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

Running Title: IMRT for Sialorrhea in Neurological Disorders

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Data Sharing Statement:
All data generated and analyzed during this study are included in this published article (and its supplementary information files).
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Abstract

Purpose: We highlight a case of a 76-year-old lady with bulbar onset Amyotrophic Lateral Sclerosis (ALS) with severe refractory sialorrhea. She was refractory to both multiple lines of anticholinergic medications and botulinum toxin injections.

Methods and Materials: We used Intensity Modulated Radiotherapy (IMRT) with 20 Gy in 4 fractions to selectively radiate the bilateral parotid and submandibular glands.

Results: This resulted in marked improvements both subjectively in standardized scores and quantitatively with measured salivary output. Eight months later, radiation of the salivary glands caused a thickened salivary output, similar to observations in head and neck cancer patients. By using another course of IMRT with 10 Gy in 2 fractions separated by 6 hours, we were able to re-irradiate the bilateral parotid and submandibular glands, decreasing salivary output further. The patient was able to avoid a tracheostomy and largely resolve her sialorrhea.

Conclusions: We highlight here how IMRT for ALS patients suffering from sialorrhea can offer another line of focal therapy, which can be further optimized based on severity and side effects.
Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder of motor neurons impacting over 12,000 patients in the US,\(^1\) with bulbar-onset ALS presenting with difficulty speaking and/or swallowing.\(^2,3\) Sialorrhea (excessive salivation) affects approximately 80% of ALS patients in which they exhibit an inability to seal their lips and suffer from a decreased coordination of the palato-lingual and/or oro-facial muscles. This leads to constant drooling contributing to the serious risk of aspiration pneumonia and limiting the use of invasive ventilation, and thus sialorrhea significantly impacts quality of life for ALS patients.

In patients suffering from sialorrhea, the initial course of treatment has been the use of oral anticholinergic medications.\(^2,3\) Unfortunately, many patients are unable to tolerate the anticholinergic side effects including constipation, drowsiness, and urinary dysfunction. Additionally, most patients will undergo many lines of anticholinergic medications and ultimately become refractory to them or intolerant to the side effects. Botulinum toxin injections in the salivary glands have posed a second line in treating sialorrhea patients. However, repeat injections are often needed in order to sustain its efficacy, and repeat injections often have waning treatment effects.\(^2\)

The salivary glands are particularly sensitive to radiation. Sparing the parotid glands in radiation therapy for head and neck cancers has been shown to significantly reduce xerostomia, helping patients to preserve salivary function.\(^4\) For sialorrhea, the opposite effect is desired, and external beam radiotherapy has been used as a treatment for ALS patients suffering from sialorrhea.\(^3\) Historically, treatment was delivered using 3D radiation plans, which broadly radiates both the major and minor salivary glands. In this case report, we used Intensity-modulated radiation therapy (IMRT) to selectively radiate the bilateral submandibular and parotid glands, which to our knowledge has not previously been reported. This conformal approach allows the minor salivary glands to be spared in an effort to help curb xerostomia (dry mouth). We found that IMRT may offer a rapid improvement in refractory sialorrhea for ALS patients and is additionally 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 amyotrophic lateral sclerosis (ALS) and progressive sialorrhea. Her salivation symptoms were significantly affecting her quality of life including profuse drooling requiring continuous lip-blotting and suctioning.

Under the guidance of her neurologist, she had tried multiple oral medications including anticholinergics atropine and glycopyrrolate, as well as a tricyclic antidepressant (TCA) 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 (PEG) tube in place for most of her nutrition, but she still had some PO intake for pleasure. She was referred to radiation oncology by her neurologist for consideration of radiation therapy for refractory sialorrhea.

First, we qualitatively and quantitatively measured her baseline degree of sialorrhea. We used the Sialorrhea Scoring Scale (SSS, Table 1)\(^5\)–\(^8\), which was developed for Parkinson’s Disease and validated for ALS, as well the Oral Secretion Scale (OSS, Table 2)\(^9\)–\(^12\), which was designed specifically for sialorrhea in ALS. These are both simple rating scales in which the patients report the severity of their sialorrhea symptoms. Additionally, we quantitatively measured the amount of salivation by weighing the amount of saliva absorbed in five cotton balls after placing them for 5 minutes consistently in the mouth. 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 day, with the patient seated and fasted for at least 1 hour, consistent with several prior studies.\(^13\)–\(^16\)

Instead of using a 3D field for treatment, we elected to treat the bilateral submandibular glands 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 utilized 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 CT (CBCT) for image guidance. The fractionation scheme was similar with prior treatments delivering two fractions per week. Given a long commute (140 miles distance), we offered to treat on consecutive days, waiting one week, and then delivering two 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 improve over time. Even after the first two fractions were delivered, we saw a reduction in the salivary weight from 3.010 g down to 0.798 g seven days later, which was further reduced 0.541 g at 49 days after
start of treatment. Subjectively, the SSS went from profuse drooling [9] to moderate drooling [4] to never drooling [1] to mild but frequent drooling [3] over the course of more than 3 months. Her OSS 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 worsening dysgeusia. Figure 3 plots the Dose Volume Histogram (DVH) for several organs illustrating the relative sparing of dose with IMRT. Of particular note is that the oral cavity containing the minor salivary glands is significantly spared. She 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 thickness of mucus. By 8 months after treatment, the saliva was further thickened, often clogging the suction tubing. She was considering a tracheostomy, but we offered the option to re-irradiate to 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 6-8 times per day down to 2-3 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 six months before sialorrhea started to return – she was then restarted on glycopyrrolate three times a day, providing her adequate control of sialorrhea She did not seek further treatment for her sialorrhea.

Discussion

This ALS patient with 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 to 3D 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 further 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 ALS patients, 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 as compared to 3D radiation. Electrons can also be used to spare dose to portions of a major salivary gland. IMRT holds this potential, as well, and may offer better targeting with daily CBCT. Further, IMRT could be combined with daily adaptation to allow for even more targeted treatment based on the size of major salivary glands on a given day.
Typically, thickening of saliva is a major side effect of using radiation to treat sialorrhea. However, IMRT allows retreatment and fine-tuning of the dose to optimize treatment effect. Here, a single retreatment controlled the patient's sialorrhea, improved quality of life and avoided tracheostomy. Our neurologists at our institution have suggested that perhaps IMRT could be considered earlier in the course of sialorrhea treatment, as some patients cannot tolerate adverse effects of anti-cholinergics and want a fast, durable option for quality-of-life improvement. Further, IMRT in the re-irradiation setting is more likely to obtain insurance authorization, which can open further investigations and optimizations.

Conclusion

IMRT to the bilateral submandibular and parotid glands offers a tailored approach for controlling sialorrhea in ALS and potentially other neuromuscular disorders. We showcase how 20 Gy in 4 fractions can initially improve subjective and objective measures of salivation. Further, retreatment with 10 Gy in 2 fractions BID 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 ALS patients for sialorrhea and might be offered earlier in the course of treatment.
Figure Captions

Figure 1. IMRT dose distributions for parotid and submandibular glands treated with 20 Gy in 4 fractions delivered in 2 fractions in consecutive days separated by 1 week. A. Coronal view showing both parotid glands and submandibular glands. B. Axial view of bilateral parotid glands. C. Axial view of bilateral submandibular glands.

Figure 2. After IMRT to the major salivary glands, there was a persistent reduction of measured salivary output (5 cotton ball weight, bottom), subjective sialorrhea (SSS, middle), and subjective oral secretion quality of life (OSS, top - y-axis inverted to represent bottom values as best). Red shaded bar indicates when the radiotherapy treatments were delivered.

Figure 3. Dose Volume Histograms for several structures show sparing of dose to sensitive Organs at Risk (OARs) with IMRT. CTV and PTV include the bilateral parotid glands and the bilateral submandibular glands.
References


Table 1. Sialorrhea Scoring Scale, scored 1 (best) to 9 (worst)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>dry, never drools</td>
</tr>
<tr>
<td>2</td>
<td>mild, only the lips are wet, occasionally</td>
</tr>
<tr>
<td>3</td>
<td>mild, only the lips are wet, frequently</td>
</tr>
<tr>
<td>4</td>
<td>moderate, wet on the lips and chin, occasionally</td>
</tr>
<tr>
<td>5</td>
<td>moderate, wet on the lips and chin, frequently</td>
</tr>
<tr>
<td>6</td>
<td>severe, drools to the extent that clothing becomes damp, occasionally</td>
</tr>
<tr>
<td>7</td>
<td>severe, drools to the extent that clothing becomes damp, frequently</td>
</tr>
<tr>
<td>8</td>
<td>profuse, clothing, hands and objects become wet, occasionally</td>
</tr>
<tr>
<td>9</td>
<td>profuse, clothing, hands and objects become wet, frequently</td>
</tr>
</tbody>
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Table 2. Oral Secretion Scale, scored 0 (worst) to 4 (best)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0 - Very Severe</td>
<td>Constant drooling requiring constant lip-blotting, regular suctioning</td>
</tr>
<tr>
<td>1 - Severe</td>
<td>Difficult conscious secretion swallowing, frequent drooling in any position, lip-blotting 12 – 30 times per hour, intermittent suctioning</td>
</tr>
<tr>
<td>2 - Moderate</td>
<td>Conscious saliva swallow required, drooling upright leaning forward, lip-blotting 4 – 6/h</td>
</tr>
<tr>
<td>3 - Minimal</td>
<td>Automatic saliva swallow decreased, infrequent drooling</td>
</tr>
<tr>
<td>4 - Normal</td>
<td>Normal automatic saliva swallow, no drooling</td>
</tr>
</tbody>
</table>
Oral Secretion Scale [4 - 0 scale]

Sialorrhea Scoring Scale [1 - 9 scale]

5 Cotton ball weight [g]

Time [Days]
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: