Evidence-Based Case Report

Salivary Gland Dysfunction and Dysphagia in Post-Chemoradiotherapy Head and Neck Malignancy Patients

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Abstract
Radiotherapy can potentially cause damage to the salivary gland, muscles, and nerve that is important to oropharyngeal swallow, leading to xerostomia and dysphagia. Reporting a case of radiotherapy-induced xerostomia and dysphagia in HNC patients. A 34 years old man with NPC stage IV B (T4N3M0) came with difficulty swallowing, dryness in the throat and mouth, coughing while eating and drinking, choking, hoarseness, and pain when swallowing. The patient had done 14 times of radiation administration with a total dose of 60 Gy with conformal 3D radiation technique. The amount of saliva measured 0.02 ml/minute. A standing secretion was found in the vallecula, right and left piriformis and postkrioid sinuses in preswallowing assessment. The presence of penetration or aspiration of secretions into the airway were detected. The patient was diagnosed with neurogenic dysphagia and advised to use NGT for diet and consult medical rehabilitation. Literature searching was conducted on March 31, 2021 in the 3 journal database, including PubMed, Cochrane, and EBSCOHost, using particular keywords based on PICO. The inclusion criteria were full text article, observational studies, case-control, cohort, randomized controlled trial, systematic review, written in English, and studies investigating the correlation between HNC patient with radiotherapy and dysphagia or xerostomia. There were 3 systematic reviews, 1 cohort, and 2 cross-sectional studies investigating the correlation between chemoradiotherapy in head and neck cancer and xerostomia/dysphagia. Chemoradiotherapy correlated with dysphagia and xerostomia in head and neck cancer. Xerostomia and disfagia were prevalent in HNC patients after radiotherapy. Besides, there was association between the dose of radiotherapy and incidence or severity of xerostomia and dysphagia. Keywords: xerostomia, dry mouth, dysphagia, radiotherapy, chemoradiotherapy, head and neck malignancy.

Disfusksi Kelenjar Saliva dan Disfagia pada Pasien Keganasan Kepala dan Leher Pasca Kemoradioterapi

Abstrak
Introduction

Head and neck cancer (HNC), accounting for 2.8% of all malignancies, is the sixth most common cancer. Treatment for HNC depends on primary site, staging, tumor resectability, and patient variable, including radiotherapy, surgery, chemotherapy, or combination treatment. Chemoradiation is the treatment of choice for most HNC because chemoradiation and surgery showed comparable survival rates. Radiotherapy can cause damage to the salivary gland, muscles, and nerve that is important to oropharyngeal swallow. Due to radiotherapy, dysphagia is a serious condition that may cause impaired quality of life (QOL), aspiration pneumonia, and impaired nutrition.

Xerostomia is a subjective complaint of dry mouth due to reduced saliva after radiotherapy, chemotherapy, long-term medication, rheumatic diseases, and metabolic diseases. Salivary gland damage after radiotherapy, may reduce salivary output, leading to oral dysfunction such as sore throat, changes in taste and voice quality, tooth decay, impaired chewing function, and difficulty of swallowing or acute dysphagia. Late dysphagia after radiotherapy can also be caused by damage of surrounding tissue, nerve, fibrosis or scar tissue formations, that lead to reduce nutritional intake and significant weight loss, affecting the patient’s general health, psychosocial, and QOL.

In HNC patients undergoing radiotherapy, the salivary gland is one of the organs affected by damage-causing dysfunction. More than 80% of patients with HNC experience xerostomia and hyposalivation after radiotherapy. Radiation therapy is usually carried out every weekday with breaks on weekends, with a duration of 3-7 weeks depend on the type and size of the cancer. The usual dose is 50 - 70 Gy once daily for five days a week or about 2 Gy per fraction. Radiation levels of more than 52 Gy can cause dysfunction in the glandular tissue. The sialometry and the calculation of saliva volume with a measuring cup are simple tests to estimate the flow rate of saliva, without or with certain stimuli.

Prevention of xerostomia induced by radiation therapy can be performed by submandibular salivary gland removal before radiation procedures, patient education, and topically or orally medication. The use of intensity-modulated radiation therapy (IMRT) have not been able to fully address xerostomia. Thus to reduce the sensitivity of salivary glands to radiation, we can use radical scavengers (amifostine, tempol), sialogogues (pilocarpine), suppressants of apoptosis (insulin growth factor/IGF 1, keratinocyte growth factor/KGF), and agents enhancing survival and proliferation of progenitor cells and expansion of ductal and acinar cells (pilocarpine, IGF 1, KGF). Pilocarpine and artificial saliva only provide temporary relief of symptoms, whereas amifostine is not commonly used because of its potential tumor-protective effects and toxicity. Currently there are still limitations in the choice of xerostomia therapy and many patients do not received appropriate therapy, thus it is necessary to establish good cooperation between clinicians so the management of post-radiation patients will be better.

The aim of this evidence-based case report (EBCR) is to show a case of induced xerostomia and dysphagia after radiotherapy in HNC. The clinical question, is in the HNC patient with or without chemotherapy and radiotherapy evidence-based case report induce dysphagia or xerostomia?

Case Presentation

A 34 years old man with NPC stage IV B (T4N3M0) came after chemoradiation. The last chemotherapy was done for 8 months and the last radiation was given 12 months ago. A total radiation dose was 60 Gy (2 Gy x 30 fractions) with conformal 3D radiation. The patient had difficulty swallowing after 14 times of radiation, dryness in the throat and mouth, coughing while eating and drinking, choking, feels hoarseness and pain when swallowing.

The patient was then put in a feeding tube after the 20th radiation. On examination of the oral cavity and swallowing function by Flexible Endoscopy Evaluation of Swallowing (FEES), the patient was cooperative and the general condition was moderately ill. The amount of saliva 0.02 ml/minute. Oral hygiene was poor and 1 cm trismus, no drooling was found and tongue movement was weak. In the pre-swallowing assessment, a standing secretion was found in the vallecula, right and left piriforms and postcricoid sinuses. The presence of penetration or aspiration of secretion into the airway were detected. Cough reflex when aspiration was absent. The epiglottis and arytenoid, as well as the vocal cords and ventricles was edematous. The measured volume of saliva in 5
minutes was 0.1 ml (0.02 ml/minute). The patient discontinued the FEES feeding because of the risk of aspiration.

The patient was diagnosed with neurogenic dysphagia in the oropharyngeal phase with increasing risk of penetration and aspiration without adequate cough reflex (silent aspiration) accompanied by severe xerostomia. Patients were advised to use nasogastric tube (NGT) for diet and consult medical rehabilitation.

Formulation of the Research
The clinical question: (P) patients with advanced stage HNC with or without chemotherapy, (I) radiotherapy, (C) without radiotherapy, (O) the prevalence of dysphagia or xerostomia, dose radiotherapy related xerostomia or dysphagia.

Evidence Research Strategy
A systematic literature searching was done on March 31, 2021 using particular keywords such as “xerostomia”, “dysphagia”, “radiotherapy”, and “head and neck malignancy” with medical subheading terms in Table 1 in the 3 journal databases, including PubMed, Cochrane, and EBSCOhost. The results were selected using inclusion criteria, exclusion criteria, and double article. The inclusion criteria were full text article, type of study (systematic review, randomized control trial, observational studies (cohort/case control), analytic cross-sectional), written in English, and studies that investigate the correlation between HNC patient with any dose of radiotherapy and dysphagia or xerostomia. This EBCR also evaluates radiotherapy as a risk factor for dysphagia or xerostomia. The exclusion criteria were articles review and studies in animal. All selected articles were appraised for the validity, importance, and applicability by two authors independently based on critical appraisal tool for etiology/harm studies, QFAITH for systematic review studies from Center for Evidence-Based Medicine (EBM), Oxford University, and JBI critical appraisal tools for prevalence studies.

Results
After performing literature searching in the 3 journal databases, using search terms in Table 1, there were 40 articles that related to our topic. After screening the full text, we found 6 articles that fulfill the inclusion and exclusion criteria, comprised of 3 systematic reviews, 1 cohort study, and 2 cross-sectional studies (Figure 1). One of the studies evaluates radiotherapy as a risk factor for dysphagia.
### Table 1. Search Terms Used in 3 Databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Terms</th>
<th>Articles Found</th>
<th>Articles Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane</td>
<td>(&quot;xerostomia&quot;:ti,ab,kw OR (&quot;dry mouth&quot;:ti,ab,kw OR (&quot;dysphagia&quot;:ti,ab,kw) AND (&quot;head and neck cancer&quot;:ti,ab,kw OR (&quot;nasopharyngeal carcinoma&quot;:ti,ab,kw OR (&quot;hypopharyngeal cancer&quot;:ti,ab,kw OR (&quot;laryngeal cancer&quot;:ti,ab,kw OR (&quot;oropharyngeal cancer&quot;:ti,ab,kw) AND (&quot;radiation&quot;:ti,ab,kw OR (&quot;radiotherapy&quot;:ti,ab,kw</td>
<td>573</td>
<td>0</td>
</tr>
<tr>
<td>EBSCO-host</td>
<td>(xerostomia or salivary gland hypofunction or dry mouth or dysphagia) AND (head and neck cancer or oral cancer or oropharyngeal cancer or hnc or nasopharyngeal cancer or hypopharyngeal cancer or laryngeal cancer) AND (radiotherapy or radiation therapy)</td>
<td>520</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 1. PRISMA Flow Chart

Xerostomia OR Dysphagia
AND
Head and Neck Malignancy
AND
Chemoradiotherapy

PubMed 746
Cochrane 573
EBSCOhost 520

Filtering double 1839

1608

Inclusion Criteria:
- Meta-analysis
- Systematic reviews
- Cohort
- Case control
- English Literature
Full-text screening

Title & Abstract Screening
40
6
6

Exclusion Criteria:
- Editorials, commentaries
- Reviews or opinion articles
- Studies in animal
- Articles already included in meta-analysis
Table 2. The Summary of Studies Included

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Study Design</th>
<th>Number of Patients (n)</th>
<th>Intervention and Control</th>
<th>Primary Endpoint</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porto de Toledo et al. (2019)</td>
<td>Systematic review and meta-analysis</td>
<td>714 patients from 17 studies</td>
<td>46 - 79 Gy dose of radiotherapy</td>
<td>Prevalence of dysphagia</td>
<td>3.6, and more than 6 months</td>
</tr>
<tr>
<td>Jensen et al. (2010)</td>
<td>Systematic review</td>
<td>184 studies</td>
<td>39-60 Gy of Radiotherapy</td>
<td>Prevalence of xerostomia</td>
<td>1-3 months, 3-6 months, 6-12 months, 1-2 years, &gt;2 years</td>
</tr>
<tr>
<td>Jiang et al. (2015)</td>
<td>Systematic review of observational studies</td>
<td>3999 patients from 20 studies</td>
<td>Radiotherapy</td>
<td>CRT as a risk factor for late dysphagia</td>
<td>&gt; 3 months</td>
</tr>
<tr>
<td>Tribius et al. (2012)</td>
<td>Cohort study</td>
<td>126 patients</td>
<td>&lt; 26 Gy of IMRT in 1 vs 2 parotid</td>
<td>Xerostomia outcome difference in radiotherapy of 1 or both parotid</td>
<td>Monthly for the first 3 months, and every 3 months thereafter</td>
</tr>
<tr>
<td>Chang et al. (2003)</td>
<td>Cross-sectional study</td>
<td>184 patients</td>
<td>70 – 80 Gy dose of Radiotherapy</td>
<td>Prevalence of xerostomia and dysphagia</td>
<td>&lt; 12 months (acute), &gt; 12 months (chronic)</td>
</tr>
<tr>
<td>Szczesniak et al. (2014)</td>
<td>Cross-sectional study</td>
<td>116 patients</td>
<td>50 – 70 Gy of 3DCRT</td>
<td>Long term prevalence of dysphagia</td>
<td>0.5-8 years</td>
</tr>
</tbody>
</table>

Summary of the six studies included in this EBCR was shown in Table 2. All of the studies were considered valid after critically appraised using appraisal tool for systematic review in Table 3, etiology study in Table 4, and prevalence studies in Table 5.

Table 3. The Result of Critical Appraisal of Systematic Review Studies Included

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Validity</th>
<th>Importance</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear PICO</td>
<td>Relevant evidence</td>
<td>Appropriate inclusion criteria</td>
<td>High-quality studies</td>
</tr>
<tr>
<td>Chemoradiotherapy as a strong evidence risk factor (3 or more than high quality studies with consistent finding)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>93% prevalence of xerostomia during irradiation and 73.6-85.3% prevalence 1-48 months after radiotherapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>41.3% of frequency of penetration of food</td>
<td>95% CI 19.7–64.9; p &lt; 0.01; n = 79; I2 = 78%</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

+ done; - not done
Jiang et al.\textsuperscript{16} reported a systematic review without a meta-analysis due to the heterogeneity and insufficient original raw data. However, this systematic review provides levels of evidence-based on the quality of the study. This review showed that chemo-radiotherapy was a strong-evidence risk factor for dysphagia. A strong level of evidence in this systematic review was defined as generally consistent findings in a minimum of 3 high-quality studies. A high-quality study was a multivariate analysis with a quality score 8 or more, evaluated using a criteria list adapted from Duckitt and Harrington’s review.\textsuperscript{16,17}

### Table 4. The Result of Critical Appraisal of Etiology Study Included

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Similar patients</th>
<th>Same outcome measurement</th>
<th>Sufficient follow-up</th>
<th>Satisfy diagnostic test for causation</th>
<th>Exposure preceded outcome</th>
<th>Dose-response gradient</th>
<th>Positive dechallenge-rechallenge</th>
<th>Consistent association</th>
<th>Biological sense</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribius et al.\textsuperscript{15} (2012)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>RR 1.332 (xerostomia); RR 2.930 (dysphagia)</td>
<td></td>
</tr>
</tbody>
</table>

+ done; - not done

### Table 5. The Result of Critical Appraisal of Prevalence Studies Included

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Appropriate sample frame</th>
<th>Appropriate recruit way</th>
<th>Adequate sample size</th>
<th>Adequate setting</th>
<th>Sufficient data analysis</th>
<th>Valid methods</th>
<th>Reliable condition measured</th>
<th>Appropriate statistical analysis</th>
<th>Adequate response rate</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al.\textsuperscript{14} (2003)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>83.2% \textit{p}&lt;0.05 (acute xerostomia); 100% \textit{p}&lt;0.05 (chronic xerostomia); 15.9% \textit{p}&lt;0.05 (acute dysphagia); 100% \textit{p}&lt;0.05 (chronic dysphagia)</td>
<td>+</td>
</tr>
<tr>
<td>Szczeniak et al.\textsuperscript{2} (2014)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>59% (prevalence of late dysphagia); 72% (response rate)</td>
<td>+</td>
</tr>
</tbody>
</table>

+ done; - not done
A systematic review by Jensen et al\textsuperscript{13} showed 93% prevalence of xerostomia during irradiation in HNC patients, 73.6-85.3% prevalence of xerostomia 1-48 months after radiotherapy, and 6.0% before radiotherapy.\textsuperscript{13} This review was unable to perform a meta-analysis due to the difference in interpretation of outcomes and effects of the studies.\textsuperscript{13}

Porto de Toledo et al\textsuperscript{1} reported a correlation between the occurrence of dysphagia and radiotherapy in HNC patients. The deglutition disorder parameter increased in post-chemoradiotherapy patients compared to prechemo-radiotherapy. Parameter of deglutition disorder was penetration of food, saliva, or liquids above the vocal fold, pharyngeal residue, and elevation of the larynx. The frequency of penetration of food was 41.3% in HNC patients less than 6 months after radiotherapy.\textsuperscript{1}

Tribius et al\textsuperscript{15} investigated (cohort) the effect of sparing radiotherapy on both parotids compared to one parotid gland on xerostomia and dysphagia (Table 4). This study concluded that xerostomia (RR 1.332) and dysphagia (RR 2.930) were significantly higher in patients who received less than 26 Gy to either right or left parotid compared to patients who received a dose of less than 26 Gy to both parotids.\textsuperscript{15}

A cross-sectional study by Chang et al\textsuperscript{14} investigated xerostomia and swallowing dysfunction using videofluoroscopic swallowing study (VFSS) in nasopharyngeal carcinoma patients after radiotherapy. The prevalence of acute xerostomia and acute dysphagia after radiotherapy in HNC patients were 83.2% and 15.9%, while chronic xerostomia and chronic dysphagia were 100% and 100%. A cross-sectional study by Szcesniak et al\textsuperscript{2} investigated the long-term prevalence of dysphagia after radiotherapy using the Sydney Swallow Questionnaire with the mean follow-up was 3 years after radiotherapy. This study showed that the prevalence of dysphagia was 59%.

**Discussion**

The prevalence of xerostomia in advanced-stage HNC patients treated with radiotherapy was 73.6% - 100% and the prevalence of dysphagia was 15.9% - 100%. The wide range difference of prevalence was caused by the difference in time to assess xerostomia and dysphagia. The difference in prevalence was also caused by the difference of tools in assessing xerostomia and dysphagia. Jiang et al\textsuperscript{16} reported that the presence of hypopharyngeal carcinoma was the strong-evidence risk factor for dysphagia, however this EBCR found only one study that correlates the dose of radiotherapy and dysphagia or xerostomia. Tribius et al\textsuperscript{15} reported that reducing the dose of radiotherapy in both parotids compared to one parotid reduces the incidence of xerostomia and dysphagia. More studies were needed since only one study evaluated this correlation and other studies were case series, so we excluded those studies.

This EBCR can compile 6 studies that evaluate the relationship between radiotherapy and dysphagia or xerostomia in HNC patients. Those studies consist of 3 systematic reviews, 2 cohorts, and 1 cross-sectional study. All of the studies were valid after critically appraised and showed similar results, namely the prevalence of xerostomia or dysphagia increase after radiotherapy. Therefore, the systematic review and cohort studies obtained provide strength to answer the questions in this EBCR. However, due to the difference in time to follow up and tools to diagnose xerostomia and dysphagia, it is necessary to determine the relationship between radiotherapy and dysphagia or xerostomia. Moreover, this EBCR searched for literature only in 3 journal databases, thus there might be a lack of study that evaluates the correlation between radiotherapy and dysphagia or xerostomia.

The saliva production is stimulated by cholinergic and adrenergic nerve fibers connected indirectly through the blood vessels that supply these glands. Saliva-producing acinar cells are predominantly postmitotic, so it is predicted that they are not very sensitive to radiation. However, radiation to the salivary glands causes a severe reduction in salivary secretion in phases 1 and 2 (0-10 days and 10-60 days post radiotherapy), indicating the salivary glands are sensitive to radiation. The cause of radiation-induced hyposalivation is still debated, whether due to apoptosis or acinar dysfunction induced membrane damage.\textsuperscript{12}

Stem cells and progenitor cells can self-renew and differentiate and replace cells that have been damaged. Therefore, the number of undamaged and remaining progenitor cells and stem cells will determine the regeneration capacity of the gland after radiation. Recovery and compensation responses have been reported in the irradiated region. This suggests the potential for stem cell/progenitor compensatory responses to regenerate salivary glandular tissue.\textsuperscript{12} The salivary glands
are superficial compared to most head and neck tumors, so ionizing radiation must pass through the salivary glands to treat tumors effectively. Tissues with fast turnover rates are more susceptible to radiation. The salivary glands have a slow turnover, but the production and quality of saliva secreted changes after radiation, thus indicating that the salivary glands are not radioresistant.

In addition to changes in the amount of saliva, there are changes in the composition of saliva, including a decrease in pH, a reduction in bicarbonate levels in saliva, an increase in the concentration of sodium, chloride, calcium and magnesium, as well as an increase in immunoproteins, lysozyme enzymes, and lactoferrin. Changes in the saliva pH to acid cause increase certain microorganisms, such as *Streptococcus mutans*, *Lactobacillus*, and *Candida*. In addition, the consistency of the saliva also turns thicker.

Dysphagia results from poor synchronization between pharyngeal contractions, opening the upper esophageal sphincter, and closing the larynx. Radiotherapy decrease the sensitivity of structures responsible for swallowing, leading to poor cough reflexes and aspiration. The risk factor for late dysphagia in HNC was the use of chemoradiotherapy and hypo-pharyngeal carcinoma as a strong-evidence risk factor and advanced tumor stage, the site of the base tongue, nasopharyngeal carcinoma, the presence of baseline dysphagia, mean radiotherapy dose as a middle-evidence risk factor.

The patient in this case report was in an advanced stage with large tumor sizes (T4), so the radiation dose given was more than 70 Gy. Patients with HNC usually receive total radiation of 50-70 Gy, which is the normal dose to kill malignant cells, which sometimes causes chronic xerostomia. The amount of radiation required to cause severe dysfunction in glandular tissue is more than 52 Gy. Radiation below this figure generally causes temporary and reversible damage. Reduced salivation after radiotherapy occurred in the radiotherapy onset period of up to 3 months after radiotherapy was completed. In the first 10 days of radiotherapy there was a massive decrease in saliva production at its worst, especially in the first week, which can be reduced by 50-60%. During this period, the flow rate of saliva is reduced compared to its original condition. Patients complained of dysphagia, lack of saliva production and thicker saliva. Serous acinar cells are more susceptible to the toxic effects of radiation; causes changes in composition and decreases in production and quality of salivary flow will be more dominant in post-radiation patients.

The diagnosis of xerostomia is based on 4 things: history, physical examination, and simple salivary flow rate measurement. The FEES test is performed to assess the side effects of xerostomia. From the physical examination, it was found that the oral cavity was dry, the production of thick saliva, the presence of dental caries. Measurement of saliva flow rate without stimulation showed very low saliva secretion, less than 0.02 ml/minutes. The swallowing reflex in was found to be slow. The presence of penetration and aspiration of food, xerostomia, weakness of the pharyngeal constrictor muscle with longer oral transit time and pharyngeal transit time on FEES are common findings in post-radiation patients. In relation to xerostomia’s presence, the patient needs therapy to overcome it and it turns out that therapy has not been done for xerostomias in this patient. Education to reduce xerostomia complaints with lifestyle modifications has been carried out in this patient.

**Conclusion**

There was an increased risk of xerostomia and dysphagia in advanced HNC patients receiving radiotherapy with a high prevalence rate. Radiotherapy can lead to xerostomia and dysphagia by affecting the salivary gland, surrounding tissue, and nerve damage. Xerostomia causing swallowing problems, affect the sense of taste and speech, which affect the QOL. Thus, it is important to assess the QOL and degree of xerostomia before, during, and after radiation. Comprehensive management is needed in the early detection of xerostomia and dysphagia disorders to increase the QOL and prevent further morbidity. Simple tests to diagnose xerostomia and dysphagia are the saliva flow rate and FEES.

**References**


