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Feasibility and Potential Value of Lipofilling in Post-treatment Oropharyngeal Dysfunction

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Objectives/Hypothesis: Head and neck cancer (HNC) patients may develop oropharyngeal dysfunction as result of volume loss or muscle atrophy of the tongue or pharyngeal musculature following treatment with surgery and/or chemoradiotherapy. If intensive swallowing therapy offers no further improvement, and the functional problems persist, transplantation of autologous adipose tissue (lipofilling) might restore functional outcomes by compensating the existing tissue defects or tissue loss.

Study Design: Case series.

Methods: In this prospective pilot feasibility study, the application of lipofilling was studied in seven HNC patients with chronic dysphagia. The procedure was carried out under general anesthesia in several sessions using the Coleman technique. Swallowing outcomes were evaluated with standard videofluoroscopy (VFS) for obtaining objective Penetration Aspiration Scale (PAS) and residue scores. Subjective Functional Oral Intake Scale scores and Swallowing Quality of Life Questionnaire were also completed. Magnetic resonance imaging was used to evaluate the post-treatment injected fat.

Results: Five patients completed the intended three lipofilling sessions, whereas two completed two injections. One patient dropped out of the study after two injections because of progressive dysphagia requiring total laryngectomy. Four of the six remaining patients showed improved PAS scores on post-treatment VFS assessments, with two patients no longer showing aspiration for a specific consistency. Two patients were no longer feeding tube dependent. Patient-reported swallowing and oral intake improved in four out of six patients.

Conclusions: Based on the results, the lipofilling technique seems safe and, in selected cases, of potential value for improving swallowing function in this small therapy-refractory HNC patient cohort.

Key Words: Head and neck neoplasms, deglutition, deglutition disorders, lipofilling, fat transfer, autologous fat injection.

Level of Evidence: 4

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INTRODUCTION

Patients with advanced head and neck cancer (HNC) are usually treated with (a combination of) surgery, radiotherapy, or chemotherapy. Despite increasing survival as a result of improved treatment modalities and combinations for most sites,¹ damage to the anatomical structures by the primary tumor or its treatment may adversely impact patients' functional outcome and

quality of life. Swallowing problems occur frequently in these patients, and may be a consequence of tissue loss, fibrosis, mucositis, xerostomia, pain and/or trismus.^{2,3} The situation may even worsen when the swallowing musculature is no longer actively used, and so-called "non-use" atrophy occurs, causing further deterioration of swallowing.⁴

Many factors contribute to dysphagia, aspiration, and even the inability to swallow. Often, due to insufficient contact between the base of tongue and posterior pharyngeal wall, the food bolus is swallowed less powerfully, leading to stagnation of food (residue), with a high risk of aspiration of the residue. A combination of decreased tongue strength, deficient/reduced hyolaryngeal elevation, lack of pharyngeal constrictor activity, lack of oropharyngeal seal, or insufficient opening of the esophageal inlet may also play a role in aspiration.^{5,6} Long-term and even lifelong feeding tube dependency is sometimes unavoidable, and quality of life in these patients is often seriously impaired.⁷

Current treatment strategies of dysphagia include continued use of swallowing musculature during treatment (the "use it or lose it" concept), by avoiding prolonged periods of nothing oral and adherence to (prophylactic) targeted swallowing exercises.⁸ Although

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TABLE I.
Patient and Tumor Characteristics at Baseline (N = 7).

Patient	Gender	Age, yr	Tumor Location	TNM	Treatment		
					CRT	Surgery	Injection
1	F	71	Base of tongue	Benign	—	2007	Base of tongue
2	M	50	Tonsil	T2N2b	2011	2012	Base of tongue
3	M	63	Vallecula	T2N2b	—	1997	Base of tongue
4	M	40	Tonsil	T4N2c	2007	—	Pharyngeal wall
5	F	59	Base of tongue	T3N2c	2004	—	Base of tongue
6	M	66	Oral cavity	T3N2c	1997	1997	Base of tongue
7	F	70	Pharyngeal wall	T3N2	2000	—	Base of tongue

CRT = chemoradiotherapy; F = female; M = male; TNM = tumor node metastasis.

promising results on pharyngeal swallowing function are reported,^{9,10} severe, therapy-refractory dysphagia may still exist in some patients.

Lipofilling, or fat grafting, is a technique for transplanting autologous, living fat cells within one individual. Due to the regenerative properties of adipose tissue—stem cells have been demonstrated at cellular level¹¹—the technique can be used for both aesthetic and reconstructive purposes. Common indications are tissue loss, pain, and/or fibrosis due to surgery, irradiation, burns, or other (post-traumatic) causes.^{12,13} To date, except for skin contouring indications,¹³ lipofilling is rarely used in HNC as there is, to the best of our knowledge, only one case history published about this technique being applied to treat oropharyngeal dysfunction following treatment for HNC.¹⁴ In that study, lipofilling filled the existing defect in the vallecula that was the cause of significant stagnation of the food bolus, and the added volume elevated the epiglottis and thus improved airway protection. In the present study, the feasibility and potential value of lipofilling in seven HNC patients with chronic, therapy-refractory dysphagia was prospectively assessed.

MATERIALS AND METHODS

The present study was designed as a small-scale prospective pilot feasibility study and was undertaken at the Department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute in collaboration with the Department of Plastic Surgery of the Academic Medical Center, in Amsterdam, the Netherlands. The study was performed according to guidelines of both institutes and those of the Helsinki Declaration.

Study Cohort

All patients had chronic dysphagia (1 year plus) as a consequence of tissue loss and/or muscle atrophy after treatment with surgery or (chemo-) radiotherapy for advanced HNC. Patients were offered to participate after their persistent, seriously debilitating dysphagia appeared to be unresponsive to intensive swallowing training by the speech language pathologist (SLP). None of the patients had been enrolled in a pretreatment prophylactic swallowing exercise program.¹⁵

The initial study cohort consisted of seven patients treated between 1997 and 2012 for advanced HNC and were in

complete remission. Six patients had a primary tumor located at the oropharynx (tonsillar arch, pharyngeal wall, base of tongue, and/or vallecula). The other patient had a primary tumor in the oral cavity. The patient and tumor characteristics of the initial patient cohort are summarized in Table I.

Informed consent was obtained, and the patients were told about the experimental design of the study. Patients were aware that due to absorption (up to 30%–50%) of adipose tissue,¹⁶ multiple (probably at least three) treatment sessions would be necessary before a therapeutic effect could be expected. All patients were free to end their participation at any time during the study.

One patient (patient 7, Table I) dropped out of the study due to progression to total laryngectomy. This patient was admitted at our institute because of severe bowel obstruction not related to her second injection 2 weeks previously. During the unavoidable hospitalization the patient's physical condition deteriorated, and she twice developed aspiration pneumonia and respiratory insufficiency, which became so problematic that a permanent tracheotomy was unavoidable. She opted to have a total laryngectomy for controlling her severely disabling and potentially life-threatening aspiration problems. This patient thus went off study and was not further analyzed, but is mentioned here for completeness of the original study cohort.

Procedure and Technique

The lipofilling procedure was carried out under general anesthesia using the Coleman technique.¹⁷ This technique aims to prevent damage to the fragile adipose cells as much as possible during transplantation and thus to promote tissue survival. The procedure starts with harvesting fat cells by aspiration from the upper abdominal wall or inner thigh, after infiltration of antibiotics and tumescence fluid (ringers lactate, lidocaine, and adrenaline). Adipose tissue from the infra-umbilical abdominal wall or inner thigh is very suitable as a donor site because of the high number of local fat cells, and the fact that no position change on the operating table is needed.¹² The fat sample is then transferred in 10 mL tubes for centrifugation, which is done for 3 minutes at 3,100 rounds per minute, producing 1,228g centrifugal force. After the centrifugation process, the specimen, in addition to fat cells, also consists of a layer of oil, a layer of fluid (including blood and tumescent fluid), and a layer of cell pellets/residue. The top supernatant oil and bottom blood cells and debris are then removed with the decanter technique (Fig. 1). The remaining, purified fat cells are then injected using 1 mL syringes with blunt tip cannulas (St'rim; Thiebaud SAS, Paris, France) at the predetermined spots, after the mucosa is first punctured using a 21-gauge needle. During



Fig. 1. After the centrifugation process, the specimen, in addition to fat cells, consists of a layer of oil, a layer of fluid (including blood and tumescent fluid), and a layer of cell pellets/residue. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

injection, small aliquots of fat are transferred with multiple passes at different depths. Control of the depth of injection is performed with the nondominant hand. This is done with multiple passes to assure even distribution within the tissue. In Figure 2, a lipofilling injection into the base of tongue is illustrated. For reasons of safety, all patients were hospitalized for observation for 1 night following the procedure.

Multidimensional Assessment

Functional data were collected using multidimensional objective and subjective outcome measures. The protocol included standard videofluoroscopy (VFS) to determine the injection sites based on the degree of contact between the base of the tongue and posterior pharyngeal wall during swallowing, and to objectively assess general swallowing function, Penetration and Aspiration Scale (PAS) scores, and overall presence of residue scores. The PAS is a tool with acceptable reliability and consists of an eight-point scale ranging from 1 to 8 (score 1: material does not enter the airway to score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject).¹⁸ The overall presence of residue score ranges from 0 to 3 (score 0: no residue to score 3: residue above and below the vallecula, with minimal residue judged as normal).^{19,20} Magnetic resonance imaging (MRI) was used to visualize the potential injection site in the oral cavity and pharynx (i.e., to estimate tongue and pharyngeal wall muscles and volumes) and the post-treatment volumes of the injected fat. Additionally, patients' perceived oral intake/nutritional status was

assessed with the validated Functional Oral Intake Scale (FOIS) ranging from 1 to 7 with score 1: nothing by mouth to score 7: total oral diet without restrictions). Patients' perception of swallowing function was assessed with the Swallowing Quality of Life (SWAL-QOL) questionnaire.²¹ The Dutch SWAL-QOL has been translated and validated for use with oral, oropharyngeal, and laryngeal cancer patients. A cut-off score of 14 points (or higher) has been established for identifying HNC patients with clinically relevant swallowing problems. A score difference of 12 points or more is proposed to be used in study designs with multiple assessments.^{22,23}

All primary outcome parameters were recorded at baseline prior to participation and approximately one to three months after the final fat injection. After each intervention, patients consulted the principal clinician at the outpatient clinic and underwent interim VFS assessments if necessary.

RESULTS

Patient Characteristics

All patients had chronic dysphagia, with four patients being (completely) dependent on permanent tube feeding (FOIS ≤ 3). The other two patients had a restricted diet of only one consistency (FOIS 4) or with specific food limitations (FOIS 6), and were included because of recurrent aspiration pneumonia. Furthermore, two patients with dysphagia were also diagnosed with some degree of dysphonia (articulation disorder).

At baseline, penetration and/or aspiration was demonstrated with VFS in all but one patient. Absent or reduced contact between the base of tongue and pharyngeal wall during swallowing was demonstrated in all six patients, resulting in more than normal contrast residue



Fig. 2. Lipofilling injection into the base of tongue (patient 7, Table I). Intraorally a long needle is arranged at the lateral tongue edge, and under palpation the tip of the needle is advanced into the base of tongue where the fat depositions are placed. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]



Fig. 3. Preoperative static videofluoroscopy image of one of the patients (patient 6) with an atrophied tongue. As can be seen, during swallowing there is hardly any contact (due to volume loss) between the base of the tongue and posterior pharyngeal wall.

above and below the hyoid bone. Figure 3 shows a static preoperative VFS image of one of the patients with a severe atrophied tongue. Furthermore, volume loss or atrophy of the tongue was confirmed with MRI in five patients. In the other patient there was reduced

tonsillar tissue (asymmetry) in the right tonsillar arch.

Procedure and Technique

In total, 17 autologous fat transplantations were carried out from October 2013 to February 2015, ranging from two to three sessions per patient with 3-month intervals. One patient (patient 4) noticed insufficient improvement following two lipofilling sessions and decided to discontinue the treatment. The other patients (N = 5) had completed the planned (three) consecutive lipofilling sessions. In total 20 to 35 cm³ adipose tissue was transplanted in these patients (Table II). Possible complications at the site of injection, such as necrosis, infection, or intravascular injection were not observed. There were also no complications such as swelling/edema with dyspnea, hematoma formation, scar formation, or damage to the underlying structures on the donor site. Postoperative pain was not reported.

Swallowing Outcomes

The functional (applicable) objective and subjective swallowing outcomes per patient pre- and post-treatment are shown in Table II. The patient (patient 4) who did not complete the protocol did not show any clinically relevant improvement on the outcome parameters. Of the remaining five patients, at 1 to 2 months follow-

TABLE II.
Functional Objective and Subjective Swallowing Outcomes Pre- and Post-treatment (N = 6).

	Injected Fat		Intake FOIS	PAS										
	No.	Amount, cm ³		Thin Liquid			Thick Liquid			Residue				
				≤3 mL	5 mL	≥10 mL	≤3 mL	5 mL	10 mL	Solid Cake	Thin	Thick	Solid	
1	3	29.5	Pre	4			3		1	1	3	3	1	3
			Post	6			3		1		1	3	3	1
			Change	+			=		=		+	=	-	+
2	3	30	Pre	1	8			4	6			3	3	
			Post	3	3	3	6	4	4	2	3	3	3	
			Change	+	+				+			=	=	
3	3	20	Pre	6	8		7	6	6			3	3	
			Post*	5	6	6	6	4	4	4	3	3	3	
			Change	-	+		+		+			=	=	
4	2	11	Pre	1	4			6				3	3	
			Post	1	8			NA				3	1	
			Change	=	-			-				=	+	
5	3	34.5	Pre	1	NA			NA					3	
			Post	6	7			6	6	6		3	3	
			Change	+	+			+				=		
6	3	32	Pre	3			4		4		3	3	3	3
			Post	6	3		4		2		3	3	3	3
			Change	+			=		+		=	=	=	=

Residue scores: range 0–3 with score 0: no residue to score 3: residue above and below the vallecula. + indicates improvement, - indicates deterioration, and = indicates equality.

*Minimal compensation maneuver (chin on chest) was applied without instruction.

FOIS = Functional Oral Intake Scale: range 1–7, higher scores mean better oral intake; NA = not applicable (i.e., no transport possible); PAS = Penetration Aspiration Scale: range 1–8, lower scores mean better/safer swallowing function.

TABLE III.
Patients' Perceived SWAL-QOL Scores Pre- and Post-treatment (N = 6).

		SWAL-QOL										
		General Burden	Food Selection	Eating Duration	Eating Desire	Fear of Eating	Sleep	Fatigue	Communication	Mental Health	Social Function	Symptom Scale
1	Pre											
	Post	75.0	50.0	88.0	17.0	63.0	38.0	8.0	50.0	5.0	20.0	61.0
	Change											
2	Pre	50.0	100.0	100.0	17.0	50.0	0	0	50.0	50.0	60.0	45.0
	Post	25.0	50.0	50.0	33.0	25.0	0	0	25.0	25.0	25.0	25.0
	Change	+	+	+	+	+	=	=	+	+	+	+
3	Pre	100.0	125.0	125.0	67.0	75.0	38.0	67.0	63.0	75.0	15.0	84.0
	Post	0	0	63.0	17.0	44.0	0	0	25.0	10.0	10.0	36.0
	Change	+	+	+	+	+	+	+	+	+	+	+
4	Pre	25.0	25.0	75.0	25.0	38.0	38.0	33.0	100.0	30.0	25.0	45.0
	Post	88.0			75.0	100.0	13.0	50.0	63.0	75.0	65.0	
	Change	-			-	-	+	-	+	-	-	
5	Pre	13.0	75.0	125.0	67.0	38.0	50.0	50.0	25.0	100.0	45.0	95.0
	Post	0	0	0	17.0	0	38.0	42.0	0	0	20.0	11.0
	Change	+	+	+	+	+	+	=	+	+	+	+
6	Pre	88.0	75.0	88.0	50.0	56.0	38.0	50.0	100.0	45.0	55.0	57.0
	Post	25.0	38.0	88.0	25.0	63.0	50.0	50.0	50.0	35.0	55.0	48.0
	Change	+	+	=	+	=	-	=	+	=	=	+

SWAL-QOL = Swallowing Quality of Life Questionnaire: range 0–120; lower scores mean better subjective swallowing function. A difference score of 12 points or more was used to demonstrate improvement (+), deterioration (-), or equality (=).

up, four patients had improved on the PAS scores, with two patients no longer showing aspiration on follow-up VFS assessments for a specific (thin or thick liquid) consistency. Two of these four patients were no longer feeding tube dependent following the lipofilling injections. Patients' subjective perspective on their swallowing function based on the SWAL-QOL sub scores had improved in these four patients, as well (Table III). All patients had distinguishable fat deposits spread out at the base of tongue in their post-treatment MRI (median follow-up 14 weeks).

Case Histories

The first case concerns a 71-year-old female who had undergone surgical resection of a large benign mucinous cyst adenoma of the tongue in 2007. Afterward, she developed functional swallowing and articulation problems, primarily based on volume loss. Following three consecutive lipofilling sessions into the base of the tongue, the patient could swallow solid food much better, as also confirmed with VFS findings, and reported improved speech.

The second patient underwent radiotherapy in 2011 followed by surgical resection and reconstruction in 2012 for a recurrent left tonsillar carcinoma. Extensive treatment by the SLP did not improve the persisting swallowing problems. However, following three fat injections into the base of the tongue, the patient perceived improvement and was able to again resume consistent oral intake alongside his tube feeding.

The third patient participated because of progressive dysphagia after a supraglottic laryngectomy and bilateral cervical lymph node dissection followed by post-operative radiotherapy for a stage IV vallecula carcinoma in 1997. VFS evaluation following the three lipofilling sessions showed no more aspiration of thick liquids, and solids were swallowed more easily.

The fourth case concerns a 40-year-old male treated with chemoradiotherapy in 2007 for a stage IV oropharyngeal carcinoma. Severe dysphagia was present directly after treatment. Previous treatments such as physical therapy, hyperbaric oxygen, esophageal dilatation, cricopharyngeal myotomy, and larynx suspension were carried out without success. After two fat injections the patient noticed insufficient improvements and decided to discontinue the treatment.

The fifth patient with a stage IV base of tongue the tumor in 2004 was treated with concurrent chemoradiotherapy. She developed severe dysphagia and dysarthria due to oropharyngeal scarring and base of the tongue atrophy. Despite intensive swallowing training, the patient remained completely dependent on tube feeding. Aspiration occurred even at 1 mL swallows. MRI showed an atrophic tongue, sagged posteriorly. After three lipofilling injections the patient was able to eat and drink again for the first time in 10 years. The patient was very satisfied, and MRI showed increased tongue volume at the right base of the tongue (Fig. 4), but VFS evaluation still showed aspiration. At 8 months post-lipofilling, she remains happy with the procedure, although safe oral intake cannot be guaranteed.

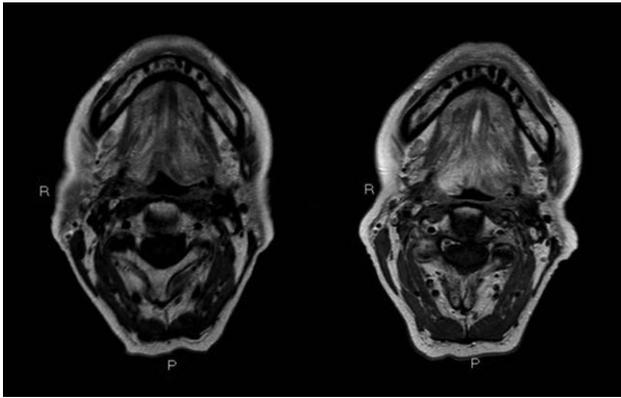


Fig. 4. Pre- and postoperative magnetic resonance imaging showing increased tongue volume as a result of several fat depositions at the right base of tongue (patient 5).

The last patient was treated with local resection, partial mandibulectomy and free fibula reconstruction, and postoperative radiotherapy in 1997 for a stage IV floor of mouth carcinoma. In 2013 he presented with progressive dysphagia requiring permanent tube feeding. Because exercise therapy for more than 1 year did not improve the persisting problems, he underwent three lipofilling procedures into the base of the tongue. Already after the second injection the patient noticed improvement in swallowing. Following the third injection he resumed oral intake and his feeding tube was removed. VFS assessment confirmed improved PAS scores for thick liquids. The effects are still maintained at 6 months post-treatment.

DISCUSSION

In this prospective pilot feasibility study, the potential value of autologous adipose tissue transplantation (lipofilling) for improvement of oropharyngeal swallowing was assessed in six HNC patients with chronic dysphagia following HNC treatment, with one additional patient taken off the study because of intercurrent disease and subsequent total laryngectomy.

Regarding feasibility and safety of the procedure, in this small series there were no complications or adverse events at the injection or donor site. All patients were admitted for observation for only 1 postoperative night, and none of the patients developed postoperative problems such as airway obstruction due to edema or swelling by the injected adipose tissue. Pain was also not an issue. Based on this limited experience, we now assume that hospital admissions might not be necessary. For future perspectives, this technique might even be performed without general anesthesia, especially in light of the need for multiple injections. It should be stressed, though, that the lipofilling injections were performed very carefully, starting with minimal (4 cm³) amounts of adipose tissue, to avoid potential respiratory problems due to postoperative swelling or overfilling in the oropharyngeal area.

The effectiveness of the procedure varied per patient. Although there was one patient who noticed no

clear benefit from the lipofilling injections and did not want to complete all three procedures (patient 4), there were four patients with severe dysphagia reporting significantly better swallowing function after the injections. At follow-up VFS assessments, these patients actually showed improvements on some of the FOIS and PAS scores, and two of them were even able to discontinue their enteral feeding. However, swallowing function was still not entirely safe in all of these patients. One patient (patient 6) experienced improvement in oral intake based on the FOIS scores, whereas there was no true improvement in function based on the PAS scores. After the lipofilling sessions she had one more episode of aspiration pneumonia treated conservatively, but this did not change her mind about her subjectively improved swallowing (as underlined in her SWAL-QOL results) and resuming her oral intake. This is in line with the literature that patient-reported outcome measures usually provide distinct but complementary information about swallowing,²⁴ and that patients' perceived swallowing function is important for quality of life.

We cannot easily explain the variability in results we observed between the patients. Adding volume is probably not always sufficient to restore swallowing function. Obviously, when there is no increase in tissue volume because of insufficient lipofilling, no benefit can be expected. However, despite the fact that a clear volume increase can be accomplished, the lipofilling injections nevertheless did not improve function in all of our patients. Currently, it is well acknowledged that dysphagia post-surgery and/or chemoradiotherapy is multifactorial in its physiological basis, which indicates that other factors such as fibrosis, reduced hyolaryngeal elevation, pharyngeal constrictor activity, and/or insufficient sphincter opening may also be an important factor besides volume loss.^{5,6} This might explain why improving just one element was not sufficient to make significant gains for some cases, though it was for others. Hence, further research will be necessary to improve the patient selection for this procedure.

Although pre- and post-treatment MRIs were available for all patients, these were not specifically made according to a protocol enabling accurate volume measurements, but merely to show the persistence of the injected adipose tissue. In fact, the fat deposits were visualized in all patients. MRIs enabling volume measurements, however, might be interesting as part of a future study protocol to substantiate the suggested beneficial effects of lipofilling in HNC.

Adipose tissue is extremely suitable for filling tissue defects because it is autologous and homogeneous in consistency, preventing possible graft-versus-host reactions, as opposed to artificial fillers that may have complications.¹¹⁻¹⁴ Nevertheless, it remains difficult to predict how much fat will be resorbed and thus how long a therapeutic effect will persist.¹⁶ With the Coleman technique, absorption of fat seems to be reduced as much as possible^{13,17}; however, three or more repeats are probably necessary to achieve and hold a therapeutic effect. According to the literature, the favorable outcomes of autologous fat injection are not only due to the filling of

soft tissue, but also to the potential regenerative effect of adipose-derived mesenchymal stem cells.^{12,16} The tissue may also become less fibrotic, yet there is no clear evidence for this.

As is often the case in clinical pilot feasibility studies, the sample size of this study was limited to only six patients, and these results should be interpreted with caution. However, the positive clinical outcomes of this study warrant further extensive investigation in larger patient cohorts to study the indications for lipofilling more precisely.

CONCLUSION

In this study, we describe the use of lipofilling in six patients with chronic dysphagia following advanced HNC treatment. The procedure seems feasible and safe, and in four out of six cases, of value for improving oropharyngeal dysfunction in this small, otherwise therapy-refractory patient cohort.

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