Using Intensity Modulated Radiation Therapy for the Treatment of Sialorrhea in Amyotrophic Lateral Sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of motor neurons affecting >12,000 patients in the United States, with bulbar-onset ALS presenting with difficulty speaking and/or swallowing. Sialorrhea (excessive salivation) affects approximately 80% of patients with ALS who exhibit an inability to seal their lips and suffer from a decreased coordination of the palato-lingual and/or oro-facial muscles. These symptoms lead to constant drooling, contributing to the serious risk of aspiration pneumonia and limiting the use of invasive ventilation. Thus, sialorrhea significantly affects the quality of life of patients with ALS.

In patients suffering from sialorrhea, the initial course of treatment has been the use of oral anticholinergic medications. Unfortunately, many patients do not tolerate the anticholinergic side effects, including constipation, drowsiness, and urinary dysfunction. Additionally, most patients undergo many lines of anticholinergic medications, and ultimately become refractory or intolerant to the side effects. Botulinum toxin injections in the salivary glands are a second line in treating patients with sialorrhea. However, repeat injections are often needed to sustain its efficacy, and repeat injections often have waning treatment effects.

The salivary glands are particularly sensitive to radiation. Sparing the parotid glands in radiation therapy (RT) for head and neck cancers has been shown to significantly reduce xerostomia (dry mouth), helping patients to preserve salivary function. For sialorrhea, the opposite effect is desired, and external beam RT has been used as a treatment for patients with ALS suffering from sialorrhea. Historically, treatment has been delivered using 3-dimensional radiation plans, which broadly radiate both the major and minor salivary glands. In this case report, we used intensity modulated RT (IMRT) to selectively radiate the bilateral submandibular and parotid glands, which, to our knowledge, has not previously been reported. This conformal approach allows for the minor salivary glands to be spared in an effort to help curb xerostomia. We found that IMRT may offer a rapid improvement in refractory sialorrhea for patients with ALS and additionally is amenable to retreatment.
Case

A 76-year-old woman with a past medical history of non-small cell lung cancer with a left lower lobe resection in 2010 presented with a 2-year history of bulbar-onset ALS and progressive sialorrhea. Her salivation symptoms were significantly affecting her quality of life, including profuse drooling that required continuous lip-blotting and suctioning.

With the guidance of her neurologist, the patient tried multiple oral medications, including anticholinergics atropine and glycopyrrolate, as well as a tricyclic antidepressant amitriptyline. However, she remained refractory to all medications. She also underwent several botulinum toxin injections to the parotid glands without sustained improvement in her drooling. She had a percutaneous endoscopic gastrostomy tube in place for most of her nutrition, but still had some oral intake for pleasure. The patient was referred to radiation oncology by her neurologist for consideration of RT for refractory sialorrhea.

First, we qualitatively and quantitatively measured the patient’s baseline degree of sialorrhea. We used the Sialorrhea Scoring Scale (Table 1),5-8 which was developed for Parkinson’s disease and validated for ALS, as well the Oral Secretion Scale (Table 2),9-12 which was designed specifically for sialorrhea in ALS. These scales are both simple rating tools in which patients report the severity of their sialorrhea symptoms. Additionally, we quantitatively measured the amount of salivation by weighing the amount of saliva absorbed in 5 cotton balls after consistent placement in the mouth for 5 minutes. Dry cotton-ball weight was first recorded and tared, then the cotton balls were placed within the oral cavity for 5 minutes. The cotton balls were taken out and weighed to measure the amount of saliva secreted. The measurements were obtained at the same time of the day, with the patient seated and fasted for at least 1 hour, which is consistent with several prior studies.13-16

Instead of using a 3-dimensional field for treatment, we elected to treat the bilateral submandibular and parotid glands more conformally using IMRT. We hypothesized that sparing the minor salivary glands may prevent undesirable effects, such as xerostomia and dysgeusia. To our knowledge, IMRT had not previously been used for the treatment of sialorrhea for ALS, perhaps because ALS is not a billable diagnosis for IMRT. IMRT also would allow for a better retreatment option if the patient’s sialorrhea were to recur.

Thus, we proceeded with treating the bilateral submandibular and parotid glands with 20 Gy in 4 fractions with daily cone beam computed tomography for image guidance. The fractionation scheme was similar to that of prior treatments delivering 2 fractions per week. Given a long commute (140 miles distance), we offered to treat on consecutive days, waiting 1 week, and then delivering 2 more fractions on consecutive days, minimizing the commute time.3,17 Figure 1 shows the dose-distribution maps for the parotid and submandibular glands.

Figure 2 depicts how both objective and subjective sialorrhea measures improved over time. Even after the first 2 fractions were delivered, the salivary weight reduced from 3.010 g to 0.798 g 7 days later, which was further reduced to 0.541 g at 49 days after the start of treatment. Subjectively, the Sialorrhea Scoring Scale changed from profuse drooling (9) to moderate drooling (4) to never drooling (1) to mild but frequent drooling (3) over the course of >3 months. The patient’s Oral Secretion Scale also went from severe constant drooling (0) to moderate (2) to minimal (3) and then to moderate (2). She tolerated radiation overall very well without experiencing adverse effects, such as mucositis, xerostomia, dermatitis, or more fractions on consecutive days, minimizing the commute time.3,17 Figure 1 shows the dose-distribution maps for the parotid and submandibular glands.

Table 2 Oral Secretion Scale, scored 0 (worst) to 4 (best)

| Score | Description |
|-------|-------------|
| 0: Very severe | Constant drooling requiring constant lip-blotting, regular suctioning |
| 1: Severe | Difficult conscious secretion swallowing, frequent drooling in any position, lip-blotting 12-30 times per hour, intermittent suctioning |
| 2: Moderate | Conscious saliva swallow required, drooling upright leaning forward, lip-blotting 4-6 per hour |
| 3: Minimal | Automatic saliva swallow decreased, infrequent drooling |
| 4: Normal | Normal automatic saliva swallow, no drooling |
worsening dysgeusia. Figure 3 plots the dose–volume histogram for several organs illustrating the relative sparing of the dose with IMRT. Of particular note is that the oral cavity containing the minor salivary glands is significantly spared. The patient did experience mild fatigue on the days of treatment.

After 4.5 months, the patient continued to have a low amount of salivary production (0.485 g). However, her subjective scores began to slightly worsen, noting that the saliva was thickened and required suctioning. She was started on liquid guaifenesin to decrease the thickness of the mucus. By 8 months after treatment, the saliva had thickened further, often clogging the suction tubing. She was considering a tracheostomy, but we offered the option to reirradiate the major salivary glands to further decrease salivary output.

We performed a second course of IMRT with 10 Gy in 2 fractions delivered twice in the same day separated by 6 hours. Two weeks later, the secretions were significantly less thick. Tracheostomy was no longer considered at the time, and the patient was able to sleep through the night. The frequency of suctioning decreased from 6 to 8 times per day to 2 to 3 times per day. Notably, as a result of this improvement in her symptoms, the patient was able to go camping. Symptom control was improved for another 6 months before sialorrhea started to return. She was restarted on glycopyrrolate 3 times per day, providing adequate control, and she did not seek further treatment for her sialorrhea.

**Discussion**

This patient with ALS and severe sialorrhea responded well to IMRT to the bilateral parotid and submandibular glands. To our knowledge, this is the first approach of invoking IMRT to selectively radiate the major salivary glands while sparing the minor salivary glands. Compared with 3-dimensional conformal RT, IMRT spares the minor salivary glands, and allows for finer control of radiation delivery to individual major salivary glands. Further optimization of radiation dosing and fractionation may permit optimal and personalized control of sialorrhea. New schemes could control duration and severity of symptoms tailored to individual patients, their particular symptoms, and overall life expectancies. Radiation offers another treatment option for patients with ALS, especially to those who become refractory to anticholinergic medications and botulinum toxin injections.

Previous studies have also examined the use of electron beam therapy for the treatment of sialorrhea with favorable outcomes. Electrons also offer a relative sparing of normal tissue compared with 3-dimensional radiation. Electrons can be used also to spare the dose to portions of a major salivary gland. IMRT holds this potential as well, and may offer better targeting with daily cone beam computed tomography. Furthermore, IMRT could be combined with daily adaptation to allow for even more targeted treatment based on the size of the major salivary glands on a given treatment day.

Typically, thickening of saliva is a major side effect of radiation to treat sialorrhea. However, IMRT allows for the retreatment and fine-tuning of the dose to optimize treatment effect. Herein, a single retreatment controlled the patient’s sialorrhea, improved her quality of life, and avoided a tracheostomy. The neurologists at our institution have suggested that perhaps IMRT could be considered earlier in the course of sialorrhea treatment, because some patients cannot tolerate adverse effects of anticholinergics and want a fast, durable option for quality-of-life improvement. Furthermore, IMRT in the reirradiation setting is more likely to obtain insurance authorization, which can open further investigations and optimizations.
Conclusions

IMRT to the bilateral submandibular and parotid glands offers a tailored approach to control sialorrhea in patients with ALS and potentially other neuromuscular disorders. We showcase how 20 Gy in 4 fractions initially can improve subjective and objective measures of salivation. Furthermore, retreatment with 10 Gy in 2 fractions two times per day can offer durable control in reducing salivation that lasts for several more months and combat
the effects of thickened secretions. Overall, IMRT can be considered more for patients with ALS for sialorrhea, and might be offered earlier in the course of treatment.

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**Figure 3** Dose–volume histograms for several structures, showing sparing of dose to sensitive organs at risk with intensity modulated radiation therapy. Clinical and planning tumor volumes include bilateral parotid and bilateral submandibular glands.