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Review

Radiotherapy and the survival of dental implants: a systematic review

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This article dedicated to Prof. Yuanwen Ouyangi.

Abstract

For patients with head and neck cancer, the effects of treatment with adjuvant radiotherapy can be devastating. Frequently there is loss of function due to tooth loss, pain and discomfort from xerostomia and mucositis, and a significant psychosocial impact. Dental implants provide an effective means of rehabilitation for many, but irradiation poses a unique set of challenges that can affect the outcome of treatment. The aims of this review were to find out whether radiotherapy in these patients affects the survival of dental implants, and to discuss details of pertinent influencing factors. An electronic search of the Medline, Web of Science, and CENTRAL databases was done to identify studies on the survival of implants in irradiated patients within specified inclusion and exclusion criteria. No restriction was placed on the year of publication. The primary outcome measure was implant survival. Seven studies involving 441 participants and 1502 implants placed into irradiated bone were included. Meta-analysis indicated that survival was significantly higher in the mandible compared with the maxilla ($p = 0.04$), and in non-irradiated cases compared with irradiated cases ($p < 0.001$). Other factors that showed a strong association with survival were radiation dose and timing of surgery. Implant-based rehabilitation is a viable option for head and neck cancer patients who have undergone radiotherapy. Whilst the short to medium-term implant survival in these cases is high, multiple factors require careful consideration for a favourable outcome. Further high-quality research and randomised controlled trials are required in this field.

Keywords: Dental; Implants; Radiotherapy; Survival

Introduction

Head and neck cancer affects almost 900,000 people each year worldwide.[1] This includes areas in the oropharynx, oral cavity, lips, larynx, hypopharynx, paranasal sinuses, and salivary glands. The most common type of head and neck cancer is squamous cell carcinoma (SCC).[2] The most significant aetiological risk factors for head and neck cancer are undoubtedly smoking and alcohol consumption.

Radiotherapy is one of the treatments for head and neck cancer. In more advanced disease it is often used in combination with surgery and/or chemotherapy, although some clinicians advocate it for selected cases of early-stage disease.[3] Head and neck cancer has high morbidity, but an upward

Abbreviations: LSGDM, Large-scale group decision making; PFS, Picture fuzzy set; PFWG, Picture fuzzy weighted geometric; MADM, Multi-attribute decision-making; T2FS, Type-2 fuzzy set; HFS, Hesitant fuzzy set; IFS, Intuitionistic fuzzy set; PFN, Picture fuzzy number; RoV, Refusal of voting; IVIFN, Interval intuitionistic fuzzy number

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trend in the survival rate of patients in recent decades[4–6] is believed to be due to the combination of improved screening programmes leading to earlier detection rates, more accurate staging methods,[7] and technological advances in treatment.[6]

Radiotherapy has several adverse side effects when used in the oral cavity, including damage to the mucosa, salivary glands, bone, and masticatory muscles.[8] These effects, combined with a higher survival rate, can result in groups of patients who will often require advanced oral rehabilitation for prolonged periods of time, whilst undergoing the challenges posed by the adverse effects of radiotherapy. Combined with the fact that many of those affected are elderly and/or have undergone extensive ablative surgery, it results in patients having teeth missing and a severely reduced quality of life.

Conventional removable prostheses are often unsuitable due to the discomfort caused by mucositis and a dry mouth, so dental implants are frequently used as an invaluable tool in the rehabilitation of such patients. The negative side effects of radiotherapy outlined above also affect the survival of implants, as do other contributing factors such as radiation dose, timing of placement, and location of the implant.

Methods

Focus question

'Does radiotherapy prior to the placement of dental implants negatively affect the outcome of implants for head and neck cancer patients?'

PICO

Population: human patients who have had a primary head and neck tumour treated with radiotherapy in native non-grafted bone.

Intervention: placement of an endosseous dental implant in an intraoral site previously exposed to radiotherapy.

Comparison: placement of an endosseous dental implant in an intraoral site not exposed to radiotherapy.

Outcome: primary measure - implant survival rate.

Search strategies

Scoping searches were done to gather information and keywords pertinent to this review, and these were then used to build a focused query. To maximise the number of relevant scientific papers, the query was entered into three electronic databases: Medline; Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). Citations and reference lists of the selected studies were also analysed manually to identify further relevant publications that were not included in the primary search.

The following medical subject headings (MeSH) were used: "dental implant" also including: implant, implant-supported, implantology, endosseous, osseointegrated, osseointegration; "radiotherapy" also including: radiation, radiation therapy, irradiation; and "cancer" also including: head, neck, oncology, carcinoma, tumour, oral, cavity, nasopharynx.

The abstracts of the studies identified were screened using the inclusion and exclusion criteria below. Any study with data missing from the abstract that related to these criteria was manually screened using the full text. The full texts of all the selected studies were then sourced and analysed.

Inclusion criteria

- Randomised controlled trials (RCT), cohort studies, case-control studies, and case reports
- Head and neck cancer patients
- Radiotherapy affecting the site of implant surgery
- Patients rehabilitated with one or more dental implant
- Follow-up period of 12 months or more after loading

Exclusion criteria

- Review articles, opinion pieces and single-patient case reports
- Unclear whether radiation had affected the site of implant surgery
- Dental implants placed into free-grafted bone
- Extraoral implants
- Patients who had received hyperbaric oxygen (HBO) therapy prior to implant placement

Types of study included

RCTs, cohort studies, case-control studies, and case series were included to maximise the amount of data available for analysis. The focus of this selection was on interventional studies on implants that had been placed following radiotherapy. Observational studies were included when enough detail had been provided regarding all the items in the inclusion and exclusion criteria.

Outcome measures

Implant survival rate.

Assessment of quality

Use of the risk of bias in non-randomised studies of interventions (ROBINS-I) tool showed that all the studies had a high risk of bias. This was primarily due to limitations in study design and data collection involving head and neck cancer patients.

Data synthesis

Data that were relevant to the aims of this systematic review were extracted and tabulated.

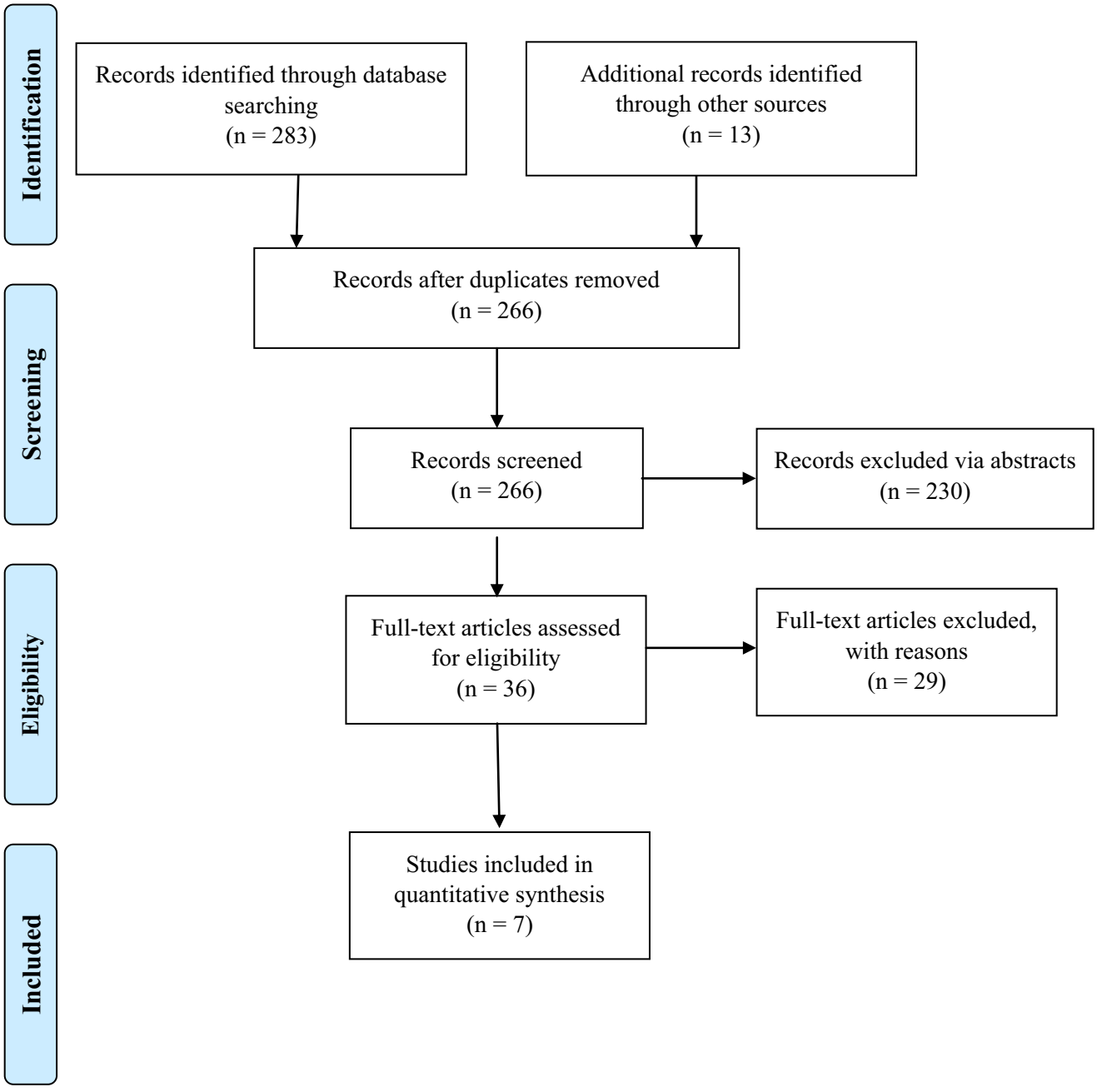

Fig. 1. Prisma flow diagram.

A meta-analysis of the available data used an aggregate patient data method for implant survival and the RevMan 5 tool (The Cochrane Collaboration, 2019). For parameters with insufficient data for meta-analysis, assessment was made via descriptive statistics.

Results

Figure 1 shows the search strategy.

Reasons for study exclusion

The most common reason for exclusion was the placement of implants into free grafted bone. Head and neck oncology surgery for advanced tumours often involves a significant loss of hard and soft tissues, and reconstruction is carried out using bone that is commonly harvested from the fibula, iliac crest, radius, and scapula. Due to the large number of variables involved in these surgeries, there is a high risk of confounding bias. Furthermore, a recent systematic review reported that while the survival of implants in grafted bone in head and neck cancer patients was promising, it was lower than that in native bone.[9] As such, to reduce the risk of overall bias, we decided that this was an important exclusion criterion.

Another common reason for exclusion was the use of HBO therapy within the cohort of patients in some studies. HBO is an adjuvant therapy that aims to increase the healing

capacity of the affected site in patients receiving radiotherapy. There is weak evidence for its efficacy in relation to the survival of dental implants in irradiated patients.[10] This, however, is based on studies with a high risk of bias, and a more recent well conducted phase 3 clinical trial identified no significant difference in the risk of osteoradionecrosis (ORN) with or without HBO.[11] HBO therapy was therefore a potential source of confounding bias so studies that used it were excluded.

Included studies

Table 1 shows the studies included for quantitative synthesis,[12–18] and Table 2, the data extracted.

Implant survival

From the available data, the survival rate was highest in the first five years after implant placement, then was reduced.

Meta-analysis

A meta-analysis was not possible in all domains due to poor outcome measures and variance in reporting. Statistical analysis was carried out only on the effects of irradiated versus non-irradiated bone, and on the site of placement on implant survival.

Irradiated vs non-irradiated bone

There was good homogeneity across studies (I^2 = 0%), meaning there was a low level of variation in study outcomes (Fig. 2). The fixed effects model showed significantly increased survival in implants placed in non-irradiated bone ($p < 0.001$) over a mean follow-up period of 1–3.8 years (odds ratio (OR) 4.77).

Maxilla vs mandible

There was a considerable level of heterogeneity (I^2 = 87%) and as such a random effects analysis model was used (Fig. 3). Implant survival in the mandible was significantly higher than it was in the maxilla ($p = 0.04$) over mean follow-up periods of 1 – 14 years (OR 5.03).

Discussion

The implant success rate was not widely reported, and a valid evaluation of this was not possible. Furthermore, this unique group of patients with several comorbidities and side-effects as a result of cancer treatment creates challenges for implant-based rehabilitation, and conventional measures of success may not be pertinent to their overall care and management. For example, a patient who has undergone radical resection and reconstruction of the jaws may not be acutely mindful of factors such as gingival recession or bone loss, as long as the implant is asymptomatic and functioning. Accordingly, implant survival rates were felt to be more applicable.

Implant survival

Following radiotherapy a series of pathophysiological processes have a negative effect on the oral environment. Several theories and studies have explored the effects related to osteoradionecrosis (ORN) of the jaw, but as specific literature relating to dental implants is limited, it is reasonable to presume that the same processes will affect implant survival. It was originally believed that a series of events following radiotherapy (related to local trauma) would induce osteomyelitis and eventually lead to necrosis.[19] It would appear then that once an implant has osseointegrated, the survival rate should be comparable to non-irradiated areas, assuming no further soft tissue trauma has taken place, but the 5–10 year data do not support this.

A widely accepted theory behind the aetiology of osteoradionecrosis is that affected tissues succumb to hypoxia, hypocellularity, and hypovascularity.[20] Furthermore, recent theories suggest a process of radiation-induced fibrosis (RIF) and atrophy,[21] which is progressive and occurs over several years.[22] This then becomes a chronic pathological process and may be a plausible explanation for the decreasing survival rate of implants over time.

Table 1
Included studies for quantitative synthesis.

First author, year, and reference	Title	Study type
Ettl 2016[12]	Impact of radiotherapy on implant-based prosthetic rehabilitation in patients with head and neck cancer: a prospective observational study on implant survival and quality of life – preliminary results	Prospective cohort
Korfage 2014[13]	Overdentures on primary mandibular implants in patients with oral cancer: a follow-up study over 14 years	Prospective cohort
Pompa 2015[14]	Survival of dental implants in patients with oral cancer treated by surgery and radiotherapy: a retrospective study	Retrospective cohort
Sammartino 2011[15]	Implant therapy in irradiated patients	Prospective cohort
Schepers 2006[16]	Effect of postoperative radiotherapy on the functional result of implants placed during ablative surgery for oral cancer	Retrospective cohort
Visch 2002[17]	A clinical evaluation of implants in irradiated oral cancer patients	Prospective cohort
Wagner 1998[18]	Osseointegration of dental implants in patients with and without radiotherapy	Retrospective cohort

Table 2
Data extracted from included studies.

First author, year, and reference	Study type	Sample size (implants in irradiated bone)	No. of patients	Mean (range) patient age	Data collection period	Follow-up period	Interval between radiotherapy and implant placement	IMRT	Radiation dose	Site of implant placement	ORN (patients/ implants)	Implant survival rate (%)	Implant success rate (%)
Ettl 2016[12]	Prospective	309	52	60 (48–82)	2009– 2014	1 year	≥ 12 months	N	61 (40–72)	Maxilla and mandible	NR	95.2	86.7
Korfage 2014[13]	Prospective	318	100	64.8 (39–88)	1998– 2010	3.8 years (median) 0-14.5 (range)	Primary placement	N	NR	NR	5 (9.6%) 10 (3.2%)	91.5	NR
Pompa 2015[14]	Retrospective	51	34	51 (32–70)	2007– 2012	22.9 months (SD 15.5)	11 – 89 months	N	40-50	Maxilla and mandible	NR	76.5	NR
Sammartino 2011[15]	Prospective	172	69	55.8 (28–63)	2004– 2006	36 months	≥ 6 months	N	<50 or >50	Maxilla and mandible	NR	78.6 for >50 Gy 93.6 for <50 Gy	NR
Schepers 2006[16]	Retrospective	61	21	Male 65 (55–75) Female 68 (58–78)	1996– 2003	29.6 months (maximum = 89 months)	9 mo (SD 3.6)	N	10–68	Mandible	NR	97%	75 prosthetic
Visch 2002[17]	Prospective	446	130	62 (34–87)	1987– 2001	≤ 14 years	6 months – 22 years	N	<50 to >72	Maxilla and mandible	NR	71 for >50 Gy 84 for <50 Gy	NR
Wagner 1998[18]	Retrospective	145	35	55 (40–76)	1987– 1997	65 months	13.02 mo (range 4-107)	N	60	Mandible	1 (2.9%) 5 (3.4%)	97.9 at 5 years 72.8 at 10 years	NR

NR = not reported

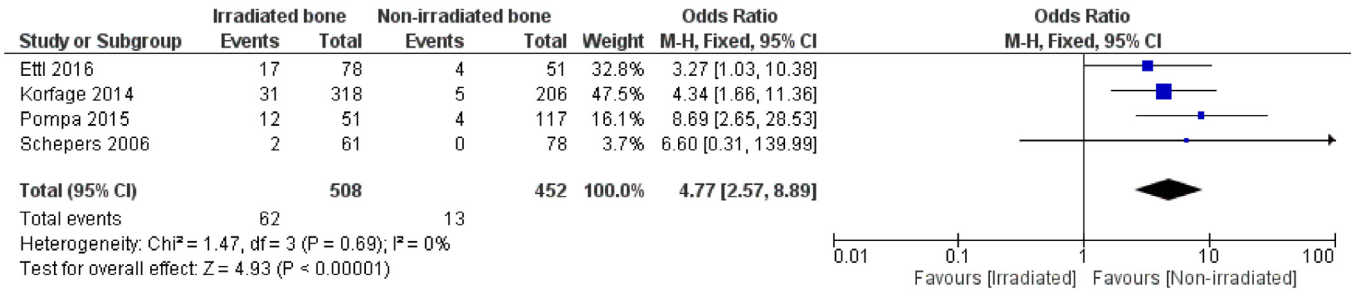

Fig. 2. Forest plot of implant survival in irradiated bone versus implant survival in non-irradiated bone.

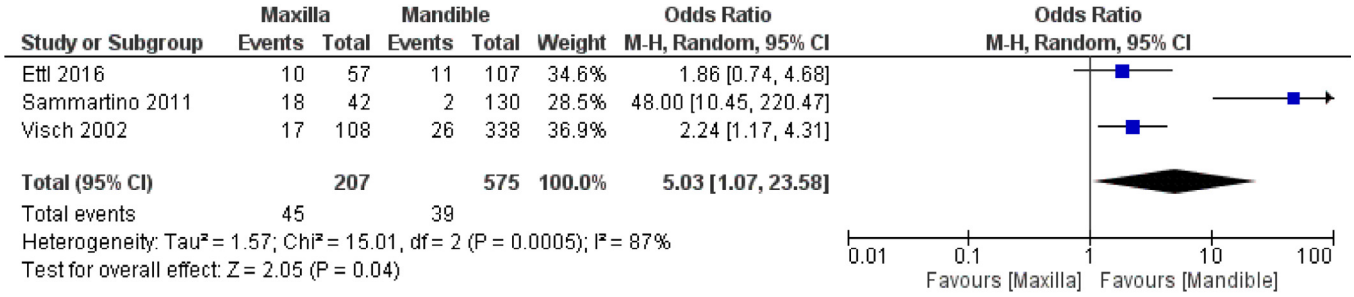

Fig. 3. Forest plot of implant survival in the maxilla versus implant survival in the mandible.

Whilst the majority of discussions relating to radiation and the cause of implant failure are related to the effects of radiation on bone, it must be remembered that there are also other causative factors. In particular, damage to salivary glands and the resulting xerostomia is well documented, and this can in turn induce a bacterial or fungal infection that will predispose the patient to peri-implantitis.[23] Furthermore, the type and size of the implants used were reported in detail in only one paper,[12] so an accurate analysis of the effect of this on implant survival was not possible.

An accurate analysis of survival rate against time was not possible due to the wide variation in reporting across the included studies, which ranged from one to 14 years and included a very limited breakdown of figures. Compared with the results found within this cohort, and as a point of reference, the 10-year survival rate in non-head and neck cancer patients has been reported as 94.9% and 92.8% for implant-retained single crowns and fixed partial dentures, respectively,[24–25] and as 97.6% for implant-retained overdentures.[26]

Timing of implant placement

There are three options for the timing of implant placement as part of head and neck cancer treatment and radiotherapy: during ablative surgery (primary placement), following surgery but prior to radiotherapy, or following surgery and radiotherapy (Table 3). There is, however, no consensus on the optimal treatment regimen and there are advantages and disadvantages for each protocol. The results of this systematic review therefore are not conclusive.

At the time of writing we know of no RCTs comparing the survival of implants and the specific timing protocols described. It is, however, important to understand the advantages and disadvantages of each protocol if we are to be able to formulate the most appropriate plan for each individual patient.

Following radiotherapy, revascularisation and neo-osteogenesis takes three to six months to commence.[27–28] Marx and Johnson[29] suggested that the acute effects of radiation subside within the first six months following exposure, and the chronic effects of vascular damage worsen after 18 months, so a 'window' of 6–18 months is advised for the placement of implants following radiotherapy. This is comparative and in agreement with most of the studies in this review. Other authors and reviews have reported similar 'optimal' timings of 6–12 months following radiotherapy.[30–32] Nevertheless, primary placement should also be considered a valid treatment option as long as there is an adequate bone structure for optimal placement.

Radiation dose

A meta-analysis showed that implant survival is significantly lower in irradiated patients compared with non-irradiated patients ($p < 0.001$). Increasing radiation doses have been shown in animal studies to systematically result in a lower implant survival rate,[33] but at the time of writing we are not aware that any RCTs have evaluated this effect in

Table 3
Advantages and disadvantages of timing protocols in implant placement related to head and neck cancer and radiotherapy.

	Advantages	Disadvantages
• Primary placement	• Faster prosthetic rehabilitation • Prevent further surgery • Reduced risk of ORN	• Optimal implant placement and angulation may not be possible due to anatomy • Implants may be lost due to cancer recurrence • Risk of radiation backscatter around implants leading to higher localised doses
• Prior to radiotherapy	• Increased surgical control in placement of implants due to availability of hard and soft tissues • Reduced risk of ORN	• Second surgery required • Potential delay in time-critical administration of radiotherapy • Risk of radiation backscatter around implants leading to higher localised doses • Implants may be lost due to cancer recurrence
• Following radiotherapy	• Increased surgical control in placement of implants due to availability of hard and soft tissues • Increased control in healing time prior to prosthetic rehabilitation • Reduced risk of loss of implants due to cancer recurrence due to increased monitoring time and effects of radiotherapy	• Second surgery required • Increased risk of ORN and complications arising from radiation (eg mucositis/limited mouth opening)

humans. The current consensus advice is based on the pooled data from studies with a myriad of confounders and sources of bias, making a valid and absolute conclusion regarding the 'safe' level of radiation dose impossible.

In a narrative publication, Anderson et al[30] provided decision-making guidelines for the placement of implants according to the exposed radiation dose:

$\leq$ 50 Gy (low risk) – standard precautions apply
50–65 Gy (moderate risk) – implant placement with caution
65–74 Gy (relatively high risk) – placement not advised unless with other precautions such as HBO therapy
75–120 Gy (high risk) – implant placement not advised

These figures are in keeping with the results found in this review in which doses of less than 50 Gy were associated with higher implant survival rates.

Location of implants

The majority of the studies supported better implant survival in the mandible than the maxilla, and a meta-analysis confirmed this to be the case ($p = 0.04$). The explanation for lower survival rates in the maxilla may be related to the poor quality of bone, which is a common characteristic that is not unique to irradiated cases, and also results in lower implant survival in native bone. It is thought that in irradiated cases, primary stability of the implant is greatest in the mandible, resulting in higher survival rates, but conversely it is theorised that long-term survival could be higher in the maxilla due to better secondary stability from increased trabecular bone and vascularity, which can withstand the chronic effects of radiation.[34] There are, however, inadequate long-term data to make a valid conclusion for either case, and whilst this is likely to be a multifactorial outcome, the vast majority of the literature and the data from this review support the claim that the survival rate in the mandible is higher than it is in the maxilla. Furthermore, there are limited data in the literature on the exact location of placement, and the influence of anterior versus posterior implants on survival may be significant irrespective of the maxilla or mandible.

Implications for clinical practice

Implant-based rehabilitation should not be considered a contraindication in the irradiated patient. Several factors can influence outcome, and management requires a comprehensive planning process with a robust understanding of the factors that can affect each stage of treatment. Of particular importance, clinicians should be aware of the effects and outcomes of the radiation dose, the timing of implant placement, and location of the implant. To gain informed consent, a complete discussion must take place with the patient to explain the likely risks and benefits, in particular the significantly lower rates of implant survival in irradiated compared with non-irradiated bone. Clinicians must ensure that patients have a realistic expectation of the treatment journey, not only the likely improvements to their quality of life, but also the common side effects experienced.

Implications for future research

Several of the key areas identified in this review are common influencing factors on implant survival and quality of life, and many have been well documented and published in the literature.

Several relevant topics are frequently not included as part of research projects, or lack sufficient data within the scientific literature. Some of these include:

- Compounding factors that may contribute to implant loss, such as the volume and quality of bone, the periodontal status, biomechanical concerns such as bruxism, smoking, oral hygiene, and systemic disease.
- The risk of implant failure, or failure of osseointegration that initiates ORN. This may eventually lead to devastating complications such as pathological fracture, which can then severely affect quality of life.
- The impact of implant failure on overall quality of life. The failure of treatment after having committed to such extensive surgery can itself affect patients psychologically. Similarly, over the period that the implants and prostheses are functioning patients may become so accustomed to their improvements that they are left in a worse state if the treatment fails and they have to cope with conventional dentures.
- The effects of intensity-modulated radiotherapy (IMRT) and other modes of radiation such as proton therapy.
- The effects of novel pharmaceutical managements for radiation-induced osteonecrosis (such as PENTOCLO) on implant survival
- Genetic factors, specifically the potential 'radiation-resistance' influence of the C-509T allele expression of the TGF-β1 gene and its effects on implant survival
- The effects of a computer-aided approach to facilitate minimally-invasive surgery, with implant placement in an optimal location in an area of bone that is least affected by radiation

Strengths and limitations

By identifying key areas of interest within the core topic, it was possible to outline the relevant details for clinical practice, with a particular focus on the impact on patients. Furthermore, exploration of these topics has generated exciting concepts for future research.

The main limitation of the review was the small number of studies that met the inclusion criteria, and ultimately their poor overall quality. The sample sizes were relatively small with short follow-up periods. The reporting of data was inconsistent and lacked detail in many areas. This is a problem that is partly due to the complex nature of treatments for head and neck cancer, the difficulties involved in carrying out RCTs ethically, and following up patients who have high morbidity and mortality. Moreover, only studies in the English language were included even though this is a topic of international interest, particularly in non-English-speaking European countries, which may have resulted in the exclusion of highly relevant studies.

Due to the lack of adequate data and high risk of bias within the included studies, quantitative synthesis was limited and a comprehensive meta-analysis was not possible. Given the limitations of the included studies, the conclusions must therefore be interpreted with caution.

Conclusion

Within the limitations of this review, the following conclusions were made:

- Implant-based rehabilitation is a viable treatment with favourable survival rates in irradiated head and neck cancer patients.
- Implant survival is significantly lower in irradiated compared with non-irradiated patients ($p < 0.001$).
- Radiation doses over 50 Gy are associated with lower survival rates.
- Implant placement should be delayed by at least six months following irradiation, although in selected cases primary placement may be favourable with good planning.
- Implant survival is significantly higher in the mandible than in the maxilla ($p = 0.04$). There are common side-effects of radiotherapy that are not amenable to improvement with implant-based rehabilitation, including xerostomia and limited mouth opening.

Further research in the form of RCTs and high-quality comparative studies is recommended to confirm the validity of these claims.

Ethics statement/confirmation of patients permission

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[See online]