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Radiotherapy and the survival of dental implants:

A systematic review

Abstract

Background and aim: The effects of head and neck cancer treatment with adjuvant radiotherapy can be devastating for patients. There is frequently loss of function due to tooth loss, pain and discomfort from xerostomia and mucositis, and a significant psycho-social impact. Dental implants provide an effective means of rehabilitation for many; however, irradiation poses a unique set of challenges that can affect the outcome of treatment. The aim of this review is to evaluate whether radiotherapy in head and neck cancer patients affects dental implant survival and discuss the details of pertinent influencing factors.

Methods: An electronic search of the Medline, Web of Science and CENTRAL databases was used to identify studies presenting 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.

Results: A total of 7 studies involving 441 participants and 1502 implants placed into irradiated bone were included. Meta-analysis indicated significantly higher survival in the mandible compared to the maxilla (p=0.04), and those in non-irradiated cases compared to irradiated cases (p<0.001). Other factors that showed a strong association with survival were identified as radiation dose and timing of surgery.
Conclusion: Implant-based rehabilitation is a viable treatment option for head and neck cancer patients who have undergone radiotherapy. Whilst the short to medium term implant survival in these cases are high, there are multiple factors that 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 etiological risk factors for head and neck cancer are undoubtedly smoking and alcohol consumption.

Radiotherapy is one of the treatment modalities for the management of head and neck cancer. It is often used in combination with surgery and/or chemotherapy in more advanced disease, although some clinicians advocate its use in select early stage diseases \(^3\).

Head and neck cancer has a high morbidity however, there has been an upwards trend in the survival rate of patients in recent decades \(^4-6\); this is believed to be due to the combination of improved screening programs 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 in their maintenance due to the adverse effects of radiotherapy.

Combined with the fact that many of the affected patients are elderly and/or have undergone extensive ablative surgery, this results in a group of patients with missing teeth that can have a severely decreased quality of life. Conventional removable prostheses are often unsuitable due to the discomfort caused from mucositis and dry mouth. As such, dental implants are frequently used as an invaluable tool in the rehabilitation of such patients. The negative side-effects of radiotherapy outlined above will also affect the
Primary measure: Implant survival rate

timing of implant placement and location of implant.

Methods

Focus Question
“Does radiotherapy prior to dental implant placement 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 intra-oral site previously exposed to radiotherapy.

Comparison
Placement of an endosseous dental implant in an intra-oral site that has not been exposed to radiotherapy.

Outcome
Primary measure: Implant survival rate
**Search Strategies**

Scoping searches were used to gather information and keywords pertinent to this review, which were then used to build a focused query. To maximise the number of relevant scientific papers, the query was carried out across three electronic databases: Medline; Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL).

Citations and reference lists of the selected studies were also manually analyzed to identify further relevant publications that were not included in the primary search.

The following Medical Subject Headings (MeSH) terms were used:

“dental implant”

Also including: implant, implant-supported, implantology, endosseous, osseointegrated, osseointegration

“radiotherapy”

Also including: radiation, radiation therapy, irradiation

“cancer”

Also including: head, neck, oncology, carcinoma, tumour, oral, cavity, nasopharynx

The abstracts for the studies identified from the literature search query were screened using the inclusion and exclusion criteria below. Any study that had missing data relating to
these criteria in the abstract was manually screened using the full text of the publication.

The full text for all selected studies were then sourced and analyzed.

**Inclusion criteria**

- RCTs, cohort studies, case-control studies and case reports
- Head and neck cancer patients
- Radiotherapy received affecting site of implant surgery
- Patients rehabilitated with one or more dental implants
- 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 site of implant surgery
- Dental implants placed into free-grafted bone
- Extra-oral implants
- Patients who had received hyperbaric oxygen (HBO) therapy prior to implant placement

**Types of study included**

Randomised control trials (RCT), cohort studies, case-control studies and case series studies were included to maximise the amount of data available for analysis. The focus of this selection was on interventional studies where implant placement had been carried out following radiotherapy. Observational studies were included when enough detail had been provided regarding all items of the inclusion and exclusion criteria.
Outcome measures

- Implant survival rate

Assessment of quality

An assessment was carried out for the risk of bias using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) for non-randomized studies. This showed that all included studies were at a high risk of bias. This was primarily due to the limitations in study design and data collection involving head and neck cancer patients.

Data synthesis

Data that was of relevance to the aims of this systematic review was extracted and tabulated.

A meta-analysis was carried out using an aggregate patient data method for implant survival using the available data and by using the RevMan 5 tool (The Cochrane Collaboration, 2019). For parameters that have insufficient data for meta-analysis, assessment will be made via descriptive statistics.

Results
**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. 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 for head and neck cancer patients is promising, it is lower than that in native bone. As such we decided that this is an important exclusion criterion to reduce the risk of overall bias. Another common reason for exclusion was the use of HBO therapy within the cohort of patients included in some studies. This is an adjuvant therapy aimed at patients receiving radiotherapy to potentially increase the healing capacity of the affected site. There is weak evidence for the efficacy of this therapy with relation to dental implant survival in irradiated patients, this is based on studies which had a high risk of bias, and a more recent well conducted phase 3 clinical trial identified no significant difference in risk of osteoradionecrosis (ORN) with or without HBO. However, as HBO therapy was a potential source of confounding bias studies using HBO were excluded.

Included studies
Table 1. Included studies for quantitative synthesis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Title</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ettl (2016) 12</td>
<td>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</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Korfage (2014) 13</td>
<td>Overdentures on primary mandibular implants in patients with oral cancer: a follow-up study over 14 years</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Sammartino (2011) 15</td>
<td>Implant Therapy in Irradiated Patients</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Schepers (2006) 16</td>
<td>Effect of postoperative radiotherapy on the functional result of implants placed during ablative surgery for oral cancer</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Wagner (2009) 18</td>
<td>Osseointegration of Dental Implants in Patients with and without Radiotherapy</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>Study</td>
<td>Study type</td>
<td>Sample size (implants in irradiated bone)</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Ettl (2016)</td>
<td>Prospective</td>
<td>309</td>
</tr>
<tr>
<td>Korfrage (2014)</td>
<td>Prospective</td>
<td>318</td>
</tr>
<tr>
<td>Pompa (2015)</td>
<td>Retrospective</td>
<td>51</td>
</tr>
<tr>
<td>Sammartino (2011)</td>
<td>Prospective</td>
<td>172</td>
</tr>
<tr>
<td>Schepers (2006)</td>
<td>Retrospective</td>
<td>61</td>
</tr>
<tr>
<td>Visch (2002)</td>
<td>Prospective</td>
<td>446</td>
</tr>
<tr>
<td>Wagner (2009)</td>
<td>Retrospective</td>
<td>145</td>
</tr>
</tbody>
</table>

Table 2. Data extraction from included studies (NR = not reported)
Implant survival

From the data that is available, the survival rate was higher in the first 5 years following implant placement and reduced in the proceeding years.

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 bone versus non-irradiated bone and site of placement on implant survival.

Irradiated vs non-irradiated bone

There was good homogeneity across studies ($I^2=0\%$) meaning there a low level of variation in study outcomes (Figure 2). The fixed effects model showed that implants placed in non-irradiated bone had a significantly increased implant survival rate ($P<0.001$) over a mean follow-up of 1-3.8 years with an odds ratio of 4.77.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Irradiated bone</th>
<th>Non-irradiated bone</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E)-(2) 2016</td>
<td>17</td>
<td>78</td>
<td>51 32.9% 3.27 [1.03, 10.36]</td>
</tr>
<tr>
<td>(F)-(3) 2014</td>
<td>31</td>
<td>318</td>
<td>5 202 47.5% 4.34 [1.66, 11.38]</td>
</tr>
<tr>
<td>(P)-(4) 2015</td>
<td>12</td>
<td>51</td>
<td>4 117 16.1% 8.69 [2.65, 28.53]</td>
</tr>
<tr>
<td>(S)-(5) 2006</td>
<td>2</td>
<td>61</td>
<td>0 78 3.7% 6.60 [0.31, 139.98]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>508</td>
<td>452</td>
<td>100.0% 4.77 [2.57, 8.89]</td>
</tr>
</tbody>
</table>

Total events 62 13

Heterogeneity: $\chi^2=14.7$, df=3 ($P=0.69$); $I^2=0\%$

Test for overall effect: $Z=4.95$ ($P<0.00001$)

Figure 1. Forest plot of implant survival in irradiated bone versus implant survival in non-irradiated bone
Maxilla vs Mandible

There was a considerable level of heterogeneity ($I^2=87\%$) and as such a random effects analysis model was used (Figure 3). Implant survival was significantly higher in the mandible compared to the maxilla ($p=0.04$) between a mean follow-up period of 1 – 14 years, with an odds ratio of 5.03.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Maxilla Events</th>
<th>Maxilla Total</th>
<th>Maxilla Weight</th>
<th>Mandible Events</th>
<th>Mandible Total</th>
<th>Mandible Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ettl 2016</td>
<td>10</td>
<td>57</td>
<td></td>
<td>11</td>
<td>107</td>
<td>34.6%</td>
<td>1.86 [0.74, 4.68]</td>
<td></td>
</tr>
<tr>
<td>Sammartino 2011</td>
<td>18</td>
<td>42</td>
<td></td>
<td>2</td>
<td>130</td>
<td>28.5%</td>
<td>48.00 [10.45, 220.47]</td>
<td></td>
</tr>
<tr>
<td>Visscher 2002</td>
<td>17</td>
<td>108</td>
<td></td>
<td>26</td>
<td>338</td>
<td>36.9%</td>
<td>2.24 [1.17, 4.31]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>207</td>
<td>575</td>
<td>100.0%</td>
<td>5.03</td>
<td>23.58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{Tau}^2 = 1.57$, $\text{Chi}^2 = 15.01$, $df = 2$ ($P = 0.003$); $I^2 = 97\%$

Test for overall effect: $Z = 2.05$ ($P = 0.04$)

Figure 2. Forest plot of implant survival in the maxilla versus implant survival in the mandible
Discussion

The aim of this systematic review was to evaluate the available literature and evidence on the survival of dental implants in patients who had received radiotherapy as part of their head and neck cancer treatment. The primary outcome measure was implant survival. Implant success rates were not widely reported, and a valid evaluation of this was not possible. Furthermore, this is a unique group of patients with several co-morbidities and side-effects as a result of cancer treatment, which create challenges in implant-based rehabilitation; as such the conventional measures of success may not be pertinent to the overall care and management of this group of patients. For example, a patient that has undergone radical resection and reconstruction of the jaws may not be acutely mindful of factors such as gingival recession or bone loss, so long as the implant is asymptomatic and functioning. Accordingly, implant survival rates was felt to be more applicable.

Implant survival

Following the administration of radiotherapy, there is a series of pathophysiological processes that negatively affects the oral environment. There have been several theories and studies exploring these effects related to osteoradionecrosis (ORN) of the jaw however, there is limited specific literature related to dental implants, but it is reasonable to presume that the same processes affect implant survival. It was originally believed that a series of events following radiotherapy related to local trauma would induce an osteomyelitis, eventually leading to necrosis. It would appear then that once an implant has osseointegrated, the survival rates should be comparable to non-irradiated areas assuming no further soft tissue trauma takes place, but the 5-10 year data does not support this.
Among the most widely accepted theories behind the aetiology of osteoradionecrosis is that of affected tissues succumbing 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 over time that may be plausible to explain the decreasing survival rates of implants with progressive years.

Whilst the majority of discussions relating to the cause of implant survival and radiation is related to the effects on bone, it must be remembered that there are also other causative factors. In particular, the 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 implants used were only reported in detail by one paper 12, and 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 in this review, due to the wide variation in reporting across the included studies, which ranged between 1 to 14 years and included a very limited breakdown of figures. In comparison to 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 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.
There is no consensus for the optimal treatment regime and there are advantages and disadvantages for each protocol. The results of this systematic review was not conclusive in this regard either. At the time of writing there have been no randomised controlled trials comparing the survival of implants and the specific timing protocols described. As such it is prudent to understand the advantages and disadvantages of each protocol to be able to formulate the most appropriate plan for each individual patient.

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **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 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 |  

Table 3. Advantages and disadvantages of timing protocols in implant placement related to head and neck cancer and radiotherapy
Following radiotherapy, revascularisation and neo-osteogenesis takes up to 3-6 months to commence\textsuperscript{27,28}. Marx and Johnson\textsuperscript{(29)} suggest that the acute effects of radiation subside within the first 6 months following exposure and that 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 to most of the studies in this review. Other authors and reviews have reported a similar ‘optimal’ timing of 6-12 months following radiotherapy\textsuperscript{30-32}. Nevertheless, primary placement should also be considered a valid treatment option as long as there is adequate bone structure for optimal placement.

**Radiation dose**

A meta-analysis showed that implant survival is significantly lower in irradiated patients compared to non-irradiated patients (\(p<0.001\)). Increasing radiation doses have been shown in animal studies to systematically result in a lower implant survival rate\textsuperscript{33} however, at the time of writing there has been no randomised controlled trials to evaluate this effect in 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, Meraw\textsuperscript{(30)} have provided decision making guidelines for the placement of implants according to exposed radiation dose:

- \(\leq 50\) Gy is classed as low risk – standard precautions apply
- 50-65 Gy is moderate risk – implant placement with caution
- 65-74 Gy is relatively high risk – placement not advised unless with other precautions such as hyperbaric oxygen therapy
- 75-120 Gy is high risk – implant placement is not advised
These figures are in keeping with the results found in this review where doses of less than 50 Gy were associated with higher implant survival rates.

**Location of implant**

The majority of the studies in this review are in support of higher implant survivals in the mandible than the maxilla. A meta-analysis confirmed that implant survival is significantly higher in the mandible than the maxilla (p=0.04). The explanation for the lower survival rates in the maxilla may be related to the poor quality of bone, which is a common characteristic and not unique to irradiated cases, resulting in lower implant survival also 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 also conversely, it is theorised that the long-term survival could be higher in the maxilla due to better secondary stability from increased trabecular bone and vascularity that can withstand the chronic effects of radiation\(^{34}\). There is inadequate long-term data available to make a valid conclusion for either case however, whilst this is likely a multi-factorial outcome, the vast majority of the literature and data from this review support the claim that there is a higher survival rate in the mandible compared to the maxilla. Furthermore, there is very limited data relating to the exact location of placement in the literature, and there may be a significant influence in anterior versus posterior implants and survival irrespective of the maxilla or mandible.

**Implications for Clinical Practice**
Implant-based rehabilitation should not be considered a contraindication in the irradiated patient. There are several factors that can influence the outcome of treatment, and management requires a comprehensive treatment 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 radiation dose, the timing of implant placement and the location of implants. A complete discussion must take place with the patient to explain the likely risks and benefits to be able to gain informed consent, in particular the significantly lower implant survival rates in irradiated bone compared to non-irradiated bone must be considered. The clinician must ensure that patients have a realistic expectation of the treatment journey and not only the likely quality of life improvements, but also the common side-effects experienced.

Implications for Future Research

There are several key areas identified in this review that are common influencing factors in implant survival and quality of life, many of which have been well documented and published in the literature. There are also several relevant topics that are frequently either not included as part of research projects, or are lacking 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 initiating ORN, that may eventually lead to devastating complications such as pathological fractures, which can then severely affect quality of life.
The impact of implant failure on overall quality of life. Perhaps the commitment to having such extensive surgery and treatment, for it to fail at a later date, 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 if the treatment does fail, they are then left in a worse state having to cope with conventional dentures.

- The effects of 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 computer aided surgery to facilitate a 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, a thorough discussion was possible to outline the relevant details for clinical practice, with a particular focus on patient impact. Furthermore, the exploration of these topics generated exciting concepts for future research. The main limitation of this 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. Reporting of data was inconsistent and lacking in detail in many
areas. This is a problem that is partly due to the complex nature of head and neck cancer treatments and the difficulties in carrying out randomised-controlled trials ethically, and following up patients who have a high morbidity and mortality. Moreover, only studies in the English language were able to be included, even though this is a topic of international interest, in particular in non-English speaking European countries, which may have resulted in excluding studies of high relevance.

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

**Conclusion**

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

- Implant-based rehabilitation is a viable treatment option with favourable survival rates in irradiated head and neck cancer patients.
- Implant survival is significantly lower in irradiated patients compared to 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 6 months following irradiation, although in select cases primary placement may be favourable with good planning.
- Implant survival is significantly higher in the mandible than 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 randomised controlled trials and high-quality comparative studies is recommended to confirm the validity of these claims.
Conflict of Interest

Nil to declare

Ethics statement/confirmation of patient permission

N/A

References


471  4.  Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early
473  5.  Lavaf A, Genden EM, Cesaretti JA, Packer S, Kao J. Adjuvant radiotherapy improves overall
474  survival for patients with lymph node-positive head and neck squamous cell carcinoma. Cancer:
478  7.  Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for
479  head and neck cancer in the United States: a site-specific analysis of the SEER database.
482  2006;7(2):175-83.
484  and bone flaps in head and neck oncology patients: a systematic review. International journal of
486  10.  Esposito M, Worthington HV. Interventions for replacing missing teeth: hyperbaric oxygen
487  therapy for irradiated patients who require dental implants. Cochrane Database of Systematic
488  Reviews. 2013(9).
490  (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): a randomized controlled trial of
491  hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible after dentoalveolar
494  on implant-based prosthetic rehabilitation in patients with head and neck cancer: A prospective
495  observational study on implant survival and quality of life-Preliminary results. J Craniomaxillofac


