ACTA OTORHINOLARYNGOLOGICA ITALICA 2022;42:243-249; doi: 10.14639/0392-100X-N1992

LARYNGOLOGY

Voice outcomes in patients with advanced laryngeal and hypopharyngeal cancer treated with chemo-radiotherapy

Risultati vocali in pazienti con cancro laringeo e ipofaringeo avanzato trattati con chemio-radioterapia

César Álvarez-Marcos[1,2], Andrea Vicente-Benito[3], Águeda Gayol-Fernández[3], Daniel Pedregal-Mallo[1,2], Paloma Sirgo-Rodríguez[3], Liliana Santamarina-Rabanal[3], José Luis Llorente[1,2], Fernando López[1,2], Juan Pablo Rodrigo[1,2]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, Hospital Universitario Central de Asturias, Oviedo, Spain; [2] Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto Universitario de Oncología del Principado de Asturias (IUOPA), University of Oviedo, CIBERONC-ISCIII, Oviedo, Spain; [3] Department of Speech Therapy, Faculty of Psychology, University of Oviedo, Oviedo, Spain

SUMMARY

Objective. Patients with locally advanced laryngeal and hypopharyngeal cancer (LHC) are often treated with chemo-radiotherapy to avoid total laryngectomy, although voice problems may occur even if not markedly manifest. We sought to evaluate the impact of chemo-radiation on voice and quality of life.

Methods. We studied 21 patients with locally advanced LHC with tumour control at least two years after chemo-radiotherapy. None manifested clinical symptoms related to the treatment and maintained an activity considered as within normal limits. All patients had a voice handicap index (VHI) of less than 15. Voice function was evaluated by perceptual vocal analysis (CAPE-V) and aerodynamic and acoustic study. Quality of life was assessed with the EORTC-H&N35 (voice items 46, 53 and 54).

Results. Voice changes were frequent, with alterations in all CAPE-V attributes, and predominantly type II and III spectrograms in acoustic analysis (78%). The EORTC-H&N35 scale showed a reduction in scores in 10-40% of items related to voice.

Conclusions. Subclinical voice disorders are common after chemo-radiotherapy. Although patients consider vocal impairment to be very minor and to not interfere with their daily life, it may contribute to a reduced quality of life.

KEY WORDS: laryngeal and hypopharyngeal cancer, quality of life, organ-preservation protocol, voice

RIASSUNTO

***Obiettivo**. I pazienti con cancro della laringe e dell'ipofaringe (LHC) localmente avanzato vengono spesso trattati con chemio-radioterapia per evitare la laringectomia totale, anche se si possono presentare problemi disfonici. Abbiamo cercato di valutare l'impatto della chemioradioterapia sulla voce e sulla qualità della vita.*

***Metodi**. Abbiamo studiato 21 pazienti con LHC localmente avanzato, con controllo locale di malattia a 2 anni dal termine dei trattamenti chemio-radioterapici. Nessuno di essi lamenta sintomi clinici correlati a detto trattamento, essendo ritornati a una normale attività di vita. Tutti i pazienti mostrano un indice di handicap vocale (VHI) inferiore a 15. La funzione vocale è stata valutata mediante analisi percettiva vocale (CAPE-V) e studio aerodinamico e acustico. La qualità della vita è stata valutata con l'EORTC-H&N35 (voci 46, 53 e 54).*

***Risultati**. I cambiamenti di voce sono risultati essere frequenti, con alterazioni del CAPE-V e spettrogrammi prevalentemente di tipo II e III nell'analisi acustica. (78%). La scala EORTC-H&N35 mostra una riduzione del punteggio tra il 10-40% nelle voci relative alla funzione vocale.*

***Conclusioni**. I disturbi della voce subclinici sono comuni dopo la chemio-radioterapia. Sebbene i pazienti considerino la compromissione vocale di minore importanza, non interferendo tali alterazioni con la loro vita quotidiana, tali disturbi potrebbero contribuire a una ridotta qualità della vita.*

PAROLE CHIAVE: *cancro laringeo e ipofaringeo, qualità della vita, protocollo di conservazione dell'organo, voce*

Received: December 29, 2021
Accepted: March 14, 2022

Correspondence
Fernando López
Department of Otorhinolaryngology, Hospital Universitario Central de Asturias
Avenida de Roma s/n, 33011 Oviedo (Spain)
E-mail: flopez_1981@yahoo.es

How to cite this article: Álvarez-Marcos C, Vicente-Benito A, Gayol-Fernández A, et al. Voice outcomes in patients with advanced laryngeal and hypopharyngeal cancer treated with chemo-radiotherapy. Acta Otorhinolaryngol Ital 2022;42:243-249. https://doi.org/10.14639/0392-100X-N1992

Introduction

Treatment of head and neck cancer (HNC) usually adversely affects voice and swallowing [1,2]. Radiotherapy (RT) or chemoradiotherapy (CRT) has become standard for the management of locally advanced laryngeal and hypopharyngeal carcinomas (LHC) [3].

RT causes laryngeal muscle atrophy and/or stiffness, fibrosis, insufficient lubrication of the laryngeal mucosa, hyperaemia, oedema and erythema [4]. These changes can lead to impaired vocal fold function [5]. In addition, the tissue effects of RT are enhanced by chemotherapy [1,5].

Voice disorders are common in patients treated with CRT [5]. Following CRT treatment, patients may present with reduced volume, low modal pitch, reduced phonic breath support, hoarseness and vocal fatigue. This is reflected in altered phonatory function tests in which impaired acoustic and aerodynamic measures of the voice are observed. In addition, patients frequently complain that the voice is highly variable and unpredictable after RT [4]. All these disorders can reduce speech intelligibility and impaired articulation can affect patients' daily life activities and interactions, which can be associated with severe functional and psychosocial problems that affect the quality of life (QoL) [6].

The presence of voice disorders after CRT in patients with advanced HCL has been studied by several authors [1,4]. In general, it has been observed that the voice worsens during CRT, improves 1-2 months after the end of treatment and reaches pre-treatment levels after 1 year or more.

Despite having an alteration in QoL, some patients with laryngeal or hypopharyngeal carcinomas treated with CRT and controlled disease do not perceive an alteration in their voice. Our aim was to detect possible subclinical voice impairment in these patients and to determine how it affects their QoL.

Methods

Patients

Since 2012, our department has followed an organ preservation protocol with CRT for patients with locally advanced LHC and, up to 2017, a total of 82 patients had been included. A cross-sectional observational cohort study was designed. To be included in the study, patients must have been tumour-free at the time of the study and without tracheostomy. None of the patients had any complaints about their voice during follow-up. Voice was assessed by the Voice Handicap Index (VHI) [7]. All patients had VHI score < 15. A cut-off score of 15 points has been established to identify patients with voice problems in daily life [4]. The minimum follow-up since the end of the treatment had to be 2 years. Patients who had undergone surgery in the head and neck area, including tracheostomy, those dependent on a feeding tube or percutaneous endoscopic gastrostomy for nutritional support, or had received specific rehabilitation by a speech therapist due to swallowing or voice disorders were excluded. Moreover, patients diagnosed with chronic obstructive pulmonary disease and pharyngo-laryngeal reflux before the start of CRT, as well as those who continued to smoke at the time of the study, were also excluded. The final sample consisted of 21 patients (25.6% of all patients treated with CRT): 16 men (76%) and 5 women (24%), with a mean age of 65 years (range 56-77 years). The selected patients underwent perceptual study, aerodynamic and acoustic analysis and QoL assessed with EORTC-H&N35 (voice items) between the second and third year after the CRT.

All patients were or had been smokers and 15 (71%) had a history of alcohol consumption. All patients stopped smoking after treatment. In 12 patients, the tumour was in the larynx (8 stage III and 4 stage IVa; all T3) and in 9 patients in the hypopharynx (6 stage III and 3 stage IVa; 3 T2 and 6 T3). All patients underwent endoscopic evaluation of the larynx prior to treatment. Unilateral vocal fold paralysis was observed in all patients with a paramedian position of the paralysed vocal fold and a glottic gap. Despite having vocal cord paralysis, no patient had been seen prior to diagnosis of the tumour for dysphonia. The mean time since CRT was 31.52 months (range 24-36). None of the patients reported symptoms related to CRT and stated that their voice was like what it was before CRT. Endoscopic examination after treatment revealed that laryngeal structures were well preserved. Ten patients had recovered vocal cord mobility, 3 had vocal paresis and 8 had not recovered vocal mobility.

The treatment with CRT consisted of a single cycle of induction chemotherapy (cisplatin, 100 mg/m^2 on day 1 plus 5-fluorouracil, 1,000 mg/m^2, for 5 days) followed by concomitant CRT (70 Gy in 7 weeks plus cisplatin, 75 mg/m^2, every 3 weeks, on days 1, 22 and 43) [8]. All participants were treated with volumetric intensity modulated radiation therapy (IMRT) in volumetric modulated arc therapy (VMAT).

Evaluation of voice

Voice outcomes were assessed at least 2 years after CRT with a maximum of 3 years. All recordings were made in a sound-treated room using a SONY ECM- DS70P condensing microphone with a flat frequency response and a SONY ICD-PX820 (16-bit) digital wave recorder with a sampling frequency of 40 kHz. The distance from the mouth to the microphone was kept constant at approximately 30 cm at a 45° angle.

Perceptual evaluation

The Consensus Protocol for Auditory-Perceptual Voice Assessment (CAPE-V) is a test designed to promote a standardised approach to assess and document auditory-perceptual judgments of vocal quality [9]. CAPE-V assesses 6 perceptual components of voice (general gravity, roughness, respiration, tension, pitch and loudness) and scores each component using a 100-mm line as a visual-analogue scale. Higher scores indicate more significant deviation from normal in such a way that the scoring scale was divided into normal (0 mm), mild (1-33 mm), moderate (34-66 mm) and severe (67-100 mm). The CAPE-V test was validated into Spanish from its initial version in English [10] and has 3 tasks that are evaluated using the visual-analogue scale of 0-100 mm: 1) a sustained vowel /e/ emitted three times during 3-5 seconds in a natural and comfortable tone, selecting the highest quality; 2) 6 sentences of the adapted CAPE-V that evaluate specific and concrete aspects of speech in a controlled linguistic environment that reveal compromised phonetic situations (articulation, glottal attacks, vocal spasms, hypo-hypernasality); 3) natural speech of 20 seconds versed in how the patient perceives his voice. The easiest task to perform this provides more consistent results in adults is the sustained vowel [11]. If the quality of all the tasks is uniform and does not show significant discrepancies, CAPE-V can be scored with a single scale to manage its results, using the highest values [10]. Two experienced speech and language pathologists (SLP; P.S-R and A. G-F), who regularly use the CAPE-V since its validation into Spanish in 2015 [10], evaluated the voice recordings randomly and independently. Ratings were established by direct observation of vocal output, and not by patient report or other means. For overall analysis of perceptual evaluation, average scores between the two raters' mean opinion scores were used to evaluate perceptual voice and speech parameters. Recordings were coded to avoid patient identification.

Aerodynamic analysis

The variable maximum phonation time (MPT) was used, which is a simple test of glottic efficiency [12]. MPT is the longest period during which a patient can sustain phonation of a vowel sound, typically /a/. The vowel /a/ is emitted effortlessly for as long as possible after a deep inspiration and time in seconds was measured with a chronometer. Typically, with no laryngeal pathology, adult males can sustain vowel sounds for between 25-35 seconds and adult females between 15-25 seconds. In cases of vocal dysfunction/laryngeal pathology, however, the MPT is considerably reduced. Arguably, therefore, MPT is of most use when glottic efficiency is poor (an MPT of 10 seconds or less) [12]. MPT is not diagnostic of laryngeal pathology, but it may be useful as an indicator of laryngeal pathology and is frequently used to monitor progress.

Acoustic analysis

The /e/ sound was analysed at comfortable levels of intensity and pitch in a soundproof environment. The computer captured 3 sec of the sound, selecting the most stable part of the broadcast, avoiding its beginning and end. Once the signal was digitised, the acoustic parameters were analysed with the PRAAT 5.6.56 programme [13]. The reference values of the acoustic variables were taken from a healthy Spanish population of the same age and gender range [14]. The acoustic parameters obtained were fundamental frequency F0 (Hertz, Hz), intensity (decibels, dB) and harmonic-noise ratio (HNR) (dB). The spectrographic analysis consisted of performing a narrow band spectrogram, using the Yanagihara classification (grades I to IV) [15].

Evaluation of Quality of life (QoL)

QoL was assessed using the European Organization for Research and Treatment of Cancer - Head and Neck questionnaire 35 (EORTC-H&N35) consists in 7 subscales with 35 items to assess QoL in head and neck cancer. It has been widely used especially in patients treated with CRT [16,17]. The subscale "speech problem" that includes three items is evaluated (46: *Have you had problems with hoarseness?* 53: *Have you had problems talking to other people?* and 54: *Have you had problems talking on the telephone?*). Each item has four-point scale (from 0 to 4; best to worst). The scale score becomes a scale from 0 to 100 and a higher score indicates a greater alteration in QoL. We use the general score of the subscale and the value of each item.

Statistical analysis

All variables were analysed with SPSS 22.0 for Windows. Descriptive statistical data (mean, standard deviation, range, median, interquartile range) were obtained. Relationships were established between the QoL questionnaire (EORTC- H&N35) and the categorical-ordinal variables of vocal alteration: perceptual (CAPE-V), aerodynamic and acoustic analysis, with Pearson and Spearman correlations, the latter in asymmetric distributions. Values of $p < 0.05$ were considered statistically significant.

Results

Voice evaluation results

Most of the participants had a mild to moderate degree of alteration for overall severity, roughness, breathiness, strain, pitch and loudness with CAPE-V (Tab. I). No patient

Table I. Perceptual values in degrees of affectation for CAPE-V.

	Overall severity	Roughness	Breathiness	Strain	Pitch	Loudness
Normal (0)	-	-	1 (4.8%)	-	-	-
Mild (1-33)	9 (42.9%)	13 (61.9%)	16 (76.2%)	15 (71.4%)	17 (81%)	20 (95.2%)
Moderate (34-66)	9 (42.9%)	7 (33.3%)	3 (14.2%)	6 (28.6%)	4 (19%)	1 (4.8%)
Severe (67-100)	3 (14.2%)	1 (4.8%)	1 (4.8%)	-	-	-

Table II. Aerodynamic and acoustic measurements.

Variables	Mean	Standard deviation	Range
MPT* (s)	13.57	5.74	5-23
HNR** (dB)	10.25	6.64	0.51-21.41
F0§ (Hz)	153.71	91.29	80.43-488.83
Intensity (dB)	79.19	2.32	71.90-83.31

**MPT: maximum phonation time; ** HNR: harmonic-to-noise ratio; §F0: fundamental frequency*

showed normality values in the total of CAPE-V attributes. Table II shows the measurements of aerodynamic and acoustic parameters. In the classification of voices in the Yanagihara scale, 4 cases (19%) showed grade I, 8 (38%) grade II and 9 (43%) grade III.

Quality of life

The values obtained for the voice items of the EORTC-H&N35 questionnaire are shown in Table III. A decrease in QoL was observed in the overall voice and in the three voice items separately, especially in item 46. Six patients (28.6%) indicated "Not at all" in all the three items.

Correlations were sought between the CAPE-V attributes with the EORTC-H&N35 voice items and the aerodynamic and acoustic variables, without observing significant values in any. Significant values were also not observed when correlating EORTC-H&N35 items with the aerodynamic and acoustic variables.

Discussion

Voice disorders are common sequelae after CRT treatment in HNC. In this work, a voice study was carried out in a selected sample of patients with LHC who underwent treatment with CRT and an organ preservation protocol. The main criterion for selection was that patients had no complaints about their voice before treatment, despite having vocal paralysis, and that they considered that their voice had not changed after CRT and was similar to their voice before treatment. A cut-off score of 15 points in the VHI-30 (97% sensitivity and 86% specificity) was established to identify patients with LHC and voice problems in daily life, as used by other authors [4]. Vocal disability perceived by all patients treated with CRT in our centre is classified according to the VHI-30 as mainly mild (90%), as observed in other studies [15,18].

It should be noted that the sample of our patients is homogeneous since all had similar location (LHC) and disease stage (III-IV) and had been treated with the same organ preservation protocol. This reduces the size of the sample that we study compared with other larger series that include other HNC locations such as oropharynx, oral cavity and nasopharynx, with expected voice sequelae of different severity and importance [4]. Furthermore, in our study there were no patients with previous surgeries in the upper aerodigestive tract, including tracheostomy, that could produce voice alterations. Another criterion that limited the sample size was the exclusion of patients with known voice disorders after CRT, rejecting those with severe mucositis and who had undergone specific rehabilitation by speech therapist. Patients who manifested swallowing disorders or had undergone a medical, instrumental, or rehabilitative procedure for dysphagia were also excluded, since this situation can cause a decrease in QoL. This must be considered because VHI-30 assesses the vocal disability perceived by the patient himself and QoL indirectly in relation to voice disorders, but does not take into account swallowing, eating and social and occupational disorders that af-

Table III. EORTC-HN35 (overall voice and items 46, 53 and 54).

Variables	Mean	Standard deviation	Median	Range
Overall voice	21.16	26.26	11.11	0-89
Item 46	39.68	39.25	50	0-100
Item 53	24.60	33.58	0	0-100
Item 54	10.31	27.11	0	0-100

fect global QoL. Therefore, the sample, although relatively small, provides very concrete and specific information on LHC treated with CRT.

The evaluation with the CAPE-V test showed a predominance of mild and moderate degrees in the vocal characteristics of patients, as also observed by other authors [15]. The perceptual evaluation with this test through the phonation of vowels in an adequate and comfortable tone allows the patient's voice to be heard without influences of the articulation of words or the beginnings and ends of phonation, in addition to serving to perform objective acoustic analysis [11]. This fact was adapted to our sample of patients, since the field of RT affects the larynx and hypopharynx where vocal articulation is less altered than other locations (oral cavity and oropharynx), as observed by others [4,19]. Our work also reflects that the vocal perception of participants is better (VHI < 15) than that collected by the researchers in the perceptual analysis with CAPE-V, as has also been published [4]. It has been reported that subjective tests (VHI-30, CAPE-V) show a lower perception of severity compared to objective tests (acoustic analysis and spectrogram) and that these tests do not usually correlate with each other when evaluating different data [10,15,20,21]. This discrepancy between patients and researchers is explained by the fact that the former tend to minimise the importance of vocal disability and its impact on QoL, since they retain their voice. Patients undergoing CRT have particular characteristics, since they assess their voice during a severe and potentially life-threatening cancer, the treatment of which could be total laryngectomy. For this reason, it is possible that at the end of a successful CRT treatment, patients may show a tendency to rate their voice as normal or slightly altered. Another aspect to be taken into account is that most patients definitively gave up their usual work activity after completion of CRT. The greatest alteration of the voice during CRT has been reported to occur during its administration or just at the end of treatment [16,17]. However, our results in CAPE-V and acoustic-aerodynamic analysis confirm that voice disorders are common, even after several years, being more evident for researchers than for the patients themselves. This can be explained for several reasons. The passage of time from the end of the CRT treatment to the completion of the QoL questionnaires (mean: 31.52, range: 24-36 months) favours adaptation to sequelae and the trend to positively judge having an intact voice. Other studies have shown that an adaptation mechanism can occur over time, as seen in swallowing disorders in the same LHC patients treated with CRT, where a self-administered test such as EAT-10 was normal, while other more specific and objective parameters were altered [22]. Several authors have pointed out that in patients with HNC treated with CRT swallowing disorders affect QoL in a more negative way than voice disorders [2,4,22,23], concluding that it is very possible that the impact of CRT on voice has not been sufficiently clarified and is generally minimised. In this regard, it has been proposed to reduce these sequelae, both vocal and swallowing, through early rehabilitation exercises and extend their use once treatment with CRT has been completed [6].

Acoustic analysis showed interesting data. On one hand, it is observed that mean F0 and vocal intensity were within normal range (154 Hz and 79 dB, respectively), although with very wide dispersion values in F0. On the contrary, spectrographic analysis of most patients showed grades II (38%) and III (43%). These results are similar to those described in other studies, which only observed grade IV in 12% of patients [15].

The QoL of the patients studied shows a worsening in both overall voice and in each individual item, ranging between 10 and 40%, as seen in Table III. Voice-related questions are very general, and thus participants tend to answer them with a more favourable score on the EORTC-H&N35. However, only 6 patients in the sample studied indicated "Not at all" in the three items. In the EORTC-H&N35 questionnaire, specific for HNC, only 3 of its 35 items are related to voice, while 20 are related to swallowing and feeding. For this reason, it is difficult to determine to what extent voice alterations intervene in QoL when they have so little weight in its global assessment. It would be beneficial if in the global calculation of QoL of patients undergoing CRT the number of items that assess vocal disorders and swallowing disorders were more balanced [2,22,23], as for example with the HADS (Scale of hospital anxiety and depression) that assesses anxiety/depression with 14 items (7 for each disorder) [24].

Other authors have compared QoL in patients with glottic laryngeal cancer and observed that those treated with RT have better QoL in the EORTC-H&N35 questionnaire in the areas of voice quality, emotional functioning and social contact in relation to those treated with surgery, although the items referred to "dry mouth" and "sticky saliva" are higher in patients with surgery [25].We have not been able to establish significant correlations between CAPE-V attributes and QoL assessed with the EORTC-H&N35 voice items, nor between them and aerodynamic and acoustic variables. Other authors have observed a relationship between the functional and physical areas of symptoms of the VHI-30 and EORTC-H&N35 [16]. However, one of the criteria established to select the sample studied was a VHI-30 value < 15, and thus it is likely that the relationship of the subjective questionnaires that evaluate the voice is altered.

There is much information in the literature on voice and

swallowing in patients with HNC treated with CRT, but it is often at variance [2,4,22]. This is due to the difficulty of obtaining uniform series in terms of tumour location, CRT modality and evaluation time with respect to treatment (during, early end, late end). In addition, other factors such as having vocal rehabilitation, tracheostoma and concomitant surgery have an influence in functional outcomes, making the data obtained in the different studies difficult to compare. On the other hand, there are many subjective questionnaires where items related to voice are usually few and superficial. These questionnaires query patients' self-perception and assess their QoL. However, they do not necessarily detect the physical state or functioning of the affected organs.

QoL of LHC patients treated with CRT is not only conditioned by functional swallowing or vocal alterations, but also by other factors that may be physical (tracheostoma, change in body scheme), emotional, cognitive and socio-occupational. Therefore, the design of a questionnaire that considers the main functional disorders in a balanced way would reflect the extent to which the alterations are related to QoL and the therapeutic modality used, both surgical (total laryngectomy, supraglottic) and CRT. They would therefore be a guide to indicate different supportive and rehabilitation therapies, as suggested by other authors [2,6,26]. Our group is conducting a study similar to the present one in the same group of patients but with diagnostic instruments and QoL questionnaires for swallowing disorders [22]. Therefore, it would be necessary to design balanced QoL questionnaires for each therapeutic modality used, both surgical (total laryngectomy, supraglottic) and CRT, since the latter preserves the anatomical structures related to voice and swallowing, while the functional impact is not the same. An exploratory factor analysis and convergent validity should be performed to create a specific questionnaire for patients with LHC treated with CRT, with more robust and balanced items between voice and swallowing disorders.

Conclusions

Patients with LHC treated with CRT, with their disease under control and without manifesting clinical voice disorders in follow-up or in self-evaluation questionnaires, frequently present vocal disorders if objective and specific subjective procedures are used. The perceptual and vocal analysis by researchers shows that the vocal quality is worse than what they perceive. These observed disorders have an impact on their QoL. Given these results, it would be advisable to evaluate both objective and subjective characteristics of the patients' voices at the end of the CRT to detect alterations that could be rehabilitated and thus avoid future impact on the QoL.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This study was supported by grants from CIBERONC (CB16/12/00390 to JPR), Ayudas a Grupos PCTI Principado de Asturias (IDI2018/155 to JPR), Fundación Bancaria Caja de Ahorros de Asturias-IUOPA and the FEDER Funding Program from the European Union.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AV-B, AG-F, DP-M, PS-R nad LS-R. CAM wrote the first draft of the manuscript and others authors commented on previous versions of the manuscript. FL, JPR and JLL wrote, supervised adn edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

All procedures were conducted in accordance with the Declaration of Helsinki and approved by Institutional Ethics Committee of the HUCA (285/18). Written informed consent was obtained from each patient.

References

1 Jacobi I, van der Molen L, Huiskens H, et al. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol 2010;267:1495-1505. https://doi.org/10.1007/s00405-010-1316-x

2 Kraaijenga SA, van der Molen L, Jacobi I, et al. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol 2015;272:3521-3531. https://doi.org/10.1007/s00405-014-3379-6

3 Machiels JP, Rene Leemans C, Golusinski W, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1462-1475. https://doi.org/10.1016/j.annonc.2020.07.011

4 Kraaijenga SA, Oskam IM, van Son RJ, et al. Assessment of voice, speech, and related quality of life in advanced head and neck cancer patients 10-years+ after chemoradiotherapy. Oral Oncol 2016;55:24-30. https://doi.org/10.1016/j.oraloncology.2016.02.001

5 Patterson JM. Late effects of organ preservation treatment on swallowing and voice; presentation, assessment, and screening. Front Oncol 2019;9:401. https://doi.org/10.3389/fonc.2019.00401

6 Carmignani I, Locatello LG, Desideri I, et al. Analysis of dysphagia in advanced-stage head-and-neck cancer patients: impact on quality of life and development of a preventive swallowing treatment. Eur

Arch Otorhinolaryngol 2018;275:2159-2167. https://doi.org/10.1007/s00405-018-5054-9

7 Núñez-Batalla F, Corte-Santos P, Señaris-González B, et al. Adaptation and validation to the Spanish of the Voice Handicap Index (VHI-30) and its shortened version (VHI-10). Acta Otorrinolaringol Esp 2007;58:386-392.

8 Urba S, Wolf G, Eisbruch A, et al. Single cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006;24:593-598. https://doi.org/10.1200/JCO.2005.01.2047

9 Kempster GB, Gerratt BR, Verdolini Abbott K, et al. Consensus auditory perceptual evaluation of voice: development of a standardized clinical protocol. Am J Speech Lang Pathol 2009;18:124-132. https://doi.org/10.1044/1058-0360(2008/08-0017

10 Núñez-Batalla F, Morato-Galán M, García-López I, et al. Validation of the spanish adaptation of the consensus auditory-perceptual evaluation of voice (CAPE-V). Acta Otorrinolaringol Esp 2015;66:249-257. https://doi.org/10.1016/j.otorri.2014.07.007

11 Zraick R, Wendel D, Smith-Olinde L. The effect of speaking task on perceptual judgment of the severity of dysphonic voice. J Voice 2005;19:574-581. https://doi.org/ 10.1016/j.jvoice.2004.08.009

12 Maslan J, Leng X, Rees C, et al. Maximum phonation time in healthy older adults. J Voice 2011;25:709-713. https://doi.org/10.1016/j.jvoice.2010.10.002

13 Boersma P, Weenink D. Praat: doing phonetics by computer. Amsterdam: Department of language and Literature, University of Amsterdam (http://www.fon.hum.uva.nl/praat/). Accessed on June 2021.

14 Delgado-Hernández J, León-Gómez NM, Izquierdo-Arteaga LM, et al. Cepstral analysis of normal and pathological voice in Spanish adults. Smoothed cepstral peak prominence in sustained vowels versus connected speech. Acta Otorrinolaringol Esp 2018;69:134-140. https://doi.org/10.1016/j.otorri.2017.05.006

15 Núñez Batalla F, Caminero Cueva MJ, Señaris González B, et al. Voice quality after endoscopic laser surgery and radiotherapy for early glottic cancer: objective measurements emphasizing the Voice Handicap Index. Eur Arch Otorhinolaryngol 2018;265:543-548. https://doi.org/10.1007/s00405-007-0512-9

16 Wan Leung S, Lee TF, Chien CY, et al. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQH& N35 questionnaires. BMC Cancer 2011;11:128. https://doi.org/10.1186/1471-2407-11-128

17 Ham JC, van Herpen CML, Driessen CML, et al. Health-related quality of life of patients treated with chemoradiotherapy plus or minus prophylactic antibiotics to reduce the number of pneumonias for locally advanced head and neck cancer, the PANTAP study. Oral Oncol 2019;96:105-112. https://doi.org/10.1016/j.oraloncology.2019.07.014

18 Rosa MED, Mituuti CT, Ghirardi ACAM. Correlation between the Voice Handicap and Swallowing Quality of Life in patients with laryngeal cancer submitted to chemoradiotherapy. Codas 2018;30:e20170060. https://doi.org/10.1590/2317-1782/20182017060

19 Nguyen NP, Abraham D, Desai A, et al. Impact of image-guided radiotherapy to reduce laryngeal edema following treatment for non-laryngeal and non-hypopharyngeal head and neck cancers. Oral Oncol 2011;47:900-904. https://doi.org/10.1016/j.oraloncology.2011.06.004

20 Woisard V, Bodin S, Yardeni E, et al. The voice handicap index: correlation between subjective patient response and quantitative assessment of voice. J Voice 2007;21:623-631. https://doi.org/10.1016/j.jvoice.2006.04.005

21 Schindler A, Mozzanica F, Vedrody M, et al. Correlation between the voice handicap index and voice measurements in four groups of patients with dysphonia. Otolaryngol Head Neck Surg 2009;141:762-769. https://doi.org/10.1016/j.otohns.2009.08.021

22 Álvarez-Marcos C, Benito AV, Fernández AG, et al. Asymptomatic swallowing disorders may be present in individuals with laryngeal and hypopharyngeal cancer treated with chemo-radiotherapy. Eur Arch Otorhinolaryngol 2022;279:995-1001. https://doi.org/10.1007/s00405-021-06861-y

23 Rinkel RN, Verdonck-de Leeuw IM, Doornaert P, et al. Prevalence of swallowing and speech problems in daily life after chemoradiation for head and neck cancer based on cut-off scores of the patient-reported outcome measures SWAL-QOL and SHI. Eur Arch Otorhinolaryngol 2016;273:1849-1855. https://doi.org/10.1007/s00405-015-3680-z

24 Danker H, Wollbrück D, Singer S, et al. Social withdrawal after laryngectomy. Eur Arch Otorhinolaryngol 2010;267:593-600. https://doi.org/10.1007/s00405-009-1087-4

25 Arias F, Arraras JI, Asin G, et al. Quality of life and voice assessment in patients with early-stage glottic cancer. Head Neck 2015;37:340-346. https://doi.org/10.1002/hed.23603

26 Sreenivas A, Sreedharan S, Narayan M, et al. Effect of vocal rehabilitation after chemoradiation for non-laryngeal head and neck cancers. Acta Otorhinolaryngol Ital 2021;41:131-141. https://doi.org/10.14639/0392-100X-N0977