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Salivary Function and Quality of Life Following Adaptive Intensity-Modulated Radiotherapy for Locally Advanced Head and Neck Cancer

Wael H. El-Sheshtawy ✉, Mostafa E. Mostafa

Clinical Oncology Department, Faculty of Medicine, Al Azhar University, Cairo, Egypt

Abstract

Background: Intensity-modulated radiotherapy (IMRT) is the standard treatment for locally advanced head and neck cancer (LAHNC). However, the potential role of adaptive radiotherapy in preserving salivary function and enhancing quality of life (QoL) remains underexplored.
Aim: This study aimed to assess salivary function and QoL following offline adaptive IMRT in patients with LAHNC undergoing concurrent chemotherapy.
Methods: Salivary function and QoL were evaluated during the last follow-up in LAHNC patients treated with a single offline adaptive IMRT. Unstimulated salivary flow rate (uSFR) was measured to assess salivary function, while QoL was evaluated using the EORTC QLQ-HN43 questionnaire.
Results: A total of 43 patients (median age: 56 years; range: 19–74) were included. Adaptive IMRT improved GTV100% and PTV95% coverage by 0.2% and 1.27%, respectively, while reducing the mean doses to the right and left parotid glands by 3.86% and 5.32%. Grade III-IV treatment-related toxicity occurred in 44% of patients. After a median follow-up of 34.8 months (range: 8.5–45.5), the 3-year disease-free and overall survival rates were 66.5% and 83%, respectively. Among the 29 assessed patients, all regained normal salivary flow (>1 ml/min), with a median uSFR of 3.3 ml/min (range: 1.5–7.4). Quality of life evaluation revealed improvements in dry mouth, sticky saliva, and 11 other scales, though four scales worsened, and two remained unchanged.
Conclusion: This phase II study suggests that a single offline adaptive IMRT approach may enhance target volume coverage, improve parotid gland sparing, and support salivary function recovery and QoL in LAHNC patients.

Keywords: Adaptive radiotherapy, head and neck cancer, intensity modulated radiotherapy, quality of life, salivary flow rate
Corresponding author: Wael H. El-Sheshtawy, MD; Clinical Oncology Department, Al Hussein University Hospital, Gawhar Al Qaed Street, Darrassa, Cairo, Egypt; Email: waelhshesh@yahoo.com
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Introduction

Radiotherapy, either alone or in combination with chemotherapy, plays a pivotal role in the treatment of head and neck malignancies, whether as a definitive or adjuvant therapy. The last few decades have witnessed significant progress in radiation therapy techniques, leading to the establishment of intensity-modulated radiotherapy (IMRT) as the standard of care for patients with head and neck cancer undergoing radiation therapy. This is primarily because IMRT can reduce the radiation dose to organs at risk while delivering highly conformal doses to multiple targets.[1]

Adaptive radiotherapy (ART) is employed to account for in-field anatomical changes during radiation therapy through periodic imaging and re-planning, either at predefined intervals (daily or after a certain number of fractions) or as needed (e.g., in cases of significant weight loss). The primary goal of ART is to reduce the dose received by organs at risk while enhancing target coverage and dose homogeneity.[2]

Radiotherapy-related toxicity still represents a significant concern; the main manifesting symptoms in such patients are xerostomia and its sequences like dental caries, dysarthria and dysphagia. Until now, using better radiotherapy

techniques Like IMRT or proton therapy has been the most successful strategy to protect the salivary function; on the other hand, some promising strategies to manage the already existing xerostomia, are being developed, like stem cell transplant and gene therapy.[3, 4]

The effects of radiation therapy on the salivary glands begin early in the course of treatment, manifesting as significant parotid gland shrinkage or morphological changes.[5-8] These changes are associated with a reduction in saliva volume and alterations in the physicochemical properties of saliva, ultimately leading to xerostomia.[9] Recovery from xerostomia depends on several factors, including the mean dose to the parotid gland, the spared volume of the contralateral parotid and submandibular glands, and other intrinsic patient factors.[10]

There are two standard methods for assessing salivary function recovery after radiotherapy. The first is through salivary flow rate (SFR) measurement.[11] The second involves salivary gland scintigraphy, which uses a PET scan with a 99mTechnetium pertechnetate radiotracer to calculate the ratio of salivary excretion fraction (rSEF) where a reduction in rSEF of more than 25% indicates salivary gland toxicity.[12]

In addition, xerostomia, along with other radiation-induced side effects, leads to significant changes in patients' quality of life (QoL). To assess this impact, several questionnaires have been used, such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-H&N35 and QLQ-HN43, which evaluate the general effects of radiotherapy on QoL.[13] In contrast, some researchers have employed more specific patient-rated questionnaires to assess the effect of radiation-induced xerostomia on salivary function and QoL.[14, 15]

The current prospective phase II longitudinal study aims to evaluate the impact of adaptive IMRT on parotid gland volume, the recovery of salivary function, and overall patient QoL.

Methods

This prospective study recruited patients with locally advanced head and neck cancer (LAHNC) between April 2019 and June 2021. All patients had histologically confirmed invasive squamous cell carcinoma, stage III-IV disease as per the American Joint Committee on Cancer (AJCC) 8th edition,[16] and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less[17]. Additionally, all patients were eligible for concurrent chemoradiotherapy (CCRT).

All patients underwent a comprehensive clinical examination, including otorhinolaryngological and dental evaluations, as well as head and neck imaging using contrast-enhanced computerized tomography (CT) and magnetic resonance imaging (MRI). For staging, contrast-enhanced CT scans of the chest and upper abdomen were performed, along with a full laboratory assessment.

Radiotherapy

Patients were simulated in a supine position using thermoplastic head and neck masks for fixation. CT scans were obtained with 2 mm slice intervals. The initial simulation CT (in-CTsim) was co-registered with pre-treatment contrast-enhanced MRI to enhance the accuracy of target and organ-at-risk (OAR) delineation. A single clinician performed the delineation to minimize inter-observer variability. Target volumes and OARs were defined according to the International Commission on Radiation Units and Measurements (ICRU) 50 and 83 reports,[18, 19] utilizing the updated consensus guidelines for nodal delineation in head and neck tumors, along with the EORTC CT-based atlas for lymph node areas and OAR delineation [20, 21]. All patients were treated with definitive IMRT, delivering 70 Gy in 33 fractions.

The radiotherapy plan was deemed acceptable if ≥98% of the planning target volume (PTV) was covered by ≥95% of the prescribed dose, with no significant volume of the PTV receiving >107% of the dose. Doses to OARs were maintained within predefined tolerance limits. The first 20 fractions were delivered according to the initially approved radiotherapy plan (in-plan).

Adaptation

At the end of in-plan, all patients were subjected to offline ART that included adaptive CT simulation (Ad-CTsim) in the same way the in-CTsim had done, re-contouring (by the same doctor) and re-planning were also done to generate a new adaptive plan (ad-plan) to be used for delivering the remaining 13 fractions. Registration was done between the Ad-CTsim (after re-contouring) and In-CTsim to calculate the cumulative dose for different volumes (PTV, parotids, and other OARs) if the patient continued to receive radiotherapy using the in-plan without adaptation. The rate of change in volumes of the target and OARs at the end of 20 fraction

(volume reduction rate) was calculated with the following equation:

Volume reduction rate = [(In-CTsim volume – Ad-CTsim volume) / In-CTsim volume] × 100

Patients received concurrent chemotherapy alongside radiotherapy in the form of either weekly cisplatin at 40 mg/m^2 or weekly carboplatin (AUC 2) for those with impaired renal function.

Follow-up and response assessment

Patients were monitored clinically on a weekly basis during treatment and then every 3 months thereafter. Response assessment was conducted 6-8 weeks post-radiotherapy using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[22] through both clinical and radiological evaluations, employing the same imaging modality used at baseline.

Salivary Function Assessment: At the last follow-up visit, salivary function recovery was evaluated by measuring the unstimulated salivary flow rate (uSFR) in surviving patients. Saliva was collected by instructing the patient to spit into a sterile container for 8 minutes. The collected saliva volume was measured using a graduated syringe and divided by the collection time (8 minutes) to calculate the uSFR. Patients with an uSFR greater than 0.1 ml/min were considered to have recovered salivary function.

Quality of life assessment

Quality of life was evaluated using the EORTC QLQ-HN43 questionnaire at two distinct time points: the first assessment took place just before the start of treatment (pre-treatment QoL), and the second was conducted at the last follow-up, at least six months after the completion of therapy (post-treatment QoL). The EORTC QLQ-HN43 examines 19 different quality-of-life scales through a total of 43 items.

The scoring system of this questionnaire employs a linear transformation to standardize scores (denoted as score S) on a scale from 0 to 100. Higher scores indicate a greater level of symptom severity or problems. Scores were calculated in accordance with the EORTC QLQ-HN43 Scoring Manual. Initially, a raw score was determined as the average response across items within each scale category. This raw score was then transformed linearly to yield the standardized score S, facilitating consistent interpretation and comparison across scales.

Endpoints

The primary endpoint of this study was to assess salivary function recovery and QoL following adaptive IMRT with CCRT for LAHNC. Secondary endpoints included evaluation of disease-free survival (DFS), overall survival (OS), and treatment-related toxicity associated with the radiotherapy technique.

Statistical methods

Descriptive statistics, including mean, standard deviation, median, interquartile range (IQR), and range, were calculated to summarize the data. For survival analysis, the Kaplan-Meier method was applied to estimate survival probabilities over time. To compare QoL means at different time points, the paired samples t-test was used, which is suitable for assessing changes in QoL scores within the same individuals across multiple intervals. The primary analysis followed a complete-case per-protocol approach without imputing missing values. A p-value of <0.05 was considered statistically significant. Data management and analysis were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY).

Results

A total of 43 patients were included in this study, with a median age of 56 years (range: 19–74). The majority of the cohort were male (32 patients, 74.4%). The most common primary tumor sites were the larynx and nasopharynx, observed in 21 patients (48.8%) and 15 patients (34.9%), respectively. Most patients presented with stage IVA disease (27 patients, 62.8%), while 16 patients (37.2%) had stage III disease (Table 1).

All patients successfully completed the prescribed 33 fractions of radiotherapy according to the treatment protocol. However, the radiotherapy course was interrupted in six patients (14%), with a median delay of five days (range: 2–17 days). The incidence of grade III-IV treatment-related toxicity was 44%. The most common severe toxicities were mucositis and dysphagia, occurring in 21 patients (36.7%) and 17 patients (34.6%), respectively. No reported grade V toxicity (Table 2).

All patients received concurrent systemic therapy alongside radiotherapy. The majority, 36 patients (83.7%), received weekly cisplatin, while six patients (14%) were treated with concurrent carboplatin, and one patient (2.3%) received concurrent cetuximab.

Table 1: Demographics and disease characteristics of 43 patients with locally advanced head and neck cancer

Variable		Description
		Median (range)
Age (years)		56 (19-74)
		***n* (%)**
Sex	Male	32 (74.4)
	Female	11 (25.6)
Smoking history	Smoker	29 (67.4)
	Non-smoker	14 (32.6)
Comorbidity	Yes	17 (39.5)
	No	26 (60.5)
Performance status	0 - 1	41 (95.3)
	2	2 (4.7)
Primary site	Larynx	21 (48.8)
	Nasopharynx	15 (34.9)
	Oropharynx	6 (14)
	Hypopharynx	1 (2.3)
Tumor grade	II	29 (67.4)
	III	14 (32.6)
T stage	T2	6 (14)
	T3	14 (32.5)
	T4	23 (53.5)
N stage	N0	13 (30.2)
	N1	18 (41.9)
	N2	5 (11.6)
	N3	7 (16.3)
Group stage	III	16 (37.2)
	VI A	27 (62.8)

The median of the mean cumulative doses to the right and left parotid glands were 24.2 Gy (range: 16–25.8 Gy) and 24.8 Gy (range: 16.6–25.6 Gy), respectively. The median maximum dose (Dmax) to the spinal cord was 42.6 Gy (range: 28.1–49.6 Gy), and to the brainstem, it was 41.4 Gy (range: 6.4–54.1 Gy).

The gross tumor volume (GTV), PTV, and both the right and left parotid glands showed significant size reductions on Ad-CTsim, with decreases of 31.26% (IQR: 45.52–26.15), 22.81% (IQR: 36.21–8.11), 13.62% (IQR: 21.72–9.81), and 17.68% (IQR: 22.41–8.41), respectively (P = 0.001) (Table 3).

Table 3 compares the initial radiotherapy plan with the adaptive plan implemented after 44 Gy, based on adaptive CT simulation. It presents changes in anatomical volumes over time, as well as differences in target volume coverage and doses received by organs at risk. The table evaluates outcomes for patients who either continued with the initial plan or transitioned to the adaptive plan.

Table 2: Most frequent treatment-related toxicity in 43 patients with locally advanced head and neck cancer treated with adaptive IMRT

Toxicity	Grade		
	Any	**I - II**	**III - IV**
	***n* (%)**	***n* (%)**	***n* (%)**
Mucositis	35 (81.3)	19 (44.2)	16 (37.2)
Xerostomia	34 (79)	27 (62.8)	7 (16.3)
Acute laryngitis	23 (53.5)	23 (53.5)	0
Acute skin toxicity	29 (67.4)	26 (60.5)	3 (7)
Dysphagia	43 (100)	28 (65)	15 (34.9)

The impact of ART on target volume coverage and doses to OARs was assessed by comparing the initial plan doses on Ad-CTsim with the adaptive plan doses on Ad-CTsim. The results showed an increase in the median GTV 100% and PTV 95% coverage by 0.2% (IQR: -0.05–2.08%) and 1.27% (IQR: 0.05–5.1%), respectively. Additionally, there was a reduction in the mean dose to the right and left parotid glands by 3.86% (IQR: 7.67–0) and 5.32% (IQR: 14.59–1.56%), respectively, as well as a decrease in the median Dmax to the spinal cord and brainstem by 3.5% (IQR: 6.56–0) and 5.28% (IQR: 7.92–2.13%), respectively. All these differences were statistically significant (P = ≤0.01) (Table 3).

The objective response rate was 93%, with 65.1% of patients (28/43) achieving complete remission, and 27.9% (12/43) showing a partial response. In contrast, only 7% (3/43) had stable disease, and no cases of progressive disease were observed.

At a median follow-up of 34.8 months (range: 8.5–45.5 months), the median DFS and OS were not reached. The 3-year DFS and OS rates were 66.5% and 83%, respectively (Figure 1).

Out of the 43 patients included in the study, 29 patients (60.5%) underwent uSFR and QoL assessments, while 8 patients (12%) died before the assessment, and 5 patients (10%) did not attend the evaluation. The uSFR was assessed once during the study. All evaluated patients had a uSFR ≥ 1.5 ml/min (within the normal range), with a median uSFR of 3.3 ml/min (range: 1.5–7.4 ml/min).

Table 3: Changes in treatment volumes and doses to organs at risk after adaptation

Volumes		Initial Plan (on Ad-CTsim)		Adaptive Plan (on Ad-CTsim)		Percent change		*p* value
GTV volume	Median (IQR)	48.3	(26.8 – 74.1)	33.2	(15 – 60)	-31.3	(-45.5 – -26.2)	<0.001
(cc)	(range)		(4.7 – 232.2)		(1.7 – 168.1)		(-80.8 – 0.02)	
GTV V100	Median (IQR)	98.4	(98.2 – 98.8)	99.12	(98.8 – 99.4)	0.2	(0 – 1)	<0.01
(%)	(range)		(97.7 – 100)		(98.1 – 99.9)		(-0.1 – 2.1)	
PTV volume	Median (IQR)	126.2	(75.8 – 224.5)	95.6	(57.2 – 136.9)	-22.8	(-36.2 – -8.1)	<0.001
(cc)	(range)		(19.4 – 855.9)		(11.6 – 601.6)		(-91.8 – 38.7)	
PTV V95	Median (IQR)	95.1	(94.8 – 95.9)	96.8	(96.2 – 97.01)	1.3	(0.6 – 2.1)	<0.01
(%)	(range)		(92.1 – 97.6)		(94.2 – 98.4)		(-0.1 – 5.1)	
Right parotid volume	Median (IQR)	30	(23.5 – 37.3)	23	(20.3 – 30.5)	-13.6	(-21.7 – -9.8)	<0.001
(cc)	(range)		(17.7 – 49)		(17.3 – 37.6)		(-35.1 – 3.8)	
Right parotid mean	Median (IQR)	24.8	(22.6 – 25.9)	23.4	(22.1 – 24.5)	-3.9	(-7.7 – 0)	<0.001
(Gy)	(range)		(15.1 – 27.3)		(15 – 27.1)		(-32.4 – 4.5)	
Left parotid volume	Median (IQR)	30.9	(25.8 – 37.3)	24	(22.3 – 30.5)	-17.7	(-22.4 – -8.4)	<0.001
(cc)	(range)		(19.5 – 48.1)		(13.9 – 42)		(-47.2 – 12.3)	
Left parotid mean	Median (IQR)	25.8	(24.1 – 26.7)	23.6	(22.7 – 24.8)	-5.3	(-14.6 – -1.6)	<0.001
(Gy)	(range)		(17.5 – 29.7)		(16.5 – 26.7)		(-33.6 – 0.4)	
Spinal cord D. max	Median (IQR)	43.4	(41.3 – 44.6)	41.4	(37.8 – 43.3)	-3.5	(-6.6 – 0)	<0.001
(Gy)	(range)		(37.1 – 49.7)		(28.1 – 47.4)		(-33.3 – 1.9)	

Ad-CTsim: Adaptive CT simulation, **GTV:** Gross tumor volume, **PTV:** Planning target volume, **IQR:** Interquartile range

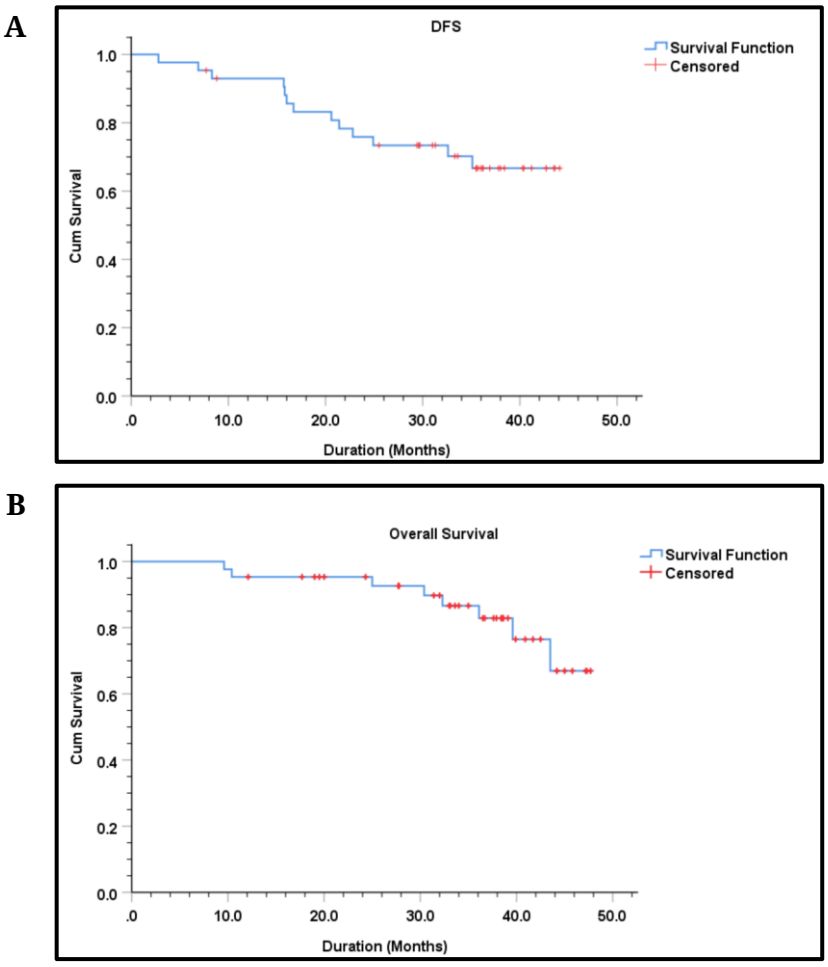

Figure 1: Kaplan-Meier disease-free (A) and overall (B) survival curves

The two EORTC QLQ-HN43 scales assessing dry mouth and sticky saliva showed a zero S score, indicating no reported symptoms among assessed patients. However, four QoL scales worsened at the last follow-up compared to pre-treatment, namely: shoulder problems (10.6 vs. 3), body image issues (8.1 vs. 0), skin problems (10.1 vs. 4), and neurological issues (21.2 vs. 3). Meanwhile, 11 other scales improved, and 2 remained unchanged (Table 4).

Table 4: EORTC QLQ-HN43 scales scores before and after treatment

Scale		Score S (0-100)	
		Pre-treatment	Post-treatment
1.	Pain in the mouth	10.6	0.8
2.	Swallowing	12.1	3.8
3.	Problems with teeth	6.1	6.1
4.	Dry mouth and sticky saliva	4.5	0.0
5.	Problems with senses	13.6	10.6
6.	Speech	26.1	9.1
7.	Body image	0.0	8.1
8.	Social eating	12.1	3.0
9.	Sexuality	7.6	7.6
10.	Problems with shoulder	3.0	10.6
11.	Skin problems	4.0	10.1
12.	Fear of progression	43.9	9.1
13.	Problems opening mouth	12.1	3.0
14.	Coughing	6.1	3.0
15.	Social contact	12.1	0.0
16.	Swelling in the neck	27.3	3.0
17.	Weight loss	0.0	3.0
18.	Problems with wound healing	3.0	0.0
19.	Neurological problems	3.0	21.2

Discussion

One of the key advantages of IMRT over conventional 3D radiotherapy in the treatment of head and neck cancer is its ability to spare the parotid glands. This was demonstrated in a study by Gupta et al., which reported a significant reduction in ≥ grade 2 xerostomia rates among patients treated with IMRT (12.5%; 95% CI: 0–29.5%) compared to those treated with conventional 3D radiotherapy (41.7%; 95% CI: 29.6–41.7%). While this difference was clinically meaningful, it showed borderline statistical significance (p = 0.082) at a median follow-up of approximately 10 years.[23] Furthermore, Ortholan et al. identified the contralateral parotid gland V40 as the most predictive dose constraint variable for complete salivary recovery 24 months post-IMRT for head and neck cancer. [24]

Significant volumetric changes are often observed within the radiation field after two weeks of radiotherapy, primarily due to tumor shrinkage, parotid gland atrophy, and patient weight loss. Other contributing factors include tissue inflammation and muscle atrophy.[25] Adaptive radiotherapy has been developed to account for these changes, aiming to improve target coverage and dose homogeneity while reducing the radiation dose to critical structures. A study by Castelli et al. reported that weekly ART improved the mean parotid gland dose by 5 Gy, leading to an 11% reduction in the risk of xerostomia.[26]

The timing and frequency of adaptations during head and neck radiotherapy are not standardized, as they depend on factors such as tumor response and weight loss. Additionally, ART is resource-intensive, increasing the workload for staff and machines. Due to logistical challenges and limited resources at our center, we performed a single offline adaptation after 44 Gy. The Re-CTsim showed a slight reduction in median GTV 100% and PTV 95% coverage by 0.2% (range: -0.05–2.08%) and 1.27% (range: -0.05–5.1%), respectively, along with a modest increase in the mean dose to the right and left parotid glands by +0.8 Gy (range: -2.2 to +8 Gy) and +0.9 Gy (range: -2.5 to +8.6 Gy).

Changes in parotid gland size during radiotherapy are closely associated with reductions in both the amount and quality of saliva, which manifests as xerostomia. Parotid gland shrinkage is dose-dependent, as demonstrated by Wang ZH et al., who found significant differences in the magnitude of parotid volume loss at mean doses below and above 30 Gy. The study reported a median 20% reduction in parotid volume by week three of radiotherapy, which continued to increase at a slower rate, reaching 27% by the end of treatment.[27]

In our study, the mean doses to the right and left parotid glands were 24.2 Gy and 24.8 Gy, respectively, with median parotid volume reductions of 13.6% and 18.2%. These rates of parotid shrinkage are lower than those reported by

Wang ZH et al.[27] likely due to differences in the mean parotid dose. This discrepancy may also be attributed to the fact that only about half of the patients in their study were treated with IMRT, while the rest received conventional 3D radiotherapy.

Several longitudinal studies have employed different questionnaires to evaluate the impact of radiotherapy on patient QoL.[13, 15, 28, 29] In a recent study by Iwanaga K. et al. the QoL of 58 head and neck cancer patients treated with radiotherapy and/or chemotherapy was monitored over two years using the EORTC-QLQ-H&N35 questionnaire. The study found that physical and social functions significantly declined during treatment but generally recovered within 1–2 years, while mental health remained stable throughout. However, persistent symptoms such as dry mouth and sticky saliva continued to affect patients over the follow-up period, emphasizing the need for ongoing management of these side effects to enhance QoL.[30]

In our study, we used the EORTC HN43 questionnaire to evaluate the effects of adaptive CCRT with IMRT. In contrast to the findings of Iwanaga K. et al.[30] all patients in our study reported no residual symptoms of xerostomia, with a zero score for both xerostomia and dysphagia after a median follow-up of 34.8 months. This difference may be attributed to variations in patient characteristics between the studies and the longer follow-up period in ours. This improvement in patient-reported xerostomia is objectively supported by the results of uSFR assessments, which demonstrated complete recovery of salivary function in all evaluated patients. The median uSFR was 3.3 ml/min (range: 1.5–7.4 ml/min), indicating that all patients achieved a normal salivary flow rate of greater than 1 ml/min.

Limitations

The relatively small sample size of 43 patients in this study may restrict the generalizability of our conclusions. The per-protocol analysis included only 29 patients who completed assessments. While this approach helps maintain the accuracy of reported findings, it may limit the broader applicability of the results. We recognize that missing data could potentially skew treatment effects if patients with poorer outcomes were disproportionately lost to follow-up. Additionally, the median follow-up period of 34.8 months might not be sufficient to fully assess changes in salivary function and QoL. While our findings indicate a beneficial role of adaptive IMRT, further research with larger cohorts and extended follow-up is necessary to confirm these results and evaluate potential late-onset toxicities.

Conclusion

The use of IMRT with even a single offline adaptation may improve the therapeutic ratio in patients with LAHNC treated through enhancing target volume coverage and reducing the dose to OARs, particularly the parotid glands. Keeping in mind the study limitations, this approach resulted in complete salivary function recovery and improved QoL in 13 out of 19 items. These findings may suggest that limited offline adaptations could be a practical alternative to more frequent offline, online, or real-time ART in busy, resource-constrained radiotherapy departments.

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Authors' contribution

Conception & Design: Both authors; Acquisition, analysis, or interpretation of data: Both authors; Drafting / revising the manuscript: Both authors; Approval of the final version of the manuscript: Both authors; Agreement to be accountable for all aspects of the work: Both authors.

Conflict of interest

The authors have no conflicts of interest to declare.

Data availability

De-identified data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical considerations

The study was approved by the Institutional Review Board of the Faculty of Medicine - Al Azhar University on 11-February-2019 (approval #: Clin.Onc.Nuc._1Med.Research_0000001). All patients included in the study signed an informed written consent.

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Study registration

Not applicable.

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