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Significance of site-specific radiation dose and technique for success of implant-based prosthetic rehabilitation in irradiated head and neck cancer patients—A cohort study

Franziska Wolf Dr. med. dent.[1] | Steffen Spoerl Dr. med.[1] | Maximilian Gottsauner Dr. med., Dr. med. dent.[1] | Christoph Klingelhöffer PD, Dr. med., Dr. med. dent.[1] | Gerrit Spanier Dr. med., Dr. med. dent.[1] | Carola Kolbeck Prof., Dr. med. dent.[3] | Torsten E. Reichert Prof., Dr. med., Dr. med. dent.[1] | Matthias G. Hautmann PD, Dr. med.[2] | Tobias Ettl Prof., Dr. med., Dr. med. dent.[1]

[1]Department of Oral and Maxillofacial Surgery, University Hospital Regensburg, Regensburg, Germany

[2]Department of Radiotherapy, University Hospital Regensburg, Regensburg, Germany

[3]Department of Prosthodontics, University Hospital Regensburg, Regensburg, Germany

Correspondence
Tobias Ettl, Department of Oral and Maxillofacial Surgery, University Hospital Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany.
Email: tobias.ettl@ukr.de

Abstract

Background: Radiotherapy aggravates implant-based prosthetic rehabilitation in patients with head and neck cancer.

Purpose: To evaluate the impact of radiation dose at implant and parotid gland site for prosthetic rehabilitation.

Material and methods: The retrospective study includes 121 irradiated head and neck cancer patients with 751 inserted implants. Radiation doses on implant bed and parotid gland site were recorded by 3-dimensional modulated radiation plans. Implant success was clinically and radiographically evaluated according to modified Albrektsson criteria and compared to treatment- and patient-specific data.

Results: Implant overall survival after 5 years was 92.4% with an implant success rate of 74.9%. Main reasons for implant failure were marginal bone resorption (20.9%), implant not in situ or unloaded (9.6%) and peri-implantitis (7.5%). A mean radiation dose of 62.6 Gy was applied with a mean parotid dose of 35 Gy. Modulating radiation techniques went along with lower grades of xerostomia ($p < 0.001$). At implant site mean doses of 57.5, 42.0, and 32.3 Gy were recorded for oral, oropharyngeal, and hypopharyngeal/laryngeal carcinoma, respectively. Implant success inversely correlated to radiation dose at implant site. Strong predictors for implant failure in uni- and multivariate analysis were implant-specific dose >50 Gy (HR 7.9), parotid dose >30 Gy (HR 2.3), bone (HR 14.5) and soft tissue (HR 4.5) transplants, bad oral hygiene (HR 3.8), nonmodulated radiation treatment planning (HR 14.5), and nontelescopic prosthetics (HR 5.2).

Matthias G. Hautmann PD, Dr. med. and Tobias Ettl Prof., Dr. med., Dr. med. dent. contributed equally to the results of this work.

Conclusion: Radiotherapy impedes implant success in a dose-dependent manner at implant site. Modern radiation techniques effectively reduce xerostomia favoring implant-based prosthetic rehabilitation. Implantation in bone grafts is more critical and telescopic-retained overdentures should be preferred.

KEYWORDS
dose, head and neck cancer, implant-specific, modulated, radiotherapy, success

1 | INTRODUCTION

Implant-based prosthetic rehabilitation is an established procedure for head and neck cancer patients as conventional prosthodontic techniques are not promising in most cases.[1-3] Ablative surgery with subsequent reconstruction results in extensive anatomical alterations.[4] Radiotherapy or chemoradiation of more than 60 Gy often causes relevant acute as well as late side effects.[5] Apart from absolute radiation dose, localization of the target volume (eg, larynx or oral cavity) and radiation technique (conventional or modulated radiation treatment planning) influence effective radiation dose for the salivary glands and the upper and lower jaw bone aggravating dental implant healing. In the literature so far, implant-based prosthetic rehabilitation is mostly evaluated comparing irradiated versus nonirradiated patients with different criteria for defining implant success or implant survival.[6-21] In some surveys, the impact of absolute radiation dose is investigated.[9,21-25] A few years ago, we reported the significance of the planned radiation target volume for success of implant based prosthetic outcome.[21,26] Just recently, a pilot study was published investigating the influence of implant-specific radiation doses on peri-implant hard and soft tissues in a small cohort of irradiated patients.[27] The present study retrospectively analyses the specific cumulative dose for every single implant inserted in a considerably large cohort of head and neck cancer patients by contouring the implants as areas of interest in the radiotherapy planning system. Moreover, radiation doses of the parotid salivary glands are evaluated depending on absolute radiation dose, localization of the target volume, and radiation technique. Long-term outcome of the inserted implants and prosthodontic restaurations is investigated by clinical and radiographical assessment.

What is known

Radiotherapy aggravates implant-based prosthetic rehabilitation in patients with head and neck cancer. There is little information about significance of implant-specific radiation dose for implant success.

What this study adds

By evaluating 3-dimensional modulated radiation plans, this study demonstrates the direct impact of implant bed-specific radiation dose on implant success in the largest cohort to date.

2 | MATERIAL AND METHODS

2.1 | Study design

A retrospective study was conducted with irradiated patients who received implant-based prosthetic rehabilitation following treatment of head and neck cancer at the Departments of Oral and Maxillofacial Surgery and Prosthodontics, between 2005 and 2018. The study was approved by the local ethic committee of the University of Regensburg, Germany (No. 17-621-101).

Our study was conducted in compliance with the appropriate EQUATOR guidelines (STROBE).

2.2 | Evaluation of patient characteristics and implant-based rehabilitation

The evaluation included demographic data (age, sex, date of birth), health status (nicotine an alcohol abuse, pre-existing medical condition, cancer type, TNM-Classification, ablative surgery, bone and/or soft tissue reconstruction) implant treatment (surgery date, date of implant exposure, type, diameter, length, site [maxilla, mandible, anterior, posterior], and augmentation [internal or external sinus floor elevation, lateral], osteoradionecrosis, prosthetic type) of each patient.

2.3 | Evaluation of radiation therapy and irradiation protocols

In all patients, the contouring and planning details of radiotherapy, fractionation, and total dose were reviewed retrospectively. The region of interest (implant site, parotid glands) could be contoured in 61 available 3-dimensional radiation plans with subsequent verification of the implant bed by later imaging until an exact match was found for every particular patient (Figure 1(A) and (B)). In this way, implant-specific radiation dose as well as dose of the parotid glands

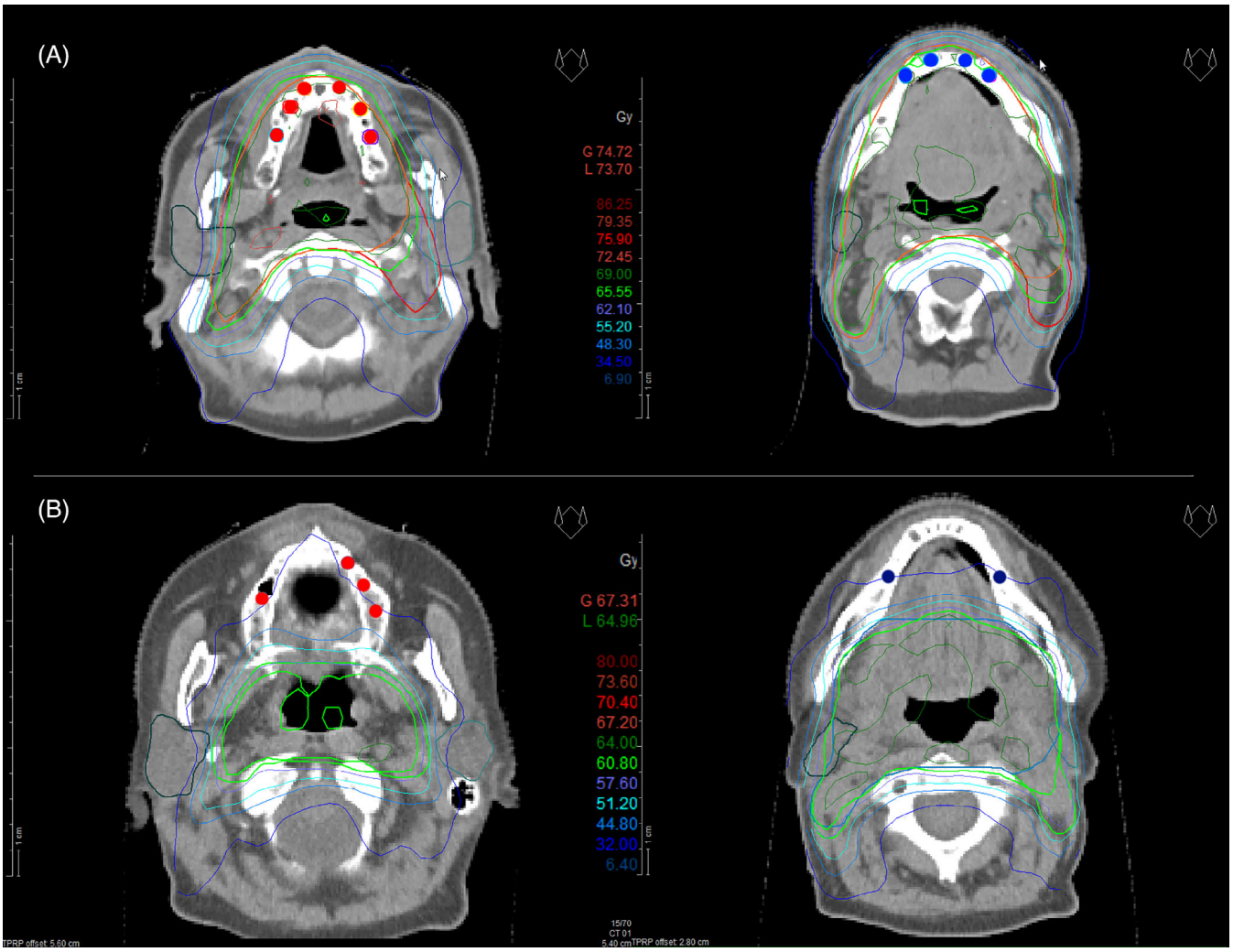


FIGURE 1 (A) (Upper row) Patient with squamous cell carcinoma of the tongue; TNM: G2 cT2 cN1 cM0; technique: Intensity Modulated Radiation Therapy; PTV: 51.6 Gy, Boost: 18 Gy; absolute radiation dose: 69.6 Gy; Ø Parotid gland dose: right 48.5 Gy, left 45.1 Gy. (B) (Lower row) Patient with squamous cell carcinoma of the supraglottis and the base of the tongue; TNM: G3 pT1 pN2 cM0; Technique: intensity modulated radiation therapy; PTV: 54 Gy; Boost: 10 Gy; absolute radiation dose: 64 Gy; Ø Parotid gland dose: right 39.1 Gy, left 36.2 Gy. Abbreviations: Gy, Gray; PTV, planning target volume; ROI, region of interest

Upper row:										
ROI	16	14	12	22	24	26	34	32	42	44
Ø Specific peri-implant dose (Gy)	70.2	69.0	68.8	68.9	69.4	69.8	66.5	68.1	66.7	66.5
Lower row:										
ROI	16	23	25	27	36	46				
Ø Specific peri-implant dose (Gy)	32.2	30.2	27.9	38.3	33.5	32.9				

(minimum, maximum, median dose; D98, D50, D2, average) were recorded for 61 patients and 365 implants. Additionally, each implant ($n = 751$) was individually classified in accordance with the original planning target volume (inside/near/outside).

2.4 | Clinical assessment

The intraoral situation of patients was documented by clinical monitoring. Probing depth (mesial, distal, lingual, buccal), recession, implant mobility, peri-implant infection, suppuration, attached gingiva, plaque-index, bleeding-index, bleeding-on-probing, neuropathy, persistent pain, and grade of xerostomia were investigated.

2.5 | Radiographic assessments

In all cases, the marginal bone status was evaluated by panoramic radiographs, which were calibrated by using the known width and length of the implants. By measuring the distance from the implant

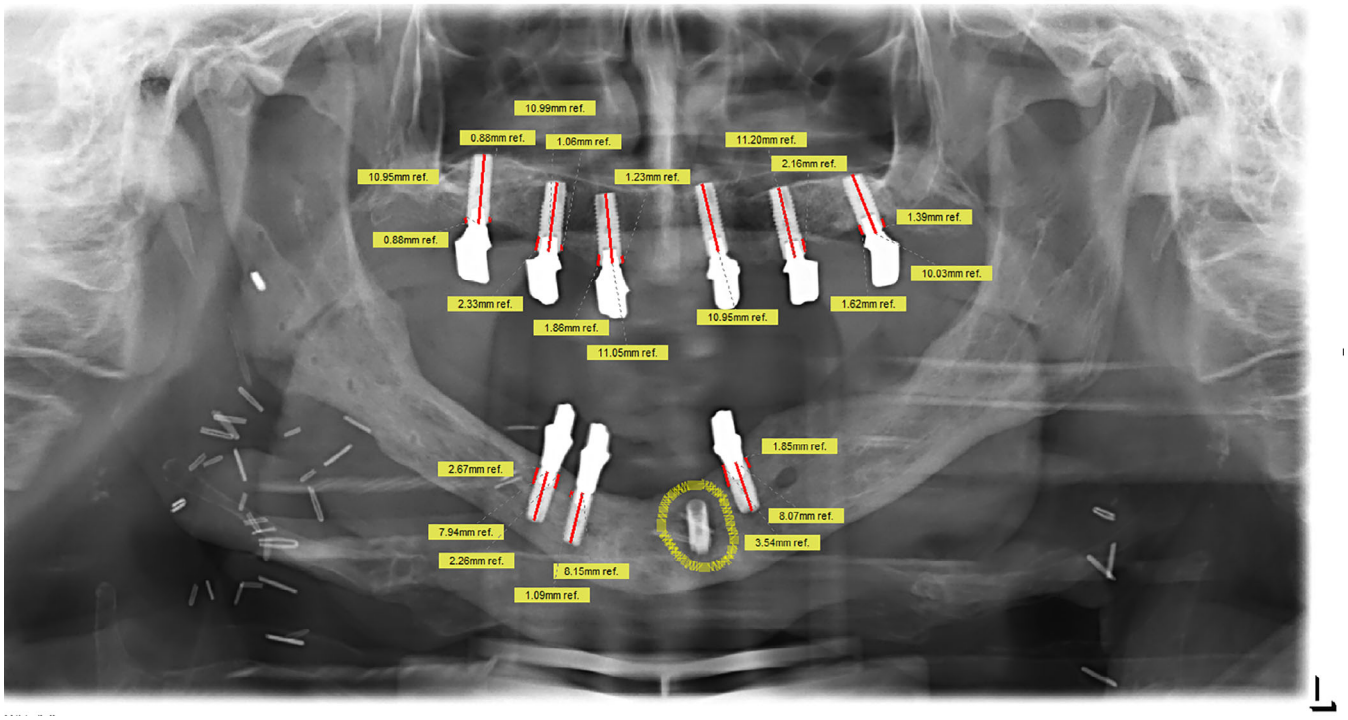


FIGURE 2 Radiographic implant follow-up after 77 months in a patient with carcinoma of the floor of mouth and reconstruction with a free fibular flap. One implant sleeping. Peri-implant bone resorption to implant shoulder is measured after calibration of implant length

shoulder to the marginal bone level mesially and distally, the marginal bone loss could be provided (Figure 2).

2.6 | Inclusion criteria

Patients who had completed implant placement and prosthetic rehabilitation after ablative surgery and/or radio(chemo)therapy due to head and neck cancer.

2.7 | Exclusion criteria

Patients were excluded in case of incomplete data.

2.8 | Patients and treatments

Four different manufacturers of implants were used in this study (Dentsply Sirona, Straumann, Camlog, Nobel Biocare). Indications for implant-based prosthetic rehabilitation were switching gaps, free end situations or edentulous jaws. Dental implants were placed either in irradiated native or grafted bone in a two-stage surgical procedure. In this study, vascularized osseous free flaps were transferred from the fibula, scapula or iliac crest (Table 1). Internal or external sinus floor elevation as well as lateral augmentation where used in case of insufficient bone supply. Average healing time after implant placement was 4–6 months (mean 23 weeks, range 8–99 weeks), depending on bone quality and different irradiation doses. Connecting elements between suprastructure and implants were individually adapted to anatomically modified conditions of each patient (bar-retained, telescopic crown, locator-retained, fixed crown, or bridge).

2.9 | Implant success

To enable a comparison to other studies, implant survival and implant success were recorded. For implant survival, loaded in-situ implants where evaluated which excludes removed and sleeping implants. Implant success was assessed using modified Albrektsson criteria[28-30] where clinical and radiological parameters were combined. If one or more parameters could not be met, the implant was rated as failure. Assessed clinical parameters included: implants in function, absence of persistent pain, no lesion of nerve; absence of mobility; absence of a clinically measurable peri-implant infection. Peri-implant infection was diagnosed in case of: suppuration, positive plaque-index, positive bleeding on probing, and probing depth of more than 4 mm. Radiological implant success (measured by radiographic investigation) was classified as follows: absent peri-implant radiolucency around the implant and absence of progressive peri-implant bone resorption of more than 1.5 mm in the first year after implant placement as well as of more than 0.2 mm during the following years.

Following secondary variables were analyzed for impact on implant success. (1) radiotherapy-related parameter: period of time between end of irradiation and implant placement; mode of radiotherapy; correlation of the planning target volume to the implant bed; total dose of radiation,

specific peri-implant radiation dose; radiation dose at both parotid glands; severity of xerostomia after irradiation; incidence of osteoradionecrosis; (2) implant specific characteristics: peri-implant hard tissue (native vs grafted); peri-implant soft tissue (local mucosa or flap tissue); augmentation (internal or external sinus floor elevation and local defects around the implant shoulder); implant length, diameter and manufacturer; site of implant location (maxilla or mandible, anterior or posterior); healing time; type of prosthodontic superstructure (telescopic, bar-retained, locator, fixed crown/bridge); (3) patient characteristics: age, sex, nicotine abuse, alcohol abuse, oral hygiene, diabetes mellitus.

2.10 | Statistical analysis

For statistical analysis SPSS (Version 25.0, IBM Corp., Armonk, NY) was used. A p-value ≤ 0.05 was defined as statistically significant. For univariate analysis, chi-square and Fisher's exact test were used to compare different groups of outcome parameters. Implant success was generated as cumulative survival rates using the Kaplan–Meier method (time-to-event) and the log-rank test for differences between group distribution. Multivariate logistic Cox regression was used to identify independent predictors of implant failure. Results were reported with hazard ratios (HRs) and 95% confidence intervals (CIs). The level of statistical significance was 5%. Only variables significant in univariate analysis were included in multivariate analysis.

3 | RESULTS

3.1 | Patients and treatment

Mean clinical follow-up period was 3.8 years (range 0.6–18.5 years) and mean radiological follow-up time was 3.4 years (range 1–18.5 years) after implant placement. This retrospective study comprised 121 irradiated head and neck cancer patients (91 male and 30 female; mean age 65.7 years, range 45–89 years), 94.2% had been treated for squamous cell carcinoma. Table 1 shows the patient characteristics.

For reconstruction of extensive intraoral hard tissue defects, 19 patients (15.7%) received a microvascular fibular transplant. Two patients received a vascularized, 18 patients (14.9%) a free non-vascularized iliac crest transplant and 2 patients (1.6%) a microvascular scapula graft. Forty-three patients (35.5%) were restored by soft tissue flaps, 21 patients (17.4%) received a microvascular radial forearm flap, 8 patients a pectoralis major flap (6.6%), 4 patients a anterolateral thigh flap (3.3%), 1 patient a latissimus dorsi flap (0.8%), 4 patients a nasolabial flap (3.3%), and 5 patients a platysma flap (4.1%).

All patients required radiotherapy with a mean dose of 62.6 Gy (range 35–74 Gy), thereof 31 definitive (25.6%) and 90 adjuvant (74.4%). Modulating radiation techniques (IMRT, IMAT VMAT, IGRT) were used in 84 (69.4%) patients whereas 37 (30.6%) patients received conventional 2-dimensional or 3-dimensional planned radiotherapy. Modern modulating planning techniques were associated with less severe xerostomia rates (50.8% grade II–III) compared to conventional techniques (68.3% grade II–III) (p < 0.001). Analysis of the available 3-dimensional radiation treatment plans (all modulated regimens) revealed a mean overall parotid gland dose of 35 Gy (range 2.4–60.9 Gy) with a mean parotid dose of 32.3 Gy for oral cancer, 38.9 Gy for oropharyngeal carcinoma, 27.8 Gy for nasopharyngeal carcinoma and 36.7 Gy for laryngo-/hypopharyngeal cancer (Table 2).

A total of 59 patients (48.8%) received chemotherapy in addition to radiotherapy. Twenty six for definitive chemoradiation (44.1%), 33 for adjuvant chemoradiation (55.9%). After radiotherapy, 111 patients

TABLE 1 Patient baseline characteristics (n = 121)

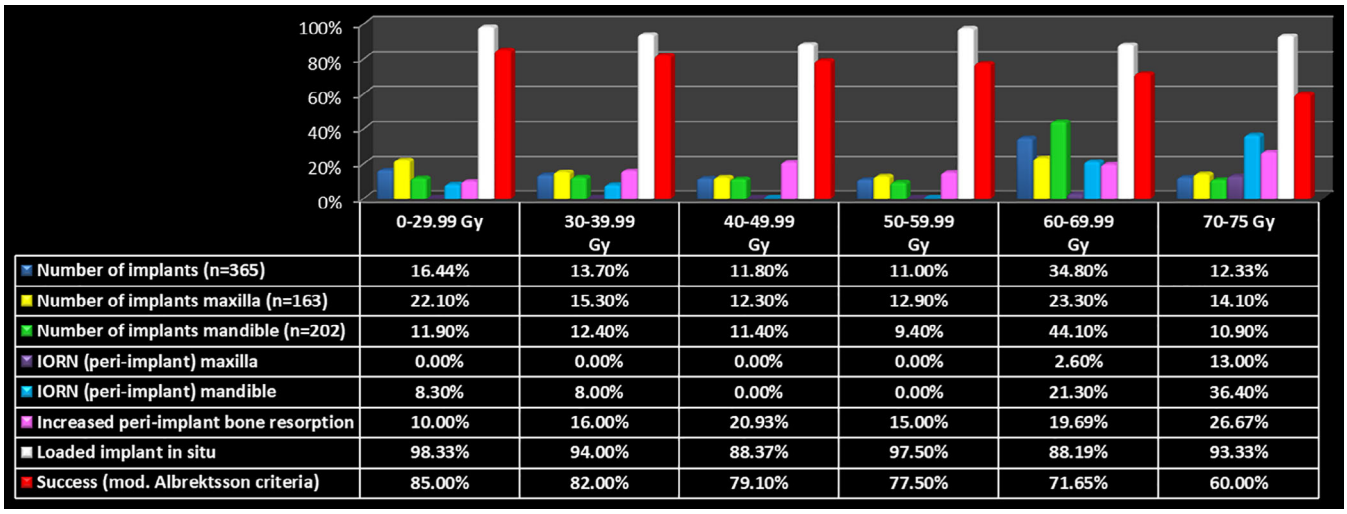
	Mean (range) or number (%)
Age, years	65.7 (45–89)
Gender	
Male	91 (75.2%)
Female	30 (24.8%)
Smoker	
At time of tumor therapy	96 (79%)
At time of implant therapy	27 (22%)
Cancer site	
Multi-level	16 (13.2%)
Oral cavity	66 (54.5%)
Oropharynx	27 (22.3%)
Larynx, Hypopharynx	8 (6.6%)
Nasopharynx, Sinus maxillaris	3 (2.5%)
Parotid gland	1 (0.8%)
Grading	
G1	3 (2.5%)
G2	88 (72.7%)
G3	26 (21.5%)
T stage	
Tx	1 (0.8%)
T1	19 (15.9%)
T2	32 (26.9%)
T3	29 (24.4%)
T4	38 (31.9%)
N status	
Nx	4 (3.5%)
N0	51 (43.6%)
N1	12 (10.3%)
N2	48 (41.1%)
N3	2 (1.7%)
Hard tissue reconstruction after intraoral local defects	
FFF	19 (15.7%)
SFF	2 (1.7%)
ICFF	20 (16.5%)
Soft tissue reconstruction	70 (57.9%)

Abbreviations: FFF, fibula free flap; ICFF, vascularized/nonvascularized iliac crest free flap; SFF, scapula free flap.

TABLE 2 Mean dose at implant and parotid site and success rate depending on tumor site

	Mean impl dose* Gy (*SD*), $n = 365$	Mean parotid dose* Gy (*SD*), $n = 365$	Impl success# $n = 751$
Oral cavity	57.5 (16.1)	32.3 (11.5)	67.3% (276/410)
Oropharynx	42.0 (22.6)	38.9 (18.3)	78.9% (198/251)
Nasopharynx	44.4 (14.0)	27.8 (3.1)	75% (18/24)
Hypopharynx/larynx	32.3 (11.5)	36.7 (3.5)	81.8% (54/66)

*$p < 0.001$ (ANOVA).
#$p = 0.008$ (Chi-Square).



	0-29.99 Gy	30-39.99 Gy	40-49.99 Gy	50-59.99 Gy	60-69.99 Gy	70-75 Gy
Number of implants (n=365)	16.44%	13.70%	11.80%	11.00%	34.80%	12.33%
Number of implants maxilla (n=163)	22.10%	15.30%	12.30%	12.90%	23.30%	14.10%
Number of implants mandible (n=202)	11.90%	12.40%	11.40%	9.40%	44.10%	10.90%
IORN (peri-implant) maxilla	0.00%	0.00%	0.00%	0.00%	2.60%	13.00%
IORN (peri-implant) mandible	8.30%	8.00%	0.00%	0.00%	21.30%	36.40%
Increased peri-implant bone resorption	10.00%	16.00%	20.93%	15.00%	19.69%	26.67%
Loaded implant in situ	98.33%	94.00%	88.37%	97.50%	88.19%	93.33%
Success (mod. Albrektsson criteria)	85.00%	82.00%	79.10%	77.50%	71.65%	60.00%

FIGURE 3 Dose-dependent implant performance und occurrence of osteoradionecrosis

(91.7%) developed therapy-induced xerostomia: 38 patients grade I (31.4%), 62 patients grade II (51.2%), and 11 patients grade III (9.1%). The mean time interval between the last day of irradiation and implantation was 48.7 months (range 3–260 months).

In a two-stage procedure, 751 implants were inserted by crestal access (maxilla: anterior 129 (17.2%), posterior 204 (27.2%); mandible: anterior 213 (28.4%), posterior 205 (27.3%)). Implant length ranged from 6 to 13 mm and diameter from 3.3 to 5 mm. With regard to the planning target volume (PTV) implants were inserted as follows: 521 in-field (69.4%), 157 near-field (20.9%), and 73 implants out-of-field (9.7%). For 365 implants (48.6%), exact irradiation dose of the implant bed (mean 38.4 Gy, range 0–76.8 Gy) could be measured. Figure 1(A), (B) and Table 2 show the differences of implant-specific dose depending on site of the primary tumor. After oral cancer treatment implants inserted at anterior oral cavity site received a cumulative mean dose of 56 Gy while 59 Gy were measured for implants inserted in the posterior oral cavity region. In case of oropharyngeal carcinoma, 42 Gy were calculated for both sites, for nasopharyngeal cancer 28 Gy were documented in anterior and 48 Gy in posterior implant site. In case of laryngo−/hypopharyngeal carcinoma, 26 Gy were measured in the anterior and 37 Gy in the posterior region of bony jaws. Out of all implants, 590 (78.6%) were inserted into native jaw bone and 161 (21.4%) implants into grafted iliac crest or fibula bone. A total of 180 (24%) implants were surrounded by soft tissue graft and 571 (76%) by local gingiva. For 152 implants located in the posterior maxilla additional sinus floor elevation (103 external; 49 internal) was performed. Lateral augmentation was necessary in 217 implant insertions (70 autologous, 34 allogeneic/xenogeneic, and 113 combinations). The mean healing time for implants was 23 weeks (range 8–99 weeks) and a mean period of 8.6 months (range 2–85) between implant uncovering and end of prosthetic rehabilitation. Different types of prosthetic superstructures were anchored on the implants, as follows: 487 telescopic-retained (64.9%), 127 individual bar-retained (16.9%), 68 locator-retained (9.1%), and 60 fixed crown or bridge (8%). A total of 37 patients (30.6%) developed osteoradionecrosis following radiation therapy: 2 in the maxilla jaw bone, 17 in the mandible jaw bone, and 18 in both of jaws. Regarding the implant bed, 72 were affected by radiation therapy-induced osteonecrosis (33 preimplantation; 39 postimplantation). Figure 3 shows the impact of increasing radiation dose at the implant bed on different parameters like development of osteoradionecrosis, peri-implant bone resorption, and Implant survival.

Finally, a total of 564 implants were clinically reviewed and evaluated: the mean plaque index was 1.09 (range 0–3), the mean bleeding index was 0.94 (range 0–3), the mean width of attached vestibular gingiva was 1.13 mm (range 0–7 mm), and the mean bleeding on probing (BOP) score was 23.61% (range 0–96%). The pocket depth on the implants was measured at 4 points (mesially:

TABLE 3 Patient and treatment-specific factors and implant success. Multivariate analysis for implant failure

Variable Coding	n Implant success (%)	Univariate analysis *p* value	Multivariate analysis Exp (*B*)	95% CI	*p* value
Smoker (tumor therapy)		0.225			
No	106/154 (68.8%)				
Yes	440/597 (73.7%)				
Smoker (implant therapy)		**0.008**	2.32	0.91–5.92	0.079
No	438 /583 (75.1%)				
Yes	108/168 (64.3%)				
Oral hygiene		**<0.001**	3.76	1.80–7.87	**<0.001**
Grade I/II	329/391 (84.1%)				
Grade III/IV	85/138 (61.6%)				
Type of radiotherapy		0.883			
Definitely	163/215 (75.8%)				
Adjuvant	383/536 (71.5%)				
Time between radiation and implantation		0.775			
≤12 months	51/68 (75.0%)				
>12 months	495/683 (72.5%)				
Technique of Radiotherapy		**0.011**	0.095	0.02–0.42	**0.002**
Conventional	138/209 (66.0%)				
Modulated	408/542 (75.3%)				
Implant bed		**0.026**	5.08	1.23–20.83	**0.025**
Near/outside PTV	180/230 (78.3%)				
Inside PTV	366/521 (70.2%)				
Radiation dose (absolute)		0.794			
≤60 Gy	173/240 (72.1%)				
>60 Gy	373/511 (73%)				
Radiation dose (specific-peri-implant)		**0.008**	7.87	2.16–28.57	**0.002**
≤50 Gy	126/153 (82.4%)				
>50 Gy	149/212 (70.3%)				
Radiation dose (parotid glands)		**0.013**	2.33	0.91–5.95	0.078
≤30 Gy	107/129 (82.9%)				
>30 Gy	168/236 (71.2%)				
Chemotherapy		0.149			
No	229/327 (70%)				
Yes	317/424 (74.8%)				
Xerostomia		**0.004**	1.53	0.67–3.49	0.31
Grade 0/I	228/290 (78.6%)				
Grade II/III	318/481 (69%)				
Osteoradionecrosis (specific-peri-implant)		**<0.001**	1.57	0.26–9.43	0.62
No	504/674 (74.8%)				
Yes	42/77 (54.5%)				
Bone transplant		**<0.001**	14.49	3.53–58.82	**<0.001**
No	452/590 (76.6%)				
Yes	94/161 (58.4%)				
Soft tissue transplant		**0.001**	4.51	1.04–19.55	**0.044**
No	431/569 (75.7%)				
Yes	113/180 (62.8%)				

(Continues)

TABLE 3 (Continued)

Variable Coding	n Implant success (%)	Univariate analysis *p* value	Multivariate analysis Exp (*B*)	95% CI	*p* value
Jaw site		0.520			
Maxilla	246/333 (73.9%)				
Mandible	300/418 (71.8%)				
Implant site		0.990			
Anterior	255/342 (74.6%)				
Posterior	291/409 (71.1%)				
Implant length		0.307			
≤10 mm	241/323 (74.6%)				
>10 mm	305/428 (71.3%)				
Implant diameter		0.613			
≤4 mm	279/388 (71.9%)				
>4 mm	267/363 (73.6%)				
Augmentation (lateral)		**0.013**	1.10	0.49–2.48	0.82
No	402/534 (75.3%)				
Yes	144/217 (66.4%)				
Healing time		0.341			
4 months	257/357 (72%)				
>4 months	266/354 (75.1%)				
Prosthetic superstructure		**<0.001**	0.19	0.09–0.42	**<0.001**
Nontelescopic	172/264 (65.2%)				
Telescopic	374/487 (76.8%)				

Notes: CI, confidence interval, significant results in bold; Chi-square and Fisher's exact test for univariate analysis. Binary logistic regression for multivariate analysis.

mean 2.57 mm, range 1–6 mm; distally: mean 2.48 mm, range 1–6.5 mm; vestibular: mean 2.13 mm, range 0–7 mm; orally: mean 2.47 mm, range 0–7 mm). With a view to the health of peri-implant tissue, 220 (39%) implants showed no signs of inflammation, 254 (45%) had a peri-implant mucositis and 56 (9.9%) showed all signs of a peri-implantitis.

3.2 | Implant survival and success

Overall 1-, 3-, 5-, and 10-year survival rates (in situ and functionally loaded) of the 751 implants were 96.5%, 94.8%, 92.4%, and 90.4% after implant placement. Sixty two implants (8.3%) were lost and removed in 32 patients (39 mandible, 23 maxilla). Main reasons were failed osseointegration ($n = 15$) and persistent peri-implantitis ($n = 39$) within 1–113 months after uncovering. Fifteen implant losses were associated with osteoradionecrosis of the implant bed (2 preimplantation, 13 postimplantation).

Ten osseointegrated implants (1.3%) were not functional loaded and remained covered (sleeper) in 8 patients (9 mandible, 1 maxilla). Twenty four of 62 removed implants were placed in transplanted bone (20 iliac crest, 4 fibular) and 38 in native bone.

The implant success rates in accordance to the modified Albrektsson criteria were 76.3%, 74.9% and 73.5% after 3-, 5-, and 10-year follow up. Increased marginal bone resorption ($n = 157$, 20.9%) was the most common reason for implant failure followed by implant not in situ or unloaded ($n = 72$, 9.6%) and peri-implantitis ($n = 56$, 7.5%). Of course some implants met more than one criteria. In terms of peri-implant bone resorption, the mean marginal bone loss after 1 year was 0.39 mm mesially and 0.44 mm distally compared to 0.82 mm mesially and 0.8 mm distally after 3 years, as well as 1.12 mesially and 1.01 mm distally after 5 years. Table 3 shows univariate associations between of tumor-related, patient- and implant-specific factors and implant success. Peri-implant osteoradionecrosis ($p < 0.001$), implantation in transplanted bone ($p < 0.001$), nontelescopic prosthetic suprastructure ($p < 0.001$), and oral hygiene ($p < 0.001$) were found to be highly associated with implant failure. Further significant factors were soft tissue transplant ($p = 0.001$), xerostomia ($p = 0.004$), conventional technique of radiotherapy ($p = 0.011$), increased peri-implant radiation dose ($p = 0.008$), smoker during implant therapy ($p = 0.008$), increased parotid salivary gland dose ($p = 0.013$), lateral augmentation ($p = 0.013$), and localization of implant bed in PTV ($p = 0.026$). Regarding the time interval between end of radiotherapy and implant placement, success rates for implantation within the first year (75%, $n = 64$)

and the second year (75.7%, $n = 222$) after irradiation are comparable whereas implant insertion after more than 2 years points to slightly worse success rates without reaching statistical significance (71%, $n = 465$) ($p = 0.394$). In multivariate analysis, peri-implant bone transplant ($p < 0.001$, HR 14.5), oral hygiene ($p < 0.001$, HR 3.8), prosthetic suprastructure ($p < 0.001$, HR 5.2), specific peri-implant radiation dose ($p = 0.002$, HR 7.9), technique of radiotherapy ($p = 0.002$, HR 10.5), localization of implant bed to PTV ($p = 0.025$, HR 5.1), and soft tissue transplant around the implant ($p = 0.044$, HR 4.5) revealed as statistically significant parameters.

4 | DISCUSSION

Implant-based prosthodontics have been established in prosthetic rehabilitation of irradiated head and neck cancer patients although implant success rates are lower than in patients without irradiation.[19,31,32] To date most studies dealing with this topic compare radiotherapy versus no radiotherapy.[6-21] Some studies are more detailed considering relation of the implant bed to the radiation target volume (in-field, near-field and out-of-field).[14,21,24,26,33] By use of the 3-dimensionalconformal treatment plans, exact dose constraints for the planned implant sites can be calculated. This adds further critical information for implant success or failure. Apart from radiation dose at implant site, it is not clear if the negative radiation effect is attributed more to the local dose at the implant site or for example to radiation-induced xerostomia.

The current study therefore evaluated the exact dose at implant site and also the dose constraints for the parotid glands, and investigated its impact, together with further patient- and treatment-specific factors, on implant success.

With view to the current literature on irradiated tumor patients, to the best of our knowledge, there exists only one just recently published study by Neckel and colleagues that specifically investigated radiation dose at the implant site by evaluating 3-dimensional radiation plans.[27] This study was conducted as a pilot study in 15 patients with 81 inserted implants. The study could show that the mean radiation dose was higher at the mandibular implant bed (46 Gy) compared to the maxillary implant bed (29 Gy) but significantly lower than the tumor bed. Interestingly this investigation did not differentiate between tumor site including carcinomas of the oral cavity as well as carcinomas of the oro- or nasopharynx. We evaluated 365 implants by this method and can confirm lower radiation doses at implant site compared to the primary tumor site, which is not surprising as soon as tumors others than located at the anterior floor of mouth are included. Nevertheless, we saw higher radiation doses at implant site for oral cancer (mean 57 Gy). Moreover, we found that it is important to differentiate the primary tumor site as carcinomas of the oropharynx (mean 42 Gy) or particularly hypopharynx and laryngeal area (mean 32 Gy) go along with significantly lower radiation doses at implant site compared to oral cancer.

Evaluation of implant success is not uniform as some studies evaluate mere implant survival which means that the implant is in situ and loaded independently from further clinical and radiographic peri-implant criteria.[10,12,13,16-18,20,22,25,27,34] Others define more detailed criteria for implant success.[35-38] In this study, evaluation of implant success was based on the most commonly accepted criteria described by Albrektsson with some modifications, particularly referring to peri-implant health.[29,30,38-41] Thorough clinical examination of peri-implant soft tissue provided reliable information about the condition of peri-implant soft tissue health. In particular, positive bleeding-on-probing (BoP) score—key parameter for clinical diagnosis of peri-implant soft tissue inflammation—or probing pocket depths over 4 mm combined with a sulcus bleeding index of 2 were defined as implant failure.[41,42] The procedure of radiographic evaluation of implants in irradiated patients with head and neck cancer does not differ from the normal cohort and is characterized by changes in the level of crestal bone. Vertical bone loss should be less than 1.5 mm for the first year and 0.2 mm annually after the first year.[38,39]

Using the described strict criteria for implant success, the present study reveals an overall 5-year success rate of 74.9%, which is lower than usually reported data. Major reasons for implant failure were advanced peri-implant bone resorption, lost or unloaded implants or peri-implantitis. Regarding mean peri-implant bone resorption, our results of about 0.8 mm after 3 years and 1.1 mm after 5 years are comparable to the results of Papi and colleagues who describe an average bone loss of 0.83 $+/-$ 12 in the 3D-CRT group and 0.74 $+/-$ 0.15 in the IMRT group after 2 years.[34] In contrast, Ernst and colleagues showed increased marginal bone resorption with 1.4 mm mesially and 1.3 mm distally as well as Neckel and colleagues with 1.5 mm for both of measurement after 3 years.[20,27] Our study demonstrates that peri-implant bone resorption increases with implant-specific radiation dose.

In univariate analysis smoking, bad oral hygiene, conventional radiotherapy, implantation inside radiation planning volume, peri-implant radiation dose >50 Gy, parotid dose >30 Gy, advanced xerostomia, osteoradionecrosis, peri-implant bone and soft tissue transplants, augmentation and nontelescopic prosthetics were associated with significant worse implant success rates. Most of these parameters like smoking, bad oral hygiene, bone transplants, and also radiotherapy are known as negative predictors for implant success.[3,21,43] An interesting result of this study is that only patients who continue smoking during implant therapy show higher failure rates whereas preimplant smokers (usually stopped with tumor treatment) present similar success rates as nonsmokers.[44] A further remarkable result is the superiority of telescopic prosthetic suprastructures to alternative methods as bar-retained or locator-retained constructions. Reasons are probably less implant deformations and bacterial load with telescopic overdentures.[45,46] With view to the ideal moment of implant insertion, our results suggest implantation after disappearance of early radiation side effects (6–24 months). In our opinion, radiation-induced fibrosis and loss of vascularization of the jaw increase over time aggravating implant success. There is an ongoing

discussion about this topic. A systematic review by Claudy and colleagues found an increased risk of failure (RR 1.34) for implants inserted between 6 and 12 months after radiotherapy. Therefore the authors recommend waiting longer than 12 months to install dental implants.[47] However, it has to be mentioned that in this review 6 out of the 10 included studies are published before 2000 and therefore include older radiation techniques. Moreover, an influence analysis indicated that there was one study responsible for the significant influence on RR. Removal of this study reduced the RR from 1.34 to 1.08. Additionally, the study with the best methodological quality in this meta-analysis pointed to a better outcome for implants inserted <12 months after radiotherapy.[47] Extension of the implant healing period to more than 4 months does also not increase implant success in irradiated patients.

The main aim of this study was to find a more distinctive impact of radiotherapy as all patients received radiation. We can demonstrate that implant success depends on radiation technique, planning target volume, and specific radiation dose at the parotid glands and at the implant site. Modern modulated radiotherapy resulted in significantly increased implant success rates, the reason for which is probably sparing of the parotid glands reducing the grade of xerostomia.[48-51] A mean parotid dose of more than 30 Gy came up with markedly higher implant failure rates compared to a mean parotid dose below 30 Gy. Similar results were obtained for xerostomia (57 Gy). Implant insertion inside the planning target volume (eg, after oral cancer) is associated with higher cumulative doses at the implant site and therefore more critical regarding success compared to implants inserted outside the planning target volume (eg, after laryngeal cancer). This relationship between tumor site and implant success rate has been described before.[21,26,33] Analyzing radiation treatment plans by contouring the implant sites as region of interest enables to calculate the specific dose constraints on every inserted implant. In doing so, we can demonstrate that radiation dose at the implant bed after treatment of laryngeal cancer is about 32 Gy whereas radiation dose at the implant site after oral cancer ranges around 57 Gy. Our results clearly show that the negative impact of radiation continuously increases with implant-specific dose. This means that implant failure is not only a matter of increased xerostomia and worse oral hygiene but also a matter of site-specific effects on the bony implant bed as fibrosis and loss of vascularization. An overall mean dose of more than 50 or 60 Gy was not decisive for implant failure in our study. However, implant specific mean doses exceeding 50 or 60 Gy are very crucial for implant performance. Also the risk for peri-implant osteoradionecrosis rapidly rises with mean doses of 60 Gy and more, particularly for mandibular implants. For these reasons, we would recommend to incorporate the radiation therapy plan into detailed implant planning.

In order to find out the most significant parameters for implant failure in irradiated head and neck cancer patients, we conducted a multivariate regression analysis which revealed peri-implant bone transplants, bad oral hygiene, conventional radiation techniques, implant-specific radiation dose >50 Gy, and nontelescopic dentures as strongest predictors of implant failure.

Of course this study has limitations as given by its retrospective nature. There is no control group. Radiographs during follow-up were not uniformly performed at the same time. Not all patients were available for clinical follow-up, some were lost due to cancer recurrence.

5 | CONCLUSION

In conclusion, this study shows that there is a dose-dependent association between cumulative irradiation dose at implant site and implant success rate. Radiation doses at implant site significantly differ depending on localization of the primary tumor. Modern modulating planning techniques effectively reduce xerostomia favoring implant-based prosthetic rehabilitation. Implantation in bone grafts implies a higher risk of failure and telescopic-retained overdentures should be preferred.

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CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest

AUTHORS' CONTRIBUTIONS

Franziska Wolf, Matthias Hautmann, and Tobias Ettl contributed to the conception and design of the work. Franziska Wolf collected the data. Franziska Wolf, Tobias Ettl, and Steffen Spoerl made the statistics. Franziska Wolf, Tobias Ettl, and Matthias Hautmann were responsible for writing. Maximilian Gottsauner, Christoph Klingelhöffer, Carola Kolbeck, and Torsten Reichert critically revised the manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Tobias Ettl https://orcid.org/0000-0002-0549-5351

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