiated bone rank around 90% after 7 years, but due to the heterogeneity of the studies, a precise general statement is difficult (Chrcanovic et al., 2016; Doll et al., 2015). However, high RT doses above 50 Gy, in particular, seem to account for lower implant survival rates (Alsaadi et al., 2008; Chen et al., 2013; Chrcanovic et al., 2016; Shugaa-Addin et al., 2016). Patients with adjuvant RCT have a 1.9-fold higher risk of losing an implant compared to patients without adjuvant RT/RCT (Doll et al., 2015). In a meta-analysis by Chrcanovic et al., a similar but even higher risk ratio of 2.18 ($p < .00001$) and an overall risk of losing an implant after radiation of about 16.4% were found when comparing implant failure between irradiated and non-irradiated patients, but up to now the dependence of an individual RT dose distribution and its effect on peri-implant tissues is still unknown (Chrcanovic et al., 2016; Doll et al., 2015; Ernst et al., 2016). Few studies have attempted to consider regional RT dose distributions preventing the risk of developing ORN, but no clinical and radiological data with the inclusion of implant-bed-specific RT doses exist (Chrcanovic et al., 2016; Heberer, Hildebrand, et al., 2011; Schoen et al., 2008).

The aim of the present study was to evaluate a new method for verifying the dependence of clinical and radiological parameters of dental implants on the specific radiation doses in their respective implant beds.

2 | MATERIAL AND METHODS

2.1 | Patients

This observational study was performed in the Department of Oral and Maxillofacial Surgery, Charité—Universitätsmedizin Berlin. A total of 10 edentulous and five partially edentulous patients were enrolled in this study. Six patients received implants in both jaws, and nine patients, in the mandible only. All implants in this study were placed in irradiated native bone. The median age of the women was 59.3 years (range, 48–71), and that of the men was 61.3 years (range, 51–71).

All patients underwent comprehensive cancer treatment including RT, followed by implant-retained prosthetic rehabilitation. At the time of diagnosis, the patients were categorized based on the tumor classification (UICC) on tumor size and nodal status (Brierley et al., 2017). Primary tumor sites were the anterior floor of the mouth ($n = 8$), oropharynx ($n = 2$), and tongue ($n = 2$), as well as the maxilla ($n = 2$) and nasopharynx ($n = 1$). Three patients received continuity resection with primary reconstruction with a free fibula flap (FFF). In two cases, a secondary resection with microvascular reconstruction via FFF was necessary.

The general characteristics of all patients are summarized in Table 1. In cases of RCT, cisplatin-based chemotherapy was given in weeks 1 and 5 of RT (days 1–5, 20 mg/m^2). The implant placement was performed six months after the end of the RT or RCT. No augmentation procedures were done in these patients prior to implant placement. To optimize soft tissue conditions, vestibuloplasty with a split skin graft was performed in each patient as previously described (Heberer et al., 2011; Heberer et al., 2011). Furthermore, each patient received a professional implant cleaning procedure every three months.

2.2 | Exclusion criteria

Exclusion criteria were smoking, untreated diabetes, and being immunocompromised (e.g., HIV infection, autoimmune diseases, cortisone treatment). Patients with implants placed in augmented or transplanted bone were also excluded.

TABLE 1 General patient characteristics and cancer treatment

Patient	Sex	Age	Number of implants	TNM classification	Tumor location	Histology	Tumor surgery	(C)RT	RT technique	RT SD (Gy)	RT TD (Gy)
1	Male	68	4 mand. 4 max.	pT2 pN2b (2/40) G2 R0 L1 V0, ECE	Tongue/ant. floor of the mouth	SCC	Tumor resection and bilateral ND (I-II)	Adjuvant SIB	IMRT	2.13	63.9
2	Male	57	4 mand.	pT2 pN2b (4/31) G3 L1 V0 Rx	Tongue / palatoglossal arch	SCC	Tumor resection bilateral ND (I-III) and secondary reconstruction with FFF after ORNJ[a]	Adjuvant SIB	VMAT	2.15	64.5
3	Female	54	4 mand.	pT1 cNx cMx G2 R2	Maxilla	SCC	Tumor resection (hemimaxillectomy)				
				Immediate cT4b cNx cMx[c]	Maxilla/mandibula	SCC		Definitive	IMRT	HART	72
4	Male	71	4 mand. 4 max.	pT2 pN0 (0/20) M0 R0 G2	Lateral border of the tongue	SCC	Tumor resection + ND (I-IV)	Adjuvant SIB	IMRT	2.13	63.9
				rpT1pN0 (0/8) G2 R0 L0 V0[b]	Ant. floor of the mouth	SCC	Tumor resection including partial resection of the mandible and ND (I-III)				
5	Male	64	4 mand.	pT4 pN0 (0/28) G2 R0 L0 V0	Ant. floor of the mouth	SCC	Tumor and continuity resection and reconstruction with FFF and ND (I-III)[a]				
				rcN3	Nodal recurrence	SCC	N/A	Def. SIB	VMAT	2.2	70.4
6	Male	60	2 mand.	pT4a pN2b (2/22) G2 R0 L0 V0	Lat. floor of mouth	SCC	Tumor and continuity resection and reconstruction with FFF and ND (I-IV)[a]	Adjuvant SIB	VMAT	2.24	56
7	Male	53	4 mand. 4 max.	pT3 pN1 (1/42) G2 R0 L0 V0	Ant. floor of mouth	SCC	Partial resection of the mandible and ND (I-III)	Adjuvant SeqB	IMRT	2	54
8	Female	69	4 mand.	cT3 cN2c M0 G3	Tonsil	SCC	N/A	Definitive	IMRT	HART	72
9	Male	63	4 mand.	pT2 pN2b (2/27) G2 R0	Ant. floor of mouth	SCC	Partial resection of the mandible ND (I-IV)	Adjuvant SIB	VMAT	2.24	56
10	Female	71	4 mand. 6 max.	cT4 cN0 M0 G3	Nasopharynx	EBV pos. Ca	N/A	Definitive	IMRT	HART	72
11	Female	54	4 mand. 4 max.	pT3 pN0 (0/8) G2 R0 L0 V0	Buccal plane	SCC	Partial resection of the maxilla reconstruction with RFF and ND (I-V)				
				rcT4b cN0 cM0[c]	Buccal plane, maxilla	SCC	NA	Definitive	VMAT	2 x 1 Gy	78.2

(Continues)

TABLE 1 (Continued)

Patient	Sex	Age	Number of implants	TNM classification	Tumor location	Histology	Tumor surgery	(C)RT	RT technique	RT SD (Gy)	RT TD (Gy)
12	Female	60	4 mand.	pT3 pN1 (1/x) Mx (pulm) RR close (1mm) G2 Lx Vx	Ant. floor of mouth	MEC	Tumor and continuity resection and reconstruction with FFF and ND (I-III)[a]	Adjuvant SeqB	3D-CRT	2	64
13	Male	65	2 mand.	pT2 pN0 (0/11) M0 G2 R0 L0 V0[c]	Ant. floor of mouth	SCC	Tumor resection and ND (I-III) followed by resection of a submental LN-metastasis.				
				rcTx rcN1 M0 V1 R2	Submandibular lymph node	SCC	Secondary continuity resection after ORNJ and reconstruction with FFF[a]	Definitive	VMAT	HART	72
14	Male	51	4 mand.	rpT1 pN0 (x/x) G2 R0 L0 V0	Ant. floor of mouth	SCC	Tumor resection and bilateral ND (I-III)				
				rcT2 rcN2b cM0[c]	Ant. floor of mouth			Definitive	IMRT	HART	72
15	Male	48	3 mand. 4 max.	cT4a cN2b M0	Tonsil	SCC	N/A	Definitive CRT	VMAT	HART	72

Abbreviations: (C)RT, (chemo)radiotherapy; mand., mandibular; max., maxillary; SD, single dose; TD, total dose; Gy, gray; SIB, simultaneous integrated boost; SeqB, sequential boost IMRT intensity-modulated radiotherapy; VMAT, volumetric-modulated radiotherapy; 3D-CRT (three-dimensional conformal radiotherapy; HART, hyperfractionated accelerated radiotherapy; ND, neck dissection; I-IV, Robins levels; FFF, free fibula flap; RFF, radial forearm flap; ORNJ, osteoradionecrosis of the jaw; ECE, extracapsular extension; SCC, squamous cell carcinoma; EBV pos. Ca, Epstein–Barr virus-positive carcinoma; ant., anterior; lat., lateral.

[a]implants in transplanted bone were excluded.

[b]secondary carcinoma.

[c]tumor recurrence.

2.3 | Surgical treatment

The implants were placed under local anesthesia (Ultracain D-S forte, adrenaline concentration 1:100,000). All implants were inserted epicrestally. All patients received an antibiotic regimen using amoxicillin/clavulanic acid 875/125 mg (1–0–1) for one day preoperatively and four days postoperatively. In cases of intolerances or allergies to penicillin, the medication was replaced by clindamycin 300 mg three times daily. The healing time of the implants was 12 weeks in the maxilla and six weeks in the mandible.

2.4 | Measurement of radiation dose

To evaluate the exact implant-specific irradiation doses for every implant, the ARIA® version 15.5 RT planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA) was used to import and register each scan and to match the initial RT planning computed tomography (CT) scan of each patient to the follow-up CT scans and/ or cone beam scans after cancer treatment. Automatic non-rigid three-dimensional (3D) image registration was performed and corrected manually if necessary. Thereafter, contouring of the implants followed: The implants with a diameter of 3.8 mm or 4.3 mm were marked in an axial slice, expanded symmetrically by 5 mm, and interpolated to be rendered in a 3D cylinder. This structure representing the "implant position" was saved in the data set and viewed along all axes to verify the position. The RT dose distribution and dose-volume histograms (DVH) were evaluated to locate the "implant" position, and the minimum (Dmin), maximum (Dmax), and mean dose (Dmean) in this volume of interest were recorded. Only the RT dose in the implant bed was therefore retrospectively evaluated using the Dmean per implant position. The method is illustrated in Figure 1.

2.5 | Radiographic evaluation

For peri-implant measurements of the bone level, routine panoramic radiographs (trademark: Planmeca ProMax; type: ProMax 3D Max, Pro Face Med Series H23 120kV) were taken in all patients 1 year (t1) and 3 years postoperatively (t2) after implantation. Using the method described by Gomez-Roman et al. (1995), peri-implant bone

level changes at the mesial (mes) and distal (dist) sites of the implants were measured with a reference point at the interface between the implant and the abutment subtracting metric distortion of the radiographs (Figure 2). A single investigator performed the measurements three times at three different time points using a digital gauge (Holex, Nürnberg, Germany). Bone level changes were calculated by subtracting the mean values of bone loss from the initial postoperative value, separately for mesial and distal sites.

2.6 | Clinical evaluation

All patients received a routine clinical evaluation using a standard protocol after implant insertion and after prosthetic restoration (Nack et al., 2015). Within the first year, the evaluation was performed every three months and was continued every 12 months thereafter. The clinical monitoring was documented after 3 years, including the measurement of the modified bleeding index (mBI) and modified plaque index (mPI) (Mombelli et al., 1987; Muehlemann, 1978). The measurements were taken mesially, distally, lingually, and buccally for both indices.

2.7 | Statistics

Differences concerning implant localization and the patients' age and gender were analyzed descriptively. The statistical analysis was performed with SPSS Statistics 25 (IBM, Armonk, New York, USA), STATA 16.1 (StataCorp LT, College Station, TX, USA), and GraphPad Prism 8 (GraphPad Software, San Diego CA, USA).

Spearman's rank correlation coefficient (Rs) was used to assess the relationship between plaque index, and sulcus bleeding index and differences in bone resorption after 1 and 3 years, respectively.

A linear mixed model with "patient" as random effect was used to assess for the relationship between implant-bed-specific radiation dose (Dmean) and differences in bone resorption for mesial and distal sites of the implants after 1 and 3 years, respectively. The analyses were done separately for maxilla and mandible, as well as per patient (both jaws). We adjusted for sex and age, and additionally for the jaw in the overall-model.

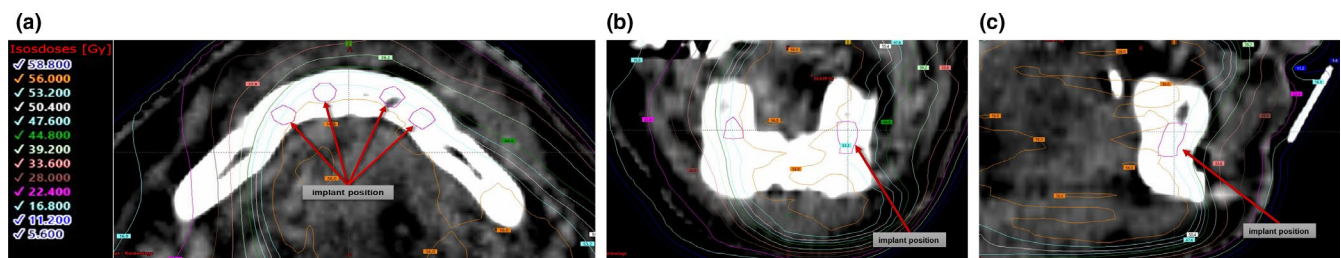A p-value <.05 was considered statistically significant.

FIGURE 1 Radiotherapy (RT) planning CT data set matched to the position of the implants (outlined in pink and indicated by the red arrows). (a) Axial view with corresponding RT isodose lines in Gy (box to the left) in the color of their respective field line. (b) Coronal view with corresponding RT isodose lines in Gy. (c) Sagittal view with corresponding RT isodose lines in Gy

2.8 | Study protocol

All persons involved had provided their informed consent prior to inclusion in the study. The study protocol was approved by the Ethics Committee of the Charité—Universitätsmedizin Berlin, Germany (EA 406,418). It conforms to the Declaration of Helsinki and the European Medicines Agency Guidelines for Good Clinical Practice
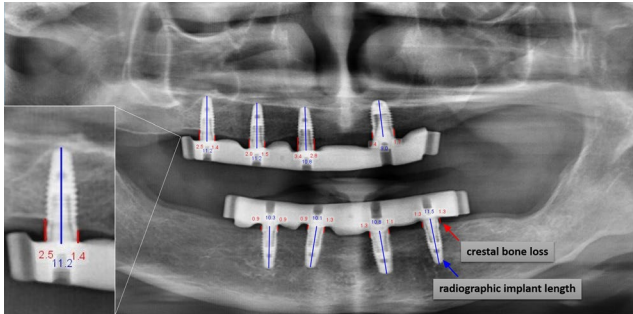

FIGURE 2 Measurement of bone loss (the blue arrow indicates radiological implant length; the red arrow indicates the crestal bone loss). The box on the left side indicates the enlarged implant exemplifying the methodology

and complies with the appropriate STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and checklist.

3 | RESULTS

3.1 | Patients and implants

A total of 81 implants (Camlog Biotechnologies AG, Basel, Switzerland) in 15 patients (six women, nine men) were analyzed. Of these, 26 implants (32.1%) were located in the upper jaw, and 55 (69.9%) were located in the lower jaw. Two implants (2.5%) were lost, both within the first three months after implantation. The success rate after 3 years was 97.5%. Dmean per implant was 40.7 Gy
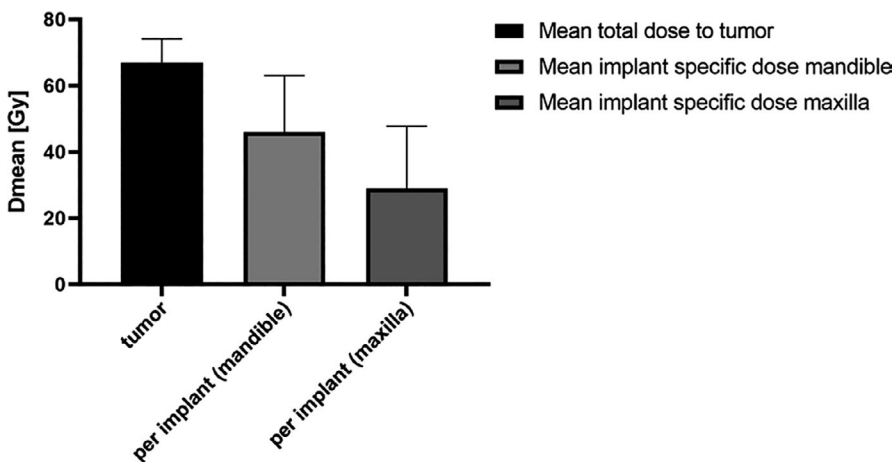
(range, 3.2–71.4), and gender-specific Dmean resulted in 34.7 Gy in women (range, 14.0–66.5) and 45.9 Gy (range, 3.2–71.4) in men. Dmean in the mandibular bone was 46.0 Gy (range, 14–71.4) and significantly higher than in the maxillary bone with a Dmean of 29.0 Gy (range, 3.2–62.4, $p < .01$). On the other hand, the mean total dose to the tumor bed in the planning target volume (PTV) was 66.9 Gy (range, 54–78.2) and significantly higher than Dmean in the mandible ($p < .01$) and the maxilla ($p < .01$) (Figure 3).

Results after 3 years revealed the following distribution of the plaque index: 46.8% of the patients demonstrated a score of 0, 36.7% a score of 1, 13.9% a score of 2, and 2.5% a score of 3. The sulcus bleeding index score was 0 in 46.8%, 1 in 29.1%, 2 in 19.0%, and 3 in 5.1% of the patients.

3.2 | Radiographic parameters

The mean amount of bone loss after 1 year (t1) was measured to be 1 mm mesially (mes) (range, 0–3.6) and 1.1 mm distally (dist) (range, 0–3.9) of the implants. After 3 years (t2), mesial bone loss was 1.5 mm (range, 0–3.6), and distal bone loss was 1.5 mm (range, 0–4.2).

The mean amount of bone loss in the mandible at t1 was 0.9 mm (range, 0–3.5) mesially and 1.1 mm (range, 0–3.9) distally. In the maxilla, mesial bone loss was 1.2 mm (range, 0–3.6), and distal bone loss was 1.1 mm (range, 0–3.1). After 3 years (t2), the mandibular bone level change was 1.5 mm (range, 0–3.5) mesially and 1.5 mm distally (range, 0–4.2). Maxillary bone loss after the same period of time accounted for 1.4 mm mesially (range, 0–2.7) and 1.3 mm distally (range, 0–2.7). The gender-specific distribution of bone loss is shown in Table 2.

Furthermore, a correlation between the plaque index (Rsmes = 0.390, 95% CI [−0.185, 0.563], Pmes < 0.01; Rsdist = 0.376, 95% CI [0.169, 0.551], Pdist < 0.01), the sulcus bleeding index (Rsmes = 0.360, 95% CI [0.151, 0.538], Pmes < 0.01; Rsdist = 0.347, 95% CI [0.136, 0.528], Pdist < 0.01), and the peri-implant bone resorption for t1 and t2 was found (plaque index: Rsmes = 0.356, 95% CI [0.137, 0.542], Pmes < 0.01; Rsdist = 0.295, 95% CI [0.0697, 0.492], Pdist = 0.01. Sulcus bleeding index: Rsmes = 0.394, 95% CI

Mean total dose to tumor
Mean implant specific dose mandible
Mean implant specific dose maxilla

FIGURE 3 Mean total tumor dose ($n = 15$, SD = 7.23) and mean implant-specific total dose (mandible: $n = 54$, SD = 17.07; maxilla $n = 24$, SD = 18.73) in gray (Gy)

[0.180, 0.572], Pmes < 0.01; Rsdist = 0.268, 95% CI [0.0404, 0.469], Pdist = 0.02).

The results show that higher implant-bed-specific radiation doses correlate significantly with higher bone resorption in both jaws (maxilla: after 1 and 3 years at distal sites; mandible: after 3 years at mesial sites). With consideration of both jaws and adjustment for maxilla and mandible, an influence of radiation dose on the peri-implant bone level after one (distally) and especially after 3 years ($p < .001$; distally and mesially) can be observed. The age was considered in all statistical models, but no association could be found. Woman did temporarily show significantly higher peri-implant bone level changes after 1 year, considering implant-bed-specific radiation doses (Table 3 and Figure 4).

4 | DISCUSSION

The present pilot study was conducted to establish a novel tool for the precise evaluation of the influence of implant-bed-specific radiation doses on peri-implant health. To date, a lack of reliable and adequate long-term data on the influence of radiotherapy on peri-implant tissues with sufficient follow-up and the consideration of multiple potential influencing factors is evident (Chrcanovic et al., 2016; Javed et al., 2010). Most studies investigated the influence of irradiation on implant survival rates, but modern radiotherapy techniques such as IMRT and VAMT

(volumetric-modulated arc therapy) can treat the individual target volume(s) with a high conformal dose distribution and a steep dose gradient, and therefore, the dose to organs and tissues of interest can vary widely (Morgan & Sher, 2020). Consequently, the radiation dose to the target (tumor) volume does not reflect the actual dose applied to the area of interest, in this case being the intended implant location. Still, sparing the jawbone is not always possible, which might explain why Papi et al. (2019) were not able to find significant differences in peri-implant bone levels and implant survival in patients who had undergone IMRT or 3D-CRT (three-dimensional conformal radiotherapy). By matching data of the individual IMRT/VMAT RT treatment plan with follow-up radiographic scans including the information for implant positioning, it is possible to overcome uncertainties concerning specific radiation doses to every single implant bed. Furthermore, most studies concentrate solely on implant survival, which insufficiently reflects peri-implant tissue health and therefore long-term treatment success, especially because the irradiated jawbone has a relevant risk of developing osteoradionecrosis due to infectious processes (Chrcanovic et al., 2016; Katsura et al., 2008; Korfage et al., 2015; Raguse et al., 2016; Schiegnitz et al., 2014, 2015). Only a few studies, on the other hand, implemented clinical and radiographic evaluation to monitor bone loss and tissue inflammation, and specific differences concerning gender and age have rarely been addressed, still lacking the comprehensive implementation of these factors (Heberer, Kilic, et al., 2011; Koszuta et al., 2015; Landes & Kovacs, 2006; Schoen et al., 2007, 2008).

TABLE 2 Bone resorption in mm after 1 year (t1) and 3 years (t2) in male and female HNC patients subdivided into mesial and distal sites

Gender	t1		t2	
	Mesial	Distal	Mesial	Distal
Male, mm (range)	0.7 (0–2.3)	0.7 (0–2.4)	1.5 (0–3.3)	1.4 (0–4.2)
Female, mm (range)	1.5 (0–3.6)	1.5 (0–3.9)	1.5 (0–3.5)	1.5 (0–4.0)

TABLE 3 Regression analysis between mean dose to mean bone level changes after 1 year (t1) and 3 years (t2) at mesial (mes) and distal (dist) sites for maxilla, mandible, and both together, adjusted for age and gender

| Localization	Mean radiation dose (Dmean) to bone level changes	Coefficient	95% confidence interval	P-value
Maxilla	t1 mes	0.054	−0.023 – 0.034	0.712
	t1 dist	0.030	0.001 – 0.059	0.043
	t3 mes	0.016	−0.015 – 0.048	0.314
	t3 dis	0.037	0.001 – 0.074	0.043
Mandible	t1 mes[a]	0.020	−0.002 – 0.042	0.074
	t1 dist	0.022	−0.002 – 0.046	0.072
	t3 mes	0.039	0.011 – 0.068	0.007
	t3 dist	0.032	0.003 – 0.067	0.073
Maxilla and mandible	t1 mes[a]	0.016	−0.001 – 0.032	0.052
	t1 dist[a]	0.023	0.006 – 0.039	0.008
	t3 mes	0.039	0.019 – 0.060	<0.001
	t3 dist	0.050	0.026 – 0.074	<0.001

[a]significant difference for gender.
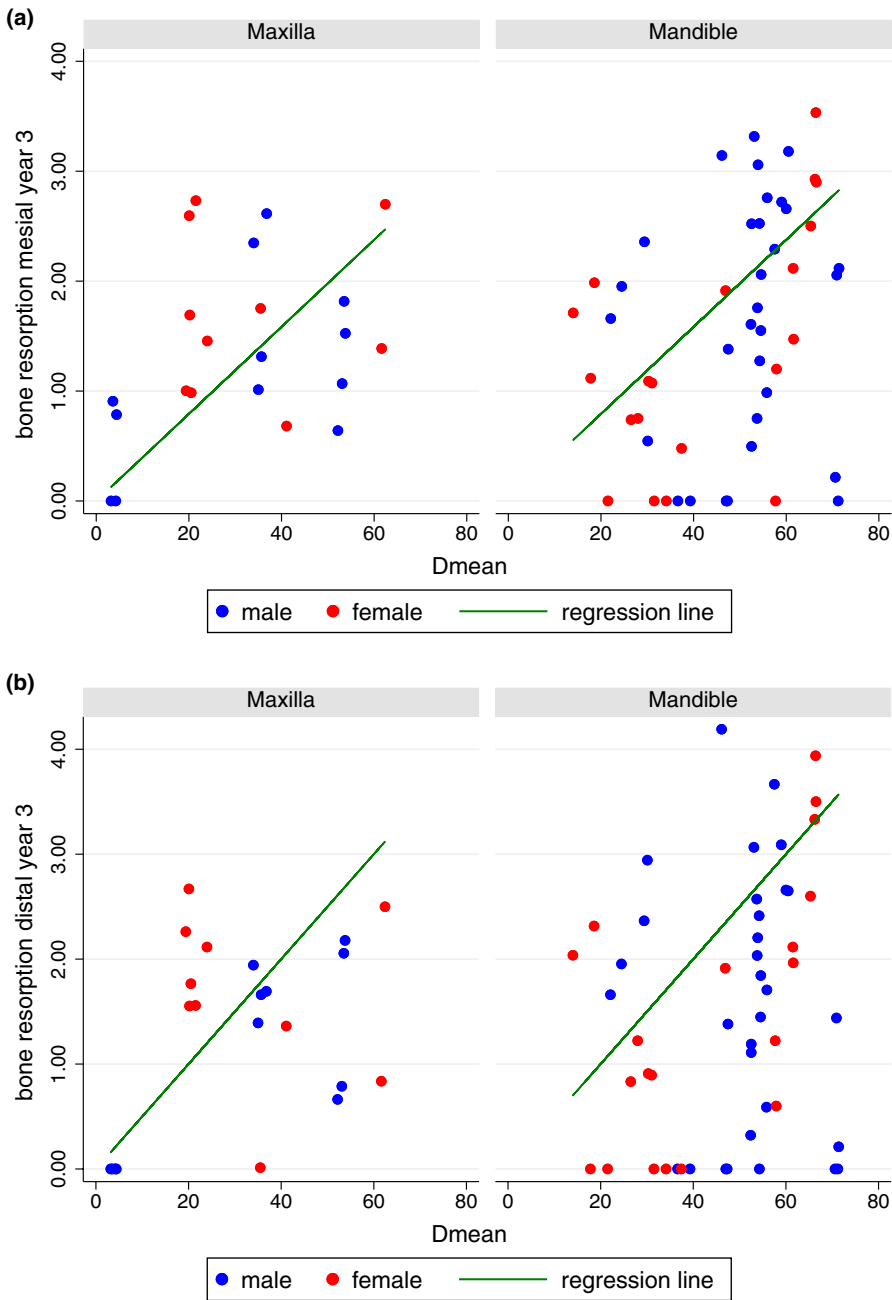
FIGURE 4 (a) Mesial bone resorption after 3 years as function of mean radiation dose (Dmean) shown for maxilla and mandible by gender. The green line indicates the estimated regression line from the linear mixed model. (b) Distal bone resorption after 3 years as function of mean radiation dose (Dmean) shown for maxilla and mandible by gender. The green line indicates the estimated regression line from the linear mixed model

Only Papi et al. (2019) did implement the calculation of radiation dosage at implant treatment sites via the analysis of radiation isodose mapping, yet focused mainly on comparing different modes of radiation. Thus, no information on sight-specific dose differences was given (e.g., mandible versus maxilla).

To the best of our knowledge, no further study exists that considers real implant-bed-specific radiation doses, and the wide range of implant-bed-specific Dmean (3.2–71.4 Gy) in the present study emphasizes the need to thoroughly distinguish implant locations in respect to tumor location and radiation planning.

The present study indicates a marginal bone loss of approximately 1 mm within the first year and of 0.5 mm within the following 2 years. The results were comparable to those found by Landes and Kovacs (2006) and Ernst et al. (2016) and are slightly higher than the data collected by Schoen et al. (2008), Nack et al. (2015), and Papi et al. (2019) 1 year after implantation. Still, due to the lack of information on sight-specific radiation differences comparability is limited. Nevertheless, in the present study, bone resorption rates 1 year after implantation were only slightly increased compared with most rates found in studies on implants in non-irradiated patients (Pardal-Peláez et al., 2020).

Follow-up scans were performed 1 and 3 years after implantation. As suspected, a higher sulcus bleeding index, as well as a higher plaque index, correlated with peri-implant bone resorption, thus indicating a relationship between oral hygiene and tissue inflammation with peri-implant soft and hard tissue health (Alassy et al., 2019; Rosing et al., 2019; Saulacic & Schaller, 2019). All patients within the present study are involved in a regular hygienist program (every three months).

Regarding localization (maxilla versus mandible), the results of measured mean bone level changes were comparable during the 3-year period.

With consideration of the implant-bed-specific radiation doses on the other hand, the results revealed an influence of radiation dose on the bone level changes within maxilla and mandible, when analyzed as separate entities. In the maxilla, a correlation with implant-specific radiation dose could be observed after 1 and 3 years, whereas a significant correlation was found after 3 years in the mandible. Comparing upper jaw and lower jaw, no significant difference was found, but a tendency can be observed, that the influence of implant-bed-specific radiation dose in the mandible appears to be higher in the long term. Nevertheless, the sample size is too small to draw definitive conclusions from this observation. Visch et al. (2002) found the outcome in the maxilla to be more favorable in irradiated patients. Taking the presented data into account, this might be due to the fact that HNC is commonly located in closer to proximity the lower jaw, potentially resulting in a high irradiation dose and damage to the mandibular bone (Funk et al., 2002; Raguse et al., 2016; Wierzbicka & Napierala, 2017). Thus, the potential bias of overestimating radiation dose in the upper jaw was ruled out by the present study design, and while the median dose to the implants in the mandible and the maxilla were still considerably high, the total radiation dose to the tumor was still significantly higher. This is an immensely relevant finding that needs to be considered for future study design in order to gain reliable results on the importance of RT dose in the "area of interest" for implant planning, on post-radiation peri-implant health, and therefore long-term success.

Taking the whole patient as reference, analysis of the presented data revealed that the mean dose to the implant bed seems to influence the bone resorption in the investigated patient cohort at both time points, but especially so after 3 years $(p < .001)$. This corresponds with the literature, which indicates that irradiation status in general has a negative influence on the long-term survival of implants (Chrcanovic et al., 2016; Granstrom et al., 1993). However, comparing studies on bone loss following irradiation, we found that conflicting data exist on whether or not irradiation status has a negative impact (Landes & Kovacs, 2006; Schoen et al., 2008). Only Schoen et al. implemented cumulative radiation doses to the interforaminal area, but implant-bed-specific differentiation in RT doses was still not implemented. The results of the present study might reflect general radiation-induced effects on adjacent structures and tissues: The long-term impact in particular seems to affect bone remodeling negatively by various potential mechanisms, such as reducing vascularization, causing endarteritis with tissue fibrosis and cell damage to osteoprogenitor cells (Chrcanovic et al., 2016; Magnus Jacobsson, 1985; Marx & Johnson, 1987; Scully & Epstein, 1996; Yerit et al., 2006). Therefore, the impact of RT observed in our study seems to be a long-term effect and was measurable despite the relatively small sample size and interindividual differences.

Concerning age, no influence on the bone level changes in connection to implant-specific radiation dose could be observed.

On the other hand, women showed higher bone resorption rates than men after 1 year, but due to men catching up on the resorption rate of females, these differences could not be observed after 3 years. Similar results were found in other investigations (Nack et al., 2015). Studies evaluating the influence of gender and age on implant success and osseointegration show conflicting results. While several studies showed no significant influence of these parameters on implant acceptance, Koszuta et al. found significant bone loss in non-irradiated female patients (Koszuta et al., 2015; van Steenberghe et al., 2002). Bone turnover in the elderly diminishes with increasing age, due to a potential decline in cell energy metabolism and various other factors, thus potentially resulting in poorer osseointegration and therefore leading to a measurably higher bone loss after 1 year (Zhang et al., 2019). Still, these effects did not seem to play a vital role when compared to younger patients in the present cohort. Nevertheless, increased age in general tends to coincide with various comorbidities, and elderly HNC patients in particular are well known to have a high prevalence of comorbidities, such as hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes, and osteoporosis, which can negatively influence implant success (Alsaadi et al., 2008; Eytan et al., 2019; Guillaume, 2016; van Steenberghe et al., 2002). Consequently, several studies suggested that the age-group of 60–70 years bears a greater risk of implant failure (Moy et al., 2005). However, age did not influence resorption rates significantly, which might in part be due to the limited sample size in this pilot study.

After 1 year, women tended to suffer from higher bone resorption than men, but these results leveled out after a period of 3 years. According to Higham and Faithfull (2015), data on hip fractures after pelvic RT suggest that older women have an increased risk of suffering from post-radiotherapy femoral neck and hip fractures, which appears to depend on the field of irradiation. This might indicate an unfavorable risk constellation in this patient cohort and could explain the adverse short-term results in older and female patients in the present study. Data on the potential influence of gender on dental implants are still controversial but indicate that postmenopausal women might have an increased risk of implant failure (Koszuta et al., 2015; Sverzut et al., 2008). Still, the effect of estrogen replacement therapy might influence bone resorption and implant success negatively in non-irradiated patients (August et al., 2001; Koszuta et al., 2015; Moy et al., 2005). Koszuta et al., for example, found higher bone resorption in a female patient group compared to postmenopausal women without hormonal replacement, but they analyzed bone loss only in non-irradiated patients. Due to the limited sample size, further subdivision of female patients was not possible in the present study, but the results after 3 years suggest that after successful osseointegration, bone resorption and long-term results are gender independent. Therefore, according to the present study, implant-bed-specific radiation dose, localization and gender could be considered as relevant risk factors for peri-implant bone resorption. Nevertheless, prospective randomized and controlled

studies with larger sample sizes need to verify these results. Modern RT techniques offer the option to integrate the patients' individual RT plan and dosimetric data to the area of interest, and this specific information should be acquired for clinical and scientific considerations.

Recent data on the timing of implantological rehabilitation published by Di Carlo et al. (2019) led the authors to the conclusion that delayed implant placement and loading after more than six months was the safest protocol. However, the optimal timing for implantation remains controversial, and some authors recommend immediate insertion since osseointegration can be achieved prior to irradiation, resulting in early rehabilitation with high denture satisfaction and thus in an improvement in the quality of life (Barber et al., 2011; Di Carlo et al., 2019; Korfage et al., 2010; Lorenzi et al., 2019; Schoen et al., 2004). Yet, the likelihood of early cancer recurrence needs to be considered since metal artifacts can negatively influence radiologic follow-up (Alberico et al., 2004; Nahmias et al., 2008). In addition, prolongation of the start of radiotherapy can potentially impair the oncological outcome. Due to the higher initial resorption rates in women, the results of the present study might call for increased caution and consideration of a more conservative implant treatment protocol in this specific cohort. Nevertheless, evidence regarding this matter is still too weak for a recommendation against early implantation and loading.

After all, the present results show that despite the aforementioned risk factors, overall bone resorption rates are low in irradiated, non-smoking patients who underwent regular follow-ups. Many studies did not actively exclude active smokers when investigating the effects of radiotherapy on dental implants and peri-implant tissues even though smoking is known to be a major risk and influencing factor (Chrcanovic et al., 2015, 2016).

In conclusion, the described assessment is a valuable tool for the precise evaluation of representative implant-bed-specific doses since these vary widely in relation to the individual field of radiation. This should not only be considered for further studies clarifying the remaining uncertainties on the impact of radiotherapy and dose variances on implant success but also calls for close clinical collaboration between surgeons and radiotherapists, potentially leading to prosthetic- and radiotherapy-driven implant planning by matching dosimetric curves with the respective implant planning software.

Short-term effects 1 year after implantation demonstrated higher bone resorption in women. Besides that, radiation dose had a tendency to negatively influence peri-implant bone resorption rate after 1 year and did so significantly after 3 years. The limitations of this study arise from its nature as a pilot study, and the presented results should, above all, serve as a springboard for further in-depth investigation on the matter. To draw direct clinical conclusions, larger prospective studies are needed which should include precise clinical information on tissue quality.

Therefore, RT dose to the area of the implant must be seen as a relevant long-term risk factor for implant health and survival. Clinical parameters for oral hygiene and inflammation correlated with bone resorption, as well. If professionally managed and with sufficient aftercare, implant-based rehabilitation of irradiated HNC patients is a relatively safe method without an equivalent alternative, after all. Still, knowledge about the influence of specific radiation doses on peri-implant tissue health is of the utmost importance for reliable treatment planning and long-term success.

CONFLICTS OF INTEREST

All authors declare that no conflict of interest exists.

AUTHOR CONTRIBUTION

Norbert Neckel: Data curation (equal); Formal analysis (equal); Investigation (lead); Methodology (equal); Software (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). Pia Wagendorf: Data curation (lead); Investigation (equal); Writing-original draft (supporting). Claudia Sachse: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Validation (equal). Carmen Stromberger: Conceptualization (lead); Data curation (equal); Investigation (equal); Methodology (equal); Software (lead); Supervision (equal); Visualization (equal); Writing-review & editing (equal). Max Heiland: Resources (lead); Supervision (supporting); Writing-review & editing (equal). Susanne Nahles: Conceptualization (lead); Data curation (lead); Formal analysis (equal); Investigation (equal); Methodology (lead); Project administration (lead); Resources (equal); Software (equal); Supervision (lead); Validation (lead); Writing-original draft (supporting); Writing-review & editing (lead).

S.N. and N.N. conceived the ideas; N.N., P.W., C.St., and C.Sa. collected the data; N.N., P.W., and S.N. analyzed the data; C.St. and C.Sa. led the data matching; N.N and P.W. led the writing; S.N. and C.St. led the manuscript review and editing; M.H., C.St., and S.N. provided the resources; M.H. and C.St. were responsible for oncological treatment; K.V. analyzed the data and performed the statistical analysis; and S.N. led the dental rehabilitation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.