Survival of Dental Implants Placed Pre-Radiotherapy Versus Post-Radiotherapy in Native Bone: A Systematic Review

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Purpose: To systematically measure the survival rate of implants placed pre- and post-radiotherapy. ***Materials and Methods:*** After performing a systematic literature exploration of 10 databases, observational and quasi-experimental studies and case series estimating the survival of dental implants in patients with head and neck cancer placed before, after, and without radiotherapy were included, with no limit on language or year of publication. The Joanna Briggs Institute Critical Appraisal was used to assess the risk of bias in eligible studies. ***Results:*** During the first screening phase, 3,445 studies were found, among which 16 met the inclusion criteria. The median follow-up period was 60 months (range: 1 to 168 months). Seven (43.7%) articles had a moderate risk of bias, four (25%) had a high risk of bias, and five (31.3%) had a low risk of bias. The survival rate for post-radiotherapy, pre-radiotherapy, and without-radiotherapy implants was 80% to 100%, 89.4% to 97%, and 92.2% to 100%, respectively. ***Conclusion:*** Despite the alterations caused by ionizing radiation in peri-implant tissues, dental implants placed pre- and post-radiotherapy had high survival rates, similar to those placed without radiotherapy, which helps improve the condition of life of patients with head and neck cancer. *Int J Oral Maxillofac Implants 2022;37:1100–1109. doi: 10.11607/jomi.9756*

Keywords: dental implant, survival rate, head and neck cancer, radiotherapy, systematic review

Head and neck cancer (HNC) is the sixth most predominant cancer type.[1,2] Most patients are diagnosed during advanced stages (III and IV) of the disease,[3–5] resulting in radical treatment that can involve surgery, radiotherapy (RDT), and chemotherapy.[6,7] Although the efficacy of RDT has been proven, it can have effects on oral health, such as reduced salivary flow rate, mucositis, radiation caries, progressive vascular fibrosis, trismus, modifications of bone morphology, and periodontal attachment loss.[6–8] Progressive vascular fibrosis reduces bone vascularity and clinically manifests as osteoradionecrosis, which is one of the most serious complications of RDT.[9,10] Osteoradionecrosis is characterized by exposed necrotic bone and pain and may present with pathologic fractures.[11,12] These factors contribute to a reduction in bone repair capacity, increasing the failure percentage of implants placed in irradiated tissues.[3,5]

Ionizing radiation in the head and neck region can cause irreversible changes such as endarteritis, which leads to hypocellularity, hypoxia, and hypovascularity.[6] These conditions seriously compromise bone healing and turnover, which interferes with the osseointegration of dental implants.[5] The bone, vessel endothelium, periosteum, connective tissue of the mucosa, and teeth can be affected by radiotherapy.[10] These conditions are favorable for the development of osteoradionecrosis and tissue dehiscence, leading to implant failure.[12]

Improved treatment for patients with HNC allows them to live for years, although with treatment sequelae, such as facial deformities, functional limitations, and the potential to develop depression.[8] These sequelae have social implications for most patients, negatively influencing their quality of life.[13] It is recommended that before initiating treatment with RDT, patients undergo screening of the oral cavity, so that oral foci, such as periodontal disease, deep carious cavities, and periapical infections, can be identified.[14] Tooth extractions can be performed before RDT to prevent post-radiation sequelae in the oral cavity.[15] Teeth loss during tumor resection surgery requires oral rehabilitation involving dental implants combined with fixed or removable prostheses.[10,16] Implant-retained restorations can restore patients' function, self-esteem, and speech, contributing to

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a better quality of life[7] and resulting in a high degree of satisfaction.[17] Dental implants are no longer contraindicated in patients treated with RDT,[13,14] despite the challenging procedure due to the anatomical and functional changes that may be caused by surgery.[7]

Implant placement can be performed after RDT (post-RDT),[15] although with a high risk of osteoradionecrosis.[18] Alternatively, implant placement can be performed before RDT (pre-RDT); however, in this procedure, implants have to be placed during the correct time interval.[19] There is an absence of studies providing an absolute indication about ionizing radiation effects on implant survival rates.[13,19] Dental implants placed in irradiated patients have varying survival rates.[20–22] Inconsistent results have been reported in the literature regarding the survival rates of dental implants placed in irradiated tissues compared with those placed in nonirradiated tissues. Thus, the most appropriate timing for implant placement is controversial and involves complex decision making. Therefore, this systematic review aimed to summarize and report the survival rates of implants in pre- and post-radiotherapy groups and compare the outcomes between the groups and to implants placed in patients without RDT.

MATERIALS AND METHODS

Study Registration

This systematic review was conducted in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[23] and the Joanna Briggs Institute (JBI) Manual.[24] The systematic review protocol was registered a priori in PROSPERO (CRD42021242331; https://www.crd.york.ac.uk/prospero/). The only deviation from the original registered protocol was that in the last version of the review, it was decided to include case series.

Research Question and Eligibility Criteria

This systematic review was intended to answer the question, "What are the individual survival rates of implants placed pre- and post-RDT compared to those placed without RDT?"

The inclusion criteria were as follows: *(1)* quasi-experimental studies, *(2)* case series, *(3)* observational studies (longitudinal retrospective or prospective), and *(4)* randomized clinical trials that evaluated implant survival in patients with HNC who obtained dental implants in native bone from the maxilla and/or mandible with or without associated chemotherapy and RDT. The exclusion criteria were as follows: *(1)* studies that exclusively included patients with cancer types that were not HNC, *(2)* studies that exclusively focused on implants placed in extraoral regions or in bone graft, *(3)* studies that exclusively included patients with comorbidities such as diabetes and osteoporosis, and *(4)* studies in which the sample was exclusively composed of patients with HNC treated without RDT and/or with hyperbaric oxygen therapy (HBOT). In addition, studies not associated with the study goal, letters to the editor/editorials, review articles, personal opinions, books/book chapters, textbooks, conference abstracts, in vitro studies, and patents were excluded. There were no limitations on language, year of publication, or type of dental implant placed.

Sources of Information and Search

The search was performed until June 2020, with search alerts as a self-updating tool, in the following databases: MEDLINE (via PubMed), Scopus, LILACS, SciELO, Embase, Cochrane Library, and Web of Science. OpenGrey, OpenThesis, and Google Scholar databases were used to fractionally obtain the "gray literature." Medical Subject Headings, Health Sciences Descriptors, and Embase Subject Headings resources were used to elect search descriptors. Furthermore, synonyms and free terms were used to enlarge the search. The Boolean operators "AND" and "OR" were also used to enhance the research strategy through several combinations (Table 1). The search terms were fitting to each database. A manual search was also performed through a systematized analysis of the references of the eligible studies.

The results of studies obtained from the bibliographic search were exported to EndNote Web software (Thomson Reuters), on which duplicates were excluded. The remaining results were then exported to Microsoft Word 2019 (Microsoft), including results obtained from the "gray literature," followed by manual removal of the remaining duplicate articles.

Study Selection

The study selection process was accomplished in three phases. The first phase focused on the analysis of article titles; those not connected to the topic were removed. In the second phase, abstracts were read, and the exclusion criteria were applied. Articles whose titles matched the study aims but did not have available abstracts were fully analyzed in this phase. In the last phase, the full texts of preliminary eligible studies were obtained and evaluated. Studies that did not meet the inclusion criteria were excluded. References of the studies included in this phase were carefully assessed for manual research.

Two reviewers (T.E.A.P. and N.T.A.R.) independently read the articles included in each phase, and doubts or disagreements between them were checked with a third reviewer (L.R.P.) to reach consensus and make a final decision. If an article could not be found online, other libraries were searched. The full texts of studies published in languages other than English or Portuguese were translated.

Table 1 Strategies for Database Search

Database	Search strategy (Jun 22, 2020)
PubMed http://www.ncbi.nlm.nih.gov/pubmed	(("Head and neck cancer" OR "Neoplasms, Head and Neck" OR "Head Neoplasms" OR "Cancer of Head" OR "Neck Neoplasms" OR "Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Neoplasms" OR "Neoplasia" OR "Tumor" OR "Cancer" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Benign Neoplasm") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous" OR "Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy") NOT ("Animal Experimentation" OR "Animal Research" OR "Animal Experimental Use" OR "In Vitro Techniques" OR "In Vitro"))
Scopus http://www.scopus.com/	(("Head and neck cancer" OR "Neoplasms, Head and Neck" OR "Head Neoplasms" OR "Cancer of Head" OR "Neck Neoplasms") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Cancer of the Mouth" OR "Mouth Cancer") AND ("Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Neoplasms" OR "Neoplasia" OR "Tumor" OR "Cancer" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Benign Neoplasm") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy"))
LILACS http://lilacs.bvsalud.org/	(("Head and neck cancer" OR "Neoplasms, Head and Neck" OR "Head Neoplasms" OR "Cancer of Head") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Neck Neoplasms" OR "Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm" OR "Oral Neoplasms") AND ("Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Cancer of Mouth" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Neoplasms" OR "Neoplasia") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Tumor" OR "Cancer" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Benign Neoplasm") AND ("Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy"))
SciELO http://www.scielo.org/	(("Head and neck cancer" OR "Neoplasms, Head and Neck") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Head Neoplasms" OR "Cancer of Head") AND ("Dental Implantation, Endosseous" OR "Endosseous Dental Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis")) (("Oral Neoplasms" OR "Cancer of Mouth" OR "Cancer of the Mouth") AND ("Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy")) (("Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy"))
Web Of Science http://apps.webofknowledge.com/	(("Head and neck cancer" OR "Neoplasms, Head and Neck" OR "Head Neoplasms" OR "Cancer of Head" OR "Neck Neoplasms" OR "Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Neoplasms" OR "Neoplasia" OR "Tumor" OR "Cancer" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Benign Neoplasm") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous" OR "Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy") NOT ("Animal Experimentation" OR "Animal Research" OR "Animal Experimental Use" OR "In Vitro Techniques" OR "In Vitro"))
Embase https://www.elsevier.com/solutions/embase-biomedical-research	('head and neck cancer'/exp OR 'head and neck cancer' OR 'neoplasms, head and neck' OR 'head neoplasms'/exp OR 'head neoplasms' OR 'cancer of head' OR 'neck neoplasms'/exp OR 'neck neoplasms' OR 'neck cancer'/exp OR 'neck cancer' OR 'oral cancer'/exp OR 'oral cancer' OR 'mouth neoplasm'/exp OR 'mouth neoplasm' OR 'oral neoplasms' OR 'cancer of mouth' OR 'cancer of the mouth' OR 'mouth cancer'/exp OR 'mouth cancer' OR 'neoplasms'/exp OR 'neoplasms' OR 'neoplasia'/exp OR 'neoplasia' OR 'tumor'/exp OR 'tumor' OR 'cancer'/exp OR 'cancer' OR 'malignant neoplasm'/exp OR 'malignant neoplasm' OR 'neoplasm, malignant' OR 'benign neoplasm'/exp OR 'benign neoplasm') AND ('dental implants'/exp OR 'dental implants' OR 'implant, dental' OR 'surgical dental prosthesis' OR 'dental implantation, endosseous'/exp OR 'dental implantation, endosseous' OR 'endosseous dental implantation' OR 'osseointegrated dental implantation' OR 'dental implantation, osseointegrated' OR 'endosseous implantation') AND ('radiotherapy'/exp OR 'radiotherapy' OR 'radiation therapy'/exp OR 'radiation therapy' OR 'radiation treatment'/exp OR 'radiation treatment' OR 'targeted radiotherapy' OR 'targeted radiation therapy') NOT ('animal experimentation'/exp OR 'animal experimentation' OR 'animal research'/exp OR 'animal research' OR 'animal experimental use' OR 'in vitro techniques'/exp OR 'in vitro techniques' OR 'in vitro'/exp OR 'in vitro')
OpenGrey http://www.opengrey.eu/	(Head and neck cancer) AND (Dental implants) AND (Radiotherapy) (Neoplasms, Head and Neck) AND (Dental implants) AND (Radiotherapy) (Head and neck cancer) AND (Dental implants) (Oral cancer) AND (Implant, Dental)
OpenThesis http://www.openthesis.org/	(Head and neck cancer) AND (Dental implants) AND (Radiotherapy) (Neoplasms, Head and Neck) AND (Dental implants) AND (Radiotherapy) (Oral cancer) AND (Dental implants) AND (Radiotherapy)
Google Scholar https://scholar.google.com	(Head and neck cancer) AND (Dental implants) AND (Radiotherapy) (Neoplasms, Head and Neck) AND (Dental implants) AND (Radiotherapy) (Oral cancer) AND (Dental implants) AND (Radiotherapy) (Mouth Neoplasm) AND (Dental implants) AND (Radiotherapy) (Head and neck cancer) AND (Dental implants) AND (Radiation therapy)
Cochrane (Trails) https://www.cochranelibrary.com	(("Head and neck cancer" OR "Neoplasms, Head and Neck" OR "Head Neoplasms" OR "Cancer of Head" OR "Neck Neoplasms" OR "Neck Cancer" OR "Oral cancer" OR "Mouth Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Neoplasms" OR "Neoplasia" OR "Tumor" OR "Cancer" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Benign Neoplasm") AND ("Dental implants" OR "Implant, Dental" OR "Surgical Dental Prosthesis" OR "Dental Implantation, Endosseous" OR "Endosseous Dental Implantation" OR "Osseointegrated Dental Implantation" OR "Dental Implantation, Osseointegrated" OR "Endosseous Implantation") AND ("Radiotherapy" OR "Radiation Therapy" OR "Radiation Treatment" OR "Targeted Radiotherapy" OR "Targeted Radiation Therapy"))

Data Collection

Data were collected from text, tables, and images. Before data extraction, to ensure consistency among reviewers, a calibration exercise consisting of simultaneous data extraction from one eligible study was performed. Any disagreement between the reviewers in this phase was also resolved through discussions, and when both reviewers disagreed, a third reviewer (L.R.P.) was consulted to make a final decision. The ethical criteria involved in the studies as well as the checklist used were collected.

Data on the following were extracted from the articles: *(1)* identification of the study (authors, country, year of publication, and study design); *(2)* sample characteristics (sample size and distribution by sex and age); *(3)* treatment characteristics (radiation doses, associated chemotherapy, moment of implant placement, and number of implants placed), and *(4)* main results (follow-up time, implant failure, loss, and survival). In cases lacking information, the corresponding author of the study was reached by email.

Risk of Bias

The JBI critical appraisal tool for systematic reviews[24] was used to assess the risk of bias and the individual quality of the selected studies. A specific tool was applied to each study design. Two reviewers (T.E.A.P. and N.T.A.R.) assessed each domain blindly and independently in terms of the potential risk of bias of the articles, as recommended by the PRISMA statement.[23] A third reviewer (L.R.P) was invited to discuss the risk of bias when consensus was not reached.

Each study was categorized according to the percentage of positive answers to the questions corresponding to the assessment tool. The risk of bias was considered high, moderate, and low when the percentage of positive answers was up to 49%, 50% to 69%, and > 70%, respectively.

Summary Measures and Syntheses of Results

A meta-analysis was performed if the data from the eligible studies were homogenous. However, methodologic and observational differences between the included studies were observed; therefore, conducting a meta-analysis was not appropriate because of significant data heterogeneity. Accordingly, descriptive analysis of the findings from the studies was performed to identify core themes related to the study aim.

RESULTS

Study Selection

The first phase of study selection yielded 3,445 articles distributed over 10 electronic databases, including the "gray literature." After removing duplicated results, 1,659 articles were retained for the analysis of the titles and abstracts. After detailed analysis, 100 studies were eligible for full-text analysis; their references were evaluated carefully, but no additional articles were selected. Subsequently, 84 studies were excluded because they did not meet the inclusion criteria or because their full texts were not found (Appendix Table 1; see Appendix in online version of this article at quintpub.com). Thus, 16 studies were selected for qualitative analysis. Figure 1 shows the process of search, identification, inclusion, and exclusion of articles.

Characteristics of Eligible Studies

Four quasi-experimental studies,[18,25–27] four cohort studies,[16,17,20,28] and eight case series[6,7,10,22,29–32] were included. The studies were published between 1996 and 2020 and were undertaken in Austria,[18] Brazil,[7] France,[32] Germany,[16,25,28] Italy,[10,22] the Netherlands,[20,26,31] Poland,[27] Spain,[17] and the United States,[6,29] with one multicenter study conducted in the United States and Japan.[30]

Most studies (n = 10) evaluated implant survival in post-radiated patients without a control group.[6,7,10,18,22,27,29–32] Four studies compared implant survival between post-radiated patients and nonirradiated patients (control group).[16,17,25,28] The other two studies compared implant survival between pre-radiated patients and nonirradiated patients (control group).[20,26]

Five studies reported the use of chemotherapy in part of their sample.[16,17,25,27,32] The mean radiation doses were 47.1 to 62 Gy, and the number of implants placed was 20 to 830. The total sample included 549 patients: 298, 52, and 199 patients in the post-RDT, pre-RDT, and without-RDT groups, respectively. However, three studies did not reveal the number of post-RDT patients.[6,27,31] The median patient age was 51 to 66.5 years.

A total of 2,994 implants were placed among patients with HNC in the 16 studies included in this systematic review. Most implants (1,784) were placed post-RDT. In the pre-RDT group, 185 implants were placed. The remaining implants (749) were placed in the without-RDT (control) group. One study[28] did not reveal the number of implants placed in each group and only indicated the total number of implants (276). The corresponding author was contacted by email, but no response was received. It was difficult to determine the number of implants placed in patients treated with chemotherapy because the studies did not specify this information. Other information regarding the demographic and clinical characteristics of the population is presented in Table 2. Only five articles[6,7,10,17,31] were approved by the Ethics Committee of their respective institutions. Informed consent was obtained from patients in six studies,[6,10,17,25,26,31] and no study described the use of any report guide.

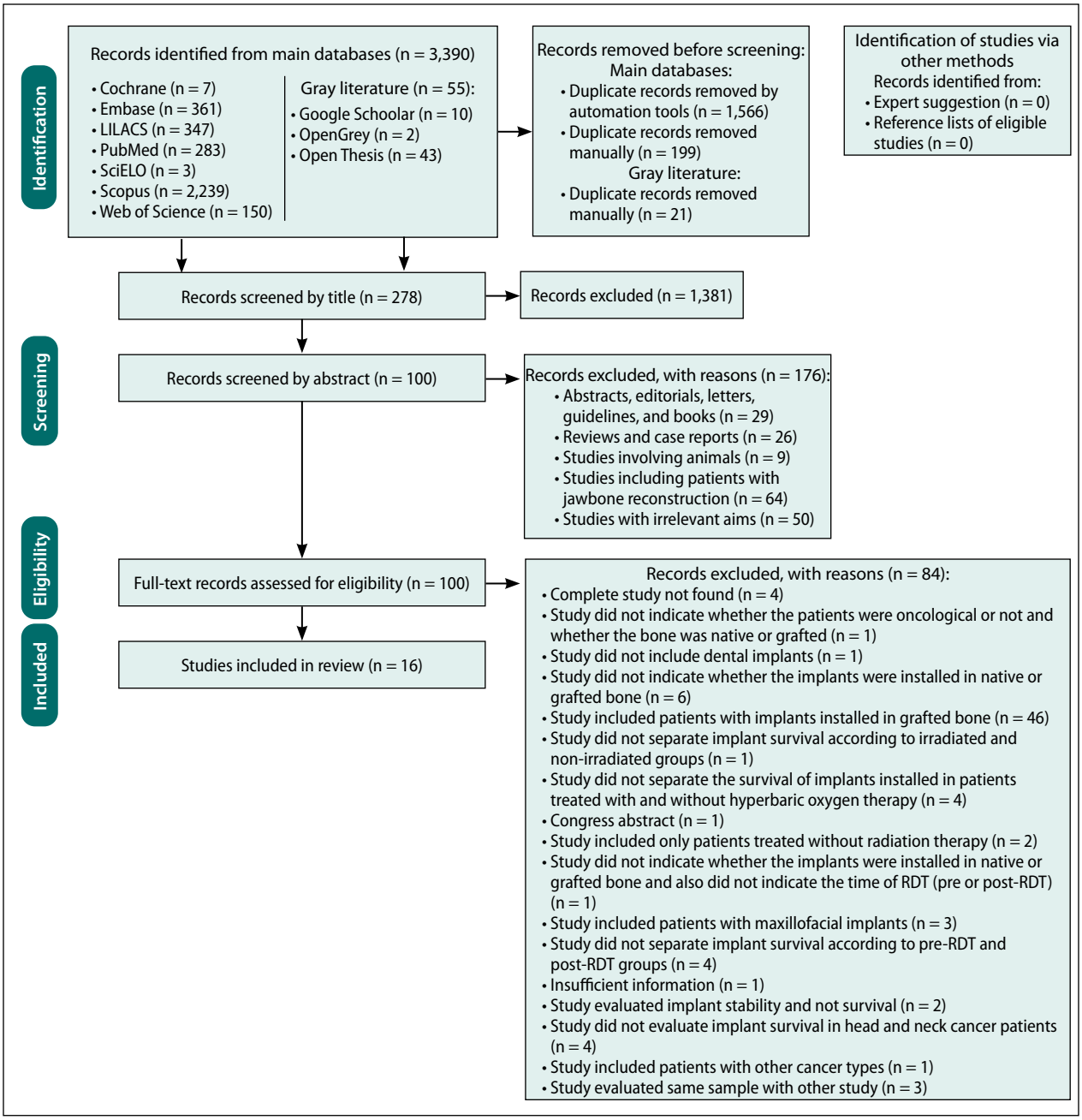

Fig 1 Process of search, identification, inclusion, and exclusion of articles.

Risk of Bias

Table 3 shows detailed information about the risk of bias of the studies included in the qualitative analysis, assessed by the Joanna Briggs Institute assessment tools.[33–35] The risk of bias of quasi-experimental studies was classified as low in one article[18] and moderate in three articles.[25–27] Two studies[18,27] received "no" for question 4 because their controls did not match the control criteria for this systematic review (nonirradiated patients). All quasi-experimental studies received "no" for question 2 because they had no uniform sample, with differences in age, HNC subtype, cancer stage, and habits (smoking and alcohol consumption) as well as the presence of associated treatment with chemotherapy.

Only one cohort study[17] had a high risk of bias,and the remaining three studies[16,20,28] had a moderate risk of bias. None of them clearly identified the confounding factors (question 4), and they did not even indicate the strategies used to deal with those confounding factors (question 5). All cohort studies had complete follow-up, which is why none showed strategies used to address incomplete follow-up (question 10).

Table 2 Summary of the Main Characteristics of the Eligible Studies Included for Qualitative Analysis

Study (year)	Study design	Associated chemo-therapy (yes/no)	Groups	Sample	Age range in years (mean ± SD)	No. of implants placed	Mean radiation doses (range)	Follow-up time (mo)	Survival rate (%)
Watzinger et al (1996)[18]	Quasi-experimental	a	Post-RDT	10	c	60	50 Gy	Mean 36	87.8
Keller et al (1997)[29]	Case series	a	Post-RDT	11 (6 male, 5 female)	24–84 (57 ± 15)	56	56 Gy (27.5–70)	Mean 120	100.0
Niimi et al (1998)[30]	Case series	a	Post-RDT	30	d	161	Between < 25 and > 66 Gy	1 to > 49	87.5
Esser et al (1999)[28]	Retrospective cohort	a	Post-RDT	28 (23 male, 5 female)	(55.3)	b	60 Gy	Mean 58.2	93.8
			Without RDT	34 (28 male, 6 female)	(54.7)	b			97.0
			Total	62 (51 male, 11 female)	a	276	60 Gy		
Visch et al (2002)[31]	Case series	a	Post-RDT	c	c	411	Between > 0–50 and > 72 Gy	Maximum 168	83.0
Landes and Kovács (2006)[25]	Quasi-experimental	b	Post-RDT	19	b	72	57 Gy	Mean 24	98.0
		b	Without RDT	11	b	42			100.0
		Yes (22 patients)	Total	30 (22 male, 8 female)	47–83 (63)	114	57 Gy		
Schepers et al (2006)[20]	Retrospective cohort	a	Pre-RDT	21	b	61	b (60–68 Gy)	Mean 29.6	97.0
			Without RDT	27	b	78			100.0
			Total	48 (29 male, 19 female)	(66.5 ± 10.3)	139	b (60–68 Gy)		
Korfage et al (2010)[26]	Quasi-experimental	a	Pre-RDT	31 (23 male, 8 female)	41–81 (59.8 ± 10.7)	124	60.1 Gy (30–70)	Mean 60	89.4
			Without RDT	19 (12 male, 7 female)	43–81 (64.2 ± 11.9)	71			98.6
			Total	50 (35 male, 15 female)	41–81 (61.5 ± 11.2)	195	60.1 Gy (30–70)		
Sammartino et al (2011)[22]	Case series	a	Post-RDT	77	a	172	a	> 36	88.3
Buddula et al (2012)[6]	Case series	a	Post-RDT	c	c	212	60.7 Gy (50.2–67.5)	Mean 84	83.0
Doll et al (2014)[16]	Prospective cohort	b	Post-RDT	55	b	292	50–72 Gy	Mean 121 (37–240)	89.5
		b	Without RDT	102	b	538			92.2
		Yes (55 patients)	Total	157 (62 male, 95 female)	16–79 (53.7)	830	50–72 Gy		
Curi et al (2018)[7]	Case series	a	Post-RDT	22	d	95	62 Gy (50–70)	Mean 89.2 (3.6–176.4)	94.1
Desoutter et al (2018)[32]	Case series	Yes (4 patients)	Post-RDT	18 (14 male, 4 female)	42–78 (57.5)	40	51.8 Gy (50–66).	Mean 89 (58–119)	80.0
Flores-Ruiz et al (2018)[17]	Retrospective cohort	b	Post-RDT	11	b	71	a	Mean 60	87.3
		b	Without RDT	6	b	20			100.0
		Yes (5 patients)	Total	17 (12 male, 5 female)	30– > 60	91			
Di Carlo et al (2019)[10]	Case series	a	Post-RDT	17 (7 male, 10 female)	(51 ± 19)	84	47.1 Gy (40–50)	Mean 22.9 (SD = 15.5)	90.5
Rolski et al (2020)[27]	Quasi-experimental	Yes (a)	Post-RDT	c	c	58	Up to a dose of 50 Gy	Mean 36	94.8

a = Not cited by the authors; b = The study did not separate the data according to the groups; c = Impossible to extract the data of native bone patients only; d = Impossible to extract the data of patients without HBOT only.

Table 3 Risk of Bias Assessed by the Joanna Briggs Institute Critical Appraisal Tools for Cohort Studies,[33] Case Series,[34] and Quasi-Experimental Studies[35]

Authors	Q.1	Q.2	Q.3	Q.4	Q.5	Q.6	Q.7	Q.8	Q.9	Q.10	Q.11	% yes/risk
Cohort studies												
Esser et al (1999)[28]	✓	✓	U	U	–	✓	✓	✓	✓	–	✓	63.6
Schepers et al (2006)[20]	✓	✓	✓	U	–	✓	U	✓	✓	–	–	54.5
Doll et al (2014)[16]	✓	✓	U	U	–	✓	U	✓	✓	–	✓	54.5
Flores-Ruiz et al (2018)[17]	✓	U	U	U	–	✓	U	✓	✓	–	–	36.4
Quasi-experimental studies												
Watzinger et al (1996)[18]	✓	–	✓	–	✓	✓	✓	U	✓			77.8
Landes and Kovács (2006)[25]	✓	–	–	✓	✓	✓	✓	U	–			55.6
Korfage et al (2010)[26]	✓	–	–	✓	✓	✓	✓	–	–			55.6
Rolski et al(2020)[27]	✓	–	–	–	✓	✓	✓	U	✓			55.6
Case series studies												
Keller et al (1997)[29]	U	–	U	–	–	✓	✓	✓	–	–		30.0
Niimi et al (1998)[30]	–	–	U	U	U	–	–	–	✓	–		10.0
Visch et al (2002)[31]	U	✓	✓	✓	✓	✓	U	U	✓	✓		70.0
Sammartino et al (2011)[22]	✓	U	–	U	–	✓	U	✓	✓	–		40.0
Buddula et al (2012)[6]	✓	✓	✓	U	✓	✓	✓	U	✓	✓		80.0
Curi et al (2018)[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		100.0
Desoutter et al (2018)[32]	✓	✓	✓	U	U	✓	✓	✓	–	–		60.0
Di Carlo et al (2019)[10]	✓	✓	✓	U	U	✓	✓	✓	✓	–		70.0

✓ = Yes; - = No; U = unclear; N/A = not applicable. Cohort studies: Q.1 = Were the two groups similar and recruited from the same population? Q.2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q.3 = Was the exposure measured in a valid and reliable way? Q.4 = Were confounding factors identified? Q.5 = Were strategies to deal with confounding factors stated? Q.6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q.7 = Were the outcomes measured in a valid and reliable way? Q.8 = Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q. 9 = Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored? Q.10 = Were strategies to address incomplete follow-up utilized? Q.11 = Was appropriate statistical analysis used?; Quasi-experimental studies: Q.1 = Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)? Q.2 = Were the participants included in any similar comparisons? Q.3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q.4 = Was there a control group? Q.5 = Were there multiple measurements of the outcome both pre- and post-intervention/exposure? Q.6 = Was follow-up complete, and if not, were differences between groups in terms of their follow-up adequately described and analyzed? Q.7 = Were the outcomes of participants included in any comparisons measured in the same way? Q.8 = Were outcomes measured in a reliable way? Q.9 = Was appropriate statistical analysis used? Case series studies: Q.1 = Were there clear criteria for inclusion in the case series? Q.2 = Was the condition measured in a standard, reliable way for all participants included in the case series? Q.3 = Were valid methods used for identification of the condition for all participants included in the case series? Q.4 = Did the case series have consecutive inclusion of participants? Q.5 = Did the case series have complete inclusion of participants? Q.6 = Was there clear reporting of the demographics of the participants in the study? Q.7 = Was there clear reporting of clinical information of the participants? Q.8 = Were the outcomes or follow-up results of cases clearly reported? Q.9 = Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q.10 = Was statistical analysis appropriate?

The risk of bias of case series studies was classified as low for four articles,[6,7,10,31] moderate for one article,[32] and high for three articles.[22,29,30]

Synthesis of Results

The follow-up period in the studies was 1 to 240 months, with a median follow-up period of 60 months in most articles. The survival rates for all groups were 80% to 100%. Implants placed post-RDT, pre-RDT, and without RDT presented survival rates of 80% to 100%, 89.4% to 97%, and 92.2% to 100%, respectively.

Among the studies that directly compared the irradiated to nonirradiated groups, a statistically significant difference was observed in only one study[17] which showed a higher survival rate for implants placed without RDT compared to implants placed post-RDT. In the remaining studies that made comparisons, no significant differences between groups[20,28] or no statistical results of the comparison[16,25,26] were reported (Tables 4 and 5). All studies that directly compared the groups showed better survival for implants placed in patients who did not undergo RDT.

DISCUSSION

The number of patients with HNC treated with RDT and rehabilitated with implant-supported prostheses has

Table 4 Implant Survival (in Months) in the Pre-RDT Group Compared to the Nonirradiated Group, According to the Follow-up Period and Radiation Doses

	Mean radiation doses (Gy)	Mean follow-up period (mo)	Survival rate: without RDT (%)	Survival rate: pre-RDT (%)
Schepers et al (2006)[20]	97.0	30	100	97
Korfage et al (2010)[26]	60.1	60	98.6	89.4

Table 5 Implant Survival (in Months) in the Post-RDT Group Compared to the Nonirradiated Group, According to the Follow-up Period and Radiation Doses

	Mean radiation doses (Gy)	Mean follow-up period (mo)	Survival rate: without RDT (%)	Survival rate: post-RDT (%)
Esser et al (1999)[28]	60	58.2	97.0	93.8
Landes and Kovács (2006)[25]	57	24	100	98
Doll et al (2014)[16]	50–72	121	92.2	89.5
Flores-Ruiz et al (2018)[17]	a	60	100	87.3

[a]Not cited by the authors.

increased over the last decade,[7,12] but the most appropriate timing for implant placement (prior to or after RDT) is controversial. This study systematically investigated the survival rate of implants placed pre-RDT and post-RDT compared to that of implants placed without RDT. The exclusion criteria included studies that exclusively involved patients with comorbidities and HBOT. Comorbidities such as diabetes and osteoporosis can significantly interfere with implant survival[7]; therefore, they could be a confounding factor in this study. The use of adjuvant HBOT is controversial, with several studies showing no influence of HBOT on implant survival, and it is an expensive treatment that is not accessible to many populations.[7,20]

In the present study, chemotherapy was not considered as an exclusion factor since limitations were noted in the included studies. Among the total of 16 studies, only 5 claimed to have included patients treated with chemotherapy (without detailed information about the chemotherapy drugs used or their dosage), and the remaining 11 did not mention whether or not patients treated with chemotherapy were included. Therefore, the exclusion of these studies would significantly decrease the total number of included studies.

Most of the drugs used in chemotherapy do not have a specific mechanism of action against tumor cells, acting on cell proliferation and thus interfering with the metabolism of healthy cells, especially those with high turnover rate (such as bone marrow cells), which can lead to reduced bone turnover, although more modern drugs tend to cause less bone damage.[36] According to some studies,[16,25,36,37] chemotherapy seems to have no significant influence on the survival of dental implants. Additionally, one study found that chemotherapy does not interfere with the number of osteoblasts produced, showing that bone metabolism is not completely compromised by chemotherapy.[38] The significantly lower survival rate of dental implants is mainly due to the effects of RDT rather than chemotherapy.[10,39]

Analysis of the survival rate according to sex, radiation techniques, and implant location was not performed. Sex does not interfere with the survival of dental implants.[28] There are different RDT techniques, such as external beam radiation, radioisotope therapy, and brachytherapy; however, different radiation techniques do not affect the survival of dental implants.[40] Implant location does not influence implant survival.[16] The results showed that dental implants placed post-RDT had a high survival rate, similar to those placed without RDT. Despite the high survival of implants placed post-RDT, the greatest number of implant failures was reported in this group. Patients have rejected offers of implant placement post-RDT because it may lead to additional surgery when patients are already exhausted.[5,14]

Implant survival is completely dependent on the osseointegration process[21]; hence, implants placed pre-RDT may show better results since osseointegration is well established before the bone is compromised by RDT, although the late effects of RDT continue for years after completion of initial treatment.[13,14] These factors may help explain the relatively high survival rate of dental implants placed pre-RDT compared to those placed post-RDT.

One of the most appropriate times for implant placement is during ablative surgery, which combines tumor surgery and implant placement, providing benefits such as implant placement in nonradiated bone (leading to a reduced risk of developing osteoradionecrosis), lack of need for additional surgery, earlier rehabilitation with an implant-supported prosthesis, and initial implant healing occurring before initiating RDT.[7,41] There

are some disadvantages, such as improper positioning of the implants (especially in patients with large defects) and difficulties in obtaining sufficient keratinized mucosa around the implants.[7,14] Another disadvantage is the risk of losing the implants due to tumor recurrence,[17] but in the present study, few implants (58) were lost due to tumor recurrence in all included studies.

This review has some limitations. Two articles[6,21] evaluated the same sample, and therefore only one was included.[6] The same happened with another set of two articles,[26,42] and once again only one article was included.[26] In both cases, the article with the longest follow-up time was included. Four articles were excluded because their full text was not found (Appendix 1), thus compromising the certainty of evidence for the present study. Only two studies were found that evaluated the survival rate of dental implants placed pre-RDT in the native bone. There was huge variation in the mean follow-up period and radiation doses between all included studies; therefore, meta-analysis could not be performed. Some data could not be extracted because they were not available in the articles. Therefore, the corresponding authors were contacted by email. Some of them responded, but the others did not. The present study did not find randomized clinical studies comparing patients with implants placed pre- or post-RDT to those with implants placed without RDT, which could enrich the study. These aspects decrease the conclusiveness of the presented findings.

CONCLUSIONS

Despite the alterations caused by ionizing radiation in peri-implant tissues, dental implants placed pre- and post-RDT seem to have high survival rates, similar to those placed without RDT, indicating that it is a relatively safe procedure. However, the available evidence is limited, with great heterogeneity in the survival rates; therefore, more well-designed studies should be performed so that accurate conclusions could be drawn.

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APPENDIX

Appendix Table 1 Studies Excluded in Reading of Full Texts and Reasons for Exclusion and Full-Text Studies Not Found (n = 84)

	Study excluded	Reason for exclusion
1	Ueda et al (1993)	Complete study not found
2	Lorant et al (1994)	Study did not indicate whether the patients were oncological or not and whether the bone was native or grafted
3	Roumanas et al (1994)	Study did not include dental implants
4	Smatt et al (1995)	Complete study not found
5	Franzén et al (1995)	Study did not indicate whether the implants were placed in native or grafted bone
6	Weischer et al (1996)	Study included patients with implants placed in grafted bone
7	Brogniez et al (1998)	Study included patients with implants placed in grafted bone
8	Arcuri et al (1997)	Study did not indicate whether the implants were placed in native or grafted bone
9	Jisander et al (1997)	Study included patients with implants placed in grafted bone
10	Weischer and Mohr (1997)	Study did not indicate whether the implants were placed in native or grafted bone
11	McGhee et al (1997)	Study included patients with implants placed in grafted bone
12	Esser and Wagner (1997)	Study included patients with implants placed in grafted bone
13	August et al (1998)	Study included patients with implants placed in grafted bone
14	Ihara et al (1998)	Study did not indicate whether the implants were placed in native or grafted bone
15	Wagner et al (1998)	Study did not separate implant survival according to irradiated and nonirradiated groups
16	Andersson et al (1998)	Study included patients with implants placed in grafted bone
17	Betz et al (1999)	Study included patients with implants placed in grafted bone
18	Grötz et al (1999)	Study included patients with implants placed in grafted bone
19	Mericske-Stern et al (1999)	Study included patients with implants placed in grafted bone
20	Schliephake et al (1999)a	Study included patients with implants placed in grafted bone
21	Schliephake et al (1999)b	Study included patients with implants placed in grafted bone
22	Weischer and Mohr (1999)	Study included patients with implants placed in grafted bone
23	Werkmeister (1999)	Study included patients with implants placed in grafted bone
24	Granström et al (1999)	Study did not separate the survival of implants placed in patients treated with and without hyperbaric oxygen therapy
25	Snauwaert et al (2000)	Study included patients with implants placed in grafted bone
26	Kwakman et al (2001)	Congress abstract
27	Kovács (2001)	Study included only patients treated without radiation therapy
28	Van Steenberghe et al (2002)	Study did not indicate whether the implants were placed in native or grafted bone
29	Goto et al (2002)	Study included patients with implants placed in grafted bone
30	Cao and Weischer (2003)	Study included patients with implants placed in grafted bone
31	Schmidt et al (2004)	Study did not indicate whether the implants were placed in native or grafted bone
32	Moy et al (2005)	Study did not indicate whether the implants were placed in native or grafted bone and also did not indicate the time of RDT (pre- or post-RDT)
33	Granström (2005)	Study included patients with maxillofacial implants
34	Shaw et al (2005)	Study included patients with implants placed in grafted bone
35	Garrett et al (2006)	Study included patients with implants placed in grafted bone
36	Bodard et al (2006)	Study did not separate implant survival according to pre-RDT and post-RDT groups
37	Yerit et al (2006)	Study included patients with implants placed in grafted bone
38	Roumanas et al (2006)	Study included patients with implants placed in grafted bone
39	Nelson et al (2007)	Study included patients with implants placed in grafted bone
40	Alsaadi et al (2007)	Insufficient information
41	Schoen et al (2007)	Study included patients with implants placed in grafted bone
42	Adell et al (2008)	Study included patients with implants placed in grafted bone
43	Bauer et al (2008)	Complete study not found
44	Schoen et al (2008)	Study evaluated same sample as Korfage et al (2010)
45	Cuesta-Gil et al (2009)	Study included patients with implants placed in grafted bone
46	Nagy et al (2009)	Study included patients with implants placed in grafted bone

Appendix Table 1 Studies Excluded in Reading of Full Texts and Reasons for Exclusion and Full-Text Studies Not Found (n = 84)

	Study excluded	Reason for exclusion
47	Barrowman et al (2011)	Study included patients with implants placed in grafted bone
48	Buddula et al (2011)	Study evaluated same sample as Buddula et al (2012)
49	Støre et al (2011)	Study did not separate the survival of implants placed in patients treated with and without hyperbaric oxygen therapy
50	Linsen et al (2012)	Study included patients with implants placed in grafted bone
51	Mancha de la Plata et al (2012)	Study included only patients treated without radiation therapy
52	Katsoulis et al (2013)	Study included patients with implants placed in grafted bone
53	Mizbah et al (2013)	Study did not separate implant survival according to pre-RDT and post-RDT groups
54	Dholam et al (2013)	Study included patients with implants placed in grafted bone
55	Gander et al (2014)	Study included patients with implants placed in grafted bone
56	Korfage et al (2014)	Study did not separate the survival of implants placed in patients treated with and without hyperbaric oxygen therapy
57	Reich et al (2015)	Complete study not found
58	Pompa et al (2015)	Study included patients with implants placed in grafted bone
59	Hessling et al (2015)	Study included patients with implants placed in grafted bone
60	Karayazgan-Saracoglu et al (2017)	Study evaluated implant stability and not survival
61	Ch'ng et al (2016)	Study included patients with implants placed in grafted bone
62	Maló et al (2016)	Study did not evaluate implant survival in head and neck cancer patients
63	Ettl et al (2016)	Study included patients with implants placed in grafted bone
64	Wu et al (2016)	Study did not separate implant survival according to pre-RDT and post-RDT groups
65	Cotic et al (2016)	Study did not separate the survival of implants placed in patients treated with and without hyperbaric oxygen therapy
66	Ernst et al (2016)	Study included patients with implants placed in grafted bone
67	Kobayashi et al (2016)	Study included patients with implants placed in grafted bone
68	Rana et al (2016)	Study included patients with implants placed in grafted bone
69	Carr et al (2017)	Study did not evaluate implant survival in head and neck cancer patients
70	Hasegawa et al (2017)	Study included patients with implants placed in grafted bone
71	Nicoli et al (2017)	Study included patients with other cancer types
72	Rolski et al (2017)	Study evaluated implant stability and not survival
73	Wetzels et al (2017)	Study included patients with implants placed in grafted bone
74	Kim et al (2018)	Study did not evaluate implant survival in head and neck cancer patients
75	Takahashi et al (2018)	Study included patients with implants placed in grafted bone
76	Butterworth (2019)	Study included patients with maxillofacial implants
77	Ettl et al (2020)	Study included patients with implants placed in grafted bone
78	Moore et al (2019)	Study included patients with maxillofacial implants
79	Nguyen et al (2019)	Study did not evaluate implant survival in head and neck cancer patients
80	Papi et al (2019)	Study included patients with implants placed in grafted bone
81	Woods et al (2019)	Study included patients with implants placed in grafted bone
82	Laverty et al (2019)	Study included patients with implants placed in grafted bone
83	Alberga et al (2020)	Study did not separate implant survival according to pre-RDT and post-RDT groups
84	Patel et al (2020)	Study included patients with implants placed in grafted bone

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