Stem cell and gene therapy interventions for the treatment of radiation-induced xerostomia: A systematic review

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Abstract

Background: Saliva is critical to our oral health and well-being. Hyposalivation, also known as xerostomia, is a common complication of radiation therapy for head and neck cancers. However, present pharmacological strategies only alleviate its symptoms and do not completely resolve the disabiling oral dryness. The purpose of this study was to conduct a systematic review of emerging strategies for treating radiation-induced xerostomia with a focus on gene and stem cell therapies since these held great promise in the direct regeneration of the hypofunctional gland.

Methods: Electronic searches were conducted in the PubMed, Ovid MEDLINE, AMED, and Europe PMC databases. The studies that met the criteria for inclusion were systematically assessed. Three reviewers independently evaluated each of the publications included in the review to ensure eligibility and to assess the risk of bias.
Results: A total of five trials were found to meet the previously stated selection and quality requirements, with four employing adenoviral-mediated transfer of the aquaporin-1 cDNA (AdhAQP1), one involving adipose tissue-derived mesenchymal stem cells (ASC). Both presented therapies were without significant adverse effects. Half of the subjects treated with AdhAQP1 improved their saliva flow by at least 50% after 42 days, while the other half remained stable or deteriorated. All participants treated with ASC (n=15) had a 50% increase in the unstimulated whole salivary flow rate at four months when compared to baseline.

Conclusions: The findings from this systematic review indicate that ASC and gene therapy have no serious side effects. The effectiveness of AdhAQP1 in the treatment of radiation-induced xerostomia is still debatable due to low salivary response rate (50%), while the ASC approach had shown more promising outcomes (response rate of 100%).

1 Introduction

Salivary glands (SG) are exocrine glands responsible for saliva production. Parotid, submandibular, and sublingual glands are the three main SG found in humans. They secrete more than 90% of total saliva (1). The majority of saliva consists of water and the rest are various electrolytes and proteins, such as enzymes, immunoglobulins, and other antimicrobial components. Saliva plays a crucial role in maintaining an appropriate dental hygiene and oral functions (2). Saliva serves several critical roles, including the following 1) Taste: substances dissolve in saliva as a result of its hypotonicity property, allowing taste buds to sense flavors; 2) Protection and lubrication: mucins in saliva coat the oral mucosa, lubricating it and facilitating mastication, speaking, and
deglutition function, as well as preventing adhesion of microorganism; 3) Cleansing: saliva has the potential to eliminate non-adherent bacteria and food debris; 4) Buffer capacity: saliva act as a buffer, ensuring that the oral cavity maintains a neutral pH level; 5) Tooth enamel integrity: the concentrations of calcium, phosphate, and fluoride in saliva promote tooth enamel remineralization; 6) Digestion: α-amylase, a salivary enzyme, is involved in the initial stages of starch digestion; 7) Antibacterial activity: immunoglobulin (IgA) in saliva neutralizes viruses, bacteria, and enzyme toxins. Additionally, it has been shown to limit bacteria’s adhesion to oral tissue (2,3). When the SG are injured, the secretory epithelia is reduced and thus saliva production decreases resulting in dry mouth or xerostomia reported symptoms.

Xerostomia is a subjective feeling of dryness in the mouth. The symptoms of xerostomia include dryness of oral mucosa, thirst, thick saliva, bad breath, hoarseness, and irritated and scratchy tongue (4). Decreased saliva secretion leads to decreased masticatory function, an increased risk of cavities, difficulties in swallowing, and susceptibility to oral infection (5). There are many causes of xerostomia such as medication side effects, radiotherapy, dehydration, and diseases. Xerostomia is one of the most prevalent side effects of radiation treatment for head and neck cancer (HNC). In 2017, 890,000 new cases of HNC were diagnosed globally, accounting for 5.3 percent of all malignancies, according to the Global Burden of Disease (GBD) research. HNC was responsible for 507 000 fatalities, or 5.3 percent of all cancer deaths (6).

Conventional radiotherapy uses gamma rays to induce double-strand breaks in the DNA sequences of target cells via free radicals intermediate formed by cellular water. The consequence of double strands breaking is cell apoptosis if the cell's self-repair
mechanism is insufficient. Radiation can cause DNA damage and cell death in salivary secretory acinar cells during HNC treatment, leading to SG hypofunction (7). Intensity-modulated radiation treatment (IMRT) is a cutting-edge technique that may be tailored to the shape of the tumor while sparing healthy tissue. However, even though IMRT has been used for HNC subjects, there are still a considerable number of subjects who continue to suffer from irreversible xerostomia. A clinical trial as shown that 41% of subjects were diagnosed with moderate or severe xerostomia when treated with IMRT (8).

At present, there are many therapies for xerostomia but most of them only relieve patients' symptoms by using saliva substitutes, or chewing gum to stimulate saliva flow (9). Sialagogues such as pilocarpine and cevimeline have been approved by the FDA for xerostomia sufferers. Pilocarpine and cevimeline are muscarinic receptor agonists that increase salivary flow rate by stimulating parasympathetic activity in the SG. However, clinical use of pilocarpine is limited due to its short duration of action (3 hours). The majority of individuals who get oral pilocarpine for xerostomia experience side effects (10). Cevimeline is a novel muscarinic agonist medication with a 5-hour duration of action. Cevimeline should be used with caution in patients who have a CYP2D6 deficit, whether suspected or proven. Hyperhidrosis, which is connected to the drug's muscarinic activity, and gastrointestinal issues such as nausea, diarrhea, and cephalalgia have been documented in phase II studies, albeit none of them are life-threatening (11).

Hyposalivation following radiotherapy has been a significant concern in patients suffering from HNC. Currently available treatments, however, mainly reduce symptoms and do not cure the disease. Recently, many pre-clinical studies have been conducted
on stem cell and gene therapy strategies to repair SG damage after radiotherapy but only a few reached a human clinical trial phase perhaps because of poor safety, tolerability and true effectiveness in animal models. Though, what strategy possesses the best safety, tolerability and effectiveness profile for SG repair in the clinic? Comparing the outcomes of randomized clinical trials will lead the field of oral medicine to gain a better clinical understanding of both stem cell and gene therapy approaches. The objective herein is to compare the safety and efficacy of registered and published stem cell and gene therapy clinical trials aimed at SG functional rescue after radiotherapy damage.

2 Methods

2.1 Study design

The 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used to perform this systematic review. The purpose of this study was to assess the safety and efficacy of various stem cell and gene therapy approaches used in clinical studies for rescuing radiation-induced xerostomia.

2.2 Search strategy

Studies were selected from PubMed, Ovid MEDLINE, AMED, Europe PMC databases by entering the search terms: "Radiotherapy" AND ("Xerostomia" OR "Dry mouth" OR "Hyposalivation") AND ("Stem Cell Transplantation" OR "Cell-based therapy" OR "Gene therapy" OR "Regeneration" OR "Mesenchymal stem cells" OR "Water channel") AND "Clinical trials" AND "Randomized controlled trials".
2.3 Study selection

This systematic review included all reports written in English language and conducted on human subjects with xerostomia with the full text available. All research papers were randomized clinical trials (Phase I–III) that were published before 15/02/2022 and were peer-reviewed. We included studies that examined the safety, tolerability, and efficacy of stem cell and gene therapy. Exclusion criteria include animal research, reviews, and the absence of freely available complete text.

2.4 Data extraction

Data extraction was independently performed by all co-authors from this study. Disagreement was resolved by discussion. The data collected included demographic information (number of patients, mean or median age, sex), study information (author, publish year, follow up time), intervention regime (type, delivery method, number of cells injected), outcome evaluation, and results of the studies.

2.5 Risk of Bias Assessment

Next, three co-authors assessed the risk of bias for each research outcome separately. The Cochrane Risk of Bias (RoB 2) technique was used to analyze the five major bias domains. This technique employs an algorithm to calculate the overall risk of bias associated with each study’s findings. To conduct a thorough risk of bias evaluation for each study finding, three authors found bias from the following sources: (1) randomization method, (2) interventions that deviated from the original design, (3) data loss, (4) outcome
measurement, and (5) outcome selection. Following each field, the signaling questions were completed, as advised by the RoB 2 tool guidelines.

Each domain was classified as having a "low risk of bias," a "moderate risk of bias," or a "high risk of bias." When all five potential sources of bias were deemed "low risk of bias," the outcomes of randomized controlled trials (RCTs) were deemed the low risk of bias for the entire evaluation. If at least one of the five areas raised "some issues" about bias, the RCT outcomes were deemed to raise "some concerns" about the total risk of bias. On the other side, if one of the five components of bias was assessed as "high risk of bias," RCT outcomes were classed as having a high risk of bias for the total evaluation. If there was a disagreement between the three co-authors, the final verdict was reached through discussion.

3 Results

3.1 Literature search results

The first step in the procedure was to conduct a search in electronic databases using precise search phrases, which resulted in the discovery of 52 papers. Following the application of the inclusion criteria, 16 records were examined by title and abstract. These studies were carefully examined after a full-text assessment. There were 5 eligible studies that met the inclusion criteria.
Figure 1. Prisma flow diagram of the systematic review process
Figure 2. Geographical map showing the location of clinical trials targeting radiation-induced xerostomia conducted worldwide. Adapted from clinicaltrials.gov database.

Clinical trials for radiation-induced xerostomia were conducted in a variety of nations, as illustrated above. North America (11 studies) is the continent with the most, followed by Canada (5), Europe (5), China (5), Southeast Asia (3), and Western Asia (2). Only 5 of the trials use stem cells or gene therapy as a therapy. As there are few clinical studies worldwide on radiation-induced xerostomia, clinicians need further guidance via more research to provide better treatment choices in the near future.
3.2 Study characteristics

The features of the five clinical studies included in this review are summarized in Table 1. The studies were done in Denmark and in the United States and were published between 2010 and 2018. All study participants are over the age of 55 on average. There is only one study that has been conducted on stem cell therapies. While there are four studies on gene therapy, but they are all from the same research group. One of them is the initial study, while the others are follow-up studies. The follow-up period for stem cells therapy was 12 months whereas gene therapy was 42 days and 3-4 years.

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Country</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Regimen</th>
<th>Regimen dose</th>
<th>Mean follow up period</th>
<th>Post-radiotherapy period</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Grønhøj 2018</td>
<td>Denmark</td>
<td>30</td>
<td>60.4</td>
<td>ASC</td>
<td>2.8 x 10^6</td>
<td>12 months</td>
<td>2 years</td>
</tr>
<tr>
<td>BJ Baum 2012</td>
<td>USA</td>
<td>11</td>
<td>59.8</td>
<td>Gene therapy</td>
<td>4.8 x 10^7 to 5.8 x 10^9</td>
<td>42 days</td>
<td>&gt;5 years</td>
</tr>
<tr>
<td>Alevizos I 2017</td>
<td>USA</td>
<td>11</td>
<td>59.8</td>
<td>Gene therapy</td>
<td>4.8 x 10^7 to 5.8 x 10^9</td>
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<td>3-4 years</td>
<td>&gt;5 years</td>
</tr>
</tbody>
</table>

3.3 Risk of bias assessment

The risk of bias assessed by co-authors are summarized in Table 2. All studies have low risk of bias in the domain of random sequencing, missing outcome data, selective reporting, and other risks of bias. While 4 out of 5 studies were identified as high
risk of bias in the domain of allocation concealment and blinding of participants, personnel, and outcome assessment.

Table 2. Risk of bias assessment of included studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Missing outcome data</th>
<th>Selective reporting</th>
<th>Other risks of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grønhøj, 2018</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
</tr>
<tr>
<td>Baum, 2012</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
</tr>
<tr>
<td>Alevizos, 2017</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
</tr>
<tr>
<td>Zheng, 2010</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
</tr>
<tr>
<td>Alevizos, 2017</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Light green</td>
<td>Light green</td>
<td>Light green</td>
</tr>
</tbody>
</table>

= Low risk of bias  = High risk of bias

3.4 Adipose tissue-derived mesenchymal stem cell (ASC) study

The salivary flow rate comparison between the two groups reveals that the ASC group had an average unstimulated whole saliva (UWS) of 0.12 ml/min and the placebo group had an average UWS of 0.16 ml/min at baseline. Both groups had comparable net UWS scores. However, when the UWS was compared to baseline, it increased by 33%
after one month and 50% after four months in the ASC group. After one month, the UWS in the placebo group decreased by 5% and increased by 0.5% after four months.

The VAS questionnaire score remained constant in the ASC group except for questions about thirst, which decreased by 22% over four months, and mouth dryness, which decreased by 2% in the solid food area. While no significant difference was seen in the placebo group. Initially, 40% of the ASC group demonstrated normal secretory function, compared to 60% of the placebo group. After four months, the ASC group has 100% of subjects with normal secretory function, compared to 80% in the placebo group. The Apparent Diffusion Coefficient (ADC), T1, and T2 sequences of MRI reveal no change between the two groups.

The tissue staining analysis of Pan-Cytokeratin marker (clones AE1/AE2) showed a notable increment in serous gland tissue in the ASC group compared to the placebo group. Moreover, the number of connective and adipose tissues was significantly decreased in the ASC group. There were no significant differences in the ratio of mucinous to serous tissue, mucinous tissue, glandular tissue, or adipose tissue between the two groups. No adverse events were detected during the primary research period. As a result, this ASC trial indicated an appropriate safety and tolerability profile and a promising outcome in terms of effectiveness towards further clinical application (12).

3.5 Gene therapy studies

3.5.1 Adenoviral-mediated transfer of the aquaporin-1 cDNA (AdhAQP1)

Saliva flow rates in targeted glands were determined prior to and following therapy, with an emphasis on the first 42 days (about 1 month and a half) following treatment.
Following therapy, both the absolute volume and proportionate change in parotid flow rates improved significantly. Further analysis of the data revealed a mixed result, with six participants having a 60–540% increase in parotid saliva flow rates at various points between days 7–42, while the other five subjects' parotid saliva flow rates remained stable or worsened (min -35%, max +10%). Six participants who improved by at least 50% were classed as responders, whereas the remaining participants were classified as non-responders. Sixty-six percent of patients in each of the first three dose groups experienced an increase in parotid saliva flow rate; in the fourth dose cohort, both subjects experienced a decrease in parotid saliva flow rate (13).

The viral-based reactivity of patients to AdhAQP1 treatment throughout the first 42 days revealed that their baseline serum anti-Ad5 NAb titers were not predictive of their response. Additionally, changes in serum NAb titers were small (zero to eightfold) and consistent between responders and non-responders. The current findings imply that minor alterations in systemic cell-mediated immune reactivity (2–3 fold change) do not rule out positive subject responses to gene transfer after Ad5 vector delivery into the parotid glands. While both innate and adaptive immune responses contribute to the host protection against adenovirus, innate immunity against virus is the most prevalent response. Indeed, it is believed that the complex innate immune response plays a critical role in limiting the efficacy of Ad vector-mediated gene transfer, accounting for up to 90% of vector clearance within the first 24 hours following intravenous Ad vector injection to transfer the aquaporin-1 cDNA. Three of the six non-responders in this investigation demonstrated a robust innate immune response with a significant increase in $^{67}$Ga citrate absorption 24 hours after treatment of the targeted parotid gland. While none of the
responders' $^{67}$Ga citrate absorption levels were greater than 11% above baseline at this time point. A 24-hour enhanced $^{67}$Ga scan may be the most straightforward and cost-effective early indicator of a negative response to Ad5-mediated gene delivery in the SG due to innate immune response to the viral particles (14).

On day 7 following AdhAQP1 administration, the Ad5 E1 gene was detected at low levels (82 copies/μl) in parotid saliva. AdhAQP1 was also detected in significant numbers (1.5 x 10^3 copies/μl). The subject under investigation presented with no symptoms, and parotid saliva samples obtained prior to and after day 7 were negative for virus and vector. A comprehensive PCR analysis of DNA extracted from the parotid saliva sample on day 7 confirmed the absence of a genetic recombination event, and no infectious viral particles were discovered (15).

Adenoviral serotype 5 vector delivery of human AQP1 cDNA (AdhAQP1) did not result in any deaths, dose-limiting toxicities, or significant adverse effects. During the first 42 days after the delivery of the AdhAQP1 vector, 65 adverse occurrences occurred as shown in Table 3. The most common categories of adverse events (AE) were gastrointestinal disorders and laboratory investigations (54.5%). The adverse effects were minor (91%) or moderate (9%), and the majority (>75%) were deemed irrelevant or unlikely to be associated to AdhAQP1 therapy. Ten of the remaining adverse effects were thought to be perhaps related to vector therapy, four were seen to be probably related, and one was thought to be definitely associated with the vector transfer treatment.

Two significant discoveries have been made through day 42 of the phase I trial done in 2012. To begin, it is safe to deliver an Adenoviral serotype 5 vector to a single parotid gland. No consistent or systematic alterations were observed in any of the clinical
safety parameters investigated. Additionally, other side effects were noted during this time span, all of which were mild or moderate in severity. The second major finding was that hAQP1 gene transfer enhanced parotid flow rate in six of eleven treated participants, indicating that the original concept could have a relevant application in humans. Notably, five of the six respondents reported an improvement in subjective symptoms (13).

**Table 3.** Summary of adverse events (AE) at each organ/system level in subjects treated with AdhAQP1 intraductal delivery (N = 11).

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Subjects with AE N (%)</th>
<th>Total AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>6 (54.5%)</td>
<td>12</td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td>6 (54.5%)</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>5 (45.5%)</td>
<td>6</td>
</tr>
<tr>
<td>Infection and infestations</td>
<td>5 (45.5%)</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (27.3%)</td>
<td>6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>4 (36.4%)</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3 (27.3%)</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal/connective tissue disorders</td>
<td>4 (36.4%)</td>
<td>4</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>2 (18.2%)</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 (9.1%)</td>
<td>2</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2 (18.2%)</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>1 (9.1%)</td>
<td>2</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2 (18.2%)</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (9.1%)</td>
<td>1</td>
</tr>
</tbody>
</table>

After the initial peak (on days 7-42) in salivary flow rate following gene transfer, each subject's parotid gland flow rate remained considerably greater than baseline.
Additionally, all individuals exhibited considerably enhanced salivary flow rates from the targeted parotid gland at their most recent research visit, which was 1086–1708 days after gene transfer surgery. When compared to the baseline visit (days 7–42), each of these five participants improved their VAS score during the initial increase in parotid salivary flow. Following that, the outcomes were more varied, although all five participants reported some improvement in their mouth's dryness and saliva production at either (or both) of the two- and three-year time intervals. Three participants reported that their mouths were nearly as dry as they were at the start of the experiment, while two said that their saliva levels were at or near the baseline. There were no adverse events of clinical significance, and laboratory results were negative (16).

4 Discussion

Xerostomia is a subjective feeling of dryness in the mouth in which the SG fail to produce enough saliva to keep your mouth moist (17). Additionally, decreased saliva output results in decreased masticatory performance, a higher prevalence of caries, difficulties swallowing, and an increased risk of oral infection (18). Xerostomia is one of the most prevalent side effects of radiation therapy in patients with HNC. However, current medications merely address the symptoms of the condition and do not cure it. As a result, there is a great desire for novel potential therapies capable of regenerating damaged SG. Gene therapy has been widely applied to the regeneration of bone (19), cartilage (20), hair (21), neural tissue (22), and muscle (23), among other tissues. Additionally, stem cell therapy has emerged as a potential treatment option as a result of numerous investigations in bone (24), dental pulp (25), liver (26), heart (27), and skin
(28). However, the number of gene therapy and stem cell therapy trials is still restricted. Only two research groups have been involved in the development of these therapies.

A systematic search technique with explicitly defined search criteria was used to select studies for this systematic review. We only took into account human studies that looked at the safety, tolerability, and effectiveness of various stem cell and gene therapies. This method limited the number of studies included in this systematic review, given the majority of investigations on gene and stem cell therapy for SG regeneration was performed in pre-clinical animal models. Only a few human studies have been performed, and only five have been completed and published, four of which are by the same research group. This could lead to a bias in our results due to a lack of comparable studies.

The findings from this review reveal that stem cell and gene therapies have no significant negative adverse complications and systemic toxicity in humans. The use of ASC therapy had no side effects, and the use of adenoviral-mediated aquaporin-1 cDNA transfer had relatively minor side effects such as dizziness, bradycardia, and hypertension. However, the number of people involved in these two therapies is small, and future clinical studies with a larger sample size are needed to reduce the risk of bias.

The ASC group's UWS flow rate grew by 50% at four months compared to baseline, while the control group such rate only increased by 5%. Hence, it holds promising results for clinical treatment. On the other hand, only half of the subjects who received gene therapy interventions responded to AdhAQP1 transfer, indicating that the efficacy of gene therapy is still debatable.
ASC is administered via local injection into submandibular glands, whereas AdhAQP1 is administered via intraductal cannulation. Intraductal cannulation delivers the therapy directly into the gland ducts and acini by retrograde flow while local injection deliver therapy into salivary gland area which contains many other structures. Thus, intraductal cannulation pathway is more effective and safer than local injection. Additionally, only one parotid gland was treated with AdhAQP1, while both submandibular glands were treated with ASC. This could affect the efficacy comparison between the two treatments as well as the frequency of adverse events.

These studies have short follow-up times, with the ASC having a mean follow-up time of 12 months and the AdhAQP1 having a mean follow-up time of 42 days, with only one research study of AdhAQP1 following the subjects for three years. Both ASC and AdhAQP1 have unknown long-term effects.

5 Conclusion

In conclusion, this systematic review findings indicate that stem cell and gene therapy strategies have no systemic serious side effects while managing radiation-induced xerostomia. The local injection of autologous ASC had no negative effects, while AdhAQP1 transfer via intraductal cannulation had only modest side effects. As for the efficacy, at 4 months, the ASC group’s unstimulated whole salivary flow rate increased by 50%, indicating that it has quite promising clinical benefits. The efficacy of adenoviral-mediated aquaporin-1 cDNA transfer is still controversial because only 50% of subjects receiving treatment responded positively to gene therapy during the 42-day follow-up
time. This study suggests that more clinical trials on stem cell therapy with a large sample size and longer follow up times should be carried out to assess long-term effects.

6 References


