The use of intraoral devices in reducing oral and dental side effects in head and neck cancer patients undergoing radiotherapy – a systematic review.

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ABSTRACT

**Purpose:** To evaluate whether intraoral devices reduce the adverse oral and dental effects of radiotherapy in head and neck cancer patients. **Materials and Methods:** A systematic search of the Medline and Embase databases for articles published before March 2019 was performed by two independent reviewers. Studies published in English that evaluated whether intraoral devices reduced the risk of radiotherapy-related complications in patients receiving radiotherapy to the head and neck region were included. The kappa statistic was used to calculate the level of inter-reviewer agreement. **Results:** Five studies met the inclusion criteria, although only one was considered to be a low risk of bias. One study reported that intraoral devices did not reduce the severity of mucositis after 7 weeks. The remaining four studies reported that intraoral devices reduced the risk of xerostomia, mucositis, trismus, dysphagia, and dental caries over 2 to 6 months. **Conclusion:** There are limited data to support the use of intraoral devices in head and neck cancer patients undergoing radiotherapy. Well-designed clinical studies that consider long-term outcomes are necessary to draw definitive conclusions. *Int J Prosthodont 2021. doi: 10.11607/ijp.6933*

INTRODUCTION:

Head and neck cancer is the sixth most common cancer worldwide with 550,000 new cases and around 300,000 deaths each year.\(^1,2\) In the United States, head and neck cancer accounts for nearly 4% of all new cancer cases whereas in the United Kingdom it accounts for 3% of all new cancers.\(^3,4\) There has been a recent significant increase in the incidence of head and neck cancer, particularly oropharyngeal carcinoma, and the human papilloma virus (HPV) has been identified as a significant factor in this.\(^5\)

Treatment for early head and neck cancer usually involves single modality therapy with either surgery or radiotherapy. Late stage disease is usually treated with a combination
of surgery, radiotherapy, chemotherapy and, more recently, immunotherapy. 6 HPV related oropharyngeal carcinoma often responds well to radiotherapy. 7 As the incidence of this type of cancer increases it is therefore likely that more patients will live longer and have to deal with the adverse effects of treatment.

The use of radiotherapy in particular is associated with multiple adverse effects that impair quality of life for head and neck cancer patients. These effects can be attributed to both the direct and indirect effects of radiation. Early effects include: mucositis, xerostomia, trismus, dysgeusia and difficulty swallowing. Late effects include: radiation caries, candidiasis, osteoradionecrosis, trismus, difficulty with removable prostheses, periodontal disease and a reduced rate of oral healing.8-13

The dental literature is replete with descriptions of intraoral devices, of various shapes and designs, which can be used to reduce or eliminate the early and late side effects of radiotherapy.14-24 These devices are typically used to displace, reposition or shield the oral hard and soft tissues or to assist in the accurate delivery of radiotherapy. Within the literature the terms appliance, device, prosthesis, shield and stent are often used interchangeably. We have used the term device throughout this paper as, according to the latest edition of the Glossary of Prosthodontic Terms, a device is something that is developed to serve a special function or purpose, particularly in the short term.25

Although intraoral devices are commonly fabricated prior to radiotherapy it is unclear if they are effective in reducing radiation dosage or the adverse effects of radiation. Intraoral devices are generally simple to fabricate but their construction often involves additional clinical visits and procedures at a challenging time for the patient and their family. 26 It is therefore important to ascertain whether these devices reduce the adverse effects of radiotherapy. The aim of this systematic review was to determine whether intraoral devices
are effective in reducing the adverse effects of radiation therapy in head and neck cancer patients.

MATERIALS AND METHODS:

A systematic review was undertaken following established guidelines. The Population, Intervention, Comparison, Outcome (PICO) framework was used to develop the following focussed question: ‘In patients receiving radiotherapy to treat head and neck cancer (P) does the use of an intraoral device (I), as opposed to no intraoral device (C), prevent or reduce the risk of complications of radiotherapy (O)?’ Studies considered for this review were then identified following a detailed search of MEDLINE via the PubMed interface outlined in Figure 1 and EMBASE prior to March 2019. The PICO question was used to develop the search strategy and this was revised appropriately for each database with the assistance of a medical librarian.

The search strategy was designed to identify all prospective and retrospective comparative clinical studies, published in English, with a minimum of 10 human subjects that investigated whether intraoral devices prevented or reduced the risk of radiotherapy related complications in patients receiving radiotherapy to the head and neck region. There was no date restriction. The following were excluded from the analysis:

1. Studies that considered the treatment of radiotherapy related complications,
2. Studies investigating brachytherapy or diagnostic radiation,
3. Studies investigating radiotherapy outside of the head and neck area,
4. Studies investigating the use of extra-oral devices,
5. Animal or laboratory studies,
6. Studies with fewer than 10 participants,
7. Studies published in languages other than English.
The title and abstract of each publication identified using the search strategy was independently appraised by two reviewers (AG and SN) to determine whether it met the inclusion criteria. When the information in the title and abstract was insufficient the full text was retrieved for analysis. The full text of any publication potentially meeting the inclusion criteria was then independently appraised by two reviewers (AM and JV). Any disagreement was resolved by discussion amongst all reviewers. The reference lists of all included studies were checked for further relevant studies. Hand searching of six journals (Journal of Prosthetic Dentistry, Journal of Prosthodontics, European Journal of Prosthodontics and Restorative Dentistry, International Journal of Prosthodontics, Journal of Cancer Research and Therapeutics, Oral Surgery Oral Medicine Oral Pathology Oral Radiology) was carried out from 2010 onwards. The year 2010 was chosen, as that was the earliest included study. The kappa statistic was used to calculate the level of inter-reviewer agreement at each stage of the review process.28

A quality assessment of each included study was undertaken using the Cochrane Collaboration tool for assessing risk of bias.29 Quality assessment was undertaken independently by two reviewers (AG and SN) and any disagreement was resolved through discussion with a third reviewer (AM). Data was then extracted from each study using a customised data collection sheet. Information on the following parameters was collected: author(s), journal, year of publication, study design, study setting, number of patients, dropouts, age range, tumour site, tumour grade, tumour stage, type of radiotherapy (external beam or intensity modulated), adjunctive chemotherapy or surgery, treatment intent (curative or palliative), type of intraoral device, adverse effects and follow up period. The outcome of interest was the difference in any adverse effect of radiotherapy between the intervention group and the control group in each comparative study. Studies were evaluated for the information they contained and no attempt was made to contact the authors for additional
information. Data was tabulated using descriptive statistics and no attempt was made to undertake a meta-analysis

RESULTS:

The searches of the Medline and EMBASE databases revealed 3573 potentially relevant studies. Of these, 3552 studies were rejected on the basis of the title and abstract and 21 studies were selected for full text analysis – as outlined in Figure 2. The weighted kappa score indicated excellent reviewer agreement at this stage (kappa = 0.9, 95% confidence interval 0.8 - 0.99).

Following full text analysis five studies were considered to meet the inclusion criteria.30-34 The remaining 16 studies were excluded because they were case reports,18,24,35,36 technique articles,15,37 investigated brachytherapy,38-41 published in Chinese,42,43 did not investigate intraoral devices44,45 or did not report on complications of radiotherapy.46 The weighted kappa score revealed perfect agreement at this stage (kappa = 1).

The design of the five studies that met the inclusion criteria are summarised in Table 1. These studies comprised three randomised controlled trials and two retrospective cohort studies. One study was considered to be at low risk of bias and the remaining four studies were considered to be at high risk of bias as summarised in Table 2. These studies were predominantly undertaken in a University or hospital setting. The primary tumour site was the tongue or floor of mouth in three studies, buccal mucosa in one study and all head and neck cancer sites were included in one study. Few studies provided information about tumour grade and stage or whether treatment had a curative or palliative intent. Radiotherapy was the primary treatment in one study; in the other four studies radiotherapy was used in conjunction with surgery and/or chemotherapy. There were three studies that used external beam radiotherapy, one study used intensity modulated radiotherapy (IMRT) and one study used both external beam and IMRT. A Cerrobend device was used to shield the teeth and alveolar
processes in one study. The other four studies investigated the use of acrylic intraoral devices to separate the maxilla and mandible whilst radiotherapy was delivered.

Collectively the five studies investigated a variety of different complications of radiotherapy: mucositis, xerostomia, saliva flow rates, salivary changes, dysgeusia, dysphagia, mucositis, pain on swallowing, dental caries and trismus. Two studies used the Radiation Therapy Oncology Group (RTOG) head and neck adverse events grading tool. The remaining three studies used different assessment tools. The results of the five studies that met the inclusion criteria are summarised in Table 3. One study found that an intraoral device did not reduce the severity of mucositis after 7 weeks. The remaining four studies found that intraoral devices reduced xerostomia and mucositis after 60 days, significantly reduced trismus after 2 months, significantly reduced pain on swallowing, mucositis, dysphagia, oral dryness and dental caries after 3 months and increased salivary flow rates and quality of life after 6 months. No attempt was made to quantitatively combine the results of the included studies as they exhibited clinical heterogeneity.

**DISCUSSION:**

The validity of any systematic review is dependent upon a comprehensive search strategy. All search strategies are imperfect and have limited sensitivity and specificity as a result of indexing inconsistencies and title and abstract imprecision. In order to identify all relevant studies we therefore reviewed the reference lists of included studies and hand-searched selected journals. This systematic review was restricted to studies published in English and it is acknowledged that this may have introduced language bias.

In order to ensure robustness of the systematic review process two reviewers appraised all potentially relevant studies. This provided protection against reviewer bias and kappa scores were calculated to determine the level of agreement over and above that
expected by chance.\textsuperscript{28} The reported kappa scores reveal excellent agreement and this should reassure the reader of the robustness of the process that has been used.

Radiotherapy is an important treatment modality for head and neck cancer but it is associated with short and long-term complications that can adversely affect quality of life.\textsuperscript{8-13} Intraoral devices have the potential to reduce the impact of these adverse effects but there appears very little evidence to support their use. The studies identified by this systematic review are at high risk of bias, exhibit significant clinical and methodological heterogeneity and do not consistently consider the same complications.\textsuperscript{29} Furthermore, none of the studies followed patients for longer than 6 months so there is no evidence pertaining to long-term adverse effects. It is therefore difficult to determine whether intraoral devices are beneficial in reducing adverse effects in patients undergoing radiotherapy to the head and neck region in the long term.

Intraoral devices are simple to fabricate but their construction can involve additional clinical visits and procedures at a challenging time for the patient and their family.\textsuperscript{26} Any device that separates the upper and lower jaws will likely reduce the radiation dose to the opposing jaw, but it is not clear that this is necessary with modern techniques such as intensity modulated radiation therapy (IMRT), which is not currently available in all head and neck units. These devices can also have a role in the accurate positioning of soft tissue structures relative to the radiotherapy source. However, head and neck cancer patients are typically immobilised by an external mask and, as Prosthodontists, we are primarily concerned with the impact that these devices have on the adverse effects of radiotherapy. This systematic review has identified a requirement for well-conducted studies, which consider long term outcomes, to determine whether intraoral devices reduce the risk of adverse effects in head and neck cancer patients undergoing radiotherapy.

CONCLUSIONS:
There is limited data to support the use of intraoral devices in head and neck cancer patients undergoing radiotherapy. This does not mean that intraoral devices are ineffective but well-designed clinical studies, which consider long-term outcomes, are necessary to draw definitive conclusions about the clinical effectiveness of these devices in reducing the adverse effects of radiotherapy in the head and neck region.

REFERENCES:


### Table 1. Design of the 5 included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Received device</th>
<th>Did not receive device</th>
<th>Drop outs</th>
<th>Site</th>
<th>Treatment</th>
<th>Device type</th>
<th>Which side effects were evaluated</th>
<th>Follow-up time(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goel et al</td>
<td>2010</td>
<td>RCT</td>
<td>24</td>
<td>24</td>
<td>0</td>
<td>Base of Tongue</td>
<td>Conventional radiotherapy</td>
<td>Custom made acrylic</td>
<td>Mucositis, Saliva changes, Dysgeusia, Trismus, Caries, Swallowing problems</td>
<td>30, 45 &amp; 60 days</td>
</tr>
<tr>
<td>Verrone et al</td>
<td>2014</td>
<td>Retrospective Cohort Study</td>
<td>19</td>
<td>14</td>
<td>N/A</td>
<td>Tongue and FOM**</td>
<td>IMRT* - alone and with other treatment modalities</td>
<td>Custom made acrylic</td>
<td>Mucositis; Dose</td>
<td>Mucositis - weekly; Dose - calculated from plans</td>
</tr>
<tr>
<td>Mall et al</td>
<td>2016</td>
<td>RCT</td>
<td>15</td>
<td>15</td>
<td>6</td>
<td>Posterior Tongue</td>
<td>Conventional radiotherapy with concurrent Cisplatin</td>
<td>Custom made acrylic</td>
<td>Unstimulated and stimulated saliva flow; Xerostomia</td>
<td>Immediately, 3 months, 6 months</td>
</tr>
<tr>
<td>Yangchen et al</td>
<td>2016</td>
<td>RCT</td>
<td>14</td>
<td>14</td>
<td>4</td>
<td>Unilateral Buccal Carcinoma</td>
<td>Conventional radiotherapy post-surgery</td>
<td>Cerrobend shielding device</td>
<td>Mucositis, Dysphagia, Saliva changes, Dysgeusia, Pain, Trismus, Caries</td>
<td>Baseline, 1 month, 3 months</td>
</tr>
<tr>
<td>Nayar et al</td>
<td>2016</td>
<td>Retrospective Cohort Study</td>
<td>24</td>
<td>31</td>
<td>N/A</td>
<td>Varied</td>
<td>Primary or adjuvant IMRT* or conventional radiotherapy</td>
<td>Custom made acrylic</td>
<td>Dosage; Mouth opening</td>
<td>1-2 months</td>
</tr>
</tbody>
</table>

*IMRT = Intensity Modulated Radiation Therapy. **FOM = Floor of Mouth.
Table 2. Risk of Bias in the 5 included studies.

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection Bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random Sequence Generation</td>
<td>Met inclusive criteria, however insufficient description of randomization.</td>
<td>Randomization software used, insufficient information.</td>
<td>Participants were randomly assigned using a computer-generated scheme by one researcher.</td>
<td>Retrospective allocation to groups according to hospital protocol.</td>
<td>Allocation done retrospectively following radiotherapy.</td>
</tr>
<tr>
<td><strong>Performance Bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Due to nature of study, could not blind participants and staff.</td>
<td>Not possible due to nature of study.</td>
<td>Participants blinded prior to commencement. Due to nature of study, could not blind researcher.</td>
<td>N/A Retrospective study.</td>
<td>No blinding possible as retrospective study.</td>
</tr>
<tr>
<td><strong>Detection Bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>None described.</td>
<td>Not possible due to nature of study.</td>
<td>Due to nature of study, could not blind outcome researchers.</td>
<td>N/A Retrospective study.</td>
<td>None described.</td>
</tr>
<tr>
<td><strong>Attrition Bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>None reported.</td>
<td>4 lost to follow-up (14%).</td>
<td>3 lost to follow-up in the control group.</td>
<td>No drop outs as retrospective.</td>
<td>No drop outs as retrospective.</td>
</tr>
<tr>
<td><strong>Reporting Bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other sources of Bias</td>
<td>None.</td>
<td>Pilot study of small group size.</td>
<td>None.</td>
<td>Multiple variables, multiple sites, large age range and retrospective study.</td>
<td>Multiple variables.</td>
</tr>
<tr>
<td><strong>Risk of Bias</strong></td>
<td><strong>High</strong></td>
<td><strong>High</strong></td>
<td><strong>Low</strong></td>
<td><strong>High</strong></td>
<td><strong>High</strong></td>
</tr>
</tbody>
</table>

This peer-reviewed, accepted manuscript will undergo final editing and production prior to publication in IJP.

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Table 3. Summary of the results of the 5 included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>Study Type</th>
<th>How were the side effects assessed?</th>
<th>Description of the difference in side effects experienced by the experimental group versus the control group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goel et al</td>
<td>2010</td>
<td>RCT***</td>
<td>RTOG HANC**** adverse events grading tool</td>
<td>Significant difference between control and experimental group for mucositis and xerostomia at all follow up times.</td>
</tr>
<tr>
<td>Verrone et al</td>
<td>2014</td>
<td>retrospective</td>
<td>Mucositis - WHO classification; Dose - mean corresponding dose of structures</td>
<td>Mucositis - no difference seen in the severity of mucositis between the two groups; Dose - lower maxillary dose and lower dose to ipsilateral parotid in experimental group</td>
</tr>
<tr>
<td>Mall et al</td>
<td>2016</td>
<td>RCT***</td>
<td>Unstimulated: saliva to pool for 60 seconds. (Repeated 4 times.) Stimulated saliva flow: same method except lemon juice was applied with a cotton bud for 2 minutes prior to collection. Xerostomia: Quality of Life indicator*****</td>
<td>Mean unstimulated and stimulated saliva flow rates at 3 months and 6 months were significantly higher in the experimental group compared with the control group. Mean quality of life scores were significantly lower in the experimental group compared with the control group.</td>
</tr>
<tr>
<td>Yangchen et al</td>
<td>2016</td>
<td>RCT***</td>
<td>RTOG HANC**** adverse events grading tool</td>
<td>At 1 month: statistically different results for pain on swallowing, saliva changes, mucositis, dysphagia and dry mouth. At 3 months: statistically different results for pain on swallowing, saliva changes, mucositis, dysphagia, dry mouth and caries</td>
</tr>
<tr>
<td>Nayar et al</td>
<td>2016</td>
<td>retrospective</td>
<td>Dose - calculated from radiotherapy plans with 10 representative areas used; Mouth opening - centimetres</td>
<td>Dose: the maxilla received a significantly lower dose in the experimental group compared with the control group (for mandibular tumours). Mouth opening: Significant difference between the two groups after completion of radiotherapy.</td>
</tr>
</tbody>
</table>

***RCT = Randomized controlled trial  
**** RTOG HANC = Radiation Therapy Oncology Group (RTOG) head and neck adverse events  
***** Module from the European Organization for Research and Treatment Quality of Life Head and Neck Module QLQ-H&N35
**Figure 1.** Medline search strategy.

1. Jaw/Radiation Effects
2. Radiation Injuries/Adverse Effects, Complications, Prevention and Control
3. Radiotherapy/Adverse Effects, Complications
4. Trismus
5. Mucositis
6. Xerostomia
7. Osteoradionecrosis
8. Radiation Caries
9. Mouth/Radiation Effects
10. Mouth mucosa/Radiation Effects
11. Radiation Dosage
12. IMRT
13. Volumetric Arc Therapy
14. Proton Therapy
15. “Head and Neck Neoplasms”/Complications, Radiotherapy, Rehabilitation
16. “Head and Neck Malignancy”/Complications, Radiotherapy, Rehabilitation
17. “Head and Neck Cancer”/Complications, Radiotherapy, Rehabilitation
18. Carcinoma, Squamous Cell/Complications, Radiotherapy, Rehabilitation
19. Carcinoma, Squamous Cell/Radiation Effects, Radiotherapy
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 19
21. Radiation Protection/Methods
22. Stents/Radiotherapy
23. Bolus Compensator
24. Dental Stents
25. Intraoral Stents
26. Radiation Carriers
27. Radiation Docking Devices
28. Radiation Protection Splints
29. Radiation Positioning Stents
30. Shielding Stents
31. Tongue Shielding Stents
32. Perioral Cone Positioning Stents
33. Radiation Shielding Stents
34. Tongue Depressing Stents
35. Tissue Recontouring Stents
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 20 AND 36
Figure 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.