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CLINICAL REVIEW

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Postimplantation radiation therapy in head and neck cancer patients: Literature review

Carine Koudougou MD[1] | Hélios Bertin MD[1,2] | Bastien Lecaplain DDS[3] | Zahi Badran DDS, PhD[3] | Julie Longis MD[1] | Pierre Corre MD, PhD[1,4] | Alain Hoornaert DDS, PhD[2,3]

[1]Service de chirurgie Maxillo-faciale et stomatologie, CHU de Nantes, 1 place Alexis Ricordeau, Nantes Cedex 1, France

[2]Laboratoire des sarcomes osseux et remodelage des tissus calcifiés, Unité Mixte de Recherche, Faculté de Médecine, 1 rue Gaston Veil, Nantes Cedex, France

[3]Faculté de Chirurgie Dentaire, 1 Place Alexis Ricordeau, Nantes, France

[4]Laboratoire d'Ingénierie Ostéo-Articulaire et Dentaire (LIOAD), Faculté de Chirurgie Dentaire, 1 Place Alexis Ricordeau, Nantes, France

Correspondence
Carine Koudougou, Service de chirurgie Maxillo-faciale et stomatologie, CHU de Nantes, 1 place Alexis Ricordeau, Nantes Cedex 1, France.
Email: koudougou.carine@hotmail.fr

Abstract

There is no recommendation regarding the timing for implant surgery in patients with head and neck cancer (HNC) who require postoperative radiation therapy (RT). This systematic review focused on the literature about the outcomes of implants placed during ablative surgery in patients with HNC who underwent postoperative RT. Implants placed after radiation therapy and implants placed in reconstructed jaws were excluded. Four comparative studies involving 755 native mandible primary implants were analyzed. The survival rate with postimplantation RT was 89.6% vs 98.6% in patients with no additional radiation. The overall success of implant-retained overdenture in patients with RT performed postimplantation was 67.4% vs 93.1% in patients with implant surgery that was carried out 1 year after the completion of radiation therapy. Only five cases of osteoradionecrosis (ORN) of the jaw were reported. The outcomes for implant survival rates appear to be positive for irradiated implants.

KEYWORDS

dental implants, head and neck cancer, implant survival, radiation therapy, radiotherapy

1 | INTRODUCTION

Curative strategies for treating head and neck cancer (HNC) frequently combine surgery, radiation therapy (RT), and chemotherapy. Consequently, the treatment often results in alteration of the facial and oral anatomy, and it can negatively impact mandibular and maxillary aesthetics and functions.[1,2] Indeed, a large mandibular or maxillary ablative surgery can impact the dentition of patients.[3] In patients requiring postoperative RT, extended dental extractions are needed in the irradiated area in order to prevent osteoradionecrosis (ORN) of the jaw. Thus, a large proportion of patients become edentulous.[4] With the development and generalization of pedicle and free flaps in reconstructive strategies of the oral cavity, the quality of life of patients with HNC has improved.[5] Furthermore, restoration of dental function by prosthetic rehabilitation represents an important part of reconstruction strategies.[2] In addition, it contributes to improvement of the aesthetic outcomes and quality of life.[3,6,7] Prosthetic rehabilitation of edentulous patients after oral cancer is a therapeutic challenge.[8] Conventional removable prosthodontic techniques are often used in first intention, but there is an elevated risk of failure in these altered anatomical situations.[3] Furthermore, it is difficult to achieve stability and retention due to the reduction of salivary secretion and due to the impairment of chewing and swallowing. Thus, masticatory functions are not restored, and it is often poorly tolerated by the patients. Many authors and systematic reviews have already shown good outcomes of implant surgery and dental implant-supported prosthetics in patients with

HNC. High implant survival rates and restoration of a good quality of life have been reported.[9-11] After facial RT, it is now commonly thought that oral implant surgery can be performed at the irradiated sites.[12-17] A low risk of implant failure has been reported for doses of less than 50 Grays (Gy).[13,18] With high doses (over 70 Gy), there is a high risk of implant failure associated with a high risk of ORN, and it is recommended that implant surgery is avoided. With doses between 50 and 70 Gy, implant placement does not appear to be advisable.[19] In these cases, various authors have advocated the use of hyperbaric oxygen treatment to reduce the risk of ORN and to improve the osseointegration, although there is scant, if any, scientific evidence to back this up.[20,21] There is currently no recommendation regarding the timing for implant surgery in patients with HNC who require postoperative RT. In most cases, implants are placed after completion of the HNC treatment, with a minimum of 6 months after the end of the RT.[12,13,20] On the other hand, some authors consider that, in addition to the restoration of osseous and soft tissues, dental rehabilitation in patients with HNC can start at the same time as the ablative surgery.[22-26] In such cases, the implantation site has not been compromised by the radiation. This promotes early oral rehabilitation of the patient and thus improvement of the quality of life. There are only a limited number of studies in the recent literature reporting the results of primary implantation with postoperative radiation, and no systematic review has focused on this topic. With regard to the effects of the radiation on previously placed dental implants, the backscattering of radiation results in an increased dose on the surrounding bone.[27-29] However, there is no scientific evidence that this phenomenon enhances the relative risk of ORN. In addition, metal artifacts generated by titanium implants are known to decrease the accuracy of tumor delineation and thus decrease the accuracy of dose delivery.[30,31] The aim of this systematic review was to assess the outcomes of implants placed during ablative surgery in patients with HNC who received postoperative RT. The influence of the following variables was assessed: the survival rates of the implants, the local impact of RT, and the success of prosthetic rehabilitation.

2 | MATERIALS AND METHODS

2.1 | Focused question

The main question asked in this review was: Does postoperative RT significantly compromise the outcome of implant surgery performed concomitant with the primary ablative surgery?

2.2 | Literature search

A systematic review was conducted of the literature published between January 2004 and June 2019. This was done by searching PubMed (MEDLINE) using the terms "dental implant," "radiation therapy," and "radiotherapy" in combination with the Boolean operators AND OR. All the abstracts retrieved were reviewed and the potentially relevant articles preselected.

2.3 | Inclusion criteria

- Original research articles based on:
  - clinical trials,
  - case-control studies,
  - cohort studies
- Involving patients with HNC who received dental implants during the ablative cancer surgery.
- Patients who underwent RT after implant placement.

2.4 | Exclusion criteria

- Implants placed only after primary surgery
- Implant placed only after RT
- Minimum follow-up of 1 year after the primary surgery
- Implants not placed in native bone (free osseous flaps)
- Case reports
- Other literature reviews
- Articles with insufficient published data

3 | RESULTS

The PubMed database searches identified 473 potentially relevant articles. Of these, 140 articles were published before 2004 and thus not considered further. The remaining 333 articles were assessed based on the abstract, and 51 articles were then selected for a review of the full text.

A total of five articles that met the inclusion criteria were selected. Upon closer inspection, two articles published by the same team used exactly the same cohort of patients. We selected the article for which the data were the most detailed. Thus, we ultimately analyzed four articles (Figure 1). In three of these studies, the implants were placed during the ablative tumor surgery for all the patients. The patients who received additional RT and the patients with no additional RT were then compared.

In one study, patients from two different head and neck oncology centers were compared. In the first cohort, the implants were placed during the ablative surgery,

whereas in the second cohort, the implant surgery was performed 1 year after completion of the oncological treatment. For all the patients, the implants were placed in the edentulous mandible, in the interforaminal region. The data and results are presented in Tables 1, 2, and 3.

3.1 | Survival rates

Implants were considered as having been lost in the following cases: osseointegration failure, resection of a recurrent tumor that included the implant(s), or the occurrence of ORN at the implantation site. The mean follow-up ranged from 29.6 months to 5 years. A total of 755 implants were placed for the patients who underwent implant surgery before RT, with an overall survival rate of 89.6% (97 implants were lost). The implant survival rates for the individual studies ranged from 82% to 96.7%.

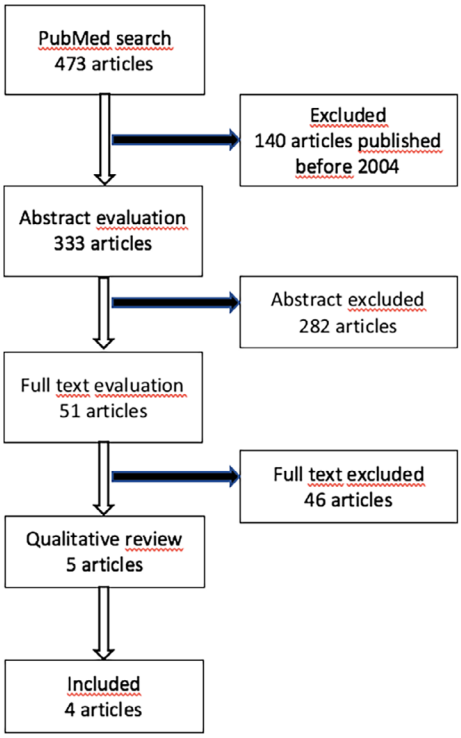

FIGURE 1 Flow chart of the selection process [Color figure can be viewed at wileyonlinelibrary.com]

A total of 356 implants were placed for the patients who did not receive RT after the implant surgery, with an overall survival rate of 98.6% (13 implants were lost). The implant survival rates for the individual studies ranged from 97.1% to 100%. There were 29 patients who underwent implant surgery 1 year after completion of the RT. Sixty-five implants were placed, with a survival rate of 90.8%. For the patients who underwent post-implantation RT, the reasons for loss of the implants were: osseointegration failure for 70 implants, resection of a recurrent tumor for 27 implants, and the occurrence of ORN for 10 implants. For the patients who did not undergo RT after implant surgery, the reasons for loss of the implants were: osseointegration failure for six implants and resection of a recurrent tumor for one implant. For the patients who underwent implant surgery, osseointegration failed with six implants.

3.2 | Radiation dose

The patients who underwent postimplantation RT were irradiated on the bed of the tumor and on the lymph nodes with conventional doses that varied from 60 to 68 Gy in two studies and unspecified doses in two studies. The average time interval between the surgery and the start of the RT was 6 weeks.

Schepers et al only specified the radiation dose at the implant site, in relation to the implants lost.[35] They reported osseointegration failure of two implants that had received a radiation dose between 20 and 40 Gy.

3.3 | The success of implant-retained overdenture

The success rate of the prosthetic rehabilitation on implants was evaluated based on two parameters: the number of patients with an implant-retained overdenture and the number of functional implants. For the patients who underwent implant surgery before the RT, the overall overdenture success rate was 67.4%, with rates ranging from 34.4% to 82.8%. For the patients who did not receive

TABLE 1 General data of the selected studies

Authors	Year	Study type	Implantation site	Number of patients	Implants	Follow-up (mean)
Schepers et al[35]	2006	Retrospective	Symphyseal Mandibular area	48	139	29,6 months
Korfage et al[25]	2010	Prospective	Interforaminal Mandibular Area	50	195	5 years
Mizbah et al.[23]	2012	Retrospective	Interforaminal Mandibular area	99	314	5 years
Korfage et al[24]	2014	Retrospective	Interforaminal Mandibular Area	164	524	3,8 years

TABLE 2 Irradiated Implants: Radiation dose, survival rate, success of the overdoverdenture

Authors	Patients	Implants	Radiation dose (Grays)		Lost implants	Survival rate	Reasons of lost implants	Patients with implant-retained overdenture	Number of functionnal implants
			Tumor bed	Implantation site					
Schepers et al[35]	21 (43,8%)	61	60-68 Gy	10-68 Gy	2	96,70%	Osseointegration failure	15/21 (71,4%)	46/61 (75,4%)
Korfage et al[25]	31 (62%)	127	Unspecified	> 40 Gy	13	89,40%	Osseointegration failure	9/31 (34,4%)	Unspecified
Mizbah et al[23]	99 (36,7%)	249	60–68 Gy	Unspecified	24	90,40%	Osseointegration failure	82/99 (82,8%)	205/249 (82,3%)
Korfage et al[24]	100 (61%)	318	Unspecified	Unspecified	58	82%	- Osseointegration failure (31 implants) - Resection of recurrent tumor (27 implants) - ORN (10 implants)	81/100 (81%)	Unspecified

Abbreviations: Gy, grays; ORN, osteoradionecrosis.

TABLE 3 Comparative groups of patients without RT or with implants placed after completion of RT

Authors	Patients	Relation to RT	Number of implants	Lost implants	Survival rate	Reasons of lost implants	Patients with implant retained overdenture	Number of functional implants
Schepers et al[35]	27 (56,2%)	No RT	78	0	100%	/	21/27 (77,8%)	59/78 (75,6%)
Korfage et al[25]	19 (38%)	No RT	72	1	98,60%	Osseointegration failure	11/19 (57,9%)	Unspecified
Mizbah et al[23]	29	Implants 1 year after completion of RT	65	6	90,80%	Osseointegration failure	27/29 (93,1%)	59/65 (90,8%)
Korfage et al[24]	64 (39%)	No RT	206	6	97,10%	Tumor (1 implant)	57/64 (89,1%)	Unspecified

Abbreviation: RT, radiotherapy.

RT, the overall overdenture success rate was 74.9%, with rates ranging from 57.9% to 89.1%.

For the patients with implant surgery that was performed 1 year after completion of the radiation therapy, 93.1% had an implant-retained overdenture. Two studies only specified the number of functional implants. Of the 310 irradiated implants, 251 were functional, representing 78.8% of the total number of irradiated implants. Of the 78 non-irradiated implants, 59 (75.6%) were functional, and of the 65 implants placed after the RT, 59 (90.8%) were functional.

4 | DISCUSSION

As a result of improvements in the surgical techniques for head and neck malignancies and advances in adjuvant cancer therapies in recent years, the number of patients going into remission has increased.

Presently, the challenge for these patients is being able to maintain a good quality of life. Restoring oral function and aesthetics is, therefore, an important consideration.[3,7]

In this context, the French national health system decided in 2013 to reimburse the placement of a maximum of four implants in the maxilla and a maximum of two implants in the mandible for patients with sequelae of HNC when stabilization of a conventional prosthesis is complicated by alteration of the oral anatomy.

Several authors have proposed guidelines for prosthodontic rehabilitation of HNC patients, based primarily on the cumulative dose received at the implantation site.[19,32-34] There is currently no consensus regarding the ideal timing of implant surgery.

In this systematic review, we sought to assess the validity of initiating implant-supported oral rehabilitation at the same time as the start of the curative treatment for HNC patient.

4.1 | Survival rates

The reported survival rates of primary implants vary from 82% in the study by Korfage et al[24] to 96.7% in the study by Schepers et al,[35] with an overall survival rate of 89.6%. In the study by Korfage et al, all the implants were inserted by a number of different surgeons and residents, which could explain their less favorable results. In the other studies, the patients were treated by a single experienced maxillofacial surgeon and a single experienced prosthodontist. It is reasonable to state that the results of Korfage et al better reflect the reality of the current practice. In concordance with the literature,[21,36-38] implants were lost more frequently in the patients who underwent RT than in the patients who had not been irradiated. For the patients who did not undergo RT after the implant surgery, the overall survival rate was 98.6%. Similar results have been reported in the literature for conventional implantology.[39] In terms of the survival rate in relation to the timing of implantation (pre- or post-RT) in this review, Mizbah et al[23] reported no statistically significant differences between implants placed before RT and implants placed after RT in native mandibular bone. Similar results have been presented by Nooh et al[14] who suggested in a literature review that postimplantation RT had a slightly better overall dental implant survival rate than preimplantation RT, although this was not scientifically proven due to the inhomogeneity of the reviewed studies.

4.2 | Anatomical sites of implant placement

In this review, all the implants were placed in the interforaminal region on the native mandibular bone, leading to more precision of the results. On the other hand, our findings can consequently not readily be extrapolated to other anatomical sites. Although a number of studies have been published on implants placed during the ablative surgery in the maxilla in the literature,[34] these were excluded from this study due to incomplete results. We decided to exclude the studies with implants placed in reconstructed mandibles. Indeed, the reconstructed mandible appears to have biomechanical properties that differ from native mandibular bone[40] and this can skew the results for survival rates. The survival rate when implants are placed after RT has been well documented. Several studies have reported a lower implant survival rate in the irradiated maxilla than in the mandible,[18,21,41,42] despite the fact that the mandible is thought to be the area that is most susceptible to ORN.[33] Thus, the high survival rates in this literature review could be explained by the mandibular placement of all of the implants in the four studies that were selected. It would be interesting to undertake a comparative study on the behavior of implants placed during ablative surgery according to the anatomical site of the implantation and including reconstructed jaws.

4.3 | Radiation dose

In this study, all the implants were placed during the primary surgery, and the tumor bed and lymph node chain were subjected to RT within 6 weeks of the surgery. The cumulative radiation dose at the implantation site depended on the location of the tumor and on the histopathology results. It could, therefore, not be predicted before

placement of the implant. Schepers et al[35] reported variation of the radiation dose at the implant site from 10 to 68 Gy. For the 61 implants that received radiation, they observed two osseointegration failures. These two implants received radiation doses of between 20 and 40 Gy. Furthermore, 17 implants with successful osseointegration received a cumulative dose >61 Gy. Therefore, when implants are placed before RT, the radiation dose does not appear to correlate with the success of osseointegration. However, this hypothesis is based on a small sample of patients and it needs to be substantiated with further scientific data. In terms of the effect of implant irradiation on the surrounding bone, Korfage et al[24] described five cases of ORN, representing 5% of the patients who underwent RT after implantation. However, they consider that for implants placed before RT the presumed risk of developing ORN due to backscattering of radiation would be lower than the risk of developing ORN when the implants are placed in an irradiated bone, albeit without presenting any scientific proof. Backscattering radiation effects have been well documented in the literature.[27-29] Ozen et al[27] showed that backscattering of radiation results in an increased dose of radiation in the surrounding bone in front of and next to the implants, with a range of 10%-21%. However, it has not been scientifically confirmed that there is a correlation between the development of ORN and radiation backscattering. Current progress in radiotherapy allows accurate distribution of the radiation dose at the tumor site, and it increases the precision of the contouring of tumors or organs at risk. Dental implants lead to metallic artifacts that result in a decrease of the contouring precision and a decrease in the accuracy of the dose calculation.[30,31] Thus, it is more difficult to deliver an accurate radiation dose to the tumor bed. Furthermore, deviations on a scale of a few millimeters can result in increased irradiation of organs at risk and they may have a significant negative impact on patient outcomes.[43] Various techniques for metal artifact reduction have been described and compared.[30,31,43] We did not find any studies that compared the accuracy of these techniques with the accuracy of the delineation in patients without sources of dental artifacts. Thus, it is difficult to determine to what extent a patient is not being given the best possible chances of success of the RT with dental artifacts generated by titanium implants. With all these observations, whether or not the risk/benefit ratio remains in favor of performing implant surgery before RT should be a consideration.

4.4 | Timing of dental implant placement

The principal aim of identifying the ideal timing of implantation surgery in relation to RT is to improve the implant survival rate, to reduce the risk of ORN, and to optimize the success of the overdenture. There are currently no validated guidelines, nor is there an official consensus in this regard. In this review, Mizbah et al[23] compared two protocols for implant placement: 1. A DAS-implant group for which the placement was during the ablative primary surgery, before the RT and a P-implant group for which the placement was during the post-therapy phase, with a minimum interval of 1 year. They did not find any statistically significant differences in terms of implant survival rates between these two groups. However, in the P-implant group, 93.1% of the implants were functional whereas this figure was 82.8% in the DAS-implant group. Korfage et al[25] reported a survival rate of 89.4% in patients who underwent postimplantation RT vs 98.6% in patients who did not receive RT, all of which were primary placed implants. For the 31 patients who underwent RT of the implants, they reported 20 patients with overdenture success at 1 year and only 9 patients (34.4%) 5 years later. Schepers et al[35] reported better outcomes, with 71.4% of the patients who underwent postimplantation RT wearing an overdenture vs 77.8% of the patients who did not receive RT, albeit with a mean follow-up of only 29.6 months. In the recent literature, most authors favor performing implant surgery after completion of the primary curative treatment (surgery, RT, chemotherapy). In most situations, implants are placed starting at 1 year after the end of the RT,[13,20] but there is still a lack of agreement regarding this matter. Claudy et al[13] suggested in a systematic review that the placement of dental implants between 6 and 12 months post-radiotherapy was associated with a 34% higher risk of failure. Conversely, in a recent review, Zen Filho et al[12] stated that the optimal time interval between irradiation and dental implantation varies from 6 to 15 months. Thus, although the timing of the implant placement does not appear to result in different survival rates, it does appear to impact the quality of the prosthodontic rehabilitation, which is the ultimate goal of the treatment. In these primary implant cases, prosthodontic success does not appear to be correlated with implant survival. There is a need for more of a focus on the factors influencing the prosthodontic success of primary implants.

4.5 | Economic perspective

Any discussion of the validity of early implantation needs to also consider the economic impact. Indeed, despite the recent inclusion of implantation surgery for HNC patients for rebates by the health system in HNC patients, the cost of implant-retained overdentures remains high. With a

mean failure rate of 32.6% of implant-retained overdentures for patients who undergo RT after implant surgery, it needs to be considered whether this procedure is indeed the most appropriate strategy. Despite this fact, Mizbah et al[23] and Schepers et al[35] both agree that nonfunctional primary placed implants remain less expensive than a secondary surgery. Wetzels et al found similar results,[44] although their opinion needs to be supported by more scientific results.

4.6 | Summary and limitation of the study

There have been no reviews in the literature that focused on primary placed implants with additional RT. The vast majority of studies to date have been regarding implants placed after RT, which explains the small number of studies selected in this review.

All the implants were placed in the inter-foraminal region of the native mandibular bone, which confers a degree of homogeneity and more precision to our conclusions. On the other hand, the results cannot be extrapolated to other parts of the jaw.

5 | CONCLUSION

There is currently a tendency to perform prosthodontic rehabilitation as soon as possible in HNC patients. Performing implant surgery at the same time as the primary tumor ablation surgery appears to be an attractive way to achieve this, even for patients who will undergo postoperative RT. Nevertheless, although the outcomes in terms of implant survival rates appear to be positive, the success of implant-retained overdentures remains hard to predict. In addition, the metallic artifacts generated by a dental implant may adversely affect the RT. Finally, the economic consequences warrant further scrutiny. There is a need for accurate identification of the patients for whom the risk-benefit ratio favors early implantation.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors mentioned in this manuscript contributed to the work reported, have read and approved the final version of this manuscript, and agree to be accountable for all aspects of work ensuring integrity and accuracy. The authors contributed as follows: conception and design, C.K., and A.H.; analysis and interpretation, C.K., B.L., and J.L.; drafting of the manuscript, C.K., H.B., and A.H.; revising of the manuscript, Z.B., H.B., P.C., and A.H.

ORCID

Hélios Bertin https://orcid.org/0000-0002-0546-079X

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