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Radiation Therapy for Hypersalivation: A Prospective Study in 50 Amyotrophic Lateral Sclerosis Patients

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Summary

Fifty amyotrophic lateral sclerosis (ALS) patients received 3-dimenstional radiation therapy (RT) on the salivary glands (10 Gy/2 fractions: n = 30 or 20 Gy/4 fractions: n = 20). Efficacy was assessed with the Sialorrhea Scoring Scale, the most effective and sensitive tool to measure sialorrhea.

Purpose: This study aimed to evaluate the efficiency and the tolerance of radiation therapy (RT) on salivary glands in a large series of amyotrophic lateral sclerosis (ALS) patients with hypersalivation.

Methods and Materials: Fifty ALS patients that had medically failure pretreatment were included in this prospective study. RT was delivered through a conventional linear accelerator with 6-MV photons and 2 opposed beams fields including both submandibular glands and two-thirds of both parotid glands. Total RT dose was 10 Gy in 2 fractions (n = 30) or 20 Gy in 4 fractions (n = 20). RT efficacy was assessed with the 9-grade Sialorrhea Scoring Scale (SSS), recently prospectively validated as the most effective and sensitive tool to measure sialorrhea in ALS patients.

Results: At the end of RT, all patients had improved: 46 had a complete response (92% CR, SSS 1-3) and 4 had a partial response (8% PR, SSS 4-5). A significant lasting salivary reduction was observed 6 months after RT completion: there was 71% CR and 26% PR, and there was a

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All patients experienced improvement: 92% had complete response (CR) and 8% partial response (PR), with no grade 3/4 toxicity. There was more CR/PR in the 20-Gy protocol ($P = .02$), and 89% of patients requiring a second RT course previously received only 10 Gy.

significant SSS reduction versus baseline ($P<10^{-6}$). There was no grade 3 to 4 toxicity, and most side effects (34%) occurred during RT. Nine patients (18%) underwent a second salivary gland RT course, with a 3-months mean delay from the first RT, resulting in a SSS decrease (−77%). Both RT dose regimens induced a significant SSS decrease with no significant toxicity. There were, however, more patients with CR/PR in the 20-Gy protocol ($P = .02$), and 8 of 9 patients (89%) receiving a second RT course had previously been treated within the 10-Gy protocol.

Conclusion: Radiation therapy of 20 Gy in 4 fractions is an efficient and safe treatment for ALS patients with sialorrhea. A shorter RT course (10 Gy in 2 fractions) may be proposed in patients in poor medical condition.

Introduction

Sialorrhea is a common disabling symptom in patients with amyotrophic lateral sclerosis (ALS) related to a facial muscle weakness and a reduced swallowing ability (1). Socially disabling, drooling may also promote bronchopulmonary infection, which was reported as the first cause of death (55%) in ALS patients (2). Moreover, a high salivary stasis score was described to correlate with the time before resorting to tracheotomy, non-invasive ventilation, and survival (3).

Low-dose radiation therapy (RT) to the salivary glands has been suggested as an effective option to safely control sialorrhea (4, 5). Conversely, drawing firm conclusions is difficult, given the small sample of reported patients (short series of <20 ALS patients) and the heterogeneity of irradiation delivered including various doses and volumes. Moreover, in 2 previous prospective studies evaluating salivary RT in ALS, patients also received concomitant botulinum toxin (6) and various RT doses (7). In another prospective study in 18 ALS patients, Andersen et al reported that a single 7-Gy fraction led to 1 case of xerostomia, whereas 1 patient experienced no effect (8).

Here, we aimed to prospectively assess the efficacy and the tolerance of a controlled RT dose and volume delivered on part of salivary glands in a cohort of 50 ALS patients, to better define the best modalities of salivary irradiation.

Methods and Materials

Study patients

This prospective study included 50 consecutive ALS patients recruited at the Paris ALS center with major drooling symptoms and referred for salivary irradiation at the Clinique de la Porte de Saint-Cloud. Patients older than 18 years, with established ALS according to revised El Escorial criteria (9), and severe sialorrhea unsuccessfully treated with medical drugs were included in the study. Patients receiving a concurrent medical treatment for drooling, with a diagnosis of dementia, who could not tolerate the supine position or who had previously undergone head-and-neck irradiation were excluded from the analysis. All patients delivered written consent, and the Regional Committee for Medical Research Ethics approved the study.

Patients' baseline characteristics are listed in Table 1. The mean age was 70 years (range, 43-92 years). Bulbar symptoms consisted of the onset of the disease in 66% of patients. Of the 50 patients, 30 (60%) were female, and most patients were in good health condition with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range, 1-4). The mean delay from the diagnosis of SLA to the onset of RT was 33.2 months (range, 7-288 months). One patient required his noninvasive ventilation device for breathing assistance during RT.

Treatment

Given the nature of palliative treatment in patients with poor prognosis and neurologic symptoms, hypofractionation was

Table 1 Patient clinical characteristics at baseline

	Overall	10 Gy	20 Gy	*P*
Total	50 (100)	30 (100)	20 (100)	
Age, y, mean (range)	70 (43-92)	66 (42-92)	73 (45-85)	.07
Sex, n (%)				
Male	20 (40)	11 (37)	9 (45)	.6
Female	30 (60)	19 (63)	11 (55)	
Performance status, n (%)				
1	34 (68)	19 (63)	15 (75)	.3
2	9 (18)	5 (17)	4 (20)	
3-4	7 (14)	6 (20)	1 (5)	
Initial symptoms, n (%)				
Bulbar	33 (66)	18 (60)	15 (75)	.008
Limb	12 (24)	11 (37)	1 (5)	
Other	2 (4)	0 (0)	2 (10)	
NA	3 (6)	1 (3)	2 (10)	
Delay, mo, ALS diagnosis to RT, mean (range)	33.2 (7-288)	40 (7-288)	26 (14-77)	.9
ALSFRS score, mean (range)				
Salivation	29.5 (13-43)	29 (13-43)	31 (21-42)	.5
Bulbar section	3.5 (0-8)	4 (0-8)	3 (0-6)	.04
Saliva section	0.85 (0-2)	0.86 (0-2)	0.82 (0-2)	.9
Mean SSS score	8 (6-9)	7.6 (6-9)	8.7 (6-9)	<.001
Mean TVAS score	5.6 (0-10)	4.9 (0-9)	6.7 (1-10)	.05

Abbreviations: ASFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; NA = not available; RT = radiation therapy; SSS = Sialorrhea Scoring Scale; TVAS = thickness visual analogue scale.

favored, as we reported previously (10, 11). From November 2010 to May 2012, 30 patients (60%) and 20 patients (40%) received a total dose of 10 Gy (2 fractions of 5 Gy, at days 1 and 3) or 20 Gy (4 fractions of 5 Gy, at days 1, 3, 8, and 10), respectively. The 20-Gy protocol was also proposed from March 2011 because several patients (7 of 12 first-included patients) needed to receive a second radiation course after the 10-Gy protocol. The 10-Gy protocol was then delivered only in patients with severe physical disability to limit displacements. RT was delivered through a 6-MV photon linear accelerator using 2 opposed beams fields including both submandibular glands and two-thirds of both parotid glands (Fig. 1). The sublingual and the upper parts of the parotid glands were preserved to avoid severe xerostomia and mucositis. All patients underwent computed tomography (CT)-based, 3-dimensional (3D) dose-planning and fixation with a thermoplastic head mask.

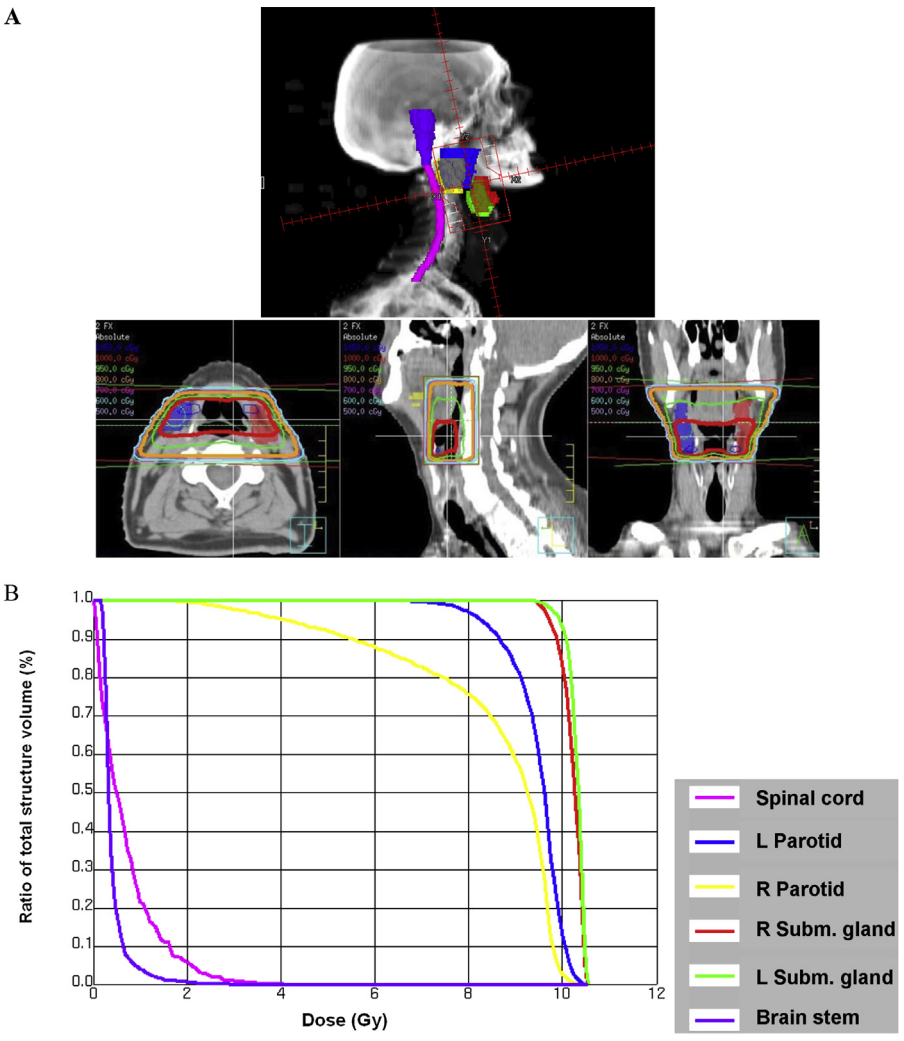
Salivary assessment

Salivation was evaluated by using the 9-grade Sialorrhea Scoring Scale (SSS), recently prospectively validated as the most effective and sensitive tool to measure sialorrhea in ALS patients (12) (Table 2), before RT and during the follow-up until 6 months after RT by both a radiation oncologist and a neurologist. Patients were classified with complete (CR, SSS, 1-3) or partial response (PR, SSS, 4-5) and absence of response (SSS, 6-9). At baseline, all 50 patients had severe hypersalivation (mean SSS, 8; range, 6-9). Mean baseline SSS and Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) were 8 (range, 6-9) and 29.6 (range, 13-43) (bulbar section, 3.5; range, 0-8; and saliva section, 0.85; range, 0-2), respectively (Table 1).

Radiation side effects were systematically prospectively assessed, with a saliva thickening visual analogue scale (TVAS; mean baseline value, 5.6; range, 0-10), xerostomia, oropharyngeal pain, change in taste, saliva thickening, and difficulty swallowing.

Statistical analysis

Unless otherwise noted, data are reported as mean ± standard deviation. The Mann-Whitney test was used to compare numerical values, and the Fisher exact test was used to compare categorical variables. Follow-up was estimated using the reverse Kaplan-



Abbreviations: R: right; L: left; Subm: submandibular gland; Gy, gray, DRR: Digital Reconstructed Radiograph.

Fig. 1. Radiation therapy dose−volume distribution in salivary glands. (A) Digital reconstructed radiograph (DRR) showing axial, sagittal, frontal dosimetric views and (B) dose−volume histogram using a 2-field technique.

Table 2 Sialorrhea Scoring Scale (SSS) grades and response criteria

Score	Description
1	Dry, never drools
2	Mild, only the lips are wet, occasionally
3	Mild, only the lips are wet, frequently
4	Moderate, wet on the lips and chin, occasionally
5	Moderate, wet on the lips and chin, frequently
6	Severe, drools to the extent that clothing becomes damp, occasionally
7	Severe, drools to the extent that clothing becomes damp, frequently
8	Profuse, clothing, hands and objects become wet, occasionally
9	Profuse, clothing, hands and objects become wet, frequently
Response criteria according to SSS	
1-3	Complete
4-5	Partial
6-9	Absence

Meier method. Patients that received a second course of RT were analyzed separately from the date of re-irradiation. P values less than .05 were considered significant.

Results

Treatment efficacy

At a median follow-up of 2.2 years from the diagnosis of ALS, 47 patients were alive. In all, 50, 50, 41, and 38 patients were assessed at the end of RT and at 1 month, 3 months, 6 months after the end of RT, respectively. In comparison with baseline values, RT induced an SSS decreased of 76%, 62%, 67%, and 65% at the end of RT and at 1 month, 3 months, and 6 months after the end of RT, respectively ($P<10^{-6}$) (Fig. 2A). At the end of RT, all patients responded with 92% CR and 8% PR. During the 6-month follow-up, we observed that two-thirds of the ALS patients had improved with a stable CR (68% CR/18% PR/14% no response (NR) at 1 month, 68% CR/27% PR/5% NR at 3 months, and 71% CR/26% PR/3% NR at 6 months after RT) (Table 3).

Toxicity

Treatment was very well tolerated, with no grade (G) 3-4 toxicity or treatment-related death. Grade 1-2 toxicities were observed in 17 patients (34%) during RT, then 4 (8%), 6 (15%), and 2 (5%) patients at 1, 3, and 6 months after the end of RT, respectively.

Toxicities observed were transitory acute taste modification, mild pain, xerostomia, saliva thickening, and swallowing difficulty (Table 4). At 6 months, 2 evaluable patients (5%) reported saliva thickening, but TVAS significantly decreased in the overall population after RT versus baseline (−9% at the end of RT, and −18%, −21%, and −26% at 1, 3, and 6 months after the end of RT, respectively; $P=.02$) (Fig. S1).

Variations with total RT dosage

Patients treated with the 20-Gy protocol had more frequently a bulbar onset form ($P=.08$), higher bulbar ALSFRS ($P=.04$), SSS ($P<.001$), and TVAS ($P=.05$) scores at baseline in comparison with patients receiving 10 Gy. The mean doses delivered to the parotids/submaxillar glands were 9.3 Gy (range, 0-11)/10.3 Gy (range, 2.9-11.1) in the 10-Gy protocol, and 18 Gy (range, 5.4-21.1)/20.5 Gy (range, 18.6-21.1) in the 20-Gy protocol. In comparison with baseline values, both protocols induced a significantly decrease in SSS scores at the end of RT, and at 1, 3, and 6 months after the end of RT, respectively (10-Gy protocol: decreases of 70%, 50%, 61%, and 60%, respectively; 20-Gy protocol: decreases of 82%, 77%; 74%, and 71%, respectively; $P<10^{-6}$ in both protocols) (Fig. 2B). There were, however, more patients with no or mild hypersalivation in the 20-Gy protocol group in comparison with the 10-Gy protocol at 1 ($P=.001$) and 6 months ($P=.02$) after RT (Table 3).

There was no difference in toxicity when comparing the 10-Gy versus the 20-Gy dosage: 30% versus 40% during RT ($P=.6$); and 7% versus 10% ($P=.6$), 22% versus 11% ($P=.4$), and 9% versus 0% ($P=.5$) at 1, 3, and 6 months after RT, respectively (Table 4). TVAS decreased after RT in comparison with baseline results in both protocols, but this was significant only in the 20-Gy protocol (−20%/−32%/−35%/−39% at the end of RT, and at 1, 3, and 6 months after the end of RT, respectively $P=.003$; 10-Gy protocol, $P=.4$) (Fig. S1).

Second RT course

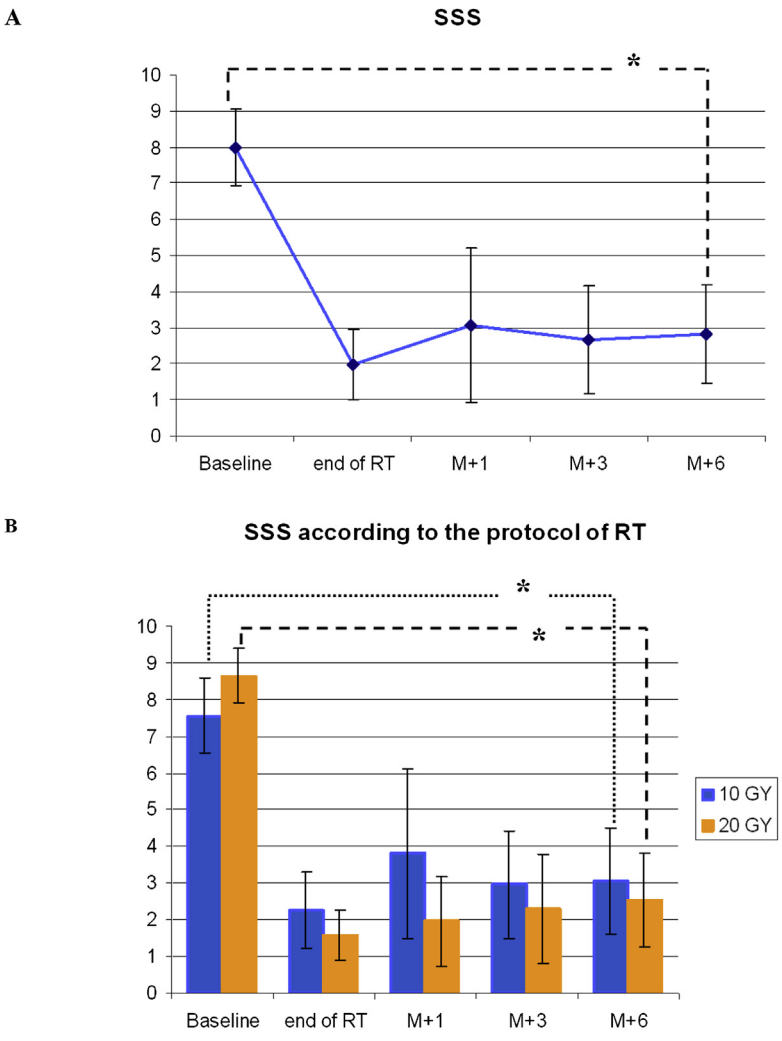
Of 50 patients, 8 (16%) who had previously received salivary glands irradiation of 10 Gy in 2 fractions alone underwent a second RT course of 10 Gy in 2 fractions (total dose of 20 Gy in 4 fractions) during the follow-up. The mean delay from the previous irradiation received was 3 months (range, 1-6 months). The second 10-Gy course helped to achieve a new response with an SSS score decrease (−77%) and TVAS (−33%) between the start of the second course of RT (mean, 6.9; range, 5-9; and mean, 5.4; range, 2-8, respectively) and the end of RT (mean, 1.6; range, 1-2; and mean, 3.7; range, 0-5, respectively). Only 1 patient (2%) in the 20-Gy protocol received another course of RT.

Discussion

To our knowledge, this is the largest prospective series of ALS medically pretreated patients receiving 3D-RT for sialorrhea and assessed with a specific validated scale (SSS). In this study, RT induced a significant decrease in hypersalivation as measured by the SSS, without severe toxicity observed.

Several medical treatments for sialorrhea, such as atropine, hyoscyamine, amitriptyline, or glycopyrrolate, are regularly used; however, there are no formal studies proving their efficacy, and numerous side effects have been observed (1, 13). Botulinum toxin injection into the salivary glands appears to be useful, as demonstrated in a small randomized controlled trial (14). However, botulinum toxin injection should be used cautiously, as it has been associated with prolonged dysphagia in patients who have ALS severe bulbar palsy (15).

Salivary RT has been previously studied in several heterogeneous disease (including Parkinson's disease), heterogeneous



RT: Radiotherapy; GY: Gray; SSS: Sialorrhea scoring scale; M: Months. *Statically significant results (Mann-Whitney test) are marked with *.*

Fig. 2. Sialorrhea Scoring Scale (SSS) score over time (A) in the 50 ALS patients and (B) according to radiation therapy (RT) dosage (10 Gy and 20 Gy).

RT technique, and smaller (n<20) retrospective (4, 5, 16) or prospective (6-8, 17) reports, with interesting results. There are, however, uncertainties concerning the use of 3D-RT or fixation systems (4, 5), and some analyses have included patients over a period of 25 years (5). Our study lasted less than 2 years and was technically controlled in volume with 3D-RT and a thermoplastic mask.

In addition, efficacy is a critical point to measure in such study. Generally, to date, patients have been evaluated with subjective scales and an objective measurement such as salivary flow or the ALSFRS item for salivation (6-8, 17). Objective methods for evaluating salivary flow and volume include saliva collection, suctioning, use of a Lashley disk over the parotid (Stensons) duct, patient-based swallowing counts, or, most commonly, by placing dental cotton pads in the mouth (18). Unfortunately, these objective tests are generally too time consuming to be of routine use in the neurology clinic and do not quantify the discomfort or social embarrassment related to sialorrhea. We used the SSS in this study. In fact, we recently prospectively validated the SSS in 69 ALS patients as the most effective and sensitive tool to measure sialorrhea in ALS patients. In addition, we showed in the same study that patients with severe salivation (SSS score, ≥6) were poorly discriminated by other scales such as the Oral Secretion Scale or ALSFRS (12).

Various schedules of RT have been reported, ranging from 4 to 48 Gy (4-8, 16, 17). A single low-dose (7-Gy) fraction was suggested to be as effective as higher total dosage in drooling reduction (5-7). On the other hand, Bourry et al reported more common positive responses with a higher total dose (≥16 Gy; 78.6%) than a lower dose (<16 Gy; 33%; $P=.07$) (19). Guy et al similarly showed that patients with sustained improvement at 6 months were treated with 20 Gy in 5 fractions in comparison with other regimens ($P=.02$) (17). In our series, both 10 Gy in 2 fractions and 20 Gy in 4 fractions induced a significant and durable SSS decrease without significant toxicity. There were, however, more patients with no or mild hypersalivation (CR and/or PR) in the 20 Gy protocol, despite higher baseline SSS values in this last subgroup (mean baseline SSS, 7.6; range, 6-9; vs mean, 8.7; range, 6-9 in patients receiving 10 Gy and 20 Gy, respectively).

Table 3 Hypersalivation results according to Sialorrhea Scoring Scale (SSS) groups among time

	End of RT n (%)	M1* n (%)	M3* n (%)	M6* n (%)
Overall population				
No. of patients assessed	50 (100)	50 (100)	41 (100)	38 (100)
Response ($P^{\dagger,\ddagger}$)	.1	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Complete	46 (92)	34 (68)	28 (68)	27 (71)
Partial	4 (8)	9 (18)	11 (27)	10 (26)
Absence	0 (0)	7 (14)	2 (5)	1 (3)
According to RT dosage				
No. of patients assessed				
10 Gy	30 (100)	30 (100)	23 (100)	21 (100)
20 Gy	20 (100)	20 (100)	18 (100)	17 (100)
Response ($P^{\dagger,\S}$)	.3	.001	.2	.02
10 Gy				
Complete	26 (87)	15 (50)	13 (56)	12 (57)
Partial	4 (13)	9 (30)	8 (35)	9 (43)
Absence	0 (0)	6 (20)	2 (87)	0 (0)
20 Gy				
Complete	20 (100)	19 (95)	15 (83)	15 (88)
Partial	0 (0)	0 (0)	2 (11)	1 (6)
Absence	0 (0)	1 (5)	1 (6)	1 (6)

Abbreviation: RT = radiation therapy.
* After RT.
† Fisher exact test.
‡ Compared to baseline results.
§ Comparison between the 2 protocols.

In our study, 89% patients who received a second RT course had received a previous total dose of 10 Gy 3 months earlier. Likewise, Scherrenberg et al reported, in a mixed series of ALS and Parkinson's disease patients treated with 12 Gy in 2 fractions, that 26 patients (55%) required re-irradiation for recurrent sialorrhea in a mean duration of 1 year. The second RT course was effective in only 62% of patients without major side effects (20). Still, partial relapse of hypersalivation may occur after a delay of more than 2 years (21). In any case, given the poor prognoses of these patients, the delay for an optimal irradiation may imply that the majority of palliative RT delivered could be successful for sialorrhea during these 'patients' remaining lifespans. Otherwise, a treatment using ionizing radiation should always be very carefully considered in nonmalignant disease, particularly for young patients with prolonged expected survival.

Table 4 Grade 1 and 2 toxicities

	During RT n (%)	M1* n (%)	M3* n (%)	M6* n (%)
Overall population				
No. of patients assessed	50 (100)	50 (100)	41 (100)	38 (100)
Total no. of toxicities	17 (34)	4 (8)	6 (15)	2 (5)
Xerostomia	3 (6)	0 (0)	1 (2)	0 (0)
Mild pain	4 (8)	0 (0)	0 (0)	0 (0)
Saliva thickening	3 (6)	4 (8)	5 (12)	2 (5)
Swallowing difficulty	2 (4)	0 (0)	0 (0)	0 (0)
Taste modification	5 (10)	0 (0)	0 (0)	0 (0)
According to RT dosage				
No. of patients assessed				
10 Gy	30 (100)	30 (100)	23 (100)	21 (100)
20 Gy	20 (100)	20 (100)	18 (100)	17 (100)
Total no. of toxicities ($P^{\dagger}$)	.6	.6	.4	.5
10 Gy	9 (30)	2 (7)	5 (22)	2 (9)
20 Gy	8 (40)	2 (10)	2 (11)	0 (0)

Abbreviation: RT = radiation therapy.
* After RT.
† Fisher's exact test.

Conclusion

Conformal 3D-RT with 20 Gy in 4 fractions for 10 days, using a 6-MV photons with 2 opposed beams fields including both submandibular glands and the two-thirds of both parotid glands, is an efficient and a safe treatment for ALS patients with sialorrhea. A shorter course of irradiation with 10 Gy in 2 fractions is an option in patients in poor medical condition. Larger prospective trials with long-term follow-up are needed to confirm these results, to properly compare RT with other medical modalities, and to specify the potential impact of RT on survival.

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