



Managing excessive saliva with salivary gland irradiation in patients with amyotrophic lateral sclerosis



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ABSTRACT

Objective: A significant fraction of patients with amyotrophic lateral sclerosis (ALS) are unable to swallow saliva, which may result in the spillage of saliva outside of the oral cavity. Although anticholinergic agents and botulinum toxin injections are considered the first line of treatment, they have not been effective for all patients. We performed a literature search on therapeutic salivary gland irradiation in patients with ALS.

Methods: We searched the PubMed for English language publications up to December 2014 on therapeutic salivary gland irradiation in patients with ALS. The search was performed using the following key words: amyotrophic lateral sclerosis, excessive salivation, sialorrhea, and radiation therapy.

Results: The majority of ALS patients with excessive salivation respond well to salivary gland irradiation. The whole bilateral submandibular, and whole or partial bilateral parotid glands have been the target tissue for radiation therapy in most of the published studies. Various radiation therapy regimens have been utilized. The response to radiation therapy lasts for several months.

Conclusions: The majority of ALS patients with excessive salivation respond well to salivary gland irradiation. Neurologists should consider this treatment option for select patients with ALS and excessive salivation.

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1. Introduction

The parotid glands are typically targets of avoidance in patients receiving radiation therapy (RT), for head and neck cancers. However, a small but growing number of studies suggest that targeting the major salivary glands directly may have a therapeutic benefit to some patients with as amyotrophic lateral sclerosis (ALS). ALS is a progressive, paralyzing condition that affects primarily lower motor neurons. It has an incidence of approximately 2–3 per 100,000 people [1]. The etiology of ALS remains unknown, but an N-methyl-D-Aspartate receptor antagonist, riluzole, has been shown to slow the progression of the disease [2]. Despite this, treatment remains generally symptomatic, and the disease typically follows a progressive, ultimately, fatal course. Up to half of patients with ALS will experience some problems with excessive salivary secretions, and refractory drooling (sialorrhea) is a major clinical problem faced by approximately 20% of these patients [3]. While the salivary glands, primarily the parotid and submandibular glands, continue to produce nearly 1.5 L of saliva per day, impaired swallowing ability leads to the accumulation and ultimate spillage of saliva outside of the oral cavity, resulting in social embarrassment, skin irritation and infection, and possible aspiration pneumonia.

While radiation therapy (RT) has been proposed as a treatment for sialorrhea, there are several other treatments that are typically tried before attempting RT. One of the first is prescribing anticholinergic agents [1], which can decrease salivary production, but symptom control can often require higher doses over time, leading to undesirable side effects such as urinary retention and constipation. Alternatively, more invasive techniques may be attempted such as botulinum toxin injections directly into the salivary glands [3–5], which is effective, though it has been associated with several severe adverse effects, including worsening dysphagia. Finally, surgical approaches exist, such as salivary duct ligation [6] and transtympanic neurectomy [7]. RT could possibly address some of the disadvantages of medical and surgical therapies in managing excessive saliva in this context. It is non-invasive, and it can be effective for several months after a finite number of treatments. In some cases, a single fraction of radiation treatment was enough to document an improvement in sialorrhea [8, 9]. We performed a literature search on therapeutic salivary gland irradiation in patients with ALS.

2. Methods

The PubMed national library database was searched for English language publications up to December 2014 on therapeutic salivary gland irradiation in patients ALS and excessive salivation. The search was performed using the following keywords: amyotrophic lateral sclerosis, excessive salivation, sialorrhea, and radiation therapy.

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The predetermined criteria for deciding which studies to include were as follows: 1. Specified outcome, 2. Radiotherapy modality described, and 3. Radiation prescription dose specified. A total of 7 reports were identified. Full articles were obtained and were reviewed. The information presented here is extracted from publications. As different investigators often present information differently, pooling data from multiple studies may be inaccurate, and a summary table is included to help the reader better understand the primary data. In addition to PubMed, we also reviewed Database of Abstracts of Reviews of Effects (DARE) and we found no Cochrane Reviews, Protocols for Cochrane Reviews, and other publications based on Cochrane Reviews. Our search of the Embase for Excerpta Medica Database did not reveal any additional published data.

3. Results

Table 1 gives a summary of studies on therapeutic salivary gland irradiation in patients with ALS. It can be seen that the majority of ALS patients with excessive saliva respond well to therapeutic salivary gland irradiation. The whole bilateral submandibular, and whole or partial bilateral parotid glands have been the target tissue for radiation therapy in most of the published studies. Various radiation therapy regimens have been utilized with dose ranges from 7 Gy in single radiation therapy fraction to 20 Gy in 5 radiation therapy fractions. The low number of radiation therapy fractions makes this therapy relatively convenient for patients with ALS. The response to irradiation lasts for several months.

4. Discussion

Though there have been relatively few studies examining the role of RT in the treatment of sialorrhea in ALS patients, there is a near universal subjective improvement in symptoms across these studies,

despite the diverse treatment volumes, doses, and patient populations. In most studies, failed treatment with either anticholinergic agents, or botulinum toxin ultimately led to a referral for treatment with RT. Toxicity of treatment was generally reported to be minimal. At the time of irradiation, commonly reported adverse effects included mild pain [8,10,11,13], erythema [13], and mucositis [11]. Long term side effects, including xerostomia [8,9,11,12] and thickened salivary secretions [9,10], were more commonly reported.

There are several points common to these studies that condition these results. First, as previously discussed, ALS has a poor prognosis; the median survival after symptom onset is three years [1], and even shorter when bulbar symptoms predominate [3]. This renders the probability of radiation-induced neoplasia relatively low, as this typically takes a decade or longer to develop. Second, the final sample sizes were often smaller than the initial sample sizes because of patient attrition, due to death and lack of follow-up. With relatively small sample sizes to begin with, many of these studies may have low power. Third, in some studies, a small number of patients needed to receive a second course of RT, to adequately control sialorrhea. Fourth, some studies looked at changes in quantitative measures of sialorrhea, while the others utilized subjective batteries. Finally, the retrospective nature of the studies could make it more difficult to ascertain the degree of improvement from RT. These are all significant limitations of this review article.

Table 1 shows that various radiation therapy regimens have been employed in the management of sialorrhea in patients with ALS. The irradiation treatment was performed with linear accelerator 4–6 MV photons with opposed lateral fields [8–12]. In some studies, 6–15 MeV electrons were utilized [11,12,14]. Whether electron irradiation is associated with less toxicity than photon irradiation, and vice versa, is not possible to conclude from the published data. 3D-CT based planning and combined approach with mixed electrons and photons could be appropriate for many patients. Plotting the response rate as a function

Table 1
Summary of studies on therapeutic salivary gland irradiation in patients with amyotrophic lateral sclerosis (ALS).

| First author | Institution | Treatment volume | Dose and fractionation | Initial sample | Response rate | Duration of response |
|-----------------------|--|--|---|----------------|---|--|
| Andersen et al. [8] | Umeå University, Sweden | Bilateral parotid gland, and posterior submandibular gland | 7.0–7.5 Gy in 1 fraction | 18 | Patients had a 57% lower salivary secretion rate two weeks after RT compared to before RT. A subjective improvement in drooling was noted in 89% of patients at 4–6 months. Visual analog scale questionnaire was utilized. | More than 6 months for 12/18 patients and 4–6 months for 6/18 patients |
| Assouline et al. [10] | Multi-institutional, France | Bilateral submandibular glands and two thirds of the parotid glands | 20 Gy in 4 fractions, or 10 Gy in 2 fractions | 50 | A complete response was reported in 71% of patients; 26% reported a partial response on the subjective Sialorrhea Scoring Scale (SSS) at 6 months. | At 6 months, 2/3 of patients had complete response |
| Bourry et al. [11] | Universite d'Auvergne, France | Bilateral submandibular and parotid glands for most patients | Varied, average of 19.1 Gy in 5 fractions | 21 | A subjective improvement in sialorrhea was noted in 65% of patients at an average of 7 months follow-up. At doses of 16 Gy or more, 78% of patients reported a subjective improvement. ALS functional rating scale was used. | 7 months for 65% of patients |
| Guy et al. [12] | Universite d'Auvergne, France | Bilateral submandibular and partial parotid glands | 20 Gy in 5 fractions, or 18 Gy in 4 fractions | 16 | A subjective improvement was seen in 80% of patients in 1 month, and 43% of patients reported improvements in 6 months utilizing a Likert and ALS functional rating scales. | 6 months for 43% of patients |
| Harriman et al. [13] | University of British Columbia, Canada | Bilateral submandibular sublingual, and tail of parotid glands | 8 Gy in 1 fraction, or 12.5 Gy in 2 fractions | 9 | An average of 1.0 g/5 min reduction of saliva production in three patients in 8 Gy group, and 0.6 g/5 min in two patients in 12.5 Gy group at 2 months follow-up. A subjective improvement in drooling seen in 67% of patients in 8 Gy group and 100% of patients in 12.5 Gy group at 2 months. Subjective degree of drooling scale was utilized. | Not reported |
| Kasarskis et al. [14] | University of Kentucky, USA | Unilateral parotid gland | 15 Gy in 3 fractions | 10 | All patients reported a subjective improvement in sialorrhea, with improvements for most starting at 2–4 weeks post-treatment, and maximal improvement 6–8 weeks post-treatment. Specific subjective assessment scale was not reported. | Not reported |
| Neppelberg et al. [9] | Haukeland University Hospital, Norway | Bilateral to submandibular glands and the majority of the parotid glands | 7.5 Gy in one fraction | 14 | Patients had an average salivary secretion rate 21% lower at 3 months post-treatment compared to pre-treatment rates. Verbal rating scale was used for subjective assessment. | Not reported |

of biologically effective dose (BED) was not possible to perform. Unfortunately, the response rate to salivary gland irradiation was not uniformly assessed, and various radiation doses were utilized.

It seems that RT provides a response that lasts for about 6 months. A half of the analyzed studies did not specify duration of response and it is difficult to draw a firm conclusion. Whether these patients required other treatment modality following RT is largely unknown. The limited published data did not fully address possible additional treatment modalities following RT. A very limited follow-up for the treated patients is another contributing factor.

Ideally, a comparison of both effectiveness and durability of response to RT to other treatment modalities would be helpful; unfortunately, this is not possible, as the published data for RT did not include such a comparison. In addition, a very limited number of the published studies, small number of treated patients, and various RT regimens preclude such an analysis at this time. The rarity of the disease is another limitation for conducting a prospective study to compare pharmacological interventions with RT in ALS patients.

As patients with ALS have limited life expectancy, the probability to see radiation induced malignancy is relatively low since it takes a decade or longer to develop following RT. Still, some patients with ALS may have extended survival and a risk for radiation induced malignancy needs to be fully addressed at the time of radiation oncologist's consolation, particularly in patients with an indolent course of ALS. Years ago, Brenner and colleagues [15] showed that the estimated risk of developing a radiation-associated second malignancy was 1 in 290 for all prostate cancer patients treated with RT, and this risk was increasing to 1 in 70 for long term survivors. Dörr and Herrmann [16] found that the majority of second cancers are observed in the volume receiving <6 Gy. Sparing normal tissue with 3D planning is important to reduce this second cancer risk.

While the management of sialorrhea in patients with ALS remains a challenge, the growing literature gives good credence to the role of RT. In all of the studies shown in Table 1, RT was given to patients whose excessive saliva and drooling was refractory to medical management with anticholinergic agents and/or botulinum toxin. Given the potential for side effects of medical treatments and the relatively well-tolerated nature of low-dose RT, it is reasonable to consider RT soon after sialorrhea becomes problematic in these patients. Dental evaluation prior to RT is encouraged, as some patients may experience severe mouth dryness following RT. With increasing prospective studies incorporating larger sample sizes such as a prospective study by Assouline and colleagues from France [10], greater credence can be gained for this effective application of RT. A dose of 20 Gy in 4 fractions on days 1, 3, 8 and 10, targeting bilateral whole submandibular and 2/3 parotid glands seems to be a reasonable approach for RT [10].

In conclusion, the majority of ALS patients with excessive saliva respond well to therapeutic salivary gland irradiation. The response to irradiation lasts for several months. Neurologists should consider this treatment option for select patients with ALS and excessive salivation.

Disclosure of interests

A. Slade: none; S. Stanic: none.

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