Dental implant survival rate in irradiated and non-radiated patients: a systematic review and meta-analysis

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Radiotherapy to head and neck has always been considered as a risk factor for rehabilitation with dental implants. Nevertheless, recent data suggest that overall, 5-year implant survival in irradiated patients can be greater than 90%. The purpose of this review was to compare the implant survival rates of irradiated and non-radiated head and neck cancer sites, and discuss the outcomes, through a systematic review approach of prospective and retrospective studies. Electronic searches were performed in the EMBASE, Cochrane, and PubMed/Medline databases up to 2019 Dec, to identify retrospective and prospective clinical studies addressing the subject. This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary variables collected from the studies were the site of tumor, age and sex of the patient, site of implant placement, radiation dosage, frequency and duration of radiotherapy, follow-up duration, implant survival and stability, hard and soft tissue changes after implant placement, any type of biological and mechanical complication, and oral health quality of life (QOL). Fifteen studies including 1097 patients and a total of 4637 implants placed in irradiated and non-irradiated sites, with a follow up duration varying from 6 to 120 months, were selected for the systematic review. The results of the quantitative synthesis suggested statistically significantly better survival rate of implants placed in non-radiated sites, as compared to irradiated sites ($p<0.00001$). However, the cumulative survival rates over a period of 7-10 years were reported to be comparable. Quality of life (QOL) after implant rehabilitation was not found to be significantly different between the compared groups. Due to the limited number of information, insufficient data was available to draw conclusion on peri-implant complication rate. No relationship was found between age, gender, and implant survival rates. Implant placement in irradiated sites is challenging and often warrants protocol modifications. Although statistically the survival rates at irradiated sites were lower in comparison to non-radiated sites, a strict inclusion criterion in patient selection, timing of implant placement after radiotherapy, radiation dosage and regular oral hygiene maintenance could minimize the chances of implant failure in irradiated patients.

"Head and neck cancer" is a term used to describe several different malignant tumours that develop in or around the throat, larynx, nose, sinuses, and mouth. These account for 4% of all the cancers

Key words: head and neck cancer, radiotherapy, implant survival, quality of life, dental implants, radiation dosage, hyperbaric oxygen therapy, irradiated patients, smoking

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in the United States (1). About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide (2). Five-year overall survival rate of patients with HNSCC is about 40-50% with about one third of patients present with early-stage disease (3). The treatment protocol for head and neck cancer involves surgeries primarily followed by radiotherapy. Surgical treatment such as partial or complete resection of the jaws, neck dissection to remove lymph nodes and reconstructive surgery in cases of large defects often causes significant jarring problems for the patients. A study demonstrated that, following successful treatment of oral cancer, the most important issues reported by patients in terms of Quality of life (QOL) were chewing, speech and swallowing, closely followed by appearance, especially in female patients (4).

Rehabilitation options for these patients are not different from healthy patients and vary from fixed prostheses (bridgework) and removable partial dentures (RPD) to implant retained fixed or removable prostheses. Dental implants have been a resolute for providing stability and support with limited pressure on soft tissues, which often are compromised after surgical therapy. Microvascular surgical techniques along with dental implants can considerably improve the rehabilitation of people with severe head and neck defects, but there may be an increased risk of implant failure in irradiated free flap bone (5). Radiotherapy significantly impedes the vascularisation and the regenerative capacity of the bone and vascular tissues. This leads to impaired regenerative and functioning ability of bone cells, leading to increased chances of osteoradionecrosis (5,6). Also, radiotherapy causes an imbalance in oral flora causing mucositis and xerostomia like conditions (6). Altered anatomy, xerostomia, chances of mucosal breakdown and graft failure are few of the factors that could contribute to implant failure in patients with radiotherapy, thereby making radiotherapy a risk factor for oral rehabilitation with dental implants (6).

However, few studies do not consider radiotherapy as an absolute contradiction to the placement of implants. Overall, 5-year survival rate of implants placed after radiotherapy was found to be 92.9% (7). The author suggested that factors like age of the patients, and time of implantation after radiation therapy had no significant impact on implant survival. However, attention should be paid towards gender of the patient, type of radiation therapy and systemic factors like diabetes and osteoporosis. Several other clinical studies have also reported that implants can osseointegrate and remain functionally stable in patients who had received radiotherapy, thus suggesting that adjunctive radiotherapy is not an absolute contraindication to implant placement (8, 9). It was reported by Alani et al in 2009 about the changing attitude of clinicians and the increase in implant placement from 43% to 93% in head and neck cancer patients (10). Despite the increasing knowledge and advancements made in the field of radiotherapy, there exists inconsistency amongst the studies regarding the appropriateness and survival rate of implants in head and neck cancer patients, particular the impression regarding success of implants due to radiotherapy and associated factors such as the restriction for site of implant placement, effects of radiation dosage, timing of implants in relation to radiation therapy, etc. With the rise in demand for implant therapy, it has become prudent for clinicians to understand the scope of implants in rehabilitation of patients with head and neck cancer.

The purpose of this systematic review was to answer the following questions:

1. What is the survival rate (SR) of implants and/or quality of life (QOL) when compared between radiated and irradiated bone?
2. How accurate is the analysis when determining the survival rate of implants between irradiated and non-radiated sites?

MATERIALS AND METHODS

An electronic search was performed on the following databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). Databases like Google scholar, Research gate, and Scopus were excluded. The last search was performed on December 31, 2019. The search terms used were: “dental implants”, “radiotherapy”, “head and neck cancer”, “implants and

radiotherapy side effects", "implant survival", implant failures after radiation". These terms were combined using Boolean operators OR and AND. Furthermore, a hand search of issues from 1999 up to the last issue available on December 15, 2019, including the "Early view" (or equivalent) section was undertaken in the following journals: British Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, Journal of Oral and Maxillofacial surgery, Oral Oncology, Clinical Oral Implants Research, Journal of Periodontology, Periodontology 2000, Journal of Prosthetic dentistry, International journal of Implant dentistry, Journal of Clinical Periodontology, Journal of Periodontal Research, Indian journal of dental research, Journal of Dental Research, Journal of clinical and experimental dentistry, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. The reference list of the retrieved reviews and the included studies was also searched for possible additional eligible studies not identified by the electronic search. The bibliography list of all relevant manuscripts and potentially eligible articles were thoroughly screened for any missed reports, not identified by electronic and manual searches. The unpublished literature or any grey articles were searched in www.opengrey.com till December 2019.

Selection of the studies

Three reviewers (SG, SP and MDF) independently screened the titles and the abstracts of the articles initially retrieved through the electronic search. The concordance between reviewers was assessed using the Cohen's Kappa coefficient. The full texts of all studies of possible relevance were independently assessed by the same two reviewers to check if they met all inclusion criteria. For articles excluded at this stage, the reason for exclusion was recorded.

Data extraction

Data were extracted by two reviewers independently (MDF and SG). Cases of disagreement were subject to joint evaluation with third reviewer (SP) until an agreement was reached.

Title and abstract analysis were used for the initial categorization of the studies. Subsequently, eligible studies were analysed and included or excluded from the total sample.

Prospective and retrospective studies comparing implant survival rate/ failure rate and QOL between irradiated and non-radiated patients/sites in same patient or between different patients in the same study were included for the systematic review and analysis. The population, intervention, comparison, and outcome (PICO) criteria, as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, were used to determine the questionnaire with appropriate exclusion and inclusion focus (11). The population (P) consisted of patients requiring oral rehabilitation with implant therapy. The intervention (I) was the placement of implants in irradiated patients, and the comparison (C) was the survival rate of implants placed in irradiated versus those placed in non-irradiated areas either in same patients or between different patients reported in the same study. The outcome (O) was the analysis of the survival rates and quality of life after rehabilitation with implant therapy.

Inclusion criteria

1. Retrospective and prospective studies comparing implant survival rate/ failure rate and QOL between irradiated and non-radiated patients/sites in same patient or between different patients in the same study.
2. Studies with a long duration of follow up of at least 1 year.
3. The studies providing details on the radiation therapy and the report of any adverse effects.

The search was limited to human studies. Restrictions were not placed regarding the publication year, however articles in English were only considered for the systematic review. No limitation on sample size was placed.

Exclusion criteria

Publications that did not meet the above inclusion criteria and those that were not dealing with original clinical cases (e.g., reviews, technical reports) were excluded. In case of multiple publications relative to subsequent phases of the same study or to enlargements of the original sample size, only the most recent data (those with the longer follow-up and the larger sample size) were considered. Also, studies focussing on the comparison between bone grafts, chemotherapy, and different types of radiation therapy as the most important outcome factor were excluded.

Assessment of the quality of the trial

The methodological qualities of the selected studies were evaluated independently by two reviewers (MDF and

SP) using ROBINS- I (Risk of Bias in Non-randomised Studies of Interventions) tools (12). The risk of bias was assessed based on any bias due of confounding, selection of participants, classification of interventions, deviations from intended exposures, any missing data, or any selective reporting of results. For each study, each criterion was scored as low risk, high risk or unclear. When all criteria were at low risk, and no more than one criterion was judged unclear, the overall risk of bias was estimated as low; if two or more criteria were judged unclear and other criteria were how-so-ever at low risk, an overall moderate risk of bias was assigned; when one or more criteria were at high risk, an overall high risk was assigned to the respective study. The authors of the included studies were contacted for providing clarifications or missing information as needed.

Statistical analysis

If three or more comparative studies presented results regarding a similar outcome variable, they were aggregated in a meta-analysis. The estimation of the effect of irradiation on implant survival/failure between implants placed in irradiated vs non-irradiated sites was expressed using Odds Ratio (OR) and 95% Confidence Intervals (CI). ORs were combined using a random effects model if at least 4 studies could be included in the meta-analysis, otherwise a fixed-effects model was adopted. Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis calculations and graphs. Forest plots were produced to graphically represent the results of meta-analysis. Reporting of these meta-analyses adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement.

RESULTS

The last electronic search was performed on December 31st, 2019. The electronic and hand search yielded a total of 636 articles from the period 1999-2019. After a first screening of the titles and abstracts a total of 21 eligible articles reporting comparisons on implant survival between radiated and irradiated sites were selected. The Cohen's Kappa among the three reviewers was between 0.88 and 0.90, indicating excellent agreement. After evaluation of the full text of these articles, only 15 studies (13-27) were considered adequate for the systematic review. These studies reported on 1097 patients and a total of 4637 implants. Fourteen studies were included in the quantitative analysis (meta-analysis) of comparative studies on implant survival (13-20, 22-27) whereas one study on quality of life (QOL) after implant rehabilitation was considered only for qualitative

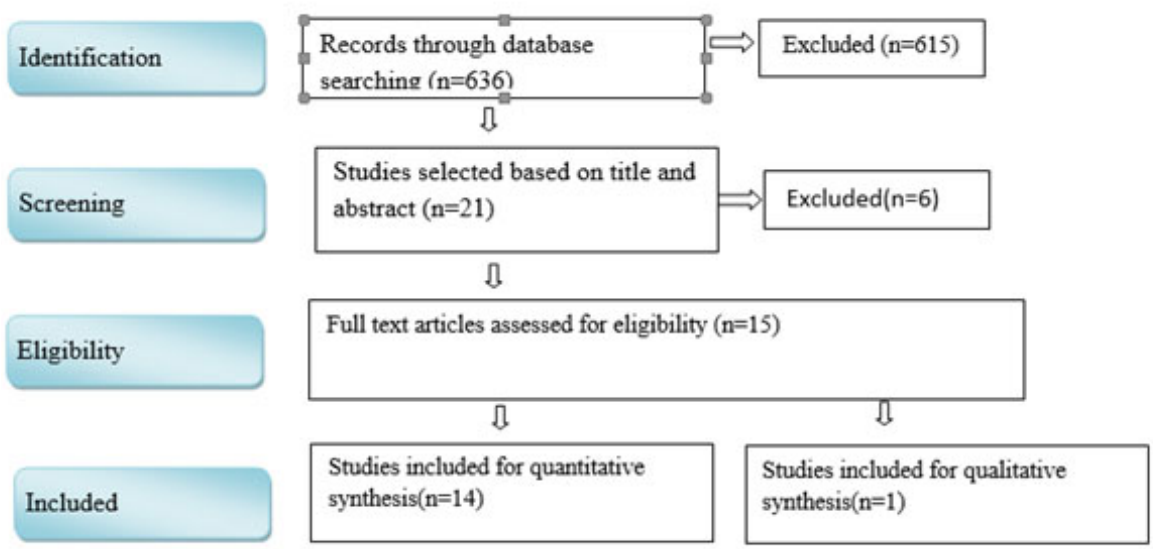

Fig. 1. *PRISMA Flowchart for selection of studies.*

analysis (21). The flowchart summarizing the screening process is presented in (Fig. 1). The results of risk of bias assessment are reported in Fig. 2 and 3.

Overall, 4 of the included studies were judged to be at low risk (13, 20, 22, 27), 8 at moderate risk (14, 17-19, 21, 23, 25, 26), and two at high risk (16, 24). The characteristics of included studies are reported in Table I-IV. The data for meta-analysis included a total of 4552 implants placed in irradiated and non-irradiated sites of 1071 patients, followed up for the duration varying from 6 to 120 months. All the patients in the present review received radiotherapy in fractions in the range of 20-72 Gy. The average age of the patients was 58.3.

Regarding the location of the implants, a total of 1056 was placed in maxilla and 2150 were placed in mandible (Table IV-V). The number of implants placed in maxilla and mandible respectively could not be discerned from the study by Dholam et al, 2013 and Granstrom et al,2005 (13, 20, 26).

Random effect model was used for the analysis as the heterogeneity between the studies evaluating the failure rates of implants placed among the irradiated and non-irradiated sites was low and relevant (Chi^2

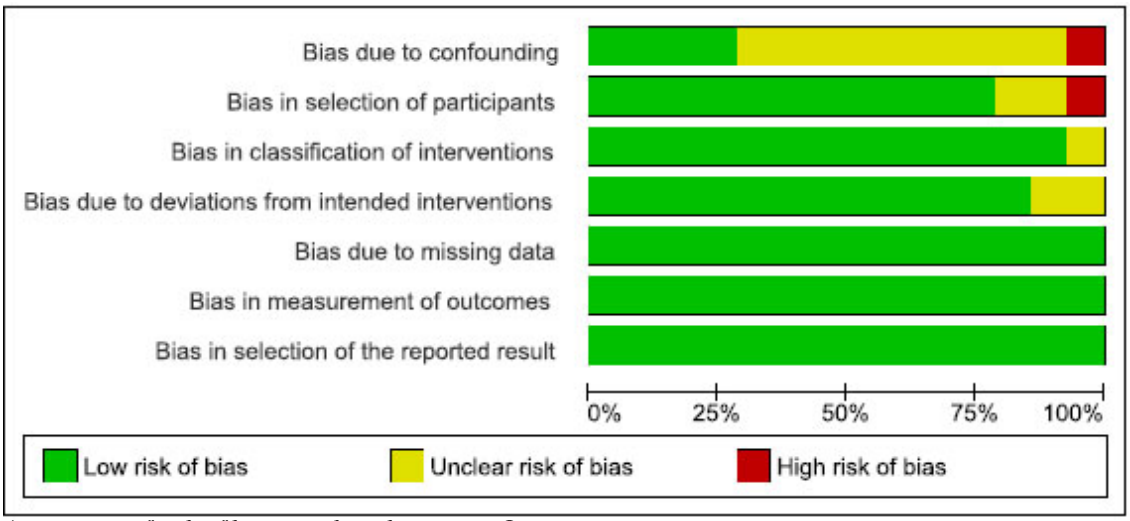

Fig. 2. *Assessment of risk of bias graph and summary I.*

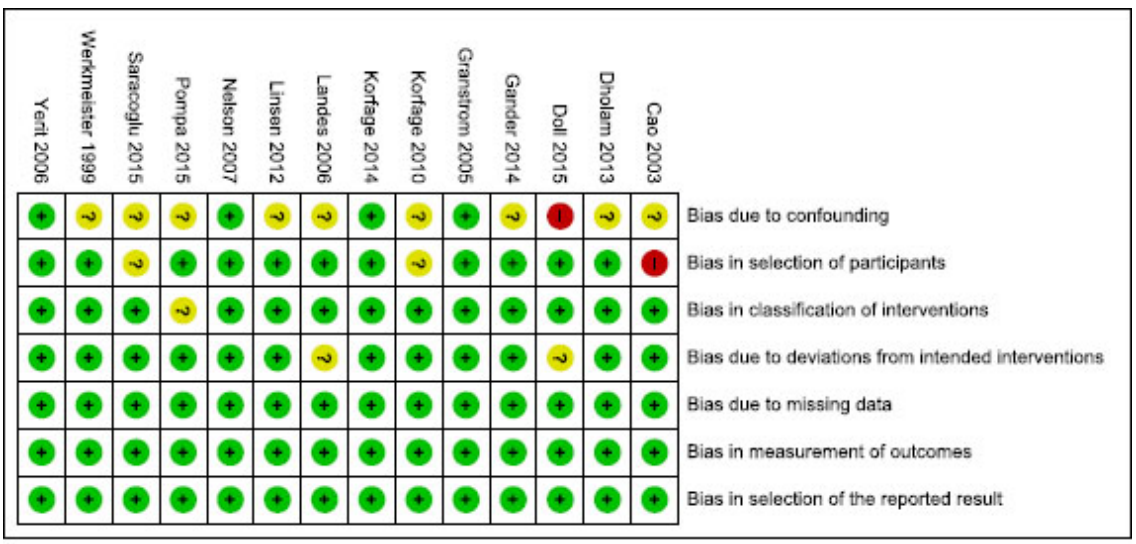

Fig. 3. *Assessment of risk of bias graph and summary II.*

Table I. *Characteristics of included studies.*

Author/ year	Cases /controls M/F Age	Dose of radiation	Implants no. and type	Time of placement after irradiation (T1) and follow up (T2)	Survival rate	QOL
Werkmeister et al, 1999 Retrospective study	IR:12 NR:17 M:23; F:6 Age: 35-79yrs	Dose: average 54Gy No HBO	Implants:109 NR:34 IR:75 Mand implants	T1: 24months T2: 3 years	Failure in IR:29.3% Failure in NR:14.7% P<0.05. No SSD between IR non grafted and grafted. P>0.05	NI
Cao, Weischer, 2003 Retrospective study	IR:12; NR:15 M:18; F:9 Age: 45-79yrs	Dose: 36-76Gy 4-5 fraction of 2-2.5Gy/week.	Implants: 131 Branemark, Frialit Maxillary implants	T1: 6 months T2: 7years	CSR of implants in IR: 49.44%, NR:77.80%, P=0.01 CSR of prosthesis: IR:75%, NR: 100% P=0.01	NI
Granstrom et al, 2005 Retrospective study	IR:107. NR:100 M:122 F:85 Age: 15-88yrs	Dose: Fractionation therapy Twice/day at 41-50 Gy Once/day at 61-70Gy HBO therapy 340 protected 291- Not protected	Implants:1245 IR:631; NR:614 Nobel biocare implants	T1: 6.3yrs T2: 20yrs	Failure of IR implants:147(23.2%) Failure of NR implants: 76(12.3%) Implant failure with HBO therapy: 29/340(8.5%) Implant failure without HBO therapy: 117/291(40.2%) P<0.001. Not SSD No effect of gender, age and smoking status on implant failure.	NI
Landes et al, 2006 Prospective study	IR: 19; NR:11 M: 22; F:8 Age: 47-83 years	Dose: 57Gy at single dose of 1.9Gy	Implants: TPS, SLA, ITI NR: 42(37%) IR: 72(63%) Mandibular implants	T1:16.5mo T2: 21mo	Implant stability better in NR(p<0.15) IR had more bone loss after 12mo post insertion of implants Success rate: 100% in NR; 98% in IR	NI
Yerit et al, 2006 Prospective study	M:56; F:15 Age: 16-84yrs	Dose: 2Gy for 25 days. Total 50 Gy	Implants: NR:84, IR:154 IMZ, Frialit, Xive. Mandibular implants	T1: mean 1.41yrs T2: 5.42-13.61yrs	Survival rate after 8 yrs: NRnb:95%, Irnb: 72% Gb:54%, P= 0.0028 No SSD diff between grafted and native bone failure.	NI
Nelson et al, 2007 Prospective study Strict inclusion criteria	IR: 93ptnts M: 63; F:30 Age: 26-89yrs Cancer sites: Max:25ptnts Mand:68 ptnts	Dose: 2Gy daily for 5days/week.	Total no: 435 IR:124(Max 41; Mand 83) NR:311(Max:113, Mand:198) Branemark, Steri-Oss, CAMLOG, ITI	T1:6 months T2:10.3yrs	Survival rate after 8 yrs: 70% in both M, F. 75%: Max and mand implants. Mand SR more than max implants after 5 years. CSR in IR @13.5yrs: 54%. Diff between IR and NR(P=0.08). SR between grafted and non-grafted: P=0.71	NI
Korfage et al, 2010 Prospective study	M:35; F:15 IR/NR:31/19 Age: 60-70yrs	>40Gy	Total: 195 Branemark, Noble biocare Mand implants	T1:6mo post implant placement T2:60m	Survival in IR:89.4%, NR:98.6%	NI
Linsen et al, 2012 Prospective study	M/F: 43/23 Max/mand: 10/56 IR/NR: 34/32 Age: 55.7yrs	2 Gy in fractions. Total of 36-60Gy	Total: 262 Branemark, Straumann IR:NR- 127:135 Max:213, Mand:49	T1: 41months T2: 82months	CSR @120 month IR: 95.6% NR: 84.7% (p=0.302)	NI
Dholam et al, 2013 Prospective study Strict incl. criteria	M/F: 18/12 Age: 13-82yrs IR/NR: 19/11	20-60Gy in fractions	Total:85 IR: 59 NR: 26 Max/Mand ant region and PMs: 6/26	T1:12 months T2:5 Years	Success rate: IR:71% NR:100% P=0.144 Native and grafted bone. P=0.465	NI
Dholam et al, 2013 Strict incl. criteria	Total:26 M/F: 17/9	20-60Gy in fractions	Total:85	Time: 18 m after implant retained dental prostheses		No SSD between IR & NR. P=0.919
Gander et al, 2014 Retrospective study	M/F: 23/10 Age: 64.15yrs	Cumulative radiation dose: 56-76Gy	Astra tech/ 136/ IR:NR-84:52 Mand implants	T1:12months T2:79m	CSR@20yr: 87.5% P=0.297	NI
Korfage et al, 2014 Prospective study	M/F: 98/66 IR/NR:100/64	Referred patients after radiotherapy. Dose unknown	Branemark/ 524/ IR:NR- 318:206 Mand implants	T1:6months post implant placement T2: 3.8 yrs	Implant loss in IR: 8.5% NR: 0.5% (p<0.0001)	IR:19.5 NR:24.6 (p=0.30)
Doll et al, 2015 Prospective study Strict inclusion criteria	M/F:62/95 IR/NR:55/102 Age: 53.7yrs	2 Gy over 6 wks. 50-72Gy total. Pre &post-op antibiotic in NR patients (Clindamycin 600mg)	Canalog, Steri-oss, Branemark, Straumann TL/ 830(450 max/380mand)/ IR:NR-292:538	T1: 6months T2:121 months	@7 yrs IR: 0.895+0.018 NR: 0.922+0.013 (P=0.011)	NI
Pompa et al, 2015 Retrospective study	M/F: 12/22 Age:50-70yrs	2 Gy given daily 5 days/week. <50Gy	Osteotite implants Total: 168 IR:NR-51:117 Mand:22; Max:12	T1:12months T2:39.5 months	Survival rate: NR:69.6%, IR:30.4% P<0.01 No SSD between implant sites. SSD in relation to time of loading of implants after radiotherapy (>6 m). P<0.01	NI
Saracoglu et al, 2015 Prospective study	M/F:42/38 Case/Cntrl: 40/40 IR/NR:40/40 Age: 51yrs	Cumulative dose: 72 Gy	Straumann/ IR:NR-40:40 Max/Mand:40/40	T1:6 months T2: 1 year	ISQ values: P<0.001 (mand) P<0.002 (maxilla)	NI

CSR: *Cumulative survival rate;* ***Max:*** *maxilla; Mand: Mandible;* ***IR:*** *Irradiated;* ***NR:*** *Non-radiated;* ***NI:*** *Not investigated;* ***SSD:*** *Statistical significant difference;* ***Yrs:*** *years. *Strict inclusion criteria refer to studies that did not include patients who were smokers, alcoholics or had poor oral hygiene.*

Table II. *Distribution of cases in maxillary region.*

Author/ year	Cases /controls M/F Age	Dose of radiation	Implants no. and type	Time of placement after irradiation (T1) and follow up (T2)	Survival rate	QOL
Cao and Weischer et al, 2003	IR:12; NR:15 M:18; F:9 Mean age: 56 year	36-76Gy 4-5 fraction of 2-2.5Gy/week.	Implants: 131 Branemark, Frialit	T1: 6 months T2: 7years	CSR: IR: 49.44% NR:77.80% p=0.01 CSR of prosthesis: IR:75% NR: 100% p=0.01	NI

CSR: *Cumulative survival rate;* ***Max:*** *maxilla; Mand: Mandible;* ***IR: I****rradiated;* ***NR:*** *Non-radiated;* ***NI:*** *Not investigated;* ***SSD:*** *Statistical significant difference;* ***Yrs:*** *years.*

Table III. *Distribution of cases in mandibular region.*

Author/ year	Cases /controls M/F Age	Dose of radiation	Implants no. and type	Time of placement after irradiation (T1) and follow up (T2)	Survival rate	QOL
Werkemeister et al,1999	IR:12 NR:17 M:23; F:6 Mean age: 55years	54Gy No HBO	Implants:109 NR:34 IR:75	T1: 24months T2:3 years	Failure rate: IR:29.3% NR:14.7% p<0.05	NI
Landes et al,2006	IR: 19; NR:11 M: 22; F:8 Mean age: 63years	57Gy at single dose of 1.9Gy	Implants: NR: 42 IR:72 TPS, SLA, ITI	T1:16.5mo T2: 21mo	Success rate: NR:100% IR: 98% Implant stability better in NR(p<0.15). IR had more bone loss after 12mo post insertion of implants	NI
Yerit et al,2006	M:56;F:15 Mean age: 57.8years	50 Gy. 2Gy for 25 days. HBO not used.	Implants: NR:84 IR:154 IMZ, Frialit, Xive.	T1: mean 1.41yrs T2: 5.42-13.61yrs	Survival rate after 8 yrs: NR:95% IR: 72% p= 0.0028	NI
Korfage et al, 2010	M:35; F:15 IR/NR:31/19 Mean age: 61.5+/- years	>40Gy	Total: 195 IR/NR:123/72 Branemark, Noble biocare Mandibular implants	T1:6mo post implant placement T2:60m	Survival rate: IR:89.4%, NR:98.6%	NI
Gander et al,2014	M/F: 23/10 IR/NR:21/12 Mean age: 64.15yrs	56-76Gy	136 IR:NR- 84:52 Astra tech	T1:12months T2:79m	CSR@20 months:87.5% p=0.297	NI
Korfage et al, 2014	M/F: 98/66 IR/NR:100/64 Mean age: 64.8 yrs	Referred patients after radiotherapy. Dose unknown	Total: 524 IR:NR –318/:206 Anterior implants Branemark	T1:6-9 months post implant placement T2: 3.8 yrs	Implant loss in IR: 8.5% NR: 0.5% (p<0.0001) Bone loss: p=0.65. Not SSD	IR:19.5 NR:24.6 (p=0.30)

CSR: *Cumulative survival rate;* ***Max:*** *maxilla; Mand: Mandible;* ***IR: I****rradiated;* ***NR:*** *Non-radiated;* ***NI:*** *Not investigated;* ***SSD:*** *Statistical significant difference;* ***Yrs:*** *years.*

=23.99, df=12, I^2 =50 %, P=0.02).

Out of 2203 implants placed in irradiated sites, 323 failures were recorded, amounting for failure rate of 14.6 %. However, in non-radiated sites, only 141 implant failures were observed out of 2349 implants, which amounts to failure rate of 6%. The Cumulative survival rate of implants placed in irradiated and non-irradiated sites was found to be

Table IV. *Distribution of cases in maxillary and mandibular region.*

Author/ year	Cases /controls M/F Age	Dose of radiation	Implants no. and type	Time of placement after irradiation (T1) and follow up (T2)	Survival rate	QOL
Granstrom et al,2005	IR:107. NR:100 M:122 F:85 Age: 15-88yrs	Dose: Fractionation therapy Twice/day at 41-50 Gy Once/day at 61-70Gy HBO therapy 340 protected 291- Not protected	Implants:1245 IR:631; NR:614 Nobel biocare implants	T1:6.3yrs T2: 20yrs	Failure of IR implants:147(23.2%) Failure of NR implants: 76(12.3%) Implant failure with HBO therapy: 29/340(8.5%) Implant failure without HBO therapy: 117/291(40.2%) P<0.001. Not SSD No effect of gender, age, and smoking status on implant failure.	NI
Nelson et al,2007	IR: 29ptnts M: 63; F:30 Age: 26- 89yrs	2Gy daily for 5days/week.	Total:435 IR:124 (Max 41; Mand 83) NR:311 (Max:113, Mand:198) Branemark, Steri-Oss, CAMLOG, ITI	T1:6 months T2:10.3yrs	Diff btwn IR and NR(p=0.08). CSR in IR @13.5yrs: 54%.	NI
Linsen et al,2012	M/F: 43/23 IR/NR: 34/32 Mean Age: 55.7yrs	36-60Gy 2 Gy in fractions.	Total: 262 Max: 213 Mand:49 IR; NR 127;135 Branemark, Straumann	T1: 41months T2:82months	CSR @120 month IR: 95.6% NR: 84.7% (p=0.302)	NI
Dholam et al,2013	M/F: 18/12 IR/NR: 19/11 Mean age: 46yrs	20-60Gy in fractions	Total:85 IR: 59 NR: 26 Max and mand implants	T1:12 months T2:5 Years	Success rate: IR:71% NR:89% (p=0.144)	NI
Dholam et al, 2013 Strict inclusion criteria	Total:26 M/F: 17/9	20-60Gy in fractions	Total:68	Time: 18 months after implant retained dental prostheses		No SSD p=0.919
Doll et al,2015 Strict inclusion criteria	M/F:62/95 IR/NR:55/102 Mean Age: 53.7yrs	50-72Gy 2 Gy over 6 wks. Pre &post-op antibiotic in NR patients (Clindamycin 600mg)	Total: 830 Max:450 Mand: 380 IR:292 (118 mand/174 max) NR:538	T1: 6months T2:121 months	SR@7 yrs IR: 89% NR: 92.5% (p=0.011) CSR@20yrs:90.8%	NI
			Canalog, Steri-oss, Branemark, Straumann			
Pompa et al,2015 Strict inclusion criteria	M/F: 12/22 MeanAge:51+/- 19 yrs	<50Gy 2 Gy daily 5 days/week.	Total:168 IR:16 NR:152 (Mand:84, Max:68) Osteotite implants	T1:12months T2:39.5 months	Survival rate: NR:69.6% IR:30.4% p<0.01 Max vs Mand: p>0.8 SSD in relation to time of loading of implants after radiotherapy (>6 months). p<0.01	NI
Saracoglu et al,2015	M/F:42/38 IR/NR:40/40 Mean age: 51.6 yrs	72 Gy	Total:80 Max/Mand:40/40 IR; NR 40/40 ITI Straumann	T1:6 months T2: 1 year	Survival rate: No SSD (p=0.37) ISQ values between IR and NR: p<0.001 (mand) P<0.002 (maxilla)	NI

CSR: *Cumulative survival rate;* ***Max:*** *maxilla; Mand: Mandible;* ***IR:*** ***I****rradiated;* ***NR:*** *Non-radiated;* ***NI:*** *Not investigated;* ***SSD:*** *Statistical significant difference;* ***Yrs:*** *years.*

85.8% and 93.9% respectively. The meta-analysis plot of total number of failure events across the irradiated and irradiated sites shows a significant favourable association of high failure rate of dental implants placed in irradiated sites (p<0.00001) with OR of 2.95 (95% CI: 1.93, 4.50) (Fig. 4).

Quality of life was only determined in two studies (21, 22). Apart from a very significant association between high implant failure rate and irradiated sites, there was not enough data to draw a correlation between Quality of life (QoL) after implant placement in irradiated sites versus radiated sites.

Table V. *Comparison amongst maxillary and mandibular implants.*

Author	Implant type	Failures	Survival rate
Werkemeister et al,1999	Mandibular	IR:26.7%; NR:14.7% p<0.05	
Cao and Weischer et al,2003	Maxillary		5-year CSR 49.44%
Granstrom et al,2005	Maxillary and Mandibular	Mandibular IR: 44%; NR: 6% Maxillary IR:12.5%; NR:6%	
Landes et al,2006	Mandibular		NR:100% IR: 98%
Yerit et al,2006	Mandibular		8-year Survival rate: NR:95%; IR:72%, P=0.0028
Nelson et al,2007	Maxillary and mandibular		8-year CSR -75% for both
Korfage et al,2010	Mandibular	IR:10.6%	Survival rate: IR:89.4%, NR:98.6%
Linsen et al,2012	Maxillary and mandibular		Survival rate: Mandible: 86.8% Maxilla: 98.6% P<0.56
Korfage et al, 2014	Mandibular	IR: 8.5% NR: 0.5% (p<0.0001)	
Doll et al,2015	Max:450 Mand: 380		p=0.845

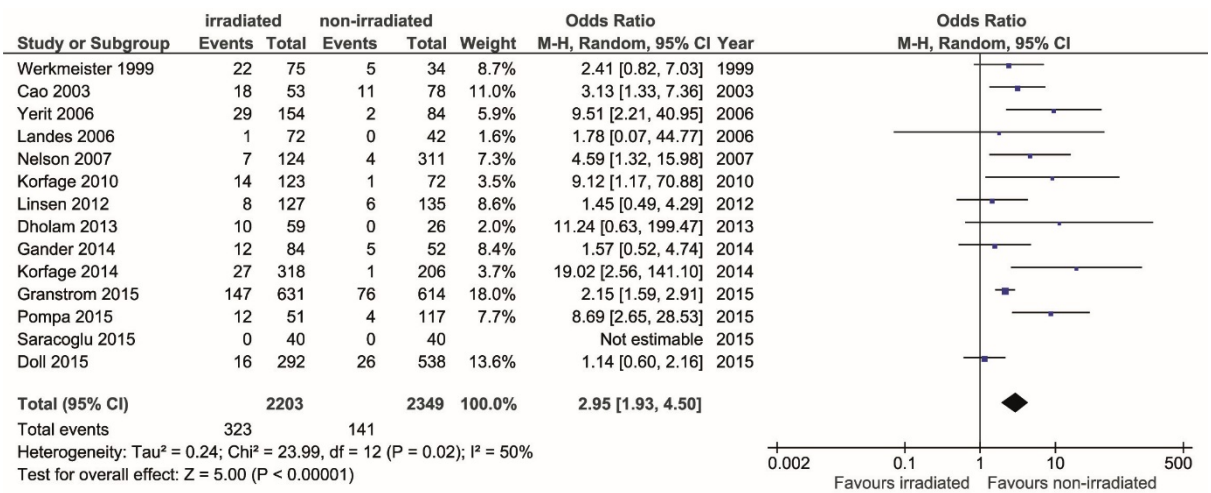

Fig. 4. *Comparison of implants installed in irradiated and non-irradiated sites.*

DISCUSSION

The present systematic review was designed to address the question: "What is the survival rate of implants in irradiated sites?" We aimed at comparing implant survival rate and postoperative quality of life between implants placed in radiated and non-radiated sites over duration of at least 1 year, through a systematic review approach. We only chose retrospective and prospective articles where implants were placed and compared between radiated / irradiated sites and patients to get evidence-based information with the best possible design.

The results of the meta-analysis demonstrated that the implant survival in irradiated sites was lower than non-radiated sites. However, the cumulative survival rates over a period of 7-10 years were reported to be comparable (18, 19, 20). This analysis agrees with current literature reviews, which report 5-year survival rate of implants placed in radiated sites ranging from 84.3%- 92.9% (9, 10, 28, 29). To understand the conflicting statistical results from different studies, it is pertinent to review the potential factors influencing the outcomes.

Radiotherapy causes tissue damage especially to the bone, periosteum, and connective tissue of mucosa along with microvascular endothelium. This leads to fibrosis and tissue changes that may cause osteoradionecrosis, ultimately endangering the osseointegration of implants. Nevertheless, some studies reported high implant survival. Franzen et al. reported successful osseointegration in 95% of implants inserted in irradiated jaws (30). Similarly, Taylor and Worthington reported that the 93% of implants in irradiated jaws achieved osseointegration (31). In clinical studies by Nelson et al. and Dholam et al., rigid inclusion criteria were followed and patients with poor oral hygiene and smoking habits were excluded from the study (13, 14). When using strict inclusion criteria, the number of late implant failures in radiated group (0.81%) was comparable to that observed in non-irradiated patients (1.29%), and the survival rate after 8 years was not significantly different between the two groups. In the study by Werkmeister et al, 14.7% of the implants placed in non-radiated bone did not osseointegrate as compared to 26.7% of the implants placed in irradiated sites and this difference was observed in many other studies included in the systematic review (15, 16, 17). Such marked difference in survival rates between different studies can be attributed to the fact that the former studies had strict inclusion criteria and subjects who were alcohol consumers or smokers and had poor oral hygiene were excluded from the study.

Alcohol and smoking are risk factors for the successful osseointegration of implants and hence can lead to early implant failure. In our present systematic review, although most of the studies included smokers and alcoholics in their studies, only 2 studies tried to determine their impact on implant survival. Study by Gander et al, 2014 evaluated the impact of smoking and alcohol on failure of implants. Smoking ($p=0.016$) and alcohol ($p=0.001$) significantly impacted implant survival (18). However, another study by Granstrom et al., 2005 in our present review evaluating the effect of smoking on implant failure rate, suggested different results. (27). In their study, amongst the irradiated group, there were 55 smokers out of 107 patients. 46 smokers fell in the category of smokers who were smoking > 20 cigarettes/day and had been smokers for more than 20 years. The data of the study demonstrated no association between the number of cigarettes ($p>0.30$) and the duration of smoking($p=0.28$) with the implant survival. DeLucas et al, 2006 through their long-term retrospective study, demonstrated that patients who were smokers at the time of implant surgery had a significantly higher implant failure rate (23.08%) than non-smokers (13.33%). Early implant failure was significantly associated with smoking at the time of stage 1 surgery and late implant failure correlated with a positive smoking history in the multivariate analysis. The study concluded that smoking is not an absolute contraindication, however, could impair the initial healing phases (32). Within the limitations of our review, it is safe to suggest that predisposing factors like smoking, alcohol, and poor oral hygiene are responsible for the lower osseointegration rates in irradiated sites.

One important factor that influences the outcome of radiotherapy is the type of radiation therapy used

to treat head and neck cancer patients. External beam therapy, brachytherapy and radio-isotope therapy are the different forms of therapy used for the treatment of head and neck cancer. In the present review, all the included studies had used conventional external form of radiotherapy. Hence, no deduction could be made regarding the influence of different forms of therapy on the outcome of implant survival. Nevertheless, it should be kept in mind that new modes of radiotherapy like IMRT, which selectively delivers the radiation dosage to targeted tumor and surrounding tissues, minimizes the radiation induced complications by manifolds and thereby increasing the survival rate of implants.

Another factor that needs attention when analysing the results of the present systematic review is the radiation dosage. Although till date, there is no consensus on the radiation dose that may have an impact on the implant survival, literature has shown that dosages between 30-40Gy given in fractions are less deleterious to the oral tissues (33, 34) as compared to the dosages over 65Gy (35). Studies included in the present systematic review confirmed this trend. Most of the studies with patients treated with radiation dosage between 36-65Gy had reported survival rate ranging between 72%-98% of implants placed in irradiated sites (19, 20) as compared to the survival rate of 48% in one study where the radiation dose was more than 72Gy (16). Another randomized controlled study noticed the difference between groups based on radiation dosage. Osseointegration and survival rate of implants was not found to be significantly different between radiated and non-radiated sites, which the authors attributed to the fact that they had excluded smokers and patients with bad oral hygiene. However, they documented that 47% of the implant failures were seen in patients receiving radiation dose between 56-60 Gy as compared to patients were exposed to radiation dosage between 50-55Gy (14).

Site of implant placement is also an important risk factor. Few systematic reviews (29, 36) have concluded that maxillary sites are at higher chances of implant failure. There are studies and reviews which demonstrate either no difference (9, 37) or increased survival rate in maxilla compared to mandible (25, 27). The results of the present study suggested that implant survival rate is higher in mandibular sites as compared to maxillary (Table 5). The increased survival rate of mandibular implants could be attributed to the fact that mandible has compact bone and high bone density, thereby attaining better implant stability and survival (25). Another factor that should be considered while interpreting the results of our review is that that there were more mandibular implants (n=2150) placed in the included studies compared to maxilla (n=1056).

Quality of life (QOL) for irradiated and non-radiated sites was not found to be significantly different in the studies included in this systematic review (21, 22). Korfage et al, in their study also reported that chewing ability had improved in radiated patients and there was no statistical significance in overall satisfaction for prosthesis function between radiated and non-radiated patients (22). These results can be explained by the fact that the patient's compare the postoperative comfort to the pre-existing disease condition. Irradiated patients seem to have more difficulty in chewing tough food, perhaps due to hyposalivation and its related consequences resulting from radiotherapy. Implant-retained prosthetic rehabilitation results in the most favourable masticatory outcomes, when compared with no prosthetic treatment (38).

Another debated and crucial factor influencing the outcomes of implant survival is the time elapsed between the end of radiation therapy and the implant placement. Higher risk of failures has been reported if implants are placed within a shorter period of less than 6 months after radiotherapy (39, 40). In the present meta-analysis, studies with implant placement within 6 months after radiotherapy reported failure rates ranging between 49%-54% (13, 15) as compared to survival rate of 96% in studies where implants were placed after 41 months (23). A higher implant survival rate was also noticed in another study where implants were placed at a mean interval of 79 months post radiotherapy (18). Doll et al, through his study presented conflicting results. Only 5.5% failures were reported even after placing the implants 6 months post radiotherapy as compared to 4.9% in non-radiated sites. This study

had excluded smokers and patients with bad oral hygiene (24). With the present evidence, due to limited number of studies, a definitive conclusion cannot be drawn between timing of implant placement and implant failures.

Absence of randomized controlled trials, small sample size, exclusion of factor like impact of oral hygiene maintenance on the implant survival rate are the main limitations of the present systematic review.

Although our meta-analysis demonstrated higher survival rate of irradiated implants as compared to non-radiated implants, it was also found that cumulative survival rate of implants placed in irradiated sites after 10 years of follow up is 89%. With the rise in demands of implants, this multifaceted question of 'What is the survival rate of implants in irradiated patients?' should be addressed after careful in-depth evaluation of a combination of factors, in particular patient's habits, site of implant placement, timing of implant placement, radiation dosage and assessment of patients' subjective functional demands.

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