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REVIEW PAPER

Survival of Dental Implants on Irradiated Jaws: A Systematic Review and Meta-analysis

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Abstract
Objectives Dental implants play a significant role in functional rehabilitation of the oral cavity after debilitating jaw surgeries for oral cavity cancers followed by radiotherapy.
Design The meta-analysis was done using Preferred Reporting Items for Systematic Review (PRISMA) guidelines published from January 1947 till August 2020. Twenty three articles consisting of 1246 participants with 4838 implants were included in our analysis.
Results The mean age of the included participants was 51.4 years. 2186 and 1685 implants were placed on irradiated and non-irradiated jaws and showed a success rate of 82.47% and 89.37% respectively. Correspondingly, publication bias of p value = 0.2129 and p-value = 0.6525 was found by Egger's and Begg's test respectively for pooled data of 16 studies. The implant success rate of 70.4% on maxillary bone and 94.5% were observed on mandibular bone. Timing of implant placement and its influence on survival rate have resulted in a 75.5% survival rate of dental implants when placed primarily in comparison with 87.7% on delayed placement. The waiting interval of 14 months in delayed implant placement has shown better results.
Conclusion Presence of radiotherapy does not play a significant role in the success rate of dental implants in oral cavity cancers. However, delayed implant placement may have a better chance of survival.

Keywords Dental implant · Oral cancer patients · Radiotherapy · Implant survival · Primary implantation

Abbreviations

GLOBOCON	The global cancer observatory
OCC	Oral cavity cancer
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	Prospective register of systematic reviews
MOOSE	Meta-analyses of observational studies in epidemiology
NOS	New castle Ottawa scale

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Introduction

Lip and oral cavity cancers are amongst the most common type of cancer worldwide and especially in the Indian subcontinent due to rampant use of tobacco and its surrogate products [1]. As per GLOBOCON 2018, in India, an estimate of more than 125,000 new oral cavity cancer (OCC) cases are diagnosed with over 70,000 deaths annually [2]. However, in recent times with the availability and access to the surgical care facility and adjuvant therapy centers, there has been an improvement in overall survival rates even in advanced oral cavity cancers [3].

Surgical treatment remains the standard of care in advanced OCC followed by radiotherapy with or without chemotherapy. Surgical management involves morbid procedures including mandibulectomies, maxillectomies with neck dissection. Studies have shown that about 40% of all the resection involves segmental mandibulectomies [3]. Segmental resection of the mandible is usually followed by reconstruction with a free fibular graft. Advanced oral cavity cancer patients with these grafts undergo radiotherapy in postoperative settings [4].

In this technically challenging procedure, oncological safety is the most important goal. Thus, dental rehabilitation takes a back seat considering its poor overall survival [5]. But with improved survival [6], cancer survivors living longer, the focus has been shifted to the quality of life. Dental rehabilitation would certainly improve the masticatory, speech functions, and aesthetic quotient of the patient [7].

Dental rehabilitation with osseointegrated implants is the gold standard. However, almost 83% of patients receive radiotherapy after surgery [8]. Radiotherapy reduces vascularization, the regenerative ability of tissues, and impedes the process of osseointegration [9]. Effects on bone after radiation can be either vascular, cellular, and metabolic. Initially following radiotherapy hyperemia is observed in tissues and later diminished vascularity is observed which can lead to osteoradionecrosis of the bone. Thus, there are many unanswered questions on the timings of dental implantation (immediate vs. delayed), their associated survival, and the differential survival rates depending on the site of the implantation. Therefore, we performed a systematic review and meta-analysis to put forth the available evidence in the literature.

Methodology

This is a systematic review and meta-analysis following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist 2009. The review protocol was registered on PROSPERO database (registry CRD-rigister@york.ac.uk/www.york.ac.UK/inst/crd) with ID CRD42020199847. This registration was done to avoid duplication of the systematic review.

Eligibility Criteria

As per PICOS criteria, P: Population consists of patients who underwent dental implant treatment oral cavity, I: Oral cavity cancer patients receiving radiation, C: Comparison of survival of implants in irradiated jaw versus non-irradiated jaw, O: Survival rates of dental implants in treated oral cavity cancer patients, S: Study—retrospective and prospective study. Our systematic review and meta-analysis were undertaken as per meta-analyses of observational studies in epidemiology (MOOSE) guidelines [10]. We searched PubMed and Cochrane database to identify studies reporting the survival rate of dental implants in treated oral cavity cancer cases along with a follow-up period of more than 6 months. All electronic searches were last updated in August 2020. The studies were also searched manually through various textbooks and journals. Search keywords used were "dental implants" AND "oral cancer," "dental implants" AND "radiation," "dental implants" AND "oral cancer" AND "radiation." Boolean operators (NOT, AND) were also used in succession to narrow and broaden the search. We also screened the references of all studies for any possible additional publications. However, we have excluded case reports and those studies with no details on dental implants. Articles published in languages other than English and articles with only abstracts were excluded. Articles with insufficient, missing data, personal communications, case series, case reports, animal studies with less than ten patients, dental implants lost due to other reasons than osseointegration like tumor recurrence, resection, and death were excluded. Two independent reviewers (S.R and H.S.) screened the literature search and assessed each study for inclusion. Any disagreement was solved by consulting a third investigator (P.K).

Data Extraction and Analysis

Two authors (H.S, S.R) independently extracted data, which included first author, publication time, study designs, site, implants in irradiated mandible and non-irradiated mandible and their survival rates, implants in maxilla/mandible with their survival rates, implants placed immediately or delayed, and their survival rates. The extracted data were checked by another author (P.K.). All the included literature was evaluated using the Newcastle-

Ottawa Scale (NOS) [11]. The highest quality of the literature was nine stars and the lowest 0 stars. It consists of eight items with three subscales, and the total maximum score of these three subsets is nine. An overall scores of ≥ 7, 5–6, and ≤ 4 are considered low, moderate, and high risk of bias, respectively.

Statistical Analysis

We performed data analyses using Stata version 12. Random-effects meta-analysis was used to calculate pooled estimated prevalence with 95% confidence intervals [12]. Interstudy heterogeneity was assessed with Cochrane's *Q*-test [13]. The percentage of total variation across studies due to heterogeneity was evaluated by the I2 measure, and values of 25%, 50%, and 75% suggested low, moderate, and high heterogeneity, respectively [14]. We have also performed subgroup analysis comparing the survival rates of implants based on the site in the oral cavity. We also compared the survival rates of implants based on the timings of their implant placement after oral cancer treatment.

For the detection of publication bias, we used direct observation of funnel plot symmetry, Egger's regression asymmetry test, and Begg's rank correlation methods. The presence of publication bias was evaluated using the Egger's and Begg's tests, where $P < 0.05$ was considered to be statistically significant. Funnel plots were used for the assessment of publication bias by graphical inspection.

Results

As per our inclusion and exclusion criteria, a comprehensive data search was performed and a total of 1346 articles were obtained (Fig. 1) of which 285 duplicates and 134 other language articles were excluded. 927 articles were then assessed for eligibility, of which 843 did not have sufficient records and 12 articles with no accessibility thus were excluded. Of the remaining 72 articles, 49 articles had incomplete data and hence finally 23 articles met our criteria and were included in our study. 23 articles were analyzed of which 21 articles were retrospective clinical studies and two were prospective clinical studies. The characteristic of the included studies is represented in Table 1. The total number of participants included in our review was 1246 with 775 males and 396 females although two studies failed to mention the number of male and female participants [19, 20]. Mean age of participants included in the study was 51.43 years. A total of 4838 implants were placed on irradiated and non-irradiated jaws. Included participants who were exposed to radiation were given a dosage of 40–72 Gy.

Results of Individual Outcome Measures

Comparison of Implant Survival Rate on the Irradiated and Non-irradiated Jaw

A total of 16 studies were included in this analysis. Fifteen studies were retrospective study while one was a prospective study. This dataset included 2186 and 1685 implants placed on irradiated and non-irradiated jaws respectively. There was a survival rate of 82.47% and 89.37% in irradiated and non-irradiated jaws, respectively. The mean follow-up period for this data set was 52.5 months. A pooled odds ratio of implant survival rate for irradiated and non-irradiated jaws of 16 studies was 0.2409 [0.1448; 0.4008] with significantly high heterogeneity observed I2 = 72.8% [55.1%; 83.5%], $P < 0.001$ (Fig. 2). The publication bias detected by Egger's tests has a *p*-value of 0.2129 and Begg's test with *p*-value of 0.6525. *P*-value for each category was > 0.05. The publication bias is shown in the funnel plot (Fig A). The results conclude that there was no difference in the survival rate of implants in irradiated patients as compared to non-irradiated patients. Our result showed that there was an 89.3% survival rate of implants placed on non-irradiated bone as compared to 82.4% survival rate of implants when placed on the irradiated bone.

Assessment of Implant Survival on the Maxilla

Three retrospective and one prospective studies were included in this subgroup analysis. A pooled analysis of maxilla gave an odds ratio of 0.7100 [0.5822; 0.8114] with high significant heterogeneity observed ($I2 = 67.7\%$, $P < 0.001$) (Fig. 3). The publication bias detected by Egger's tests has a *p*-value of 0.7924 and Begg's test with *p*-value of 0.4969 which was not significant (Fig B). In this study, a total of 260 implants were placed on the maxillary bone of which 183 survived consequently giving a 70.4% survival rate.

Assessment of Implant Survival Rate on the Mandible

The implant survival rate with random effect model which showed a pooled implant survival rate in mandible 0.9614 [0.9099; 0.9840] with significantly high heterogeneity observed ($I2 = 70.3\%$; $P < 0.001$) (Fig. 4). The publication bias detected by Egger's tests has a *p*-value of 0.079 and Begg's test with *p*-value of 0.174 (Fig C). A total of 592 implants were placed on the mandible of which 560 survived, and hence the survival rate was found to be 94.5%.

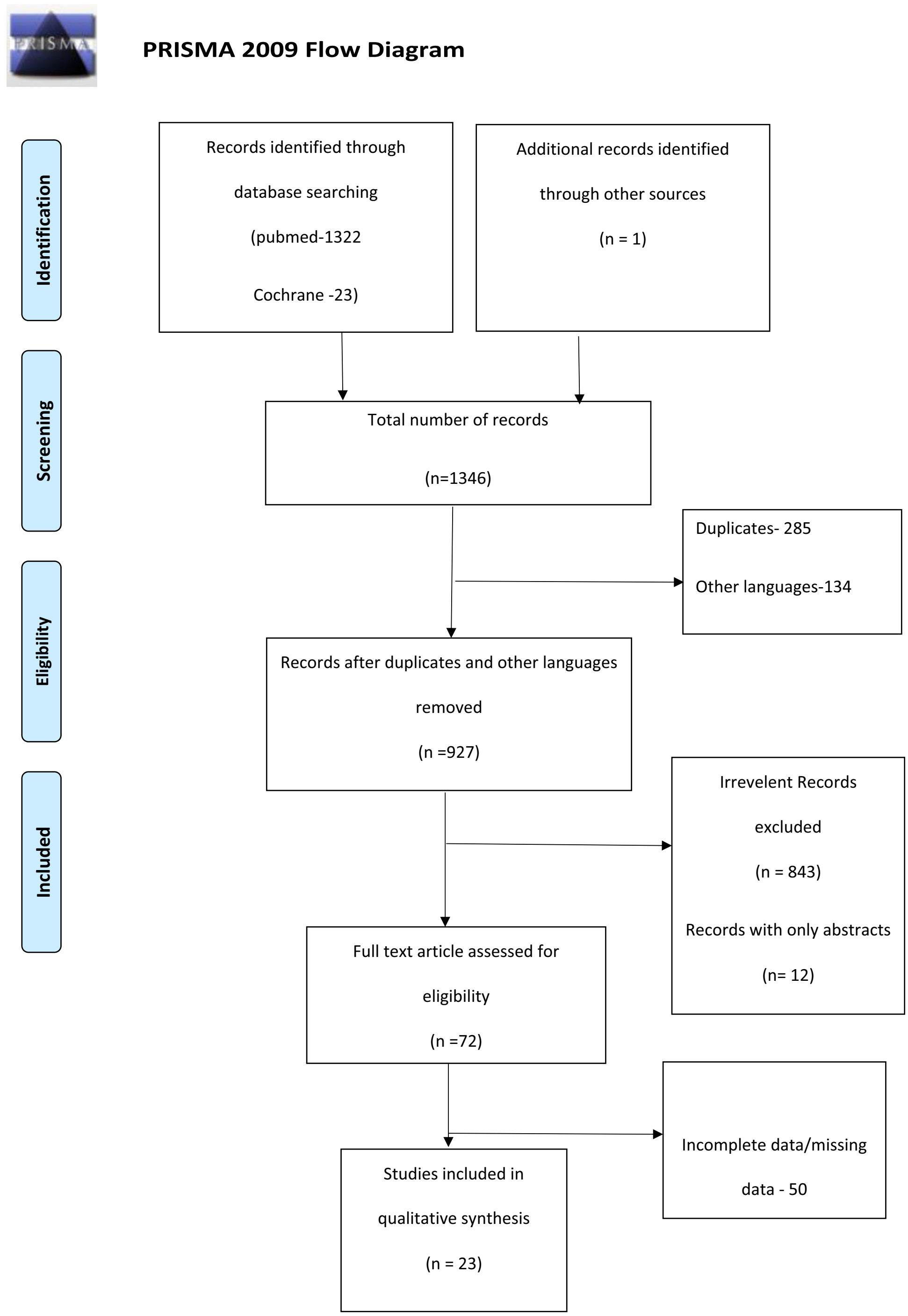


Fig. 1 Prisma flowchart

Assessment of Survival of Immediately Placed Implants

Seven retrospective studies were included, and a pooled data analysis of immediate Implants gave an odds ratio of 0.75 [0.58 0.81] with highly significant heterogeneity observed (I2 = 94.30%, $P < 0.001$) (Fig. 5). The publication bias detected by Egger's tests has a p-value of 0.136 and Begg's test with p-value of 0.293 (Fig D). The publication bias showed in the funnel plot. Immediate implant insertion of 523 implants was reported of which 395 had survived hence the survival rate was 75.5%.

Assessment of Survival of Delayed Placed Implants

A random-effect model showed a pooled data analysis of delayed placed implants with an odds ratio 0.94 [0.88; 0.97] with significantly high heterogeneity observed (I2 = 94.60%, $P < 0.001$) (Fig. 6). The publication bias

Table 1 Characteristics of included studies

Sr. no	Author	Study type	Year	Sample size	Total no. of implants	Mean age (year)	Male	Female	Quality score
1	Chang et al. [15]	Retrospective type	2016	246	1132	59	166	80	7
2	Chispasco et al. [16]	Retrospective type	2005	16	71	48.7	12	4	6
3	Dholam et al. [17]	Retrospective type	2013	30	85	46	18	12	8
4	Eckert et al. [18]	Retrospective type	1996	20	89	NA	NA	NA	5
5	Fenlon et al. [19]	Retrospective type	2009	41	145	NA	NA	NA	5
6	Granstorm et al. [20]	Retrospective type	1999	78	335	64.9	47	31	8
7	Jackson et al. [21]	Retrospective type	2015	46	15	58	31	15	8
8	Katsoulis et al. [22]	Retrospective type	2011	46	104	57 ± 7	31	15	6
9	Kobayashi et al. [23]	Retrospective type	2016	41	134	61.5	27	14	5
10	Korfage et al. [24]	prospective type	2010	64	195	61.5 ± 11.2	35	15	7
11	Linsen et al. [25]	Retrospective type	2009	66	262	55.7	43	23	7
12	Mancha et al. [9]	Retrospective type	2012	50	335	55.5	38	12	6
13	Menapace et al. [26]	Retrospective type	2018	23	121	62.4	16	7	6
14	Nelson et al. [27]	Retrospective type	2007	93	435	59	63	30	6
15	Pellagrino et al. [28]	Retrospective type	2018	21	108	49.6	15	6	5
16	Pompa et al. [29]	Retrospective type	2015	34	144	51 ± 19	12	22	7
17	Sammartino et al. [30]	prospective type	2011	77	172	55.8	51	26	5
18	Sandoval et al. [31]	Retrospective type	2019	20	29	62.5	15	5	7
19	Scalroff et al. [32]	Retrospective type	1994	22	114	58.6	16	6	5
20	Schepers et al. [33]	Retrospective type	2006	48	139	66.4	29	19	6
21	Schliephake et al. [34]	Retrospective type	1999	83	409	51.9	59	24	5
22	Werkmiester et al. [35]	Retrospective type	1999	29	109	55	23	6	6
23	Woods et al. [36]	Retrospective type	2017	52	156	43	28	24	7

detected by Egger's tests has a *p*-value of 0.201 (Fig E). A total of 587 implants survived of the 669 implants which were placed post-radiotherapy, and an 87.7% survival rate was observed in the included study. Pooled meta-analysis results of individual outcome measures were analyzed.

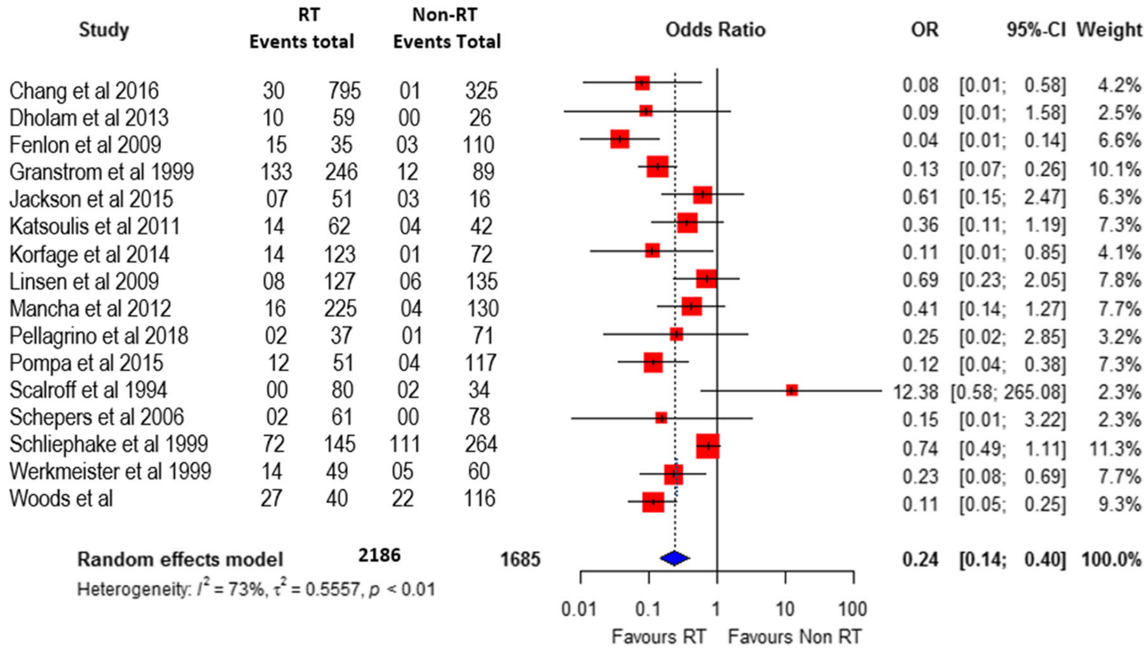


Fig. 2 Forest plot representing pooled analysis of data for survival rate of dental implants on irradiated and non-irradiated bone

Fig. 3 Forest plot representing pooled analysis of data for survival rate of dental implants on maxilla

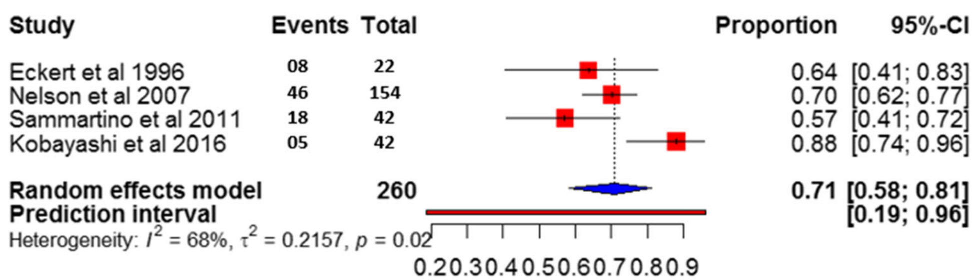
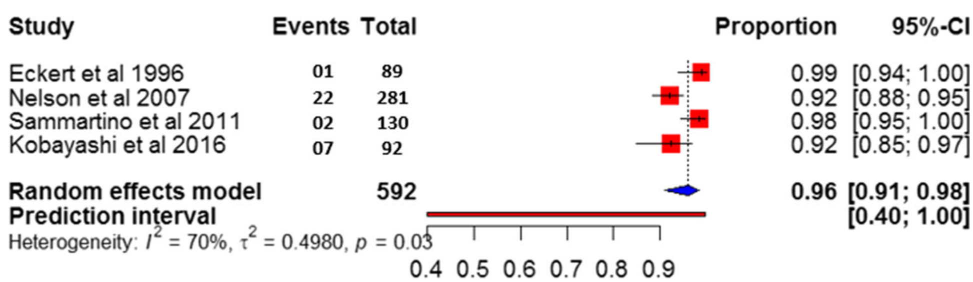


Fig. 4 Forest plot representing pooled analysis of data for survival rate of dental implants on mandible



Discussion

Over the past decade, dental implant rehabilitation following surgical resection and radiation is gaining more scientific experience. Cuesta gill et al. [38] in their study concluded that implant-supported prosthesis is the only useful form of dental rehabilitation in patients with oral oncological problems subjected to additional radiotherapy.

In a 2016 meta-analysis [39], comparisons between the survival rate of dental implants on irradiated and non-irradiated jaws were reported with 40 included studies and had concluded with 15% failure rate in irradiated jaws and showed a significant difference. However, our study noted that there was no difference in the survival rate of implants in oral cancer patients' post-radiation therapy as compared to those patients without radiation therapy. This difference in results can be attributed to the addition of six new articles [15, 21, 24, 28, 29, 36, 37], of which three [21, 29, 36, 37] with comparatively higher weightage showed a significantly improved survival rate for implants placed in the irradiated bone as compared to the previous studies. Several clinical trials are reported with the

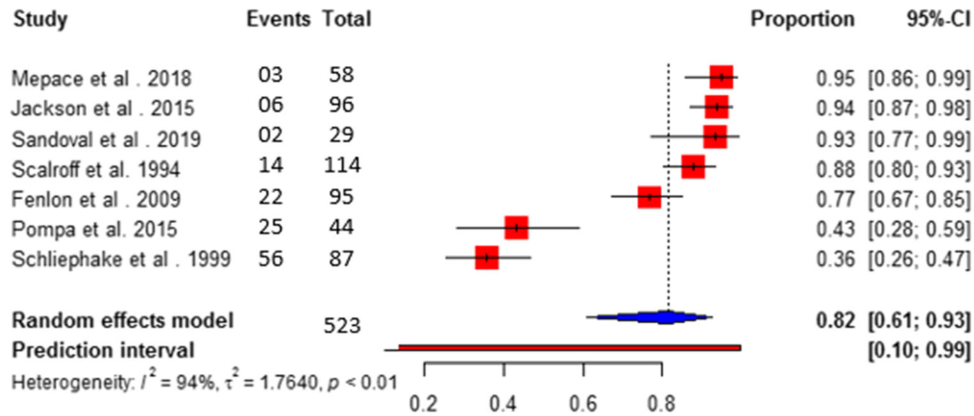


Fig. 5 Forest plot representing pooled analysis of data for survival rate of dental implants placed immediately

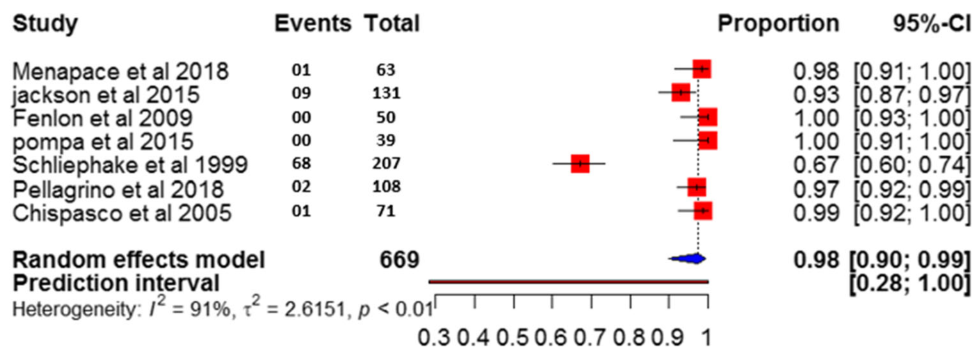


Fig. 6 Forest plot representing pooled analysis of data for survival rate of delayed placed dental implants

majority supporting in favor of improved survival rate of implants on non-irradiated bone and has found to have better osseointegration and reduced complication rates [19, 20, 32, 35]. Few clinical trials have presented no significant difference in survival rates; nevertheless, we have not found any meta-analysis in favor of this argument [22, 25, 28]. We have observed in our meta-analysis a non-significant difference of dental implants when placed on either irradiated or non-irradiated jaw which gives us a change in perspective that was not found in any earlier literature. Non-significant results in our study can be also explained due to a higher percentage of delayed placed implants with a mean waiting interval of 14.3 months. The effect of radiation dosage on the jaw bone and its impact on survival of dental implants have been controversial and as evidenced by Visch et al. [40] that there was an increased failure rate of dental implants when placed on the bone that was irradiated with > 50 Gy when compared with the bone that was irradiated with < 50 Gray with mean waiting interval of 145 months. Our analysis supported these results as 10 studies reported use of > 50 Gray of radiation dosage and resulted in an 88.3% survival rate on the non-irradiated jaw as compared to 75.4% survival rate on irradiated jaws.

It may be assumed that the site of implant placement may also contribute to the success and failure of implant treatment. Literature has shown varied survival rates on maxilla and mandible. A study by Linsen et al. [25] 2009 (n = 66) showed a 98% survival rate on maxilla which can be due to increased vascularity in the maxillary area thus proving secondary stability. Non-significant results were obtained by two studies: Chang et al. [15] and Curi et al. [7], whereas our meta-analysis has included four retrospective studies exhibiting a significant success rate of implants when placed on the mandible. Better survival on the mandible can be explained due to its anatomy and bone density accordingly providing primary stability. Both primary stability and secondary stability are important for the long-term survival of implants; as vascularity will be affected due to irradiation, it might hamper the secondary stability, thus leading to the increased failure rate of dental implants on irradiated jaws [41]. However, the literature shows a higher incidence of osteoradionecrosis after radiation therapy in the mandible as compared to maxilla due to axial pattern vasculature of the mandible.

The interval between the definitive therapy of oral cancer and the installation of dental implants may contribute to the success or failure of osteointegration. We have included seven retrospective studies which favor delayed placement as it provides better osteointegration and stability. This study concluded that implants placed after an average of 14 months of oral cancer treatment had better survival rates. This can be on account of various factors that implants placed immediately following surgery may cause inappropriate implant positioning, early tumor recurrence, and alteration of bone anatomy post-surgery as previously explained by Pompa et al. [29]. However, there was no significant difference observed in dental implant survival by delaying the waiting interval of > 12 months when compared with implants placed with < 12 months waiting for interval as evidenced by Sammartino et al. [30]. In patients with oral cavity cancer, dental rehabilitation has the potential to significantly improve quality of life functionally in the form of mastication, speech and improve facial support [42]. Therefore, limitations observed in our study was due to inclusion of retrospective and prospective studies as no randomized clinical trials were available in the database. The survival rate of dental implants based on type of irradiated bone was not assessed in our study as there were only 9 articles [15, 17, 19–21, 24, 25, 28, 33] that clearly defined the type of irradiated bone; although 3 articles [17, 21, 28] included patients reconstructed with fibula, other 6 articles [15, 19–21, 24, 25, 33] mentioned about patients being grafted with different osseocutaneous flaps. Due to these differential data, we intended to focus our study strictly on survival of implants on irradiated jaws. Our study showed implants placed in mandible had better survival; however, its data on the radiation exposure or whether it was placed on mandible or reconstructed mandible are not available. These variables are confounding factors to influence the survival of implants after definitive treatment of oral cavity cancers. We could not find the relevant literature to analyze the influence of loading of implants on their failure rates. Studies included in our analysis lacked the information on the type of radiation therapy. However, this is the first study to analyze the latest data available in the literature to give the overview of the prognosis of implants based on radiation factor, time after definitive treatment, and according to the site of the implants placed.

Conclusion

Our study concluded that there were no significant results with the dental implant when placed on the non-irradiated bone and irradiated bone. Site-wise survival for dental implants was better in the mandible than the maxilla. Lastly, delayed placement of dental implants has shown better results as compared to immediately placed implants.

Declarations

Conflict of interest The authors have no conflicts of interest.

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