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Managing Editor
M. Ansarin

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Review

Loss of smell in COVID-19 patients: a critical review with emphasis on the use of olfactory tests

COVID-19 e olfatto: revisione critica della letteratura sulla valutazione olfattiva

Rosario Marchese-Ragona[1], Domenico Antonio Restivo[2], Eugenio De Corso[3], Andrea Vianello[4], Piero Nicolai[1], Giancarlo Ottaviano[1]

[1] Department of Neuroscience, Otolaryngology Section, University of Padua, Italy; [2] Department of Medicine, Neurological Unit and Service of Clinical Neurophysiology, Garibaldi Hospital, Catania, Italy; [3] Fondazione Policlinico Universitario A. Gemelli IRCCS, Unità Operativa di Otorinolaringoiatria, Università Cattolica del Sacro Cuore, Rome, Italy; [4] Department of Cardiological, Thoracic and Vascular Sciences, Respiratory Pathophysiology Unit, University of Padua, Italy

SUMMARY

Since December 2019, an outbreak of a newly isolated coronavirus (SARS-CoV-2) appeared in Wuhan, China, and then spread worldwide. Recently, it has emerged that a number of patients may present with sudden hyposmia, sometimes without other symptoms of the disease. We performed a critical review on the methods used to date to investigate the olfactory function in COVID-19 patients in order to establish which should be considered the most appropriate to use during this pandemic. Literature analysis showed that the diagnosis of hyposmia in COVID-19 patients was mainly made through subjective symptomatology collected by questionnaires and/or interview. Psychophysical tests were carried out in a few studies showing significant discrepancies between the self-reported sense of smell and test results. To date the methods used by authors to investigate smell impairment in COVID-19 patients have been very heterogeneous and predominantly based on self-reported questionnaires leading to confusing and inconclusive results. We suggest that simple validated self-administered psychophysical olfactory tests could be a valuable instrument to investigate isolated/quarantined or hospitalised COVID-19 patients referring smell impairment in order to confirm olfactory dysfunction.

KEY WORDS: hyposmia, COVID-19, SARS-CoV-2, olfaction, olfactory test, surveys

RIASSUNTO

Da dicembre 2019, in seguito alla comparsa in Cina di una nuova infezione da Coronavirus (COVID-19), si è assistito alla diffusione di una pandemia. In un numero significativo di pazienti è stata riscontrata la comparsa di alterazioni dell'olfatto anche in assenza di altri sintomi tipici dell'infezione. In questa revisione della letteratura sono stati inclusi gli articoli pubblicati da gennaio 2020 sull'alterazione olfattiva nei pazienti COVID-19 e in particolare i metodi utilizzati per la diagnosi. L'analisi della letteratura ha mostrato che la diagnosi dell'alterazione olfattiva in questi pazienti è stata eseguita principalmente mediante questionari. Pochi studi si sono basati sulla valutazione olfattiva mediante test psicofisici validati. Sono emerse discrepanze tra l'alterazione olfattiva riportata nei questionari e la valutazione olfattiva eseguita mediante test psicofisici. Ad oggi lo studio dell'olfatto nei pazienti COVID-19 è stato eseguito in maniera eterogenea e principalmente basata sui sintomi riferiti dai pazienti portando a risultati spesso contrastanti. Gli autori suggeriscono di utilizzare test olfattivi psicofisici, semplici, validati e somministrabili anche in assenza di un operatore al fine di confermare l'alterazione olfattiva in questi pazienti che spesso sono in quarantena, isolati o ospedalizzati.

PAROLE CHIAVE: *iposmia, anosmia, COVID-19, SARS-CoV-2, olfatto, test olfattivi, questionari*

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Correspondence
Giancarlo Ottaviano
Department Neurosciences, Otolaryngology Section, University of Padova, via Giustiniani 2, 35100 Padua, Italy
Tel. +39 049 8214470. Fax +39 049 8213113
E-mail: giancarlo.ottaviano@unipd.it

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Introduction

Since December 2019, a novel coronavirus SARS-CoV-2 (COVID-19) outbreak emerged in Wuhan, China, and subsequently rapidly spread to several countries [1].

The clinical manifestations of COVID-19 range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome. Guan et al. [2], in a comprehensive review of patients affected by SARS-CoV-2, described the clinical presentation of 7,736 patients who were hospitalised in China. Fever, the most frequent symptom, was present in 43.8% to 88.7% of cases. Other reported symptoms included cough (67.8%), fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), myalgia or arthralgia (14.9%), sore throat (13.9%), headache (13.6%), chills (11.5%), nausea or vomiting (5%), diarrhoea (3.8%), nasal congestion (4.8%), haemoptysis (0.9%) and conjunctival congestion (0.8%). Alterations in taste or smell were not reported among the clinical symptoms. Mao et al. [3], studying 214 consecutive patients with laboratory-confirmed diagnosis of SARS-COV-2, reported in 36.4% both central and peripheral nervous system manifestations. Among the latter, hypogeusia and hyposmia were reported in 5.6 and 5.1% of cases, respectively. After this first report, numerous other cases of hyposmia in patients suffering from COVID-19 have been reported in the media and scientific journals, especially otolaryngology journals, so that a less serious variant of COVID-19 responsible for this symptomatology has been hypothesised [4]. Given these reports, the British Rhinological Society (BRS), as well as the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), recommended that the smell loss should be considered a marker of COVID-19 infection [5,6].

Herein, we critically reviewed reports about the methods used to date to quantify olfactory loss in COVID-19 patients, highlighting the limitations of subjective olfactory assessment and the importance of using validated olfactory tests during this pandemic.

Methodology of search strategy

We performed a full systematic review of the literature including English-language articles that were screened from several databases (PubMed, Medline, Web of Science and Google Scholar) and published from January 2020. Literature searches were performed in the beginning of May 2020. We searched articles using MeSH-terms, and/or text words such as "COVID-19", "SARS-CoV-2", "smell", "smell loss", "anosmia", "hyposmia" and "olfactory dysfunction". Titles were screened for relevance, followed by review of the abstract and full text. We only included peer-reviewed papers. This resulted in 24 papers that were discussed in this review. A total of 45 references were used in the full document. We did not include in this critical review articles reporting on 10 or less confirmed SARS-CoV-2 positive patients, unless a validated olfactory test was performed. Generally, we excluded articles with the lack of confirmed COVID-19 status. We divided the identified studies in two major groups, based on the methodology used to detect impairment of smell, and specifically studies using simple surveys or data extracted by medical records and studies using validated olfactory tests.

Sense of smell evaluation in confirmed COVID-19 patients by survey, questionnaires, or medical records

The majority of published studies concerning olfactory dysfunction in patients with COVID-19 infection have used survey questionnaires.

Hopkins et al. [5], of 2,428 subjects (most of them unconfirmed for COVID-19) who complained of smell loss, identified 74.4% reporting anosmia and 17.3% very severe smell loss. Interestingly, of the 80 patients who underwent nasopharyngeal swabs for COVID-19, only 74% tested positive for the virus.

Via telephone interview, Lee and co-workers [7] evaluated 3,191 laboratory confirmed COVID-19 patients complaining of acute anosmia or ageusia. Smell/taste loss was reported by 15.3% of patients (n = 488). Among these, only olfactory loss was reported by 27.7% of patients, ageusia by 20.3% and both by 52%. Similarly, Heidari et al., Clemency et al. and Gudbjartsson et al. evaluated their COVID-19 patients who complained of olfactory dysfunction through a telephone interview/verbal questionnaire [8-10]. A multicentre questionnaire study [11], based on 417 mild-moderate COVID-19 patients, reported olfactory dysfunction in 85.6% of cases (n = 357). Among these, 284 (79.6%) referred anosmia, while 73 (20.4%) hyposmia. Furthermore, phantosmia and parosmia affected 12.6% and 32.4% of patients, respectively. Olfactory dysfunction appeared before (11.8%), after (65.4%) or simultaneously (22.8%) to the appearance of general or ENT symptoms. According to the authors, 25.5% of patients recovered both their sense of smell and taste during the 2 weeks following resolution of general symptoms. Among the cured patients who had residual gustatory and/or olfactory dysfunction, 53.9% complained of isolated olfactory dysfunction, while 22.5% of isolated gustatory dysfunction and 23.6% of both. Females seemed to be more affected by smell and taste dysfunctions than males [11]. Leichien et al. [12] evaluated by questionnaire 1,420 mild-moderate COVID-19 positive patients. Anosmia

was one of most prevalent symptoms and was reported in about 70.2% of patients. Smell loss lasted at least 7 days after the disease in 37.5% of healed patients. Benezit et al. [13], evaluating 259 COVID-19 positive patients through a web-based questionnaire, found that 20% of the respondents complained of hyposmia, 24% of hypogeusia and 17% of both. Other authors have reported anosmia/hyposmia through surveys in COVID-19 positive patients. Among these, Kaye et al. [14] reported that 237 COVID-19 patients, using the AAO-HNS COVID-19 Anosmia Reporting Tool for clinicians [15], complained of anosmia. In particular, 73% reported anosmia before a diagnosis of COVID-19, while 27% after. Adding smell loss to a symptom tracker phone app, Menni et al. [16] obtained surveys from 7178 subjects who reported having been tested positive for COVID-19. Of these, 65.03% complained of smell/taste loss.

Some papers reported the results of case-control studies. Beltran-Corbellini et al. [17], studying 79 SARS-CoV2 positive patients and 40 controls (patients positive for influenza) by surveys, found that smell and taste complaints were significantly more frequent in cases than in controls. Furthermore, considering only the study group, they found that the patients complaining of smell/taste alterations were significantly younger than patients without these complaints. Similarly, studying 59 COVID patients and 203 controls (COVID-19 negative patients with influenza-like symptoms) Yan et al. [18] found that the referred smell/taste impairments was independently and strongly associated with COVID-19-positivity. Finally Wee et al. [19], studying 154 patients positive to COVID-19 and 71 patients tested positive for other respiratory viruses, found olfactory/taste dysfunction being self-reported by 22.7% of the patients of the former group and by only 2.8% of the patients of the latter. The authors concluded that self-reported olfactory dysfunction had high specificity as a screening criterion for COVID-19.

Studying retrospectively smell and taste data from 128 COVID-19 patients, Yan et al. [20] observed that only 26 (20.1%) required hospitalisation. Very interestingly, referred anosmia was found to be an independent factor for outpatient care. The authors concluded that smell loss in COVID-19 might be associated with a milder clinical course, as already hypothesised by Gane and coworkers [4] and Lee and co-workers [7]. This could be one of the reasons why hospitalised patients usually complain less of smell/taste dysfunction. Aggarwal et al. [21], evaluating 43 COVID-19 positive hospitalised patients (16 of whom hospitalised for the infection), observed that on surveys smell/taste loss was reported in a very low percentage of patients (19%). The mean population age was 65.5 and 75% were males. Giacomelli et al. [22] found that 33.9% of COVID-19 hospitalised patients reported on surveys either taste or olfactory alterations, while 18.6% reported both. Similar results, obtained mainly on hospitalised patients, were reported by Klopfenstein and coworkers who observed in surveys that 47% of their 114 COVID-19 patients reported olfactory alteration (anosmia) and about 85% (46 patients) also suffered of dysgeusia [23].

Some studies evaluated the reported sense of smell symptom together with patients reported outcome measures (PROMS), such as VAS (visual analogue scale) or SNOT 22 (sinonasal outcome test-22). Yan et al. [18] studied 59 COVID-19 patients and asked them to fill in a VAS for smell and taste. After showing that 40 patients (68%) reported smell and 42 (71%) gustatory impairment, the authors described a referred improvement of both senses with the clinical resolution of the infection in the majority of the patients. SNOT-22 has also been used in order to study the rhinological symptoms of 202 COVID-19 patients. In this study, 64% of the patients interviewed referred altered sense of smell/taste. At SNOT-22, among the patients complaining of olfactory dysfunction, 34% also complained nasal obstruction. Smell loss, as isolated symptoms, was reported by only 6 patients [24].

Sense of smell evaluation in confirmed COVID-19 patients by olfactory test

Few studies in the literature have adopted validated olfactory tests to confirm the olfactory loss reported by COVID-19 patients and to assess its severity.

Eliezer et al. [25] described the case of a 40-year-old woman, COVID-19 positive with acute hyposmia. A five-odour identification test confirmed the olfactory alteration, while CT scans and MRI of the nasal cavities showed bilateral inflammatory obstruction of the olfactory fissures without abnormalities of the bulbs and olfactory traits. Ottaviano et al. [26] studied 6 COVID-19 patients complaining of sudden hyposmia by the "Le Nez du Vin" test, a six-odours smell identification test and in all cases found an olfactory deficit. In a study by Lechien et al. [27], of 78 subjects complaining of isolated sudden hyposmia, 46 COVID-19 positive patients underwent the "Sniffin Sticks" identification sub-test (16 odours). The authors found that 52% of the patients were anosmic, 11 (24%) were hyposmic. It should be noted that 11 patients had normal olfaction (24%).

In a case-control study by Moein et al. [28], 60 patients with COVID-19 (not necessarily complaining of olfactory dysfunction) carried out an olfactory study using the Persian version of the University of Pennsylvania Smell Identification Test (UPSIT). Only 35% of COVID-19 patients were aware of their olfactory deficiency, while the

olfactory test showed that almost all patients (98%) had a measured olfactory dysfunction. According to UPSIT standards, 58% of patients were either severely hyposmic or anosmic, 27% had a moderate hyposmia, 13% a mild hyposmia and only one patient (2%) had normal sense of smell.

Vaira et al. [29] evaluated 72 COVID-19 patients using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, finding that the majority of the patients (about 83%) were affected by smell dysfunction (either hyposmia or anosmia), although only 61% of patients reported having or having had olfactory loss. Of importance, 28 patients who no longer referred olfactory dysfunction at the time of the visit were found to be hyposmic at the smell test [29].

Discussion

Olfactory dysfunction can be either conductive, mainly caused by sinusitis and rhinitis due to the physical blockage of odours in reaching the receptors of olfactory neurons, or sensorineural, involving the interruption of the pathway between olfactory receptors and the olfactory cortex, mainly caused by viral infections, head injuries or neurodegenerative diseases (i.e.: Parkinson's and Alzheimer's diseases) [30-32].

In general, three different types of olfactory (no radiological) testing exist: subjective (patient reported) olfactory assessment, psychophysical olfactory assessment and olfactory assessment based on electrophysiological studies [31,33]. The method used for assessing olfactory dysfunction is extremely important for accurate diagnosis, reporting outcomes and tracking olfactory changes over time [31]. This should be considered even more important during an outbreak in which olfactory dysfunction seems to be one of the most frequently reported symptoms.

Validated questionnaires or recognised forms of evaluation, possibly quantitative and/or anchored, such as a VAS, can be used in the study of hyposmia. Nevertheless, self-assessment is not well related to the measured olfactory function [30,31,33], as it has been well shown in the few studies where olfactory tests have been performed in COVID-19 positive patients. In particular, Lechein et al. [27] found that 24% of COVID-19 patients complaining of olfactory loss were normal by the smell test, whereas Moein and colleagues [28] and Vaira et al. [29] observed an underestimation of the self-reported smell dysfunction. In this regard, it is known that in the general population only for anosmia is there correspondence between self-reported olfactory function and the measured one [31,33]. Due to this lack of precision, subjective evaluation of the sense of smell should always be associated with a validated olfactory test to determine the severity of the dysfunction. Furthermore, the measurement of the olfactory function with validated olfactory tests allow quantification of the extent of smell reduction and to evaluate it during clinical follow-up [31,33].

Psychophysical and electrophysiological procedures are the most effective approaches to assess the integrity of the olfactory system in humans. Electrophysiological tests, such as olfactory event-related potentials, give an objective measure of smell, but are complex and necessitate of expensive equipment, so their clinical use is limited and are mainly reserved for research purposes [30,32,33]. Psychophysical tests, in which subjects are requested to provide a volitional response to the presentation of odourant stimuli, are much more known. Being easy to use, these tests are the most widely employed for quantifying olfactory function in clinical practice [31,32,34].

Psychophysical olfactory tests can be divided into the threshold and supra-threshold tests. The olfactory threshold is the concentration of an odour in which 50% of stimuli are detected and 50% remain imperceptible to a subject. The supra-threshold olfactory test involves the presentation of the odour with stimuli of sufficient concentration so that they are detectable to the subject. Among commercially available psychophysical olfactory tests, the most widely known are the UPSIT and the Sniffin' Sticks. UPSIT is a standardised microencapsulated odourant identification test where 40 odourants are presented in a scratch and sniff format with 4 response alternatives accompanying each odour, able to identify normosmia, mild, medium, severe hyposmia and anosmia. Sniffin' Sticks uses reusable pen-like odour dispensing devices that are presented to the subject by an examiner and consists of three subtests, which allow the study of odour threshold (for n-butanol/phenyl ethyl alcohol), discrimination of 16 odourant triplets and identification of 16 odours. The latter subtest is performed using a multiple-choice task (identification of individual odours is performed from lists of four descriptors for each odour). The sum of the 3 subtest results gives a composite score, known as TDI, which can indicate normal olfactory function, hyposmia, or anosmia [30-33,35,36]. CCCRC is also a composite test, being based on threshold for n-butanol and identification of 10 odour subtests [32]. Some shortened psychophysical olfactory tests are also available, mainly based on odour identification [31-33,37]. The number of items presented can range from 4 (4-Item Pocket Smell Test) to 12 odours [Screening 12 test, Cross-Cultural Smell Identification Test (CC-SIT)] [32,33,37]. When based on a small number of odours (up to 12), smell identification tests are mainly considered screening olfactory tests. Nevertheless, the use of these psychophysical instruments should be considered preferable to subjective assessment

alone, as questionnaires on self-represented symptoms are not as sensitive or specific as odour identification tests, particularly for mild hyposmia [31-33].

Viral infections of the upper respiratory tract are the most common cause of hyposmia or permanent anosmia. This loss of smell can reflect damage not only to the olfactory epithelium, but also to central olfactory structures following a viral invasion into the brain. Suzuki et al. [38] identified coronavirus in nasal secretions in a patient with post-viral olfactory dysfunction. The potential route of entry into the central nervous system of SARS-CoV-2 has not yet been established, but several mechanisms including invasion of olfactory nerves and retrograde invasion of the CNS, haematogenous or lymphatic routes all seem to be possible [39]. The movement of the COVID-19 virus to the brain via the cribriform plate close to the olfactory bulb has been proposed as possible route for the virus to reach the brain [40]. An olfactory cleft disease has also been hypothesised as a cause of olfactory loss in patients with COVID-19 [25]. Interestingly, very recently, neurobiologists from Harvard Medical School analysed bulk and single-cell RNA-Seq datasets to identify cell types in the olfactory epithelium that express molecules that mediate infection by SARS-CoV-2. They found in both mouse and human datasets that olfactory sensory neurons do not express two key genes required for CoV-2 entry, ACE2 and TMPRSS2. In contrast, non-neural cells in the olfactory epithelium, olfactory epithelial support cells and stem cells of olfactory epithelium express both of these genes, suggesting that infection of these cells could directly or indirectly lead to olfactory dysfunction [41].

Conclusions

The human sense of smell can be evaluated through subjective methods and/or either psychophysical or electrophysiological olfactory tests. To date, the methods

Table I. Screening and olfactory testing methods used in COVID-19 positive patients.

	Patients complaining of or with smell alterations	Verbal questionnaire	Online questionnaire	Telephone interview	Smart-phone app	UPSIT	Sniffin' sticks	Nez du vin	Simple odourants	CCCRC	PROMS
Mao [3]	11	X									
Hopkins [5]	2,428#		X								
Lee [7]	389			X							
Lechien [11]	357	X									
Lechien [12]	997	X		X##							
Bénézit [13]	95		X								
Kaye [14]	237		X								
Menni [16]	4,668				X*						
Beltrán-Corbellini [17]	25	X									
Yan [18]	40		X								X
Wee [19]	35	X									
Yan [20]	75	X°	X°	X°							
Giacomelli [22]	31	X									
Klopfenstein [23]	54	X									
Spinato [24]	130			X							X
Eliezer [25]	1								X^		
Ottaviano [26]	6							X§			X
Lechien [27]	78	X					X^^				
Moein [28]	59					X**					
Vaira [29]	72	X***								X	
Heidari [8]	23	X									
Clemency [9]	110			X							
Gudbjartsson [10]	119°°			X							

** COVID-19 symptom tracking. Android and IOS app; ** Persian version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT); *** Not clear if questionnaire or telephone interview; ^ Smell test with 5 odourants: flower rose, caramel, goat cheese, fruits, manure; ^^ Sniffin sticks 16 odours identification sub-test only in 46; § Identification test (6 odours); # Lack of confirmed COVID-19 status in most of the cases; ## In cases of patient isolation; ° Data obtained by electronic medical records. If data were not available, patients were either emailed or called; °° Loss of smell and taste were reported together.*

used to investigate smell impairment in COVID-19 patients have been very heterogeneous (Tab. I). Most of the publications that we identified in this review are based on olfactory self-assessment that is unreliable in COVID-19 patients compared to psychophysical tests [27-29,42], especially in the context of a pandemic scenario and consequent restrictions in social life [43]. The authors probably opted for self-administered questionnaire because it can be very difficult to perform an olfactory test during SARS-CoV-2 outbreak, especially when testing recently infected patients. In fact, these patients are isolated or hospitalised, some olfactory tests require an operator who can alter the test result with the protective suit, while other tests are not disposable. For all these reasons, the results of the available studies are not conclusive and many questions remain unanswered about the actual incidence of smell impairment during COVID- 19 infection, its predictive value of a mild- moderate severity of the disease and the percentage of patients recovering.

Given to their simplicity, psychophysical tests, in which the subjects are requested to provide a volitional response to the presentation of odourant stimuli, are the most widely employed for quantifying olfactory dysfunction. Among these, odour identification tests are the most simple and fast [32]. It would also be important to use disposable tests, since SARS-CoV-2 can remain viable on plastic, stainless steel and cardboard for up to 72 hours [44]. Although home-quarantined/isolated COVID-19 patients were able to perform the CCCRC in a self-administered way [45], the UPSIT, being self-administered and readily available, should be preferred. Other shorter validated psychophysical tests, such as the CC-SIT (12 odours), the smell Diskettes Test (8 odours) and "Le Nez du Vin" (6 odours), being disposable and not requiring the supervision of a physician/nurse, could also be proposed to test patients in quarantine/isolation and possibly still contagious patients.

The involvement of taste in COVID-19 patients with chemosensory symptoms could be most probably secondary to smell loss [30,31]. Based on gustatory screening test, some authors found that 47% of patients studied with COVID-19 had taste changes [29]. To confirm these data, full gustatory testing, i.e. using taste strips [31], should be performed to confirm and quantify the taste dysfunction in COVID-19 patients.

In March 2020, the AAOHNS and BRS proposed that hyposmia and dysgeusia (in the absence of other respiratory diseases) should be added to the symptoms used to screen for CoV-2 infection [5,6]. We suggest that validated psychophysical self-administered tests could be valuable methods to investigate smell impairment in COVID-19 patients to identify as accurately as possible cases needing of closer post-infection follow-up.

More extensive studies based on validated psychophysical olfactory tests (systematically performed during active infection) may help to assess the frequency of hyposmia among COVID-19 patients, its pathogenesis, duration and potential role as a marker of disease progression or severity.

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HEAD AND NECK

Anatomic and radiologic relationships of neck structures to cervical spine: implications for anterior surgical approaches

Rapporti anatomici e radiologici delle strutture cervicali in relazione al rachide: implicazioni per gli approcci cervicotomici anteriori al rachide

Matteo Alicandri-Ciufelli[1,2], Matteo Fermi[1], Giulia Molinari[1], Elisa Aggazzotti Cavazza[1], Anna Maria Billi[4], Giuliano Giliberto[2], Francesca Cavalleri[3], Giacomo Pavesi[2], Livio Presutti[1]

[1] Otorhinolaryngology-Head and Neck Surgery Department, University Hospital of Modena, Italy; [2] Neurosurgery Department, New Civil Hospital Sant'Agostino-Estense, Baggiovara (MO), Italy; [3] Neuroradiology Department, New Civil Hospital Sant'Agostino-Estense, Baggiovara (MO), Italy; [4] Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

SUMMARY

The position of the pharyngolaryngeal framework is very important in choosing the best surgical approach for cervical spine disease. The aim of the present paper is to investigate the position of the hyoid bone and cricoid cartilage in relation to the cervical spine. Moreover, the surgical implications for anterior transcervical approaches to the upper spine and the prevertebral space are discussed. To minimise complication rates and increase surgical effectiveness, the location and extent of the cervical spine disease should be evaluated in the context of the patient's specific anatomy. A retrospective analysis of 100 cervical spine MRIs was conducted. Patients with diseases that could alter anatomic relationships of cervical structures were excluded. The mid-sagittal view of the hyoid and the inferior margin of the cricoid cartilage were projected perpendicularly to the anterior surface of the cervical vertebrae. The distance between these two landmarks was measured on the same view. The distribution of hyoid projections ranged between C2-C3 and C4-C5 intervertebral space, while the cricoid cartilage ranged between C4-C5 and C7-T1 intervertebral spaces. The mean distance between these two landmarks was 49.1 ± 7.7 mm, with statistically significant differences between males and females. The position of the cricoid cartilage significantly influenced the length of the pharyngolaryngeal framework, while the position of hyoid did not. A wide range of variability in the position of the hyoid bone and the cricoid cartilage in relation to cervical levels exists. This implies that an *a priori* association of a cervical level to neck structures at risk might be inaccurate. The use of these easily identifiable landmarks on pre-operative imaging may help to guide the choice among different anterior surgical approaches to cervical spine and reduce the risk of surgical complications.

KEY WORDS: cervical vertebrae, recurrent laryngeal nerve, vocal cord paralysis, swallowing disorders, hypoglossal nerve

RIASSUNTO

La posizione del framework faringolaringeo è importante nel decidere quale approccio al rachide cervicale adottare. L'obiettivo dello studio è di analizzare la posizione dell'osso ioide e della cartilagine cricoide in relazione ai livelli del rachide cervicale e discuterne le possibili implicazioni per gli accessi cervicotomici al rachide cervicale ed allo spazio prevertebrale. Infatti, per ridurre al minimo le complicanze legate a tale chirurgia ed incrementare l'efficacia del trattamento, la posizione ed estensione del processo patologico a carico del rachide dovrebbe essere inquadrata rispetto ai rapporti anatomici con l'asse faringo-laringeo del singolo paziente. È stata condotta un'analisi retrospettiva di 100 risonanze magnetiche cervicali, escludendo i pazienti che presentavano lesioni che potessero alterare i rapporti anatomici con le vertebre cervicali. Prendendo in esame le scansioni sagittali sulla linea mediana, l'osso ioide ed il margine inferiore della cricoide sono stati proiettati perpendicolarmente sulla superficie anteriore del rachide ed è stata misurata la distanza di queste dal punto di proiezione sulla colonna vertebrale. La distribuzione delle proiezioni dell'osso ioide si attestava tra gli spazi intervertebrali

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Correspondence
Matteo Fermi
Department of Otorhinolaryngology,
Head & Neck Surgery, University Hospital
of Modena, largo del Pozzo 71, 41125 Modena, Italy
Tel. +39 059 4222402. Fax +39 059 4222454
E-mail: matteo.fermi.med@gmail.com

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C2-C3 and C4-C5, mentre quella della cartilagine cricoide tra C4-C5 e C7-T1. La distanza media tra queste due strutture era di 49,1 ± 7,7 mm e vi era differenza statisticamente significativa tra sesso maschile e femminile. La posizione della cricoide influenzava significativamente la lunghezza dell'asse faringo-laringeo, mentre la posizione dell'osso ioide era spesso costante. Da quanto osservato, si evince che esista un ampio raggio di variabilità nella posizione dell'osso ioide e della cartilagine cricoidea rispetto ai livelli delle vertebre cervicali. Da ciò ne deriva che una associazione a priori tra specifici livelli cervicali e strutture del collo a rischio sarebbe poco accurata. L'utilizzo dei reperi proposti, facilmente identificabili radiologicamente, può guidare la scelta tra i diversi approcci cervicotomici anteriori al rachide cervicale, riducendo il rischio di complicanze chirurgiche.

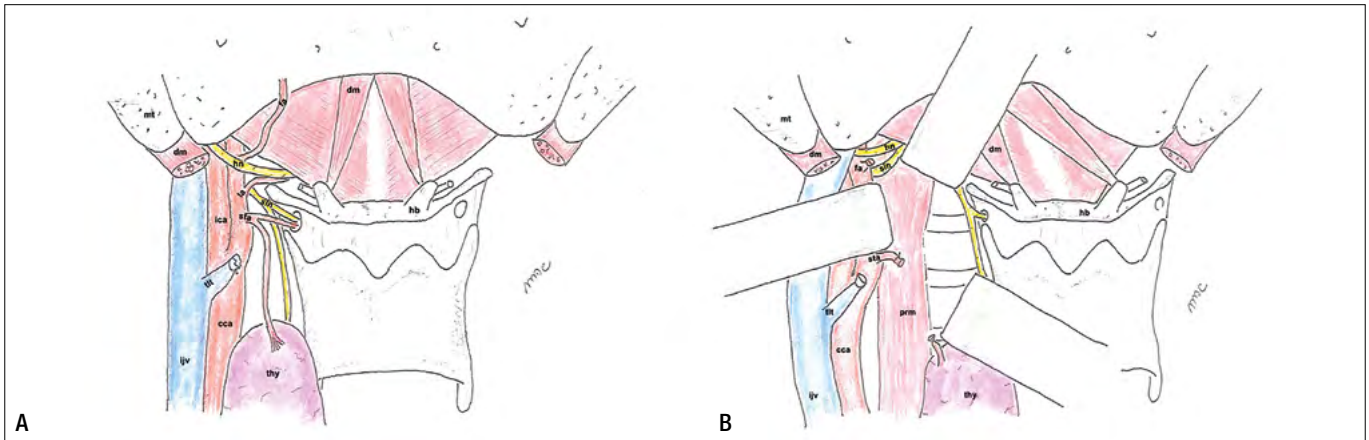
PAROLE CHIAVE: *vertebre cervicali, nervo laringeo ricorrente, paralisi delle corde vocali, disfagia, nervo ipoglosso*

Introduction

The cervical region is a delicate anatomic site, crossed by several vascular, nervous, respiratory and digestive structures, whose injury can lead to serious complications during or after surgery [1]. Several surgical approaches provide access to the cervical spine (CS). Among these, anterior, lateral and posterior approaches have been described [2]. Cervical disc herniation is traditionally treated by anterior surgical approaches, as described by Cloward in 1958 [3]. The Cloward technique provides an anterior horizontal neck incision, and a dissection performed through an "avascular" pathway between the superficial cervical fascia and the middle layer of the deep cervical fascia. The location and extent of the CS lesion to treat are the major determinants that influence the selection of the most appropriate surgical approach. Moreover, the surgeon should select the approach that allows the widest and most comfortable surgical field and the lowest rate of morbidity. The location and extent of the CS disease should be evaluated in the context of the patient's specific anatomy in order to minimise complication rates and increase surgical effectiveness. Pre-operative imaging, mostly CS magnetic resonance imaging (MRI), provides clear visualisation of the area that has to be treated, as well as some surgical landmarks in the neck. When the upper CS (C0-C2) is affected by the disease, the Cloward approach may not guarantee an adequate area of exposure and manoeuvring. Thus, wider incisions and appropriate dissection of superior laryngeal nerve (SLN), hypoglossal nerve (HN), and external carotid artery branches are required, possibly in cooperation with a head and neck surgeon. The hyoid bone (HB) has a central position in the neck, and it has a close relationship with all the above-mentioned structures (Fig. 1).

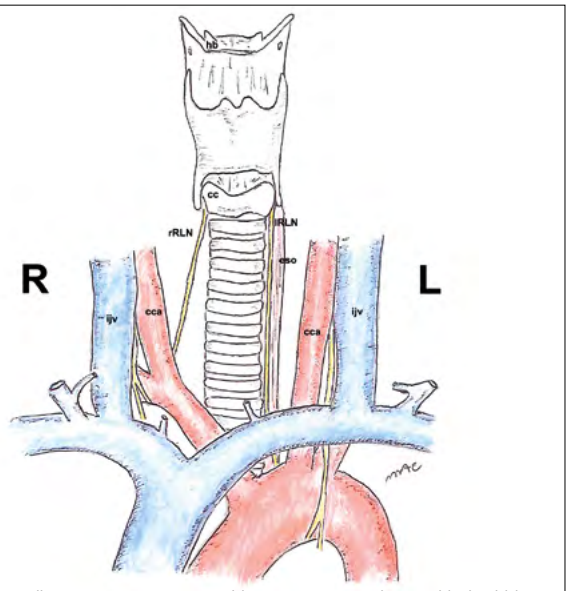
The primary aim of this radiologic study is to evaluate the position and variability of HB in relation to the cervical spine (i.e. level of vertebrae or discs) in a cohort of patients. Relationship of the HB with the CS may help in planning the best approach based on the position of the pathology relative to the HB.

Another important structure that can be encountered during anterior cervical spine (ACS) approaches is the recurrent laryngeal nerve (RLN). As is well known, the RLN has a different path between the right and left side, having a more lateral course on the right side and thus being traditionally considered at greater risk of iatrogenic damage on this side (Fig. 2). The RLN enters the larynx at the level of the inferior margin of the cricoid cartilage (IMCC). Therefore, as a



mt: mastoid tip; dm: digastric muscle; fa: facial artery; hn: hypoglossal nerve; la: lingual artery; sln: superior laryngeal nerve; sta: superior thyroid artery; ica:internal carotid artery; tlt: thyrolingual trunk; cca: common carotid artery; ijv: internal jugular vein; thy: thyroid; prm: prevertebral muscles; hb: hyoid bone

Figure 1. Anterior cervical region, coronal view. (**A**) anatomic structures to be aware of during a high prevascular retrovisceral approach. Note the anatomic relationship among the superior laryngeal nerve and the hyoid bone; (**B**) ligature of the superior thyroid artery and retraction of the neurovascular bundle to expose the prevertebral muscles and the upper/mid cervical spine. Careful cranial retraction of the hypoglossal nerve and the superior laryngeal nerve can widen the surgical space.



cc: cricoid cartilage; cca: common carotid artery; eso: esophagus; hb: hyoid bone; ijv: internal jugular vein; lRLN: left recurrent laryngeal nerve; rRLN: right recurrent laryngeal nerve

Figure 2. Anterior cervical region, coronal view. Schematic drawing showing the pathway of inferior laryngeal nerves. Note the oblique direction on the right side toward the inferior margin of the cricoid cartilage.

secondary outcome, the position of the IMCC compared to CS level and its variability are analysed. This finding may help surgeons to choose the optimal side of the approach.

Materials and methods

The CS MRIs of 100 patients were randomly selected among MRIs performed between 2005 and 2017. 50 males and 50 females (age range: 25-96) were selected. MRI was performed at the same institution using a 1.5-T scanner (Intera; Philips Medical Systems, Best, The Netherlands). Being a purely retrospective observational radiologic study, neither institutional research board/ethics committee approval nor patient consent were required at our institution.

Poor-quality MRI images, such as those with movement artefacts or with inappropriate radiologic positioning of the patient, were discarded. Patients with a cervical pathology markedly altering the anatomy of the neck or of the spine were excluded. All the distances and projections were assessed by an experienced neuroradiologist (F.C.) on either T1 weighted or T2 weighted MRI on sagittal plane, depending on which sequence had the best image definition of HB, IMCC and CS vertebrae. The anatomical landmark usually used to describe the RLN's relationships was the inferior cornua of the thyroid cartilage. Nevertheless, the IMCC was chosen as a radiologic landmark due to its easier detection on MRI images. The position of the HB and IMCC were assessed, choosing the cut where their entire sagittal image was visualised. To determine their projection on the cervical spine, a roughly parallel line to the anterior surface of the cervical vertebrae was considered. The centre of the sagittal view of the HB and the posterior edge of the IMCC were projected perpendicularly on this line. Specifically, when the projection was either on the intervertebral disk, the superior quarter of the lower vertebral body (VB), or the inferior quarter of the upper vertebral body, the projection level was C (number of the superior VB) - C (number of the inferior VB). When the projection level was on the central two quarters of the VB, the level attribution was C (number of that VB).

To define the length of the laryngeal framework, the distance between the HB and the IMCC was measured in the same view, drawing a perpendicular line between the centre of the HB and the line passing through the IMCC (Fig. 3).

All data were tabulated and results for continuous variables are presented as mean ± standard deviation. All statistic analyses were conducted with SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA). The data were analysed with a Student's t test for continuous variables. HB and IMCC projections on the spine were subgrouped for statistical analysis as follows: C2-C3/C3, C3-C4/C4, C4-C5/C5, C5-C6/C6 and C6-C7/C7. To analyse the relationships between HB and IMCC projections on the spine (categorical variables) and the distance between the HB and IMCC

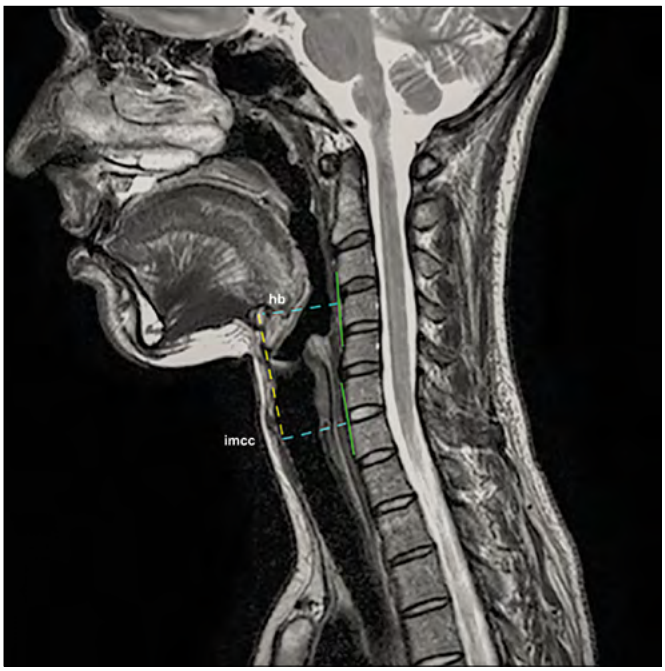


Figure 3. Magnetic resonance imaging, sagittal plane, T2-weighted. Green line: roughly parallel line to the anterior surface of the cervical vertebrae bodies; blue line: projection of the hyoid bone and inferior margin of cricoid cartilage to the cervical spine; yellow line: distance between the hyoid bone and the inferior margin of cricoid cartilage (length of the laryngeal framework).

(continuous variables), one-way analysis of variance tests (ANOVA) were performed. Bonferroni post-hoc test was applied to the results. A P value < 0.05 were considered statistically significant.

Results

The mean distance between the HB and the IMCC was 49.1 ± 7.7 mm. Significant differences between males and females were observed: the mean distance was 53.5 ± 6.1 mm and 44.7 ± 6.5 mm, respectively (p = 0.00). The projections of the HB and the IMCC on the CS were evaluated. The distribution of HB projections ranged between C2-C3 and C4-C5 intervertebral space with 4% located at C2-C3 intervertebral space, 23% at C3 vertebral body, 33% at C3-C4 space, 34% at C4 vertebral body and 6% at C4-C5 intervertebral space (Fig. 4). These data were compared between males and females, with no statistical differences between groups (p = 0.06).

The distribution of IMCC projections ranged between C4-C5 and C7-T1 intervertebral spaces with 2% among C4-C5, 12% at C5 body level, 23% at C5-C6 intervertebral space, 39% at C6 vertebral body, 20% at C6-C7 intervertebral space, 3% at the level of C7 body and just in one case below C7 (1%). In the female group, none

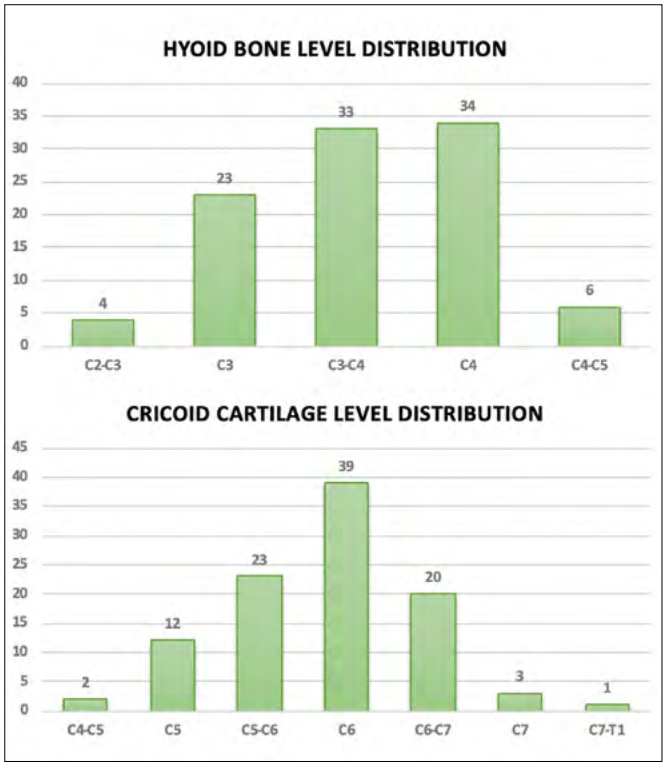


Figure 4. Histograms showing the distribution of projection on the cervical spine of hyoid bone (HB) and inferior margin of cricoid cartilage (IMCC) in the case series analysed.

of the cricoid cartilages was located more caudally than C6-C7 intervertebral space. (Fig. 4) These data as well were compared in men and women, showing significant differences (p = 0.03).

The one-way analysis of variance tests (ANOVA) showed no significant relationship among HB-IMCC distance and HB projections on the spine (p > 0.05), while statistical significance was found among HB-IMCC distance and IMCC projections, in particular among C4-C5/C5 and C6-C7/C7 subgroups (p = 0.00) and C5-C6/C6 and C6-C7/C7 subgroups (p = 0.002).

Discussion

The anterior approach to the cervical spine is a widely used technique to deal with diseases that arise primarily from the anterior spinal column, such as trauma or degenerative conditions. Since 1958, when it was first described by Cloward RB and Smith GW, it was evident that the main obstacles to the achievement of the anterior aspect of the cervical spine were anatomical [3-5]. Various authors made the effort to thoroughly describe the key anatomical structures (e.g. SLN, superior thyroid artery, RLN, inferior thyroid artery, sympathetic trunk, oesophagus, etc.) that surgeons had to be aware of during dissection [6-10]. Nevertheless, different intraoperative and postoperative complications can still occur. Accurate location and extent of the skin incision are helpful to decrease technical difficulties and surgical time in ACS surgery. Adequate exposure of the surgical field can ease surgical manoeuvring, increase light, and reduce retraction of soft tissues, with less pressure damage to vital organs. Spine surgeons can use neck palpatory landmarks (e.g. HB, thyroid cartilage and cricoid cartilage) to decide the site of the surgical incision, which should be performed at the midpoint of the level of surgery [11]. However, Liu et al. demonstrated in their radiologic study that the HB, the thyroid and cricoid cartilages were not reliable to predict cervical levels, while the angle of the mandible was found to be the most accurate landmark for identifying C2/C2-C3 disc space [12]. They postulated that, due to a great variability in intraoperative neck flexo-extension and spinal degeneration, those superficial landmarks were not reliable to decide the site of the incision.

Haller et al. investigated the anatomic relationship of the HN, SLN and its branches, superior thyroid and laryngeal artery with the cervical spine to demonstrate their vulnerability during upper ACS surgery. They postulated that spine surgeons can be aware of which neurovascular structures are at risk at a given cervical level [13]. Nevertheless, the relationship between cervical spine levels and neck structures can be highly variable, so that *a priori* association of a cervical level to structures

at risk, as described by Haller et al, can be inaccurate [13]. As shown in the present radiologic study, a wide range of variability in terms of the size of the pharyngo-laryngeal framework and the projections of two key landmarks of the neck (HB and IMCC) to cervical levels does exist. Since this was a radiologic study, the position of the patient while performing the MRI could vary from the final position in the operative room, where in most cases the head is more extended. However, it is common for spinal surgeons to perform an intraoperative x-ray in latero-lateral projection to choose the position of the incision. Since the HB and IMCC are easily identifiable on radiographs, this intraoperative imaging would possibly help in confirming the optimal approach selected on the basis of the MRI. Moreover, patients with CS disease usually have neck stiffness and can rarely modify their extension significantly. Melamed et al. thoroughly described the SLN anatomy and its position posteriorly to the superior thyroid pedicle at the level of the HB. Its damage often results in the loss of the high-pitched tones and in decreasing of the sensitive reflexes of the supraglottic and hypopharyngeal regions, leading to increased risk of dysphagia and aspiration [9]. Dysphagia is a common complication after ACS surgery, and its occurrence is possibly due not only to SLN damage, but also to RLN impairment, HN damage, oesophageal ischemia, reperfusion injury, or soft tissue swelling. The reported incidence of dysphagia is widely variable in the literature. However, an incidence up to 71% during the two postoperative weeks has been reported in well-designed prospective studies [14]. The wide variation may be partially explained by the fact that dysphagia is routinely underestimated. Tasiou et al. reported that the incidence of dysphagia was 11% when based on physician's notes, while it increased to 57% when the patients were surveyed [15].

HN injury, which is a well-documented complication after soft tissue surgery of the neck, is a rare event after ACS surgery. It can lead to persistent or transient dysphagia of the oral phase and dysarthria. It occurs more frequently in upper ACS surgery, and the reason is anatomical [16,17]. HN exits the posterior skull base through the hypoglossal canal in the occipital bone and runs inferiorly towards the carotid sheath, together with the vagus nerve in its first segment. Below C1/C2, it proceeds between the carotid artery and the internal jugular vein, while below C2/C3 it runs medially [13]. At this level, during a retropharyngeal approach to the upper CS, the hypoglossal nerve may mimic a venous vessel crossing the field, so great caution should be taken when interrupting venous-like structures in this location [17]. Below C2/C3, the path of the HN becomes lateral and it does not appear in the operative field during ACS surgery [16]. Careful preoperative assessment of the position of the HB and its projection on the cervical spine may improve the management of the SLN and its branches, leading to a significant reduction in postoperative dysphagia or dysarthria. Our results demonstrated that the position of the HB was inconstant. The position ranged between C2-C3 and C4-C5 intervertebral spaces with no significant differences among males and females. Thus, it might be postulated that, based on the position of the disease with respect to this landmark, a specific anterior approach could be indicated in order to limit the possible complications involving the SLN and the HN. When the disease was located more cephalad to the HB, a standard anterolateral approach could be inadequate due to the limited exposure of important landmarks such as the SLN and the HN and could expose patients to the above-mentioned complications.

In these cases, a longitudinal cervical incision, possibly extending anteriorly toward submandibular/submental spaces might be more appropriate. Pre-emptive identification and isolation of the SLN and HN should be performed. Moreover, ligation of the thyrolingual trunk could help to further improve manoeuvring and exposure. Furthermore, identification and ligation of the external carotid artery branches could be performed à la *demande* to extend the dissection even more cranially in order to reach the upmost tract of the cervical spine (C1-C2) by an upper prevascular retrovisceral approach (Tab. I) [18].

The incidence of vocal cord palsy/paralysis due to RLN injury during ACS surgery ranges from 2.3% to 24.2% [19]. The differences in percentages are possibly due to significant heterogeneity in study designs and definition of vocal cord impairment by various authors. Moreover, some studies suggested that RLN palsy (RNLP) is underreported [15]. Indeed, asymptomatic RLNPs are more frequent than symptomatic ones with hoarseness [20]. This may explain why this complication may be underestimated. Different authors have described the anatomy of the RLN and its relationship to vascular and fascial structures [10]. Jung et al. showed that a left-sided approach in ACS surgery significantly reduced the incidence of both early postoperative and permanent (3-months follow up) RLNP from 24.2% and 13.3% respectively, to 14% and 6.5% [21].This is probably

Table I. Surgical approaches suggested based on disease extension compared to neck structures: hyoid bone (HB); inferior margin of cricoid cartilage (IMCC).

Disease level related to neck structures	Surgical anterior approach
Cranial to HB	High prevascular retrovisceral approach HPRA
Between HB and IMCC	Standard Cloward approach
Caudal to IMCC	Standard Cloward approach (left side preferred)

due to the more vertical course of the nerve on the left side, where it lies in a relatively protected position within the oesophagotracheal groove [6]. Nevertheless, it is sometimes mandatory to reach the CS from the right side (e.g. right spinal cervical nerve compression) and some authors still prefer the right-sided approach to the lower CS due to easier dissection for right-handed surgeons [11]. Shan et al. postulated that the pathway of the right RLN in the space between the carotid and visceral sheaths is located below the C7-T1 disc [10]. This would imply that the IMCC would lie at this level or below. On the contrary, based on our findings, the RLN extends cranially even to C4/C5 intervertebral disc in some patients, and is located more cephalad to C7 and C6 in 96% and 37% of cases, respectively. These results have direct impact on the surgical approach for ACS and underline the importance of careful preoperative assessment of the location of the lesion with respect to the IMCC, especially in case of any disease that has to be approached by anterior access from the right side, where the pathway of the RLN is oblique and where it might be jeopardised by the retraction applied to the trachea/oesophagus and neurovascular bundle (Tab. I). Moreover, when deemed appropriate, an x-ray can be performed intraoperatively in order to verify the cervical spine level and to check the relationship with the cartilaginous skeleton of the larynx. The present authors are aware that surgeons' habits and experience can play a major role in choosing the surgical approach (e.g. the side based on handiness), but the aim of the study was to stimulate the surgical community to consider the variability in neck structures in relation with the CS and foster cooperation among spinal and head and neck surgeons for selected CS surgeries, when deemed appropriate.

Conclusions

A wide range of variability in the projections of the HB and IMCC to cervical spine levels and in the length of the pharyngo-laryngeal framework exists. This implies that an *a priori* association of a cervical level to specific anatomical structures at risk can be inaccurate. Instead, the use of anatomical landmarks that are easily identifiable on pre-operative and intra-operative radiology, such as HB and IMCC, can help guide the choice of anterior surgical approach in terms of level, side and type of incision. Thus, thorough evaluation of pre-operative MRI, especially in sagittal planes, is recommended to better understand the position of critical anatomic structures in the neck area and to define the best surgical approach for each specific case.

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Thyroid

Total thyroidectomy versus lobectomy: surgical approach to T1-T2 papillary thyroid cancer

Tiroidectomia totale versus emitiroidectomia: approccio chirurgico al carcinoma papillare della tiroide T1-T2

Luigi Di Filippo[1*], Gioacchino Giugliano[2*], Marta Tagliabue[2], Sara Gandini[3], Federica Sileo[1], Agnese Allora[1], Enrica Grosso[2], Michele Proh[2], Veronica Basso[2], Donatella Scaglione[4], Marco Federico Manzoni[1,2**], Mohssen Ansarin[2**]

[1] Departments of General Medicine and Endocrine Tumor Unit, San Raffaele Scientific Institute, IRCCS, Milano, Italy; [2] Division of Otolaryngology and Head and Neck Surgery, IEO, European Institute of Oncology, IRCCS, Milan, Italy; [3] Department of Experimental Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [4] Division of Data Manager, IEO, European Institute of Oncology, IRCCS, Milan, Italy

** Co-first authors L. Di Filippo and G. Giugliano contributed equally to this work.*

*** Co-last authors M.F. Manzoni and M. Ansarin share co-last authorship.*

SUMMARY

The incidence of papillary thyroid carcinoma, which accounts for 80-90% of all thyroid cancers, has recently been increasing. The current study aimed to compare the oncological and functional outcomes of total thyroidectomy (TT) and thyroid lobectomy (TL). To this end, a retrospective single-centre cohort study involving a tertiary care institution was conducted. Data regarding demographics, clinicopathology and postoperative complications from 586 patients with papillary thyroid cancer treated in a single institution were collected. Cox proportional-hazards models were utilised to determine differences in outcomes stratified according to propensity score. Our data suggested no significant difference in the risk for locoregional recurrence or distant metastasis between TL and TT among patients with pT1-2 pN0 papillary carcinoma. TT plays an important role in improving prognosis among patients with metastatic lymph nodes in the central neck compartment (pN1a) ($p = 0.001$). Moreover, TT had significantly higher rates of postoperative hypocalcaemia and recurrent laryngeal nerve paralysis compared to TL ($p < 0.001$ and $p = 0.02$, respectively).

KEY WORDS: total thyroidectomy, thyroid lobectomy, papillary thyroid cancer, hypocalcaemia, recurrent laryngeal nerve paralysis

RIASSUNTO

Il carcinoma papillare della tiroide rappresenta l'80-90% dei tumori tiroidei e la sua incidenza è attualmente in aumento. Vogliamo valutare i risultati oncologici e funzionali del trattamento chirurgico del cancro della tiroide: tiroidectomia totale versus emitiroidectomia. Abbiamo effettuato uno studio monocentrico di coorte storica in un centro di riferimento terziario. Abbiamo raccolto i dati demografici, clinicopatologici e complicanze post operatorie di 586 pazienti trattati nel nostro istituto per carcinoma papillare della tiroide. Sono stati applicati modelli di rischio proporzionale Cox per valutare le differenze nei risultati, stratificandoli con il propensity score. I nostri dati suggeriscono che l'emitiroidectomia non porta ad un aumento del rischio di ricaduta locoregionale né a distanza rispetto alla tiroidectomia totale nei pazienti affetti da carcinoma in stadio T1-2 N0. La tiroidectomia totale riveste un ruolo importante in termini di miglioramento della prognosi nei casi di metastasi linfonodali del comparto centrale del collo (pN1a) ($p = 0,001$). Nella nostra casistica la tiroidectomia totale ha un rischio più elevato di complicanze chirurgiche in termini di ipocalcemia post operatoria e paralisi ricorrenziali ($p < 0,001$ e $p = 0,02$ rispettivamente).

PAROLE CHIAVE: *tiroidectomia totale, emitiroidectomia, carcinoma papillare tiroideo, ipocalcemia, paralisi ricorrenziale*

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Correspondence
Marta Tagliabue
Division of Otolaryngology and Head & Neck Surgery European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy
Tel. +39 02 57489490. Fax +39 02 94379216
E-mail: marta.tagliabue@ieo.it

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Introduction

The incidence of papillary thyroid carcinoma (PTC), which accounts for 80-90% of all thyroid cancers, has currently been increasing due to increased diagnostic scrutiny and better diagnostic technology [1]. The widespread availability and improved sensitivity of neck ultrasonography (US) and fine-needle aspiration cytology (FNAC), accounting partly as overdiagnosis, and effects of environmental and lifestyle changes, may be responsible for such an increase [2,3]. The Surveillance, Epidemiology and End Results (SEER) database reported that incidence rates for PTC increased 2.4-fold during the few last decades predominantly among those with low-risk intrathyroidal T1-T2 carcinoma [4,5]. Despite its high prevalence, thyroid cancer is rarely deadly with an excellent prognosis and a 10-year survival rate exceeding 90% [6-9]. Unfortunately, disease recurrence and postoperative surgical complications remain very common [10]. No universal agreement on the management of PTCs, especially the smallest lesions, has been established given that confidently differentiating between aggressive and slowly progressing diseases is not yet possible. To date, thyroid surgery has been the main treatment for PTCs. The extent of curative surgery has long been a controversial topic, with evidence for both conservative surgery (lobectomy) and radical surgery (total thyroidectomy). Although the 2009 American Thyroid Association (ATA) guidelines had recommended total thyroidectomy (TT) for PTCs > 1 cm, the recent 2016 ATA guidelines recommend lobectomy alone for low-risk, 1-4 cm PTCs [11,12]. Recent studies have observed that surgery type did not affect patient outcomes and were much more related to cancer intrinsic risk factors or patients themselves [13-20]. Other studies have reported that thyroid lobectomy (TL) had a higher risk for recurrence compared to TT [9,21,22]. Furthermore, adverse surgical events, such as hypocalcaemia and recurrent laryngeal nerve injury, are more frequent and severe after TT than after lobectomy alone [23,24]. As confirmed by the latest ATA guidelines, accurate preoperative staging and risk evaluation is crucial to determine the proper surgical approach and post-surgical management [12]. While some potential risk factors, such as histological features, vascular invasion and extrathyroidal extension (ETE), are difficult to evaluate preoperatively, others, like age, sex, familial history, BRAFV600E mutation and lymph node (LN) involvement can be readily assessed preoperatively [25-30]. To date, the role of surgical extension among patients with PTC remains controversial. As such, the present study aimed to compare long-term outcomes of TT and TL among patients with T1-T2 PTC and evaluate postoperative complication rates. To minimise selection bias, various statistical analyses were performed to categorise our cohort according to the presence or absence of lymphadenectomy (central neck dissection) while accounting for prognostic and confounding factors.

Materials and methods

Study population

This retrospective single-centre cohort study was approved by the European Institute of Oncology Ethics Committee. From January 1995 to January 2018, a total of 3,013 patients underwent surgical treatment at the Otolaryngology and Head and Neck Surgery Department of the European Institute of Oncology IRCCS, Milan, Italy. Patients (n = 2,424) with the following characteristics were excluded: age less than 18 years, benign disease, previous thyroid treatment, mixed-type PTC, tumour size > 4 cm, pT3-pT4 stage, cN1b, distant metastasis, follow-up < 6 months and contralateral TL completion performed for reasons other than suspected or proved recurrence. Ultimately, 586 patients with pT1 or pT2 PTC were enrolled and assigned to two groups according to whether they received TT (group; n = 412) or TL (group; n = 174). Patient demographics and surgical and histopathologic details (histological features, lesion size, multifocality and LN metastases) were determined from the IEO electronic archive. To minimise selection bias, we divided our cohort in two groups according to the presence of central neck dissection during surgical planning, considering that most locoregional recurrences (LRRs) involve locoregional cervical lymph nodes.

Patient management

Preoperative patient evaluation included a complete clinical examination, routine blood tests, laryngeal fibroscopy to determine vocal cord mobility, US to estimate size, possible ETE and LN metastases in the central area (VI level) and FNAC [31]. Most cases underwent FNAC for preoperative diagnosis of PTC, whereas others were diagnosed incidentally through surgical specimens from patients undergoing treatment for a cytologically benign disease.

Surgical approach

TL was performed among patients with no evidence of ETE, no bilateral carcinoma and a lesion size of < 2 cm in diameter when FNAC was positive for carcinoma and > 2 and < 4 cm when preoperative FNAC was Tyr 2. TT was performed among cases with bilateral carcinoma, oncological lesion ≤ 4 cm, benign lesion > 4 cm, bilateral goiter,

familial history of thyroid cancer and uncertain contralateral nodules. All surgical approaches were determined through multidisciplinary team decisions with the patient's consent. Clinically node-negative patients underwent prophylactic central neck dissection when thyroid FNAC was Tyr 3, 4, or 5, as recommended by the multidisciplinary team, or when macroscopic ETEs were detected during preoperative US or following surgery [12,32-34].

The aforementioned surgical management was standardised at our Institute starting in 2010, during which a more efficient, minimally invasive surgery and systematic use of surgical loupes for all surgeons were introduced.

Radicalisation was proposed when central neck metastasis or ETE were discovered to allow for radioactive iodine treatment (RAIT) in TL cases.

Surgical complications and follow-up

An analysis of the two most frequent postoperative thyroidectomy complications (i.e., transient or permanent hypocalcaemia and transient or permanent recurrent laryngeal nerve paralysis) was performed. Only euthyroid patients with normal preoperative calcium and PTH levels were included. As suggested by American Association of Clinical Endocrinologists guidelines, hypocalcaemia was defined as a serum albumin-corrected total calcium level lower than 2.1 mmol/L (8.5 mg/dL) regardless of signs and symptoms [35]. Permanent hypocalcaemia was defined as requirement of vitamin D and calcium supplementation for more than 12 months after surgery, independent of calcium values [35]. Patients with aggressive cancer features and risk factors, such as pT2 stage and/or central node involvement, underwent RAIT according to current guidelines [12,33,34]. The postoperative follow-up included clinical evaluation consisting of physical examination, laryngeal fibroscopy, neck US, iodine-131 scan (for TT) and serum thyroglobulin samples at 6- to 12-month intervals (for TT and TL). Outcomes evaluated included LRR, metastasis occurrences, and mortality. LRR was defined as a new lesion in the thyroidectomy bed or cervical LNs detected through clinical examination with neck US and increased thyroglobulin levels and confirmed using FNAC or histopathological samples from the re-intervention. Metastasis was detected using iodine-131 scans (for TT), computed tomography, or cytology and histology. Recurrence-free survival (RFS) was defined as the time interval, expressed in months, between the first surgery and detection of recurrence (both LRR and distant metastasis).

Statistical analyses

All analyses comparing the type of thyroidectomy were stratified according to the presence or absence of lymphadenectomy. Categorical variables were presented as relative frequencies (percentages). Continuous variables were reported as median and interquartile range. Categorical variables were compared using Fisher's exact test, while continuous variables were compared using the Wilcoxon signed-rank test. The Kaplan-Meier method was utilised to generate survival curves, which were compared using the log-rank test. To reduce the impact of confounding factors and treatment selection bias, a propensity score was used to identify factors significantly associated with thyroidectomy type. Cox proportional-hazards models were stratified according to the propensity score. All tests were two-sided with a p-value of < 0.05 considered statistically significant.

Results

Patient characteristics and surgical technique(s)

Demographics and clinicopathological features of the 586 patients are presented in Table I. Patients had a median age of 48 years [interquartile range (IQR): 39-58 years], among whom 461 were women (78.7%). Multifocality was found in 182 patients (31.1%). Moreover, 494 patients had pT1 PTC (84.3%), while 92 had pT2 PTC (15.7%). Among the 586 patients who satisfied the selection criteria, 412 (70.3%) underwent TT and 174 (29.7%) underwent TL. The median follow-up duration was 58 months (IQR: 24-102 months). None of the patients developed distant metastasis. Significant differences in age [50 (41-59) vs 43 (36-52) years; $p < 0.001$], multifocality (37.6% vs 15.5%; $p < 0.001$) and central neck dissection (62.1% vs 47.7%; $p = 0.0012$) were observed between the TT and TL groups, respectively, as expected from the pre-surgical studies (Tab. I). No significant differences in sex and pT stage were observed between groups ($p = 0.52$ and 0.86, respectively). Central lymphadenectomy was performed in 339 patients (57.8%). Demographics and clinicopathological features of those who did and did not undergo central lymphadenectomy are summarised in Tables II and III.

Postoperative follow-up of patients who underwent central neck dissection

No deaths related to thyroid disease occurred among patients who underwent central neck dissection. A total of four patients (1.17%) developed local relapse (two with LN metastases and two in the contralateral lobe), among whom three underwent TL and one TT. Among those who underwent central lymphadenectomy, significant differences in multifocality (43.4% vs 13.3%; $p < 0.001$), central LN metastasis (42.2% vs 15.7%; $p < 0.001$) and age ($p = 0.05$) were found between the TT and TL groups (Tab. II). To evaluate survival curves of TT and TL groups,

Table I. Prognostic factors according to type of surgery.

		Lobectomy (LT)	Total Thyroidectomy (TT)	Total	P-value
		174 (100)	412 (100)	586 (100)	
pT	1	146 (83.9)	348 (84.5)	494 (84.3)	0.8653
	2	28 (16.1)	64 (15.5)	92 (15.7)	
Sex	Females	134 (77)	327 (79.4)	461 (78.7)	0.5244
	Males	40 (23)	85 (20.6)	125 (21.3)	
Multifocality	No	147 (84.5)	257 (62.4)	404 (68.9)	< 0.0001
	Yes	27 (15.5)	155 (37.6)	182 (31.1)	
Year of surgery	≤ 2010	122 (70.1)	249 (60.4)	371 (63.3)	0.0263
	> 2010	52 (29.9)	163 (39.6)	215 (36.7)	
Age	< 48	117 (67.2)	189 (45.9)	306 (52.2)	< 0.0001
	≥ 48	57 (32.8)	223 (54.1)	280 (47.8)	
Lymphadenectomy	No	91 (52.3)	156 (37.9)	247 (42.2)	0.0012
	Yes	83 (47.7)	256 (62.1)	339 (57.8)	

Table II. Central lymphadenectomy group - prognostic factors according to type of surgery.

		Lobectomy (LT)	Total Thyroidectomy (TT)	Total	P-value
		83 (100)	256 (100)	339 (100)	
pT	1	77 (92.8)	214 (83.6)	291 (85.8)	0.037
	2	6 (7.2)	42 (16.4)	48 (14.2)	
Sex	Females	59 (71.1)	194 (75.8)	253 (74.6)	0.393
	Males	24 (28.9)	62 (24.2)	86 (25.4)	
Multifocality	No	72 (86.7)	145 (56.6)	217 (64)	< 0.0001
	Yes	11 (13.3)	111 (43.4)	122 (36)	
Year of surgery	≤ 2010	42 (50.6)	137 (53.5)	179 (52.8)	0.644
	> 2010	41 (49.4)	119 (46.5)	160 (47.2)	
Age*	< 48	56 (67.5)	142 (55.5)	198 (58.4)	0.054
	≥ 48	27 (32.5)	114 (44.5)	141 (41.6)	
pN1a	No	70 (84.3)	148 (57.8)	218 (64.3)	< 0.0001
	Yes	13 (15.7)	108 (42.2)	121 (35.7)	

** median value; p-values of Chi-square test.*

Table III. No central lymphadenectomy group - prognostic factors according to type of surgery.

		Lobectomy (LT)	Total Thyroidectomy (TT)	Total	P-value
		91 (100)	156 (100)	247 (100)	
pT	1	69 (75.8)	134 (85.9)	203 (82.2)	0.046
	2	22 (24.2)	22 (14.1)	44 (17.8)	
Sex	Females	75 (82.4)	133 (85.3)	208 (84.2)	0.555
	Males	16 (17.6)	23 (14.7)	39 (15.8)	
Multifocality	No	75 (82.4)	112 (71.8)	187 (75.7)	0.056
	Yes	16 (17.6)	44 (28.2)	60 (24.3)	
Year of surgery	≤ 2010	80 (87.9)	112 (71.8)	192 (77.7)	0.003
	> 2010	11 (12.1)	44 (28.2)	55 (22.3)	
Age*	< 48	61 (67)	47 (30.1)	108 (43.7)	< 0.0001
	≥ 48	30 (33)	109 (69.9)	139 (56.3)	

P-values of Chi-square test.

Table IV. Multivariate logistic models to determine propensity scores used in the Cox models - prognostic factors significantly associated with type of surgery: association between hemi-thyroidectomy vs. thyroidectomy.

			OR	Low 95% CI	High 95% CI	P-values
Central lymphadenectomy	Multifocality	No vs yes	4.78	2.37	9.61	< 0.0001
	pN	No vs yes	4.30	2.18	8.49	< 0.0001
	Age		0.97	0.95	0.99	0.0127
No central lymphadenectomy	Multifocality	No vs yes	2.30	1.14	4.65	0.0204
	Age		0.93	0.91	0.96	< 0.0001
	Year of surgery	> 2010 vs ≤ 2010	0.34	0.16	0.74	0.0063

CI: Confidence Interval.

multivariate logistic models were created to determine propensity scores using prognostic factors that were significantly associated with type of surgery: multifocality, LN involvements and age (Tab. IV). Our analyses found that RFS rates differed significantly between the TT and TL groups [p = 0.041; hazard ratio (HR): 11.127, 95% confidence interval (CI): 1.117-110.8)] (Tab. V, Fig. 1). In particular, this difference was found only among patients with central LN metastasis (pN1a) and not among those with pN0 (p = 0.001 and 0.16, respectively) (Figs. 2A, B).

Postoperative follow-up of patients without central neck dissection

No deaths related to thyroid disease occurred among patients who did not undergo central neck dissection. A total of six patients (2.43%) developed local relapse (three with lateral neck metastases, two in the contralateral thyroid lobe and one with both lateral neck and contralateral thyroid lobe metastases), among whom three underwent TL and three TT. Among those who did not undergo central lymphadenectomy, significant differences in age (p ≤ 0.001) and year of surgery were observed between the TT and TL groups (p = 0.003) (Tab. III). To evaluate survival curves of TT and TL groups, multivariate logistic models were established to determine propensity scores using prognostic factors that were significantly associated with type of surgery: multifocality, year of surgery and age (Tab. IV). Our analyses found no significant difference in RFS between TT and TL groups (p = 0.73; HR: 1.364, 95% CI: 0.228-8.159) (Tab. V; Fig. 2C).

Differences in complications rates between groups

Serum calcium levels were collected in 419 patients after surgery. Using the previously established definition for hypocalcaemia, 243 (58%) and 22 patients (5.2%) were determined to have postoperative transient and permanent hypocalcaemia, respectively. Transient hypocalcaemia was significantly more common in the TT group than in the TL group (64.9% vs 19.1%; p < 0.001), whereas no significant difference in permanent hypocalcaemia was observed,

Table V. Multivariate Cox proportional hazard models stratified by propensity scores - analyses are carried out in the two groups by lymphadenectomy.

	HR	Low 95%CI	Up 95%CI	P-values
Central lymphadenectomy	11.127	1.117	110.8	0.041
No central lymphadenectomy	1.364	0.228	8.159	0.733

Hazard ratio (HR) of relapse and 95% confidence intervals refer to type of surgery: hemi-thyroidectomy vs total thyroidectomy.

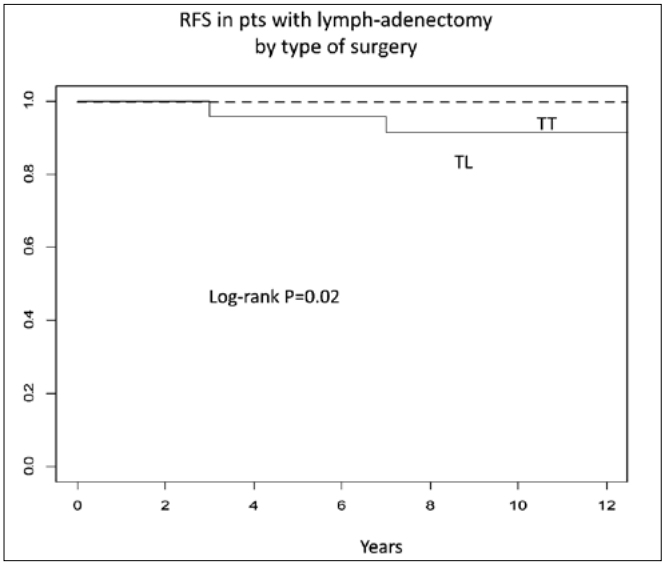

Figure 1. Recurrence-free survival (RFS) in patients receiving lymphadenectomy according to type of surgery: Total Thyroidectomy (TT) vs Thyroid Lobectomy (TL).

perhaps due to the number of subjects evaluated (Tab. VI). More cases of transient recurrent laryngeal nerve paralysis were observed among those who underwent TT than those who underwent TL (p = 0.02; Tab. VI). Only two patients developed permanent recurrent laryngeal nerve paralysis, both of whom belonged to the TT group (Tab. VI). One patient needed tracheostomy, which was removed at 4 months after surgery for movement in one vocal cord. The second one reported unilateral permanent vocal cord paralysis without respiratory problems.

No upper laryngeal nerve damage was noted, while none of

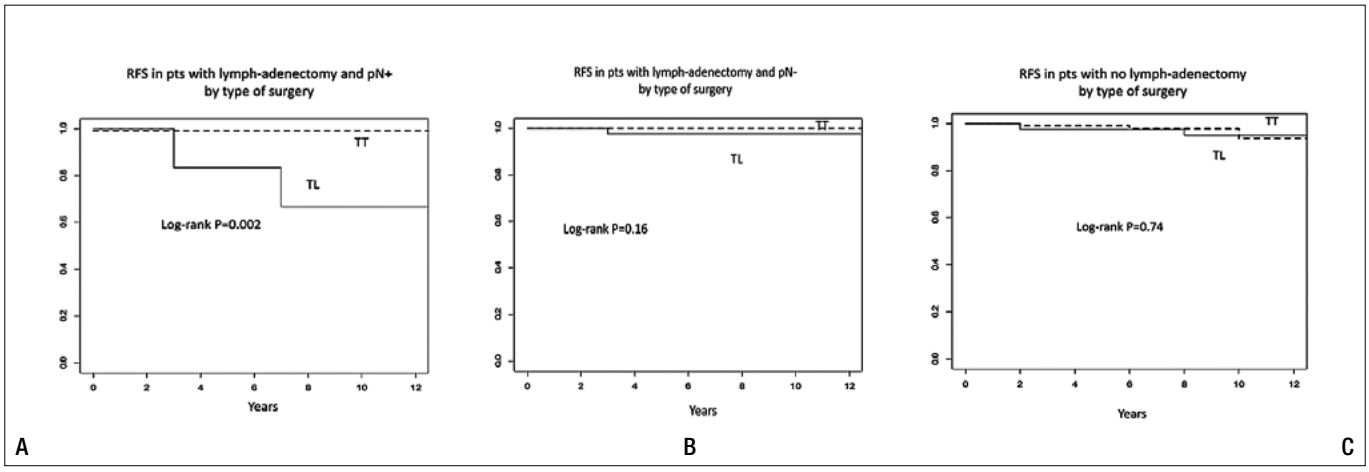

Figure 2. (**A**) recurrence-free survival (RFS) in patients receiving lymphadenectomy and pN+ according to type of surgery: Total Thyroidectomy (TT) vs Thyroid Lobectomy (TL); (**B**) recurrence-free survival (RFS) in patients receiving lymphadenectomy and pN– according to type of surgery: Total Thyroidectomy (TT) vs Thyroid Lobectomy (TL); (**C**) recurrence-free survival (RFS) in patients no receiving lymphadenectomy according to type of surgery: Total Thyroidectomy (TT) vs Thyroid Lobectomy (TL).

Table VI. Complications by type of surgery.

		Lobectomy (LT)	Total Thyroidectomy (TT)	Total	P-value
		174 (100)	412 (100)	586 (100)	
Parathyroidectomy	No	165 (94.8)	357 (86.7)	522 (89.1)	0.0037
	Yes	9 (5.2)	55 (13.3)	64 (10.9)	
Vocal cord transient paralysis	No	168 (96.6)	376 (91.3)	544 (92.8)	0.0233
	Yes	6 (3.4)	36 (8.7)	42 (7.2)	
Vocal cord permanent paralysis	No	6 (3.4)	34 (8.3)	40 (6.8)	0.5541
	Yes	0 (0)	2 (0.5)	2 (0.3)	
		Lobectomy (LT)	**Total Thyroidectomy (TT)**	**Total**	**p-value**
		63 (100)	356 (100)	419 (100)	
Transient hypocalcaemia	No	51 (80.9)	125 (35.1)	176 (42)	< 0.0001
	Yes	12 (19.1)	231 (64.9)	243 (58)	
Persistent hypocalcaemia	Yes	0 (0)	22 (6.2)	22 (5.2)	0.2434

P-values of Chi-square tests.

the patients reported swallowing disorders due to impaired sensitivity during bolus passage.

Discussion

Despite the increasing incidence of PTC, mortality rates remain constant, while prognosis remains excellent [4].
The excellent behaviour of this tumour has led to ongoing debates regarding the necessity of surgical management [5,8]. Two large studies by Bilimoria et al. (2007) and Adam et al. (2014) had reached opposite conclusions. Accordingly, Bilimoria et al. found that among 52,173 patients, those with PTC > 1 cm who underwent conservative surgery exhibited increased rates of recurrence [9]. However, that study had several limitations mainly due to the use of administrative registries from which clinicopathological variables were missing. Conversely, Adam et al., who examined 61,775 patients with 1-4 cm PTC, found that OS was similar between patients who underwent conservative and radical surgery after multivariable adjustment for clinical and pathological factors [14]. Supporters of TT underline the lower risk of recurrence, possibility of thyroglobulin administration during follow-up, and use of I-131 for both diagnostic and therapeutic aims [36]. On the other hand, lobectomy has been preferred for its lower postsurgical morbidity and the absence of lifelong replacement therapy [23,24,37]. Moreover, supporters of lobectomy have stated that several studies found no

difference in recurrence rates and that patients who develop recurrence can still be successfully treated without increasing disease-specific mortality [15]. The latest ATA guidelines on thyroid carcinoma management concluded that lobectomy alone may be sufficient for low-risk PTC of 1-4 cm[12]. This indicates that thyroid cancer management must be tailored to each patient according to both stage and risk factors [18-20,25-30]. This approach challenges the predominant role of tumour size in the management of PTC [38,39]. Moreover, studies have proposed that an active surveillance approach toward managing microPTC (PTC < 1 cm) among those with very low-risk (old age, unifocal and well-defined thyroid nodule margins, and no signs of extrathyroidal extension and neck lymph node involvement on US) seems to be a safe and effective alternative to surgical resection [40,41].

The results of our study substantiate the hypothesis that TL does not promote greater risk of recurrence/LRR or distant metastasis among patients with pT1-2 pN0 papillary carcinoma. Our findings showed that TT had a significantly higher rates of postoperative hypocalcaemia and recurrent laryngeal nerve paralysis than TL.

Moreover, 22 patients determined to have permanent hypocalcaemia need continuous replacement therapy to maintain serum calcium levels in the lower reference range. Unfortunately, we have no data on the incidence of osteoporosis and osteoporotic fractures in permanent hypocalcaemia. However, it is not known if the incidence could be influenced by other factors, such as BMI, heredity, sex, age, other conditions, or medical therapies. This should be considered together with an estimate of the financial costs of both treatments given the increasing interest in cost estimation nowadays. A cost-effectiveness analysis conducted at our institution revealed that TL and TT had a direct cost of € 3,167 (2,800-3,200) and € 5,099 (4,880-5,200), respectively [42]. Several limitations of the current study need to be noted. First is the retrospective nature of the analyses with potential confounding variables and treatment selection bias. We note that prospective studies on this disease are very difficult to conduct given the extended life expectancy, extensive follow-up duration, costs associated with such a study and related ethical issues. Another limitation is the small sample size, as well as the short median follow-up duration. On the other hand, this is a single-centre cohort study with complete and accurate medical records. Moreover, the current study utilised propensity scores to reduce the bias of confounding variables related to treatment effect evaluation arising from simply comparing outcomes among those who did and did not receive treatment. This method attempts to do in a retrospective study what randomisation does in a prospective study. TT, on the other hand, plays an important role in the management of metastatic lymph nodes in the central compartment (pN1a), which leads us to highlight the importance of preoperative study to avoid staging errors and reduce the number of subsequent TLs for oncological radicalisation.

Conclusions

The present study found that TL did not increase the risk for LRR or distant metastasis among those within pT1–2 pN0 PTC and had no effect on RFS. Moreover, TT promoted significantly higher rates of postoperative complications, such as postoperative hypocalcaemia and recurrent laryngeal nerve damage, compared to TL. Additional studies with larger sample sizes and longer follow-up duration would be useful to confirm our data. Although a randomised prospective study would provide much greater statistical power, it may not be feasible considering the characteristics of the disease.

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Laryngology

Voice aspects in sulcus coexisting with benign lesions of the vocal folds

Caratteristiche della voce in pazienti con sulcus e lesioni benigne delle corde vocali

Beata Miaśkiewicz[1], Aleksandra Panasiewicz[1], Elżbieta Gos[2], Agata Szkiełkowska[1], Piotr H. Skarżyński[2], Elżbieta Włodarczyk[2]

[1] Audiology and Phoniatrics Clinic, Institute of Physiology and Pathology of Hearing, Kajetany, Warsaw, Poland; [2] Teleaudiology and Screening Department, Institute of Physiology and Pathology of Hearing, Kajetany, Warsaw, Poland

SUMMARY

The purpose of this study was to measure the clinical profile of patients with sulcus who had concomitant benign lesions such as polyp, oedema, cyst, nodules, or fibrous mass of the vocal fold. We reviewed the medical charts of 38 patients who had a diagnosis of sulcus type 2 or 3 (according to Ford). The patients were classified into two groups. The study group consisted of 16 subjects who had sulcus and associated benign lesion; 22 patients diagnosed with sulcus alone were enrolled in a control group. We analysed psychosocial (Voice Handicap Index-30), auditory-perceptual (GRBAS), acoustic measures and videostroboscopic images. In the study group, the mean VHI-30 scores of all subscales ranged from moderate to severe handicap. The difference between groups was significant on the emotional ($p = 0.004$) and physical ($p = 0.007$) subscales. On GRBAS scale, the majority of patients from both groups exhibited mild hoarseness, breathiness, asthenic or strained voice, although roughness was more frequently rated moderate; the differences between groups were not statistically significant. The most abnormally increased values were achieved for amplitude values of acoustic parameters, but significant difference between groups was found in Soft Phonation Index only ($p = 0.049$). Concerning glottal closure, the most frequent finding was irregular chink in the study group, and spindle glottic chink in controls; we found significant differences between groups ($p = 0.004$). In both series of patients, the most frequent abnormal findings were moderately diminished amplitude and moderately restricted mucosal wave, with no significant difference between groups. Patients with sulcus and coexisting benign lesions were more handicapped on the emotional and physical subscales of VHI-30. The most characteristic shape of the glottal gap was irregular chink in the study group, and spindle chink in the control group. Acoustic evaluation of voice showed that the most severe disturbances affected amplitude parameters. The clinical characteristics indicated that the presence of sulcus primarily determines the quality of voice, and that additional benign pathologies do not drastically affect further voice deterioration. The coexistence of secondary benign vocal fold lesions aggravates the difficulties in making a preoperative diagnosis of sulcus. It is important to clinically suspect the possibility of coexistent sulcus to plan the correct treatment and obtain better voice outcomes.

KEY WORDS: larynx, laryngoscopy, polyps, vocal folds, hoarseness

RIASSUNTO

Lo scopo di questo lavoro è valutare il profilo clinico dei pazienti con sulcus ed affetti contestualmente da lesioni benigne come polipi, edema, cisti, noduli o fibromi delle corde vocali. Abbiamo analizzato le cartelle cliniche di 38 pazienti con diagnosi di sulcus di tipo 2 o 3 (secondo FORD). I pazienti sono stati suddivisi in due gruppi. Il gruppo di studio è composto da 16 pazienti con sulcus e lesioni benigne cordali; il gruppo di controllo è costituito da 22 pazienti con diagnosi di sulcus senza altre lesioni cordali associate. Abbiamo valutato il Voice Handicap Index-30, GRBAS, misurazione acustica ed immagini videostroboscopiche. Nel gruppo di studio i punteggi medi del VHI-30 sono compresi in un range di handicap dal moderato al severo. Sono emerse delle differenze statisticamente significative nei due gruppi nelle valutazioni emozionali e fisiche (rispettivamente $p = 0,004$ e $p = 0,007$). Sulla scala GRBAS, la maggior parte dei pazienti di entrambi i gruppi ha mostrato raucedine di grado lieve, respiro affannoso, voce astenica o tesa, sebbene l'irregolarità fosse risultata più frequentemente di grado moderato, con differenze statisticamente non significative nei due

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Correspondence
Beata Miaśkiewicz
Audiology and Phoniatrics Clinic, Institute of Physiology and Pathology of Hearing, Mokra 17 Str., Kajetany, 05-830 Nadarzyn, Warsaw, Poland
Tel. +48 22 356 03 51. Fax +48 22 356 03 86
E-mail: b.miaskiewicz@ifps.org.pl

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gruppi. L'alterazione più evidente dei valori è risultata essere quella a carico dell'ampiezza dei parametric acustici, tuttavia l'unica differenza statisticamente significativa è risultata a carico del Soft Phonation Index (p = 0,049). Per quanto concerne la chiusura glottica, l'alterazione più frequente nel gruppo di studio è stata una rima glottica irregolare mentre nel gruppo dei controlli, una rima glottica fusiforme, (p = 0,004). In entrambe le serie di pazienti le alterazioni più frequenti sono state l'ampiezza moderatamente ridotta e l'onda della mucosa moderatamente limitata, ma non abbiamo riscontrato differenze significative tra i due gruppi.

Le caratteristiche cliniche indicano che la presenza di solco influisce in manieradeterminante sulla qualità della voce mentre le ulteriori patologie benigne associate al sulcus influiscono solo parzialmente sulla disfonia. La coesistenza di lesioni secondarie benigne delle corde vocali rende più difficile formulare una diagnosi preoperatoria di sulcus. È importante sospettare clinicamente la possibilità di un sulcus coesistente per pianificare il giusto trattamento al fine di ottenere un migliore risultato vocale.

PAROLE CHIAVE: *laringe, laringoscopia, polipi, corde vocali, raucedine*

Introduction

Sulcus is a laryngeal condition linked to a clinically inhomogeneous defect of the epithelium covering the vocal folds in which there is a structural malformation, ranging from minor invagination to a deep focal pouch.

The classifications of sulci used today were introduced by Bouchayer and Cornut [1], and Ford [2]. Bouchayer and Cornut proposed to distinguish sulcus vergeture (which Ford named sulcus type 2) and sulcus vocalis (the open epidermoid cyst which Ford named sulcus type 3) as two distinct anatomical phenomena [1]. Vergeture is characterised as an atrophic groove under the free edge of the vocal fold that extends close to the vocal ligament. Sulcus vocalis refers to a pocket lined with a thick epithelium extending into the Reinke's space as deep as the vocal ligament or muscle [1]. It is characterised by tissue loss throughout the entire lamina propria [3]. Ford and colleagues [2] extended this classification to account for variability in clinical appearance. In addition types 2 and 3, they distinguished type 1 as involving an asymptomatic subtle depression along the free edge with normal or minimally altered mucosal wave and an intact layered structure of the lamina propria.

To date, there is no consensus regarding the aetiology of sulcus. Arguments for congenital origin link sulcus to epidermoid cyst and mucosal bridge of the vocal fold, representing the fourth and sixth branchial arch anomalies [1,4]. Keratin debris (fibrous mass) embedded deep within the sulcus or a concomitant scar are not unusual intraoperative findings [5,6]. Nakayama and colleagues found a high incidence (48%) of sulcus deformities in pathological examinations for laryngeal cancer, and suggested an acquired origin resulting from local trauma and/or chronic inflammation [7]. A mechanism similar to the development of middle ear cholesteatoma was considered by Lee et al. [4].

Sulcus leads to vocal fold stiffness and deformity of the medial edge, resulting in glottal insufficiency; consequently, patients very often present supra-glottal and glottal hyperactivity or even a severe compression that may result in development of other concomitant benign lesions, such as polyp, oedema, or vocal fold nodules. The incidence of concomitant lesions in sulcus cases is reported to be 6.4% to 64% [8-14]. The presence of such benign lesions can reveal the underlying condition (sulcus) and may influence voice quality. Proper diagnosis based on thorough clinical examination allows for specific treatment and rehabilitation, and also provides reliable prognosis for voice improvement. There is only a handful of studies related to specific voice characteristics of patients with sulcus and coexistent benign lesions of the vocal folds.

The goal of the present study was to analyse the clinical characteristics of patients with sulcus and concomitant benign lesions; the analysis considered psycho-social handicap, auditory-perceptual ratings, acoustic measurements and vibratory patterns.

Materials and methods

We carried out a retrospective study based on charts of 38 patients with diagnosed sulcus (with and without coexistent benign lesions) who were treated surgically at the Institute of Physiology and Pathology of Hearing between 2011 and 2017. The diagnosis and classification of sulcus were made by a laryngologist following stroboscopic examination. Diagnoses were confirmed or revised by the same laryngologist during subsequent direct microlaryngoscopy. Patients undergoing intervention for a benign lesion of the vocal fold e.g. polyp, nodules, oedema, in whom sulcus was discovered during palpation with a blunt micro-instrument were included in this study based on the intraoperative diagnosis. The final inclusion criterion in this study was the presence of sulcus (with and without concomitant lesions) during surgery.

The exclusion criteria were: sulcus suspected during videolaryngostroboscopy but not confirmed in microlaryngoscopy, incomplete medical charts and prior laryngeal surgeries.

Patients were classified into two groups. The study group consisted of 16 subjects who had sulcus and associated benign lesions. Twenty-two patients with isolated sulcus were included in the control group.

The study group consisted of 13 women and 3 men aged from 28 to 66 years (M = 39.62; SD = 10.171). There were 7 patients with type 2 sulcus and 9 with type 3. Eight patients were diagnosed with unilateral sulcus and 8 with bilateral sulci. In cases of bilateral sulci they were of the same type on both vocal folds. In 7 subjects sulcus presented with concomitant vocal fold fibrous mass, while a polyp coexisted in 3 patients, mucosal bridge in 3, Reinke oedema in 2, vocal nodules in 1, epidermoid cyst in 1, scar in 1 and presbylarynx in 1 patient. Additionally, 3 patients had two lesions that simultaneously presented a fibrous mass and mucosal bridge, fibrous mass and polyp and vocal nodules with mucosal bridge. In 10 cases the concomitant lesions were found unilaterally (on the same vocal fold as the sulcus) and in 6 subjects bilaterally.

The control group consisted of 22 subjects diagnosed with sulcus alone: 11 women and 11 men aged from 22 to 70 years (M = 46.05; SD = 12.96). There were unilateral sulci in 6 patients and bilateral ones in 16. Most patients presented with type 2 sulcus (15 cases) or type 3 sulcus (7 cases). In cases of bilateral sulci, there was the same type of sulcus on both vocal folds.

The complaints driving diagnostic procedures and conservative or surgical treatment involved: hoarseness, diminished voice intensity and range of voice, vocal fatigue, and strained, breathy or unstable voice. Prior to surgery, 52% of patients had undergone speech therapy without satisfactory voice improvement. The remaining 48% were unable to attend preoperative therapy sessions due to a considerable distance from their home or lack of time.

Patient evaluation included psychosocial, auditory-perceptual and acoustic assessments, as well as laryngovideostroboscopy (LVS).

The Voice Handicap Index questionnaire (VHI-30) was administered to evaluate self-perception of voice [15]. The VHI-30 total score (VHI-T) and its components, emotional (VHI-E), physical (VHI-P) and functional (VHI-F) subscale scores, were all calculated.

An auditory – perceptual evaluation of voice was carried out with the GRBAS scale [16] in which a clinician estimates the grade of hoarseness (G), roughness (R), breathiness (B), asthenia (A) and strain in the voice (S) on a scale from 0 to 3 (0, normal; 1, mild; 2, moderate; 3, severe). Ratings, based on sustained phonation and a short speech sample, were made by a senior laryngologist – phoniatrist (BM) upon initial clinical presentation. The same researcher then retrospectively performed blinded evaluation of the recorded voice samples.

An objective acoustic voice analysis was performed with a Computerised Speech Lab (CSL) 4,500 external module from Kay Elemetrics Corporation (Lincoln Park NJ). All voices were recorded with an ECM 800 microphone (Behringer) positioned approximately 15 cm away from the mouth at an angle of 45° to reduce airflow effects. Analysis of a voice sample recorded at a sample rate of 25 kHz was done using the Multidimensional Voice Program software (MDVP 5105 version 2.7.0). Three samples of the sustained vowel "a" in modal voice were used for analysis; only the middle portion of the uttered vowel was used (min. 0.6 sec), avoiding onset and offset effects [17-19]. The following acoustic parameters were calculated: average fundamental frequency (F0), frequency variations (% Jitter; Relative Average Perturbation, RAP; Pitch Perturbation Quotient, PPQ; Smoothed Pitch Perturbation Quotient, sPPQ; Fundamental Frequency Coefficient Variation, vF0), amplitude variations (% Shimmer; Amplitude Perturbation Quotient, APQ; Smoothed Amplitude Perturbation Quotient, sAPQ; Peak-to-Peak Amplitude Coefficient of Variation, vAm), and noise-related parameters (Noise to Harmonic Ratio, NHR; Soft Phonation Index, SPI).

To analyse the acoustic characteristics of patients with sulcus and coexisting benign lesions, we used the normative thresholds as proposed by Delijsky [20], as well as the norms provided by Kay Elemetrics Corporation which refer to adults in the general population [21]. For each parameter, we determined a cut-off point separating the patients into two groups: one with low values of the given parameter (lower than the normative value) and another with high values (above the norm).

Laryngovideostroboscopy (LVS) was performed with a 70° rigid laryngoscope (EndoStrob DX Xion 327, GmbH, Germany), while glottal closure and vibration characteristics of the vocal folds were assessed subjectively.

The pattern of glottal closure was rated on a 6-point scale according to Lim's proposal [22] as follows: 0, complete closure; 1, anterior glottic chink; 2, posterior chink; 3, spindle glottic chink; 4, irregular glottic chink; 5, incomplete glottic closure (no glottal contact).

Amplitude and mucosal wave were evaluated with a 4-point scale. Amplitude was rated as: 0, normal; 1, mildly diminished; 2, moderately diminished; 3, severely diminished; and mucosal wave: 0, normal; 1, mildly restricted; 2, moderately restricted; 3, completely lacking. All stroboscopic videos were evaluated preoperatively, and the recordings were retrospectively assessed in an anonymous fashion by the same senior laryngologist-phoniatrist who performed auditory-perceptual ratings.

Operations were performed under general anaesthesia with suspended microlaryngoscopy and endotracheal intubation. In the first step of the procedure, the vocal folds were inspected under magnification with an operating microscope and palpated with a blunt instrument to assess

the type of pathology or search for any other unexpected lesions.

If the coexistent benign lesion was present, it was removed during the same surgical procedure. The surgical technique for sulcus was based on the concept by Bouchayer and Cornut with Remacle's modification [1,8,23].

In cases of coexisted vocal nodules and polyp the medial microflap technique was applied, whereas epidermoid cyst, Reinke's oedema, scar and fibrous mass were treated by the lateral microflap technique.

If there was a significant vocal fold atrophy, injection laryngoplasty was performed during the same operation. We used two injectable materials: hyaluronic acid (HA; Surgiderm 24 XP, Allergan) and calcium hydroxylapatite (CaHa; Radiesse Voice Implant, Merck). Postsurgical voice therapy was mandatory in all subjects and involved one session a week for 2-5 months, or patients were referred to hospitalisation with voice rehabilitation.

Statistical analysis

The normality assumption of quantitative variables (the VHI scores and acoustic parameters) was examined by the Shapiro-Wilk test. Afterwards, a two-sample t-test or the Mann-Whitney U test was conducted. A chi-square test was used to test differences between the study group and control group in terms of categorical variables (the results for GRBAS and for assessment of glottal closure, amplitude and mucosal wave). Data analysis was done using IBM SPSS Statistics v. 24.

Results

Voice Handicap Index

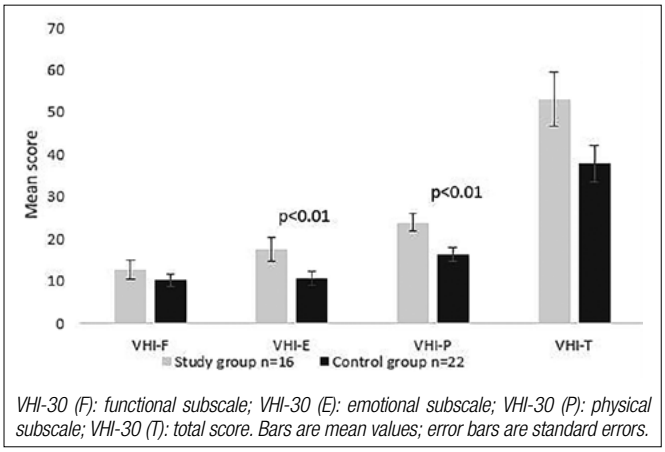
Summary statistics for the VHI-30 subscale scores and total score for patients from the study group are presented in Table I. According to the criteria described by Jacobson et al. [11] the mean scores of all subscales ranged from moderate (functional) to severe (physical, emotional) handicap, and the total score was moderate.

Figure 1 compares the VHI-30 scores between patients from the study group and controls (the sulcus group).

Table I. Descriptive statistics for VHI-30 scores (for patients with benign lesions (n = 16).

	Min	Max	M	SD	Me
VHI-F	0	26	12.69	8.48	11.00
VHI-E	2	40	17.38	11.63	16.00
VHI-P	9	36	23.88	8.91	26.50
VHI-T	15	99	53.00	25.66	44.50

Min: minimum; Max: maximum; M: mean; SD: standard deviation; Me: median; VHI-30 (F): functional subscale; VHI-30 (E): emotional subscale; VHI-30 (P): physical subscale; VHI-30 (T): total score.



VHI-30 (F): functional subscale; VHI-30 (E): emotional subscale; VHI-30 (P): physical subscale; VHI-30 (T): total score. Bars are mean values; error bars are standard errors.

Figure 1. Comparison of VHI- 30 scores between study group and controls.

The difference between groups in VHI scores was significant for the emotional (p = 0.004) and physical (p = 0.007) subscales, indicating that patients with concomitant benign lesions were more handicapped in both these domains than patients without coexisting benign lesions. On the functional subscale, the groups did not differ (p = 0.330). For the global VHI-30 score the p value was 0.05, and the 95% confidence interval of the difference was [-0.015; 30.615] (it spanned 0), so the difference cannot be considered significant.

Perceptual evaluation (GRBAS)

Data on GRBAS parameters are presented in Table II, which shows the number of subjects and percentages (in brackets). The majority of patients in the study group presented with a mild grade of hoarseness (69%), whereas 31% had a normal voice in the perceptual assessment. Concerning the R parameter, most patients had a moderate (50%) or mild (37.5%) grade of roughness. Breathiness appeared mostly mild (62.5%), as did strained voice (69%). Asthenia was present in 56% of cases, and was mild.

Comparison of GRBAS indices showed similar values in both groups. For all GRBAS domains, the differences between the study group and controls were not significant (p > 0.05).

Acoustic assessment

The percentage of high and low values for MDVP is shown in Table III. The values for frequency were above the norm in most individuals in the study group. For vF0, 93.8% of subjects were above the norm.

High values of amplitude parameters were also observed in the majority of patients, especially for vAm (100%) and Shim (93.8%). Elevated values of SPI (37.5%) and NHR (18.2%) were less commonly found.

Table II. Comparison of GRBAS parameters for study group (n = 16) and control group (n = 22).

	Grade				
	Normal voice (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**	
Study group	5 (31%)	11 (69%)	0	0	$\chi^2 = 1.27$; p = 0.530
Control group	9 (41%)	12 (54.5%)	1 (4.5%)	0	
	Roughness				
	Normal voice (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**	
Study group	0	6 (37.5%)	8 (50%)	2 (12.5%)	$\chi^2 = 2.65$; p = 0.449
Control group	1(5%)	4 (18%)	15 (68%)	2 (9%)	
	Breathiness				
	Normal voice (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**	
Study group	4 (25%)	10 (62.5%)	2 (12.5%)	0	$\chi^2 = 0.17$; p = 0.919
Control group	5 (23%)	15 (68%)	2 (9%)	0	
	Asthenia				
	Normal voice (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**	
Study group	7 (44%)	9 (56%)	0	0	$\chi^2 = 0.21$; p = 0.646
Control group	8 (36%)	14 (64%)	0	0	
	Strain				
	Normal voice (0)	**Mild (1)**	**Moderate (2)**	**Severe (3)**	
Study group	2 (12%)	11 (69 %)	3 (19 %)	0	$\chi^2 = 1.60$; p = 0.660
Control group	2 (9%)	14 (64%)	4 (18%)	2 (9%)	

Table III. Percentage of patients in the study group (n = 16) having high or low MDVP parameters. Abbreviations as in Materials and methods.

	Below norm (%)	**Above norm (%)**
Jitt	31.2	68.8
RAP	31.2	68.8
PPQ	43.8	56.2
sPPQ	37.5	62.5
vF0	6.2	93.8
Shim	6.2	93.8
APQ	25.0	75.0
sAPQ	25.0	75.0
vAm	0.0	100.0
NHR	81.3	18.2
SPI	62.5	37.5

Table IV. Comparison of MDVP parameters. Abbreviations as in Materials and methods.

	Study group n = 16		**Control group n = 22**		**Test statistic**	**P-value**
	M	**SD**	**M**	**SD**		
F0	202.29	64.87	195.38	41.64	t = 0.40	0.692
Jitt	1.98	1.21	1.71	1.15	U = 144.00	0.344
RAP	1.17	0.71	1.02	0.68	U = 145.00	0.359
PPQ	1.21	0.76	1.00	0.70	U = 134.50	0.220
sPPQ	1.54	0.91	1.27	0.64	U = 139.50	0.280
vF0	3.55	2.79	2.85	1.81	U = 151.00	0.460
Shim	6.82	3.54	5.79	2.30	U = 44.50	0.352
APQ	5.06	2.97	4.23	1.62	U = 160.00	0.636
sAPQ	7.74	6.33	6.30	1.87	U = 168.00	0.813
vAm	22.88	10.55	17.89	7.70	U = 114.00	0.067
NHR	0.17	0.06	0.16	0.05	U = 172.00	0.906
SPI	11.45	4.89	15.12	5.90	t = 2.03	0.049

M: mean; SD: standard deviation; t: result of t-test; U: result of Mann-Whitney test.

Table IV compares the values of the voice parameters in the study group with those in the control group. The analysis showed that, for the SPI parameter, there was a significant difference between groups with the mean value being lower in patients with sulcus and coexisting benign lesions (p = 0.049). The vAm was also elevated, but failed to reach statistical significance (p = 0.067). For the remaining parameters, no significant changes were observed between groups.

The percentages of high and low MDVP values were compared between groups (patients with sulcus benign lesions and the controls) using a chi-square test, but no significant differences were found.

Laryngovideostroboscopy

In the study group, preoperative stroboscopic examination revealed sulcus vocalis or vergeture in 11 patients. In the remaining 5 cases, other laryngeal disorders were diagnosed (polyp in 2, nodules in 1, Reinke oedema in 2) and sulcus

was only diagnosed during microlaryngoscopy (Figs. 2, 3). Data on glottal gap measurements are presented in Table V. We did not observe complete glottal closure in any patient in the study group, but it was present in 9% of individuals in the control group. The most frequent finding in the study group was irregular chink (56%), whereas it was rarely seen in controls (5%). The most characteristic shape of glottal closure in the control group was spindle glottic chink (68%), which we observed in only 19% individuals in the study group.

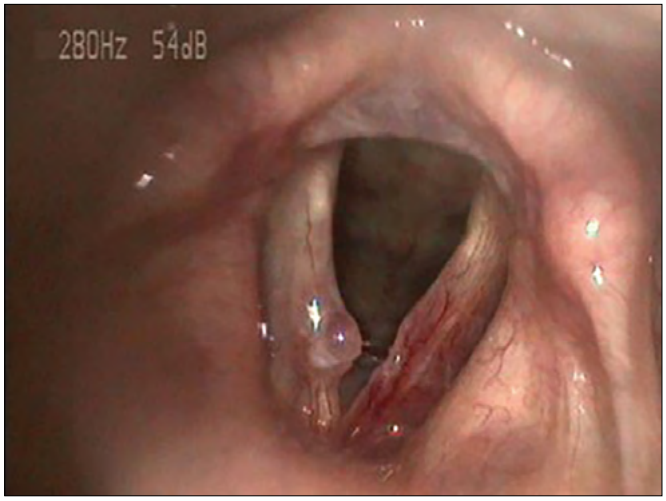


Figure 2. Laryngovideostroboscopy of a polyp on the right vocal fold and sulcus type 3 on the left vocal fold.

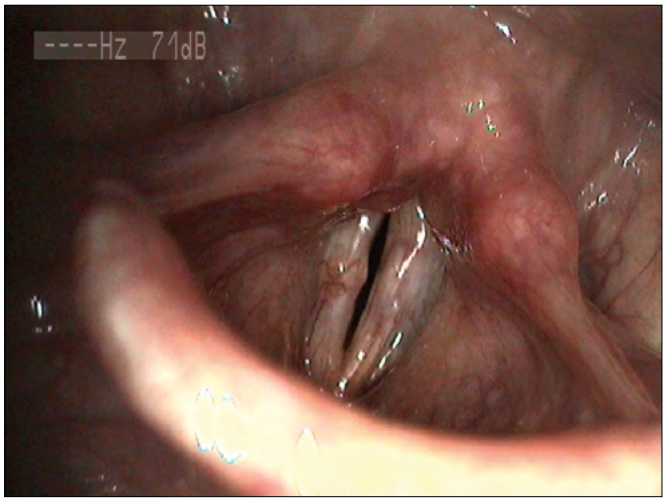


Figure 3. Laryngovideostroboscopy of bilateral sulcus type 3 and bilateral fibrous mass of the vocal folds.

In terms of glottal closure, significant differences between the groups were found ($p = 0.004$).

In most patients in the study group the amplitude of vibration was diminished to a moderate degree (56%); for 31% it was mild and severely diminished in 13%. We did not note normal amplitude in any patient. The mucosal wave was moderately restricted in 75% of patients and severely in 25%. We did not observe any patients with normal and mildly restricted mucosal wave.

The most frequent finding in the control group was moderately (46%) and mildly (36%) diminished amplitude; in 9% it was normal and severely diminished in 9%. Regarding the mucosal wave it was moderately restricted in 64% individuals; in 18% it was mild and in 18% it was severely restricted. We did not find any subject with a normal mucosal wave.

Regarding comparison of the amplitude and the mucosal wave, there was no significant differences between groups ($p > 0.05$). In both groups the most frequent abnormal findings were moderately diminished amplitude and moderately restricted mucosal wave. Even though in the study group there were more patients with severely diminished amplitude (13%) and severely restricted mucosal wave (25%), the differences were not significant.

Discussion

Sulcus is not a rare vocal fold pathology, but it is difficult to diagnose. The heterogeneity in origin and clinical appearance makes the diagnosis and treatment of sulci a challenge [5,13]. This laryngeal condition frequently goes undetected and is only suspected after stroboscopic study.

The presence of a concave medial edge of the vocal fold with glottal incompetence leads to the development of secondary hyperfunction and makes the vocal folds more susceptible to vocal abuse, which may predispose the patient to development of speech-trauma related lesions. In our cases, sulcus was associated with vocal fold fibrous mass, epidermoid cyst, mucosal bridge, polyp, nodules, and Reinke's oedema. According to the literature, sulcus may be detected or confirmed in approximately 30-40% of patients undergoing surgery for such lesions, thus confirming that sulcus is not easy to diagnose during stroboscopy [8,12,23]. Eckley and colleagues [9,23]. reported that the incidence of sulcus in those with polyps ranges from 22.2 to 36.4%. Coexistence of a mucosal bridge and an epidermoid cyst,

Table V. Comparison of glottal closure in the study group (n = 16) and control group (n = 22).

	Complete closure	Anterior chink	Posterior chink	Spindle shaped	Irregular	Incomplete closure	
Study group	0	1 (6)	1 (6)	3 (19)	9 (56)	2 (13)	$\chi^2 = 17.22$; $p = 0.004$
Control group	2 (9)	0	2 (9)	15 (68)	1 (5)	2 (9)	

in conjunction with sulcus vocalis, tends to reinforce a congenital origin, and indicates that these three lesions may represent different evolutionary stages [1].

Structural vocal fold abnormalities in the sulcus lead to asymmetric vibrations and unbalanced muscular activity of the vocal folds [23]. Deformity of the vocal fold edge, abnormal glottis closure, irregular amplitude vibration and restricted mucosal wave seem to play a key role in the development of these benign lesions.

The most frequent finding in the study group was irregular chink (56%), whereas in the controls it was spindle shaped closure (68%). Intuitively, some coexisting lesions (i.e. nodules, polyp, oedema, cyst) may contribute to a reduction of glottal gap during phonation. Such a glottal configuration was also consistent with acoustic parameter Soft Phonation Index. The significantly lower values of SPI in patients with sulcus and coexistent lesions (in comparison to those with sulcus alone) may indicate that some concomitant lesions decrease the width of the glottal gap [21].

The lack of complete glottal closure creates an air leak which reduces the patient's ability to produce a constant sound, leading to changes in vibratory amplitude that contribute to auditory-perceptual and acoustic measurements [19]. In the auditory-perceptual evaluation, the majority of patients in both groups had a mild grade of hoarseness, roughness, or breathiness as well as an asthenic or strained voice quality, which is consistent with other reports [24,25]. The only exception was that moderate roughness was observed in most subjects in the control group.

In objective acoustic assessments, the most abnormally increased values were amplitude parameters. Peak-to-peak vibratory amplitudes (vAm) were higher in cases of sulcus with concomitant lesions (although the difference was not statistically significant in comparison to sulcus alone). The mean values of frequency parameters were slightly elevated. The lack of significant differences between groups, except for SPI, suggests that acoustic structure of the voice in both series of patients was determined by the presence of sulcus. Many authors report a large discrepancy between acoustic measurements and VHI-30 [26,27]. As in other reports, the VHI-30 scores in the study group were influenced by gender allocation [15]. The control group had an even sex distribution, whereas in the study group there was a prevalence of women, in contrast with the literature [24,28,29]. Patients with sulcus and concomitant benign lesions had significantly higher emotional and functional VHI-30 scores. The high score on the emotional subscale may stem from a clear prevalence of women in our study group since vocal nodules, cyst, or Reinke's oedema are more common in females [30]. Despite the lack of statistical significance ($p = 0.050$) between the groups, the total VHI score was higher in the study group. Welham et al. [3] reported similar observations in a group with sulcus and concomitant scar/oedema. This suggests that sulcus with coexisting lesions is more handicapping than is sulcus alone.

Our study design has some limitations and the data should be interpreted carefully. Importantly, only 16 patients with sulcus and concomitant lesions were included in the study group. This is a small sample, especially considering the heterogeneity in clinical presentation. We gathered subjects with two types of sulcus (types 2 and 3) with different concomitant laryngeal disorders afflicting one or both vocal folds. Our findings reflect the clinical complexity of these patients, but the small number also limits direct comparison between the study and control groups. It is worth noting the inhomogeneity in gender between the two groups.

Conclusions

The clinical characteristics indicate that the presence of sulcus primarily determines the quality of voice, and that the additional benign pathologies do not drastically affect further voice deterioration. The coexistence of secondary benign vocal fold lesions aggravates the difficulties in making a preoperative diagnosis of sulcus. Therefore, it is important to clinically suspect the possibility of coexistent sulcus to individualise treatment, including surgery, to obtain better voice outcomes and decrease the chance of recurrence of benign lesions involving the vocal fold.

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LARYNGOLOGY

A one-year time frame for voice prosthesis management. What should the physician expect? Is it an overrated job?

Finestra di un anno sulla gestione di pazienti con protesi fonatoria. È un carico clinico sovrastimato?

Claudio Parrilla[1], Ylenia Longobardi[1], Gaetano Paludetti[1], Maria Elisabetta Marenda[1], Lucia D'Alatri[1], Francesco Bussu[2,3], Emanuele Scarano[3], Jacopo Galli[1]

[1] Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Istituto di Otorinolaringoiatria, Rome, Italy; [2] Otolaryngology Division AOU, Sassari, Italy; [3] Università Cattolica del Sacro Cuore, Istituto di Otorinolaringoiatria, Rome, Italy

SUMMARY

Management of late complications represents the main reason for reluctance in using voice prosthesis rehabilitation. The aim of this paper is to report our experience by describing the one-year management of a large cohort of patients in order to clarify how demanding management is in terms of burden on clinicians. Between June 2017 and June 2018, each access made at the Otolaryngology Clinic of our Institute for issues related to prosthesis by 70 laryngectomised patients rehabilitated by voice prosthesis was registered in a specific database. A review of the data provided information on the incidence, management and outcomes of adverse events encountered during the selected time frame. In addition, a T test was used to evaluate the differences between irradiated and non-irradiated patients and between primary and secondary tracheo-oesophageal-puncture. Leakage through the prosthesis was the most common cause for access (51.86%). The median number of accesses per patient per year was 3.47. The speech therapist autonomously managed 18.1% of accesses. The median number of accesses per patient per year needing a physician was 2.84. The median lifetime of the prosthesis was 4.85 months. Radiotherapy or modality (primary or secondary) of the puncture did not influence the number of accesses per year or the prosthesis lifetime. This retrospective analysis of results highlighted the most frequent issues and the most effective measures to deal with them, which allowed us to define a systematic algorithm to standardise and ease long-term outpatient management.

KEY WORDS: total laryngectomy, voice prosthesis, post-laryngectomy, rehabilitation, multidisciplinary

RIASSUNTO

La gestione delle complicanze tardive rappresenta il motivo principale della riluttanza nell'uso della riabilitazione con protesi fonatoria dopo laringectomia totale. Lo scopo del presente lavoro è descrivere un anno di gestione di un'ampia coorte di pazienti, al fine di chiarire quanto impegnativo sia il management in termini di carico lavorativo per i clinici dedicati. Nel periodo compreso tra giugno 2017 e giugno 2018, ogni accesso effettuato, presso la Clinica di Otorinolaringoiatria del nostro Istituto, da 70 pazienti laringectomizzati riabilitati con protesi fonatoria per problematiche legate al dispositivo protesico, è stato registrato su uno specifico database. L'analisi dei dati ha fornito informazioni sull'incidenza, la gestione e gli outcomes relativi a tutti gli eventi avversi riscontrati durante il periodo preso in esame. Al fine di valutare le differenze tra pazienti irradiati e non irradiati e pazienti sottoposti a posizionamento simultaneo e sequenziale/ritardato è stato, inoltre, utilizzato il test T di Student. Il leakage intravalvolare è stata la causa di accesso più frequente (51,86%). Il numero medio di accessi per paziente per anno è stato pari a 3,47. La logopedista ha gestito autonomamente il 18,1% degli accessi. Di conseguenza, il numero medio di accessi per paziente per anno che hanno necessitato di visita medica è stato pari a 2,84. La durata media del dispositivo protesico è stata pari a 4,85 mesi. La radioterapia o la tecnica di posizionamento utilizzata (simultanea o sequenziale/ritardata) non ha influen-

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Correspondence
Ylenia Longobardi
Otolaryngology Head and Neck Surgery Department,
Catholic University of the Sacred Heart,
l.go F. Vito 1, 00168 Rome, Italy
E-mail: ylenia.longobardi@guest.policlinicogemelli.it

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zato il numero di accessi per anno né la durata della protesi fonatoria. L'analisi retrospettiva dei risultati ha evidenziato le problematiche più frequenti e le misure più efficaci per affrontarle, permettendo la creazione di un algoritmo sistematico che agevoli e standardizzi il management a lungo termine di questi pazienti.

PAROLE CHIAVE: *laringectomia totale, protesi fonatoria, post-laringectomia, riabilitazione, multidisciplinare*

Introduction

Over the last 30 years, trachea-oesophageal speech (TES) has become the gold standard for rehabilitation following total laryngectomy [1] thanks to a more natural sounding voice, superior voice quality, shorter rehabilitation time [2,3] and a higher success rate (ranging from 60 to 90%) [4] compared with other rehabilitation methods.

Generally speaking, it is recognised that four main reasons hinder the widespread use of TES: surgical complications (early complications), long-term voice prosthesis/fistula troubles (late complications), cost of devices and burden on physicians.

Early complications are in most cases "minor" (e.g. trauma to the lips/teeth, superficial mucosal lacerations), both in primary and secondary settings [5]. Major complications (e.g. oesophageal perforation) are quite rare and always related to difficult secondary puncture [6-10]. Diagnosis and management of early minor and major complications is beyond the scope of this paper, but the general worldwide orientation is a preference, as much as possible, for primary punctures to reduce the risk of major, life-threatening complications.

Our focus is on late complications, which could be considered unavoidable consequences of the fistula and/or of the presence of a foreign body (i.e. voice prosthesis). The management of these issues is considered time demanding, often causes anxiety in non-experienced non-specifically trained specialists and, in the real world, it represents the main obstacle for many physicians to voice prosthesis rehabilitation. Voice prosthesis patients are, in fact, notoriously characterised by much more frequent visits to healthcare professionals than oesophageal speakers. Some late sequelae are easy to manage, whereas others may challenge even the most experienced clinician [11].

The lifetime of voice prostheses is one of the limitations of TES, representing the need for ongoing replacement of the valve [12]. The main cause (80%) for replacement of an indwelling device is internal leakage (intravalvular leakage) due to the contamination by a biofilm of bacteria and yeasts that renders the valve incompetent [13,14].

Other reasons for device replacement/adjustment are leakage around the device, fistula-related problems including formation of granulation tissue, or infection [15,16].

Leakage around the prosthesis is often due to the gradual thinning of the tracheo-oesophageal-puncture site (TEP), and consequent shortening of the prosthesis is a natural course of events, representing about 10% of all voice prosthesis substitutions [17-21].

In addition, functional issues (immediate or delayed aphonia or dysphonia) represent a frequent problem that brings the patient to the hospital to be treated accordingly [22,23].

The aim of this paper is to analyse a 1-year window of troubleshooting in a multidisciplinary setting for a large cohort of voice prosthesis rehabilitated patients, to quantify how demanding management is and to propose an algorithm that is useful to minimise the time and burden for dedicated clinicians.

Materials and methods

Between June 2017 and June 2018, 70 voice prosthesis patients made 243 accesses at the Otolaryngology Clinic and Phoniatric Unit of our Institute for issues related to their prosthesis. In our centre, there is a dedicated team for management of voice prosthesis patients consisting of 2 ENT surgeons and 3 speech therapists. Each team member has specific training and is able to perform patient visits to evaluate the voice prosthesis, fistula and peristomal tissues.

The median age was 65.12 ± 6.53 years (range 54-80 years). All patients had undergone total laryngectomy with bilateral neck dissection and TEP for voice restoration. All patients included in the study had undergone primary closure of the pharynx, except for three free flap non-tubed reconstructions (2-anterolateral thigh and 1 forearm) in the salvage setting after concomitant radio-chemotherapy.

Forty-six patients had been subjected to primary (n = 12/26.08%) or adjuvant (n = 34 /73.91%) radiotherapy. In 28 of 70 patients (40%), a secondary TEP was chosen.

The interval between total laryngectomy and prosthesis implantation varied from 2 to 108 months (25.38 ± 27.55). All patients were primarily trained by the speech therapist in the use and maintenance of the fistula and prosthesis. Speech therapy rehabilitation began on the 10^{th}-12^{th} post-operative day for patients undergoing primary TEP, after the removal of the nasogastric tube. For patients with secondary TEP, rehabilitation started 24 hours after the operation. Speech therapy provided coordination exercises, which included breath and digital stoma occlusion, production of vocalisations, bi-syllabic and polysyllabic words, automatic series and sentences with increasing

length. Subsequently, patients worked on the production of exclamatory or interrogative sentences, reading short passages and conversations. Finally, specific training was carried out to improve the control of rhythm and modulation and intensity variations. Speech therapy had variable timing based on each individual case (from 10 to 20 sessions, with a median of 12 sessions). No patient ever used the Electrolarynx.

Since June 1st, 2017, each access was registered in a specific database. A review of these medical records provided information on the incidence, management and outcomes of adverse events encountered during the selected time frame (1 June 2017 - 1 June 2018). The data were managed as hand-entry during routine practice and the records were then interrogated as a chart/case review. The appointed person for managing this data was speech therapist.

Data used were retrospectively gathered from existing data sources. Approval from the Local Ethics Committee was obtained.

Statistical analysis

Statistical analysis was performed using JMP software, release 7.0.1, from the SAS Institute. The α level was fixed at 0.05.

Paired T test was used to evaluate the differences between patients subjected to radiotherapy vs non-irradiated patients and between primary and secondary TEP.

Results

Leakage through the prosthesis occurred in 125 accesses (51.86% of overall accesses). In 15 of 125 internal leakages, the speech therapist resolved the issue. In 110 of 125 accesses, the physician resolved the issue. The solutions adopted are summarised in Table I.

Leakage around the prosthesis was noted in 60 accesses made by 29 of 70 patients (24.69% of overall accesses, 41.42% of patients). On most occasions, it was due to an over-long prosthesis moving back to create a piston-effect. Before coming to medical examination, 14 cases were resolved by the speech therapist. In 46 of 60 accesses, the leakage around the prosthesis was resolved by a physician. The solutions adopted are summarised in Table II.

Some patients developed aphonia or dysphonia, immediate or delayed, showing excessive vocal effort (28 accesses, 11.52%). The first step in the management of this problem was speech therapist evaluation, who resolved it in 10 of 28 cases. In 14 of 28 cases, the dysphonia/aphonia was resolved by a physician. Three of 14 patients were treated with chemical denervation with botulinum toxin. In 4 accesses (3 of which by the same patient), no attempt was successful in resolving the excessive vocal effort. The solutions used are summarised in Table III.

A growing circumferential granuloma at the tracheal wall of the puncture was observed in 16 accesses (6.58%). In three cases, the replacement was avoided by the speech therapist. In 13 of 16 accesses, the physician resolved the issue. The solutions used are summarised in Table IV.

On 8 occasions patients presented to our clinic because > 8 months has passed since the last substitution (3.29%). They had no leakage or any other complication. They underwent a check-up by a speech therapist to assess the condition of the prosthesis. 2 of these 8 patients (25%) did not require a replacement. 6 patients underwent replacement because of the poor condition of the prosthesis (75%), in particular 1 replacement with a longer one (16.6%), 4 with an analogous one (66.6%) and 1 with a shorter one (16.6%).

Two patients who ingested the voice prosthesis (0.82%) were managed by reinsertion of the prosthesis in the operating room by secondary technique.

In two patients, granuloma formation caused voice prosthesis spontaneous extrusion (0.82%). In one case, the prosthesis was immediately reinserted using the retrograde technique. For the remaining patient, it was necessary to replace the prothesis in the operating theatre.

Finally, we recorded a dislocated prosthesis (0.36%) that was resolved by replacement with an analogous one and an oesophageal pocket (0.36%) caused by overgrowth of mucosa, which was resolved by replacing the voice prosthesis with a longer one via retrograde technique.

In our series, the median number of accesses per patient

Table I. Solutions used in 125 cases of internal leakage.

Leakages through the prosthesis solved by speech therapist	Deep cleaning of the prosthesis with brush, flush and aspirator	**15/125 (12%)**
Prosthesis reinsertion in leakages through the prosthesis		**110/125 (88%)**
	TEP replaced with analogous one	78/110 (70.90%)
	TEP replaced with shorter one	25/110 (22.72%)
	TEP replaced with longer one	3/110 (2.72%)
	TEP replaced with specialised one equipped with tiny magnets (ProvoxActiValve ATOS®)	3/110 (2.72%)
	TEP replaced with longer one via retrograde technique	1/110 (0.90%)

Table II. Solutions used in 60 cases of leakage around the prosthesis.

Leakages solved by speech therapist	Deep cleaning of the prosthesis or its relocation in situ	**14/60 (23.33%)**
Prosthesis reinsertion in leakages around the prosthesis		**39/60 (65%)**
	TEP replaced with a shorter one	22/39 (56.41%)
	TEP replaced with analogous one via overshooting replacement	12/39 (30.76%)
	TEP replaced with specialised one with double oesophageal flange (ProvoxXtra-seal ATOS®)	3/39 (7.69%)
	TEP replaced with a longer one	2/39 (5.12%)
Leakages solved with a silicon ring		**4/60 (6.66%)**
Leakages solved with injectable silicone		**3/60 (5%)**

Table III. Solutions used in 28 cases of aphonia/dysphonia.

Aphonia/dysphonia solved by speech therapist	Relaxation exercises for the cervical area, manipulation, facilitating manoeuvres, change of posture, relaxed phonation with pulmonary support, decrease of volume and soft voice attack	**10/28 (35.71%)**
Prosthesis reinsertion in aphonia/dysphonia		**11/28 (39.28%)**
	TEP replaced with analogous one via an overshooting replacement	6/11 (54.54%)
	TEP replaced with a longer one	3/11 (27.27%)
	TEP replaced with a shorter one	1/11 (9.09%)
	TEP replaced with a longer one via retrograde technique	1/11 (9.09%)
Aphonia/dysphonia resolved with botox injection	60 units, 15 units in 4 different points, under electromyographic monitoring	**3/28 (10.71%)**

Table IV. Solutions used in 16 cases of granuloma.

Issue solved by speech therapist	Relocation in situ of the prosthesis	**3/16 (18.75%)**
Prosthesis reinsertion in granuloma		**13/16 (81.25%)**
	TEP replaced with analogous one via overshooting	6/13 (46.15%)
	TEP replaced with a longer one	6/13 (46.15%)
	TEP replaced with a longer one via retrograde technique	1/13 (7.69%)

per year was 3.47. The total number of exclusive speech therapist treatments was 44 of 243 (18.1%), and in these cases the surgeon or phoniatrician did not see the patient. In the case of exclusive management by a speech therapist, the prostheses had an average lifetime of 6.07 ± 6.49 weeks (range 1-27.57 weeks).

Consequently, the median number of accesses per patient per year needing physician treatment was 2.84. The median prosthesis lifetime was 4.85 months.

Student's T test showed that radiotherapy did not influence the number of accesses per year. No statistically significant difference between the irradiated group and non-irradiated group of patients was found (respectively 3.63 ± 2.98 vs 3.54 ± 2.57, $p > 0.05$). In addition, comparison of the prosthesis lifetime between irradiated and non-irradiated patients did not show any significant difference (respectively 4.27 vs 4.88 months, $p > 0.05$). The same result was found comparing the median number of accesses of patients undergoing primary puncture with patients undergoing secondary puncture. The difference was not significant (respectively, 3.13 and 4.13, $p > 0.05$). We did not analyse the differences between primary pharynx closure vs. free flap reconstruction because the latter was performed on only 3 of the 70 patients in our cohort.

Discussion

It is well demonstrated that voice prosthesis currently represents the gold standard in rehabilitation of laryngectomised patients [24,25]. Nevertheless, reluctance with regards to the widespread use of these devices is still present among surgeons, phoniatricians and speech therapists.

The main reason for this reticence arises from the burdensome management of late sequelae together with the cost of devices. To address the first issue, we analysed a 1-year time frame of management in a large cohort of voice prosthesis rehabilitated patients and, as a result, we developed a trouble-shooting algorithm with a technical flow chart to achieve quick and correct identification and adequate treatment of complications (Fig. 1).

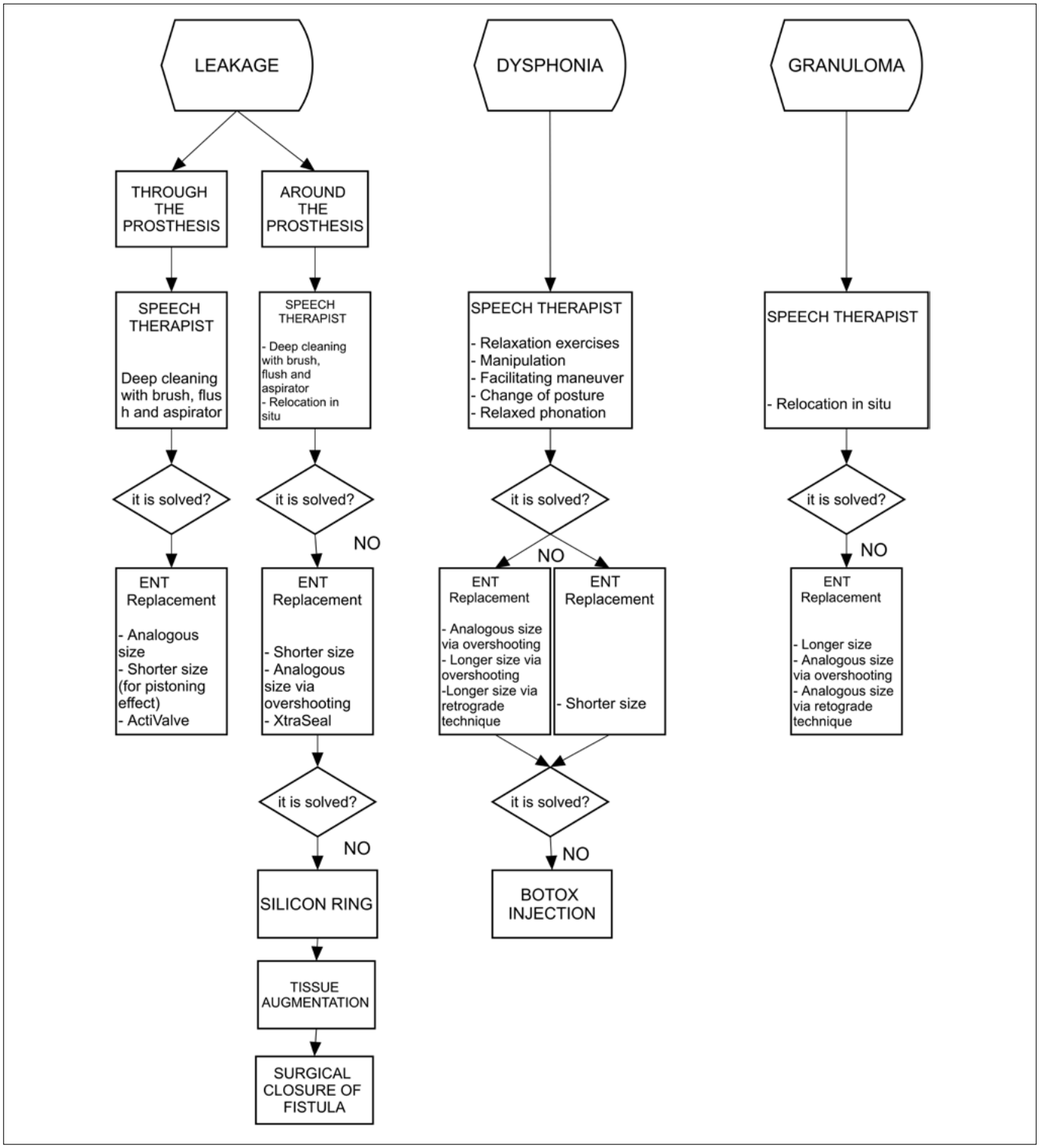

Figure 1. Trouble-shooting algorithm for complications of tracheo-oesophageal prostheses.

Our results show that it is important to verify the status of the prosthetic device at each outpatient evaluation, and, if there are any problems, to establish their exact nature, determine the indication for replacement (leakage through or around, infection of the fistula tract, etc.) and determine the required length of the new prosthesis.

Specifically, when an intravalvular leakage (the most frequent issue) occurred, an analogous prosthesis is the

solution in most cases (70.9 % of cases in our series), because in this specific case we are dealing with a prosthesis-related problem. However, our experience suggested that we should never automatically replace the existing device with another of the same size. In fact, even if the leakage is intravalvular, a different length of prosthesis is sometimes needed. In most of these cases (in our series 22.72%), a shorter prosthesis is needed because of shrinkage of the tracheoesophageal wall, otherwise a perivalvular leakage or speaking effort because of the piston effect on the posterior oesophageal wall may be experienced. Rarely (2.72% in our series), a longer prosthesis can be indicated because of the synchronous presence of hypertrophic/granulation tissue.

When intravalvular leakage occurs too frequently and patients experience a device lifetime of 4 to 8 weeks, or even less [26], it is necessary to adopt a specialised voice prosthesis equipped with tiny magnets to effectively close the valve, and Candida-resistant material to decrease fungal colonisation [27] (Provox ActiValve ATOS® Atos Medical AB, Horby, Sweden). This solution was used in our series in only 2.72% of cases.

According to the literature [28] and in the present series, the second most common reason for voice prosthesis replacement is peripheral leakage. In these cases, our approach considers the following sequence: downsizing (insertion of a shorter prosthesis); replacement with an analogous prosthesis (same size) via overshooting if leakage is due to dislocation of the oesophageal flange into the wall; extra-flange prosthesis (in our experience the Xtra-seal prosthesis-ATOS® Atos Medical AB, Horby, Sweden); ring application; tissue augmentation (to increase the TEP tract with injectable silicone or autologous fat); surgical closure of the fistula (when required). We intentionally excluded purse string sutures on the fistula tract because in our experience it did not resolve a single case of periprosthetic leakage. In most cases, in fact, it depends on party wall resorption, and therefore the solution is not to shrink it but to augment it. Massive TEP enlargement occurs very seldom, but this adverse event can be a considerable burden on patients and head and neck teams. Some clinicians suggest temporary prosthesis removal allowing the TEP to shrink, but this requires a feeding tube and a cuffed cannula and this is not very appealing to patients. Some authors [29] suggest that a massive TEP enlargement is the result of a prolonged use of a voice prosthesis that is too long because of its pistoning effect. Precise analysis of this aspect and a proper solution (shorter prosthesis) is the key indication to avoid this troublesome complication.

In cases of effort in voicing due to a hypertonicity or spasm of the pharyngo-oesophageal musculature, confirmed in the diagnostic work-up by a lidocaine test, the solution was Botulinum toxin injection. We have never used neurectomy of plexus pharingeus and secondary myotomy. In two of 5 patients who underwent botulinum toxin injections, we temporarily resolved the problem and an additional injection was programmed.

Interestingly, in our series, patients who had undergone radiotherapy (preoperative or post-operative) did not show any significant differences from non-irradiated patients in terms of number of accesses to the outpatient clinic or prosthesis lifetime. These data confirm what has already been demonstrated in the literature regarding equivalent late complication rates in the two subgroups of patients [30-32].

Similarly, no significant differences in the incidence of late complications or management were detected between patients with primary puncture and secondary puncture, according to the literature. In fact, only an intraoperative or early post-operative different rate of complications was demonstrated between the two techniques [7-9]. In particular, major surgery-related complications are described only in secondary punctures. This explains our recent orientation towards primary puncture, reserving secondary punctures for patients from other centres who have failed oesophageal vocal rehabilitation or who are not satisfied with their vocal quality.

Finally, our results showed the central role of the speech therapist in the management of TES patients. In fact, 18.1% of accesses were resolved exclusively by speech therapists, reducing the number of accesses needing physician treatment/advice, and leading to a significant reduction in costs and time.

Our study highlights the importance of a systematic approach in the management of late complications in voice prosthesis rehabilitated patients. A flow chart with a trouble-shooting algorithm may guide clinicians in the precise detection and adequate treatment.

Conclusions

The management of late complications is one of the main reasons for the reluctance in using voice prosthesis rehabilitation. Problems occur, despite surgeons' best efforts, as an unavoidable consequence of the presence of a foreign body, represented by the prosthesis. Strict adherence to a tailored trouble-shooting algorithm may offer an easy solution to the most common complications. In a multidisciplinary setting, an initial visit by a speech therapist is useful to render the burden of voice prosthesis management reasonably acceptable for the surgeon, especially in a tertiary referral centre where the high number of patients may become a highly demanding task.

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Laryngology

Correlations between bedside and instrumental endoscopic parameters in determining severity of dysphagia: an integrated clinical evaluation of safety and efficiency

Correlazioni tra parametri non strumentali e strumentali endoscopici nel determinare la severità della disfagia: una valutazione clinica integrata di sicurezza ed efficienza

Daniele Farneti[1], Elisabetta Genovese[2]

[1] Audiology and Phoniatrics Department - Romagna Health Service, Rimini Hospital, Rimini, Italy; [2] Audiology Service, University of Modena and Reggio Emilia, Policlinico Hospital of Modena, Italy

SUMMARY

Interaction between bedside and endoscopic parameters is of great interest in the management of patients with swallowing disorders. Our aim is to document if and how bedside parameters correlate with severity using endoscopic assessment. 556 consecutive patients (318 M/238 F, mean age 65.56 ± 10.36 years, range 18-91), were evaluated in our Swallowing Centre during 2008. All underwent bedside evaluation and fiberoptic endoscopic evaluation of swallowing (FEES), considering the pooling score (p-score) and the pooling sensation, collaboration and age score (p-SCA score) to express criteria of clinical severity of dysphagia. The correlation between the two tests (Spearman correlation coefficient) and their agreement to classify severity (Cohen's kappa) was defined. After dichotomisation (cut-off: no risk/any kind of risk of aspiration), values of sensitivity and specificity were obtained after comparison with FEES results (gold standard). A close and significant correlation between the p-score and p-SCA score was found (rho = 0.88; $p < 0.001$). The agreement among scores in attributing the categories of risk is moderate (Cohen's Kappa = 0.46; $p < 0.001$).The p-score had a sensitivity of 96% and specificity of 60%, while the p-SCA score has a sensitivity of 98% and specificity of 40%. Our results suggest that including even a few parameter from bedside evaluation to an endoscopic score, the level of severity expressed by the latter, decreases. The evaluation of patients with swallowing disorders should consider as many elements as possible, deriving from non-instrumental and instrumental evaluation (integrated clinical evaluation).

KEY WORDS: swallowing, deglutition disorders, aspiration, residue, FEES, p-score

RIASSUNTO

L'interazione tra parametri bedside e parametri endoscopici è di grande interesse nella gestione di pazienti con disturbi di deglutizione. Il nostro obiettivo è documentare se e come i parametri bedside modificano la gravità espressa dalla valutazione endoscopica, per definire un criterio di gravità che meglio aderisca al reale contesto clinico. 556 pazienti consecutivi (318 M/238 F, età media 65,56 ± 10,36 anni, intervallo 18-91 anni), sono stati valutati nel nostro Centro Disfagie durante il 2008. Tutti sono stati sottoposti a una valutazione bedside e una valutazione endoscopica della deglutizione, considerando il punteggio del pooling score (p-score) e del pooling sensibilità, collaborazione ed età score (p-SCA ascore) per esprimere i criteri di gravità clinica della disfagia. È stata definita la correlazione tra i due test (coefficiente di correlazione di Spearman) e il loro accordo per classificare la gravità (kappa di Cohen). Dopo la dicotomizzazione (cut-off: nessun rischio / qualunque rischio di aspirazione) sono stati ottenuti valori di sensibilità, specificità, dal confronto con i risultati FEES (gold standard). È stata trovata una stretta correlazione tra il p-score e il p-SCA score (rho = 0,88): la correlazione è significativa ($p < 0,001$). L'accordo tra i punteggi nell'attribuzione delle categorie di rischio è moderato (Cohen's Kappa = 0,46; $p < 0,001$). Il p-score ha raggiunto valori di sensibilità del 96% e specificità del

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Correspondence
Daniele Farneti
Audiology and Phoniatrics Service, Infermi Hospital, via Settembrini 2, 47923 Rimini, Italy
Tel./Fax +39 0541 705146
E-mail: lele.doc@libero.it

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60%, mentre il punteggio p-SCA ha raggiunto valori di sensibilità del 98% e specificità del 40%. I nostri risultati suggeriscono che, includendo anche pochi elementi dalla valutazione bedside a un punteggio endoscopico, il livello di gravità espresso da quest'ultimo diminuisce. La valutazione di pazienti con disturbi della deglutizione dovrebbe considerare il maggior numero possibile di elementi, derivanti dalla valutazione non strumentale e strumentale (valutazione clinica integrata).

PAROLE CHIAVE: *deglutizione, disturbi della degradazione, aspirazione, ristagni, FEES, p-score*

Introduction

Swallowing is a complex neuromuscular act, which requires sensory input and automated neuromuscular activities under real-time modulation guaranteed by the central nervous system in all its parts [1]. In optimal physiological and functional conditions, all the ingested bolus is transferred to the stomach, for digestive processing, without invasion of the airway (false route) or residue. In dysfunctional or pathological conditions, material pooling or residue can invade the respiratory tract, upwards and/or downwards, leading to respiratory or nutritional complications (ineffective / inefficient swallow or dysphagia), respectively [2]. Several conditions, acting as morbidity or comorbidities, can affect the quality of life (QOL) of dysphagic patients, offering a wide variety of events that are able to influence each other in guiding the clinical options adopted by the multidisciplinary team (MDT) that manages the patient [3].

During the processing of data leading to therapeutic planning, conditions of ineffective/inefficient swallowing (i.e. airway invasion/residue) must be documented with instrumental assessment. However, complete strategic planning cannot disregard other clinical not instrumental information, which is no less important in suggesting therapeutic strategies, even when apparently in contrast with instrumental evaluation. Data from the literature show that clinical non-instrumental evaluation alone tends to underestimate the risk of aspiration, while endoscopic evaluation tends to overestimate it [4]. A reasonable balance between non-instrumental and instrumental evaluation seems to be the best combination that can offer the optimal strategy to the MDT, in order to obtain the best compliance of patients and caregivers. The balance mentioned above also seems to be the best way to achieve a concrete and reasonable evaluation of severity of impaired swallowing and the risk of complications [5]. In addition, the real and logistical aspects of clinical practice must also be considered, as well as the availability of local resources [3].

In our Swallowing Center all patient referring swallowing disorders are routinely submitted to Bedside Swallowing Evaluation (BSE) [6] and endoscopic evaluation of the upper aerodigestive tract, performing a dynamic test with bolus for the study of swallowing (fiberoptic endoscopic evaluation of swallowing; FEES) [7]. The evaluation of the oral and oesophageal phases of swallowing (O-FEES and E-FEES, respectively) [5] is performed considering the patient's specific complaints or to answer to specific questions that the clinician poses. These approaches, only recently introduced in clinical practice, are not yet adequately supported by the international literature, but their value is purely local and far from any research intent.

The pooling score (p-score) and the pooling Sensation, Collaboration and Age score (p-SCA score) [8] are simple scores used in our endoscopic practice to define a criterion of severity of impaired swallowing, considering the material pooling/residue and the risk of aspiration. Material pooling/residue is evaluated in the hypopharynx/laryngotracheal cavities, considering specific anatomical landmarks, but also considering its amount and management (Tab. I).

After these preliminary considerations, the aims of this study are to evaluate: 1) how the severity of dysphagia, endoscopically defined, changes when BSE parameters are considered together with FEES parameters; and 2) the weight of BSE parameters in determining severity, as mentioned above.

Materials and methods

In this prospective study a sample of 556 consecutive patients (318 M/238 F, mean age 65.56 ± 10.36 years, range 18-91 years) seen at our Swallowing Centre during 2008 was considered. All patients underwent BSE performed alternately by two speech-language pathologists (SLPs) and a phoniatrician. During BSE a preliminary collection of information on pathologies, interventions and drugs was made. Subsequently, cognitive and language skills were assessed, observing the patient's facies and carrying out manual exploration of the mouth and oropharynx. Finally, assessment of swallowing skills was performed with boluses of different consistency and volume, verifying the appearance of cough, throat clearing and modification of vocal quality.

After BSE, all patients were evaluated by a phoniatrician and submitted to FEES according to a protocol in use at our centre [3]. Endoscopic evaluation was performed with a Storz endoscope (model 11101RP2, 30 cm long, 3.5 mm in diameter) and recorded with a workstation (Richard Wolf GmbH, Knittlingen, Germany). The patients were given three trials of different consistencies: 5 cc pureed,

Table I. Anatomical landmarks and bedside parameters with relative values.

Pooling	Endoscopic landmarks	Bedside parameters		
		Sensation	Collaboration	Age (years)
Site	Vallecule: 1 Marginal zone: 1 Pyriform sinus: 2 Vestibule/vocal cords: 3 Lower vocal cords: 4	Presence = -1 Absence = +1	Presence = -1 Absence = +1	+1 (< 65) +2 (65-75) +3 (> 75)
Amount	Coating: 1 Minimum: 2 Maximum: 3			
Management	< 2 2 </> 5 > 5			
Score	p: 4-11		p-SCA: 3-16	

p: pooling; p-SCA: pooling-sensation-collaboration-age. P-score: 4-5 = minimum score, corresponding to no dysphagia; 6-7 = low score, corresponding to a mild dysphagia; 8-9 = middle score, corresponding to a moderate dysphagia; 10-11 = high score, corresponding to a severe dysphagia. P-SCA score: 3-4 = minimum score, corresponding to no dysphagia; 5-8 = low score, corresponding to a mild dysphagia; 9-12 = middle score, corresponding to a moderate dysphagia; 13-16 = high score, corresponding to a severe dysphagia.

5 cc liquid dyed with 5% methylene blue and 1/4 cracker. After each consistency the p-score and the p-SCA score were obtained (Tab. I). The p-score expresses a continuum of severity, summarised in a simple number ranging from 4 to 11, and clinically distributed over 4 levels of severity. The p-SCA score [8] is the p-score enriched with simple information achieved from BSE, namely sensation, collaboration and age: it ranges from 3 to 16, with the same clinical application on 4 levels of severity. The inter-rater and intra-rater reliability of the p-score was recently determined [8]. The p-score considers the risk of aspiration occurring over the time (before, during and after swallowing) as an interaction between material pooling and false route (ineffective/inefficient swallowing). The correlation between material pooling and false route, i.e. safety and efficiency, has been recently evaluated [9,10].

Statistical analysis

The correlation between the p-score and p-SCA was determined with Spearman's correlation coefficient. The agreement between the two scores was calculated (Cohen's Kappa) considering the categories of risk corresponding to the total scores (no dysphagia, mild, moderate, severe). The categories of risk individualised with the two scores was studied with the aim of underlining possible systematic divergences in the attribution of the severity to individual cases. Subsequently, the p-score and the p-SCA score were dichotomised, dividing patients without risk from those with middle and high risk of aspiration. By comparison of dichotomic scores with the results of FEES (considered as the gold standard), the values of sensitivity and specificity were obtained.

All patients were over 18 years of age and consenting, in accordance with the Declaration of Helsinki. The study was approved by the local Ethical Research Committee. Statistical analysis was performed with Intercooled STATA 8.0 for Windows software.

Results

A sample of 556 consecutive patients (318M/238F, mean age 65.56 ± 10.36 years, range 18-91 years) was evaluated. A close correlation between the p-score and p-SCA score in determining dysphagia severity (rho = 0.88) was found (Figs. 1A, B). The agreement among scores regarding the categories of risk showed moderate correlation (Cohen's Kappa = 0.46; $p < 0.001$). Table II shows how the two scores classified patients in different categories of risk. Table III summarises the percentage of patients classified by the two scores: the two scores are correlated (Wilcoxon signed-rank test, $p < 0.001$). Subsequently, the judgement expressed by the scores was dichotomised, setting the cut-off point between patients without risk and those with any risk, with the purpose of comparing the scores with the results of FEES in terms of "aspiration" and to obtain, for both, values of sensitivity and specificity. The values of sensitivity and specificity are reported in Table IV.

Discussion

In daily clinical practice the possibility of correlating signs and symptoms with residue/aspiration in patients with deglutition disorders due to different aetiologies is an important goal, and is needed to obtain better guidance for MDTs and prevent complications [10]. The interaction between signs (instrumentally documented) and symptoms is a complex and intriguing relationship, but nonetheless is likely the best way to offset the trend of instrumental

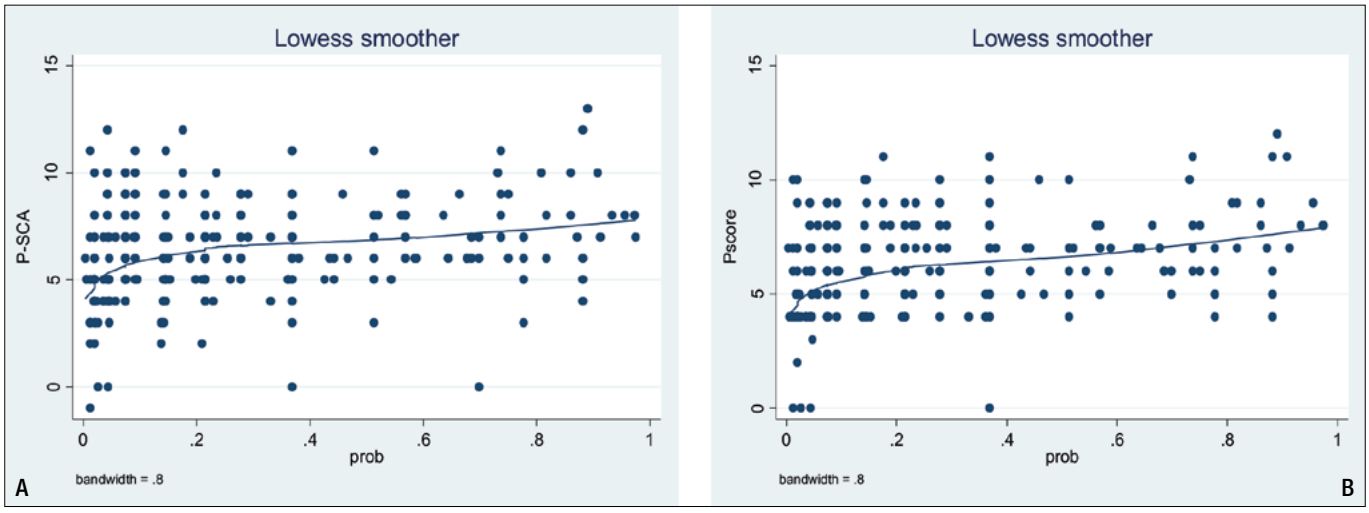

Figure 1. Scatterplot whit non-parametric regression curve (Lowess smoother): (**A**) p-score; (**B**) p-SCA score.

Table II. Comparison of P-score and P-SCA score and classification of risk.

	P-SCA score				
P-score	**No**	**Mild**	**Moderate**	**Severe**	**Total**
No	163 61.98	100 38.02	0 0.00	0 0.00	263 100.00
Mild	11 7.33	139 92.67	0 0.00	0 0.00	150 100.00
Moderate	0 0.00	43 55.18	35 44.87	0 0.00	78 100.00
Severe	0 00.0	12 36.36	20 60.61	1 3.03	33 100.00
Total	174 33.21	294 55.61	55 10.50	1 0.19	524 100.00

Table III. P-score and P-SCA score and risk of aspiration.

	Frequency	**Percentage**
P-score		
No dysphagia	264	50.29
At risk	261	49.71
Total	525	100.00
P-SCA score		
No dysphagia	174	33.21
At risk	350	66.79
Total	524	100.00

assessments to overestimate risks. With the contribution of instrumental evaluation, the risk of lost episodes of silent aspiration/penetration at the bedside is less, but the risk in generalising pathological random or extraordinary airway invasion events is higher [11,12]. Considering our data, the p-score and p-SCA score are both useful tools to define severity, and both show the same statistical significant trend (Figs. 1A, B). However, considering the categories of risk attributed, the two scores seem to work in a different way.

Table IV. Screening properties of the scores considering no risk and any risk of aspiration.

	Sensitivity	**Specificity**	**Correctly classified**	**ROC Area [95% Conf. Interval]**
P-score	95.56%	59.77%	65.90%	0.7766 (0.73908 0.81205)
P-SCA score	97.78%	39.63%	49.62%	0.6870 (0.64539 0.72653)

The p-SCA score tends to increase severity in the category with lower risk, while in those with higher risk it tends to be more cautious, attributing a category with lower severity in comparison to p-score (Tab. II). Overall, the patients classified as at risk of aspiration by the p-score are 50%, while the p-SCA score considers 67% of patients to be at risk (Tab. III). After dichotomisation (cut-off: no risk/any risk class) and comparison with the gold standard (aspiration documented during FEES), the two scores still show a different trend, offering different levels of sensitivity and specificity (Tab. IV). It is as if the p-SCA score recognises more patients at risk, more sensitive than the p-score, but also less specific with a greater risk of identifying false positive patients. In other words, both have high sensitivity to identify patients with any risk of aspiration, from minimal to high, but the p-score is more specific, and better at recognising false positives and therefore more reliable in correctly classifying patient without dysphagia and those with a risk of swallowing disorders. The low specificity of the p-SCA score also expresses a low ability of the score to identify patients who do not have swallowing disorders or who have low swallowing concerns, despite the more precise contribution of endoscopy results.

It is worth noting, as previously mentioned, that BSE alone, even if well conducted, underestimates the risk of silent aspiration, while endoscopy leads to generalisation of occasional episodes of false routes and residues. In addition, aspiration, as a marker of impaired swallowing, it is the most significant but not the only one, capable of determining the clinical severity of dysphagia and suitable for guiding the treatment plan and the activities of the MDT.

Conclusions

The simplest conclusion of the current experience, in accordance with our aims, seems to be that, by including even a few factors from the BSE in an instrumental score, the level of severity expressed by the latter decreases. Namely, the simple evaluation of sensation, collaboration and age tends to mitigate the judgment of severity expressed by the p-score, putting patients back into categories with lower risk: not only, but the greater impact of this contamination affects the ability of a "hybrid" score to correctly identify false negative patients, with a decrease in specificity. This experience also statistically quantified the weight of BSE parameters in reducing the specificity of a FEES parameter, such as the p-score.

The most relevant clinical implication of our work seems to be that the evaluation of patients with swallowing disorders should consider as many elements as possible, deriving from both non-instrumental and instrumental clinical evaluation: this could be considered as integrated clinical evaluation [5].

The main limitation of this preliminary work is that the p-SCA score considers a limited number of BSE parameters, although the logic supporting it is strong [10].

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Rhinology

Odontogenic sinusitis and sinonasal complications of dental treatments: a retrospective case series of 480 patients with critical assessment of the current classification

Sinusiti odontogene e complicanze nasosinusali di trattamenti dentali: una casistica retrospettiva di 480 pazienti con analisi critica della classificazione attuale

Marco Molteni[1], Antonio Mario Bulfamante[1], Carlotta Pipolo[1], Paolo Lozza[1], Fabiana Allevi[2], Antonia Pisani[1], Matteo Chiapasco[3], Sara Maria Portaleone[1], Alberto Scotti[1], Alberto Maccari[1], Roberto Borloni[1], Giovanni Felisati[1], Alberto Maria Saibene[1]

[1] Otolaryngology Unit, Department of Health Sciences, San Paolo Hospital, University of Milan, Italy; [2] Maxillofacial Unit, Department of Health Sciences, San Paolo Hospital, University of Milan, Italy; [3] Oral Surgery Unit, Department of Health Sciences, San Paolo Hospital, University of Milan, Italy

SUMMARY

The term odontogenic sinusitis (OS) has proved less and less suitable to describe a series of pathological conditions related to dental procedures. We have introduced the term and classification 'sinonasal complications of dental disease or treatment' (SCDDT). This study aimed to review our cases and evaluate whether the classification used is applicable to everyday clinical practice. The sample was composed of patients treated for SCDDT from 2002 to 2018 in our Department of Otorhinolaryngology. All presented signs and symptoms of sinusitis and had a recent history of dental disease or treatment. All patients underwent multidisciplinary evaluation, flexible endoscopy and computed tomography (CT) scan. Patients were allocated into three groups depending on the aetiology of the complication, following the classification proposed by Felisati et al. The sample comprised 480 patients (44% men, 56% women) with a mean age of 52.36 years. Of these, 43 patients (9%) belonged to group 1 (class A), 105 (21%) to group 2 (50, 2A; 5, 2B; 27, 2C; 23, 2D) and 332 (70%) to group 3 (119, 3A; 213, 3B). A total of 454 patients (94.5%) had unilateral maxillary opacification, while only 26 cases (5.4%) started as bilateral inflammation. Nine of the latter cases (34.6%) presented a bilateral odontogenic focus, while the other 17 (65.4%) had a history of unilateral dental pathology. The results of this study suggest that SCDDT is a complex entity that needs a careful diagnostic approach based on CT scans and presurgical endoscopy.

KEY WORDS: paranasal sinuses, dental diseases, transnasal endoscopic surgery

RIASSUNTO

Il termine sinusite odontogena (OS) si è progressivamente dimostrato meno adatto a descrivere tutta una serie di condizioni patologiche legate alle procedure odontoiatriche e, per tale motivo, il nostro gruppo ha introdotto il termine "Complicanza nasosinusale di malattia o trattamento odontoiatrico" (SCDDT) e una classificazione correlata. Il presente lavoro ha lo scopo di esaminare la nostra casistica e di valutare l'applicabilità della classificazione utilizzata alla pratica clinica quotidiana. Il campione è composto da pazienti trattati per SCDDT dal 2002 al 2018 presso il nostro Dipartimento di otorinolaringoiatria. Ogni paziente presentava segni e sintomi di sinusite e aveva una recente malattia dentale o storia di trattamento. Tutti i pazienti hanno subito una valutazione multidisciplinare, un'endoscopia flessibile e una TAC. I pazienti sono stati suddivisi in tre gruppi a seconda dell'eziologia della complicanza, secondo la classificazione proposta da Felisati. Il campione era composto da 480 pazienti (44% uomini, 56% donne) con un'età media di 52,36 anni. 43 pazienti (9%) appartenevano al gruppo 1 (classe A), 105 pazienti (21%) al gruppo 2 (50, 2A; 5, 2B; 27, 2C; 23, 2D) e 332 (70%) al gruppo 3 (119, 3A; 213, 3B). 454 pazienti (94,5%)

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Correspondence
Antonio Mario Bulfamante
Otolaryngology Department, San Paolo Hospital, via A. di Rudinì 8, 20142 Milan, Italy
Tel. +39 02 8184 4249. Fax +39 02 5032 3166
E-mail: antonio.bulfamante90@gmail.com

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presentavano un'opacizzazione mascellare unilaterale, con un coinvolgimento del seno mascellare sinistro in 259 casi (53,9%) e destro in 195 casi (40,6%), mentre solo 26 casi (5,4%) esordivano come infiammazione bilaterale. 9 di questi ultimi (34,6%) presentavano un interessamento odontogeno bilaterale, mentre gli altri 17 (65,4%) avevano una storia di patologia dentale monolaterale. I risultati di questo studio indicano SCDDT come un'entità complessa necessitante di un approccio diagnostico basato su TAC e endoscopia prechirurgica. La nostra analisi ha evidenziato anche alcuni punti deboli dell'attuale classificazione, portando alla decisione di produrne una nuova, più pratica e applicabile.

PAROLE CHIAVE: *seni paranasali, patologia dentaria, chirurgia endoscopica transnasale*

Introduction

Maxillary sinusitis is inflammation of the maxillary sinus, which can be acute or chronic, based on the duration of symptoms (less or more than 12 weeks) [1]. While the main aetiology of sinusitis being rhinologic, dental pathology can represent the primary cause of unilateral maxillary sinusitis [2]. The proximity of the teeth to the floor of the sinus allows odontogenic infections to penetrate from the oral cavity to the maxillary chamber, violating the mucosal lining (Schneiderian membrane) [3,4]. Historically, dental diseases such as periodontitis, periodontal abscesses or periapical diseases, as well as dental trauma, have been reported to be responsible for 10-12% of maxillary sinusitis [5,6], but the real incidence is now considered to be up to 30% [7]. According to recent publications, 8% of endoscopic nasal surgery aims to treat odontogenic sinusitis (OS) [8]. However, in recent years, the term OS has proven less and less suitable to describe a range of pathological conditions related to dental procedures, including implant displacement, oroantral communication (OAC) following dental extractions and sinus floor elevation, because these do not always lead to sinus infection or inflammation [9]. For this reason, in 2013 our group introduced the term "sinonasal complication of dental disease or treatment" (SCDDT) to the literature, to describe all these dental aetiologic mechanisms [10,11]. The clinical presentation of OS varies and is often not specific, but left untreated it may reduce quality of life and lead to serious complications. Microbiology, pathophysiology and management of odontogenic and rhinogenic sinusitis are substantially different, and OS frequently requires a multidisciplinary approach involving ear, nose and throat (ENT) specialists, maxillofacial specialists and radiologists [12]. When medical therapy fails, functional endoscopic sinus surgery (FESS) is required to correct sinus drainage and ventilation, while oral accesses help prevent possible relapse of infection [13]. Although SCDDTs have become far more common and the incidence of OS has increased [8], only a few systematic studies have addressed the real rate of SCDDT and the importance of extra-maxillary extension [8,9]. Through analysis of a relevant case series, our study aimed to clarify this complex matter and to evaluate whether the classification used is solid and applicable to everyday clinical practice. To describe demographics of OS, aetiology, response to treatment and ease of categorisation into existing classifications, we collected a retrospective cohort of 480 consecutive patients treated for OS from 2002 to 2018. We categorised and analysed them using the Felisati et al. classification system for sinonasal complications [10,14]. We also correlated clinical and radiological features with intraoperative findings to determine the real prevalence of extra-maxillary extension and reported data on surgical treatment of these patients and treatment success rates.

Materials and methods

We enrolled 480 consecutive patients treated for SCDDT from 2002 to 2018 in our Department of Otorhinolaryngology - Head and Neck Surgery (San Paolo Hospital, University of Milan, Italy). We performed a 16-year retrospective study, analysing clinical findings, demographic factors (sex and age), causes and course of disease, imaging, and surgical and medical management. This study followed the Declaration of Helsinki on medical protocol and ethics. Institutional ethics committee approval and informed consent were unnecessary, as we performed a retrospective study.

The inclusion criteria were: (1) a clinical diagnosis of sinusitis of suspected odontogenic origin, supported either by radiology or endoscopy, not responding to medical treatment; (2) ENT specialist and dentist or maxillofacial surgeon agreement on the odontogenic focus; (3) execution of an endoscopic sinus surgery procedure with or without a combined oral approach to treat the sinonasal condition; and (4) the availability of a presurgical maxillofacial computed tomography (CT) scan, with or without contrast). The exclusion criterion was a history of chronic rhinosinusitis, with or without polyps, predating the dental treatments and condition(s).

With regards to clinical findings, all patients included referred sinusitis signs and symptoms, including purulent rhinorrhoea, unilateral and bilateral nasal obstruction, maxillary pain and postnasal drip. These symptoms appeared after dental treatments or diseases and did not respond to medical therapy, which comprised topical nasal steroids and decongestants, associated with systemic antibiotic and mucolytic therapy. Nasal endoscopy with

a flexible endoscope was performed on each patient, to explore the sinuses and identify inflammation foci, dislocated dental implants or anatomical variations (nasal polyps, septal deviation and turbinate anomalies). All these were examined and grouped as contributing causes of sinusitis. An accurate oral exam checked for dental lesions or OAC. The clinical diagnosis was confirmed by a CT scan without contrast medium (triplanar or three-dimensional) of the paranasal sinuses, which showed the location, extent and severity of the disease.

Patients were allocated into three macro-groups depending on the aetiology of the complication, following the classification protocol proposed by Felisati et al. in 2013 [10] (Tab. I). Group 1 included pre-implantologic treatment complications with OAC (sinus augmentation or outcomes of Le Fort osteotomies), group 2 included complications related to implant placement and group 3 included classical odontogenic complications, related to dental procedures or diseases. Each group was divided into different classes based on the clinical situation and therapeutic options. Seven classes were identified.

In our original classification, group 1 had only one class, including all complications stemming from pre-implantologic treatments. Patients were not differentiated on the presence of an OAC as proposed by Fadda and colleagues [15], since we regarded these patients as either having an existent OAC or requiring surgical creation of an OAC to approach the sinus from the combined access.

Group 2 had four classes. Class 2A included all cases of peri-implant osteitis around infected endosseous or subperiosteal implants, with sinusitis and oroantral fistula. Class 2B consisted of implant dislocation into the nasal and paranasal cavities, with development of sinusitis and OAC. Class 2C was related to implant dislocation with sinusitis, without OAC. Class 2D included all cases in which implant dislocation had been recognised before sinusitis development.

Patients in group 3 showed OS caused by dental diseases or treatments, including pulpal necrosis in deep caries, periodontitis, odontogenic cysts, endodontic procedures and tooth extractions. These patients were further divided into two classes by the presence (3A) or absence (3B) of OAC.

The Felisati et al. classification offers also a ranking system to select the most complex patients. Class 1A includes the most difficult cases to treat, and class 3B the simplest. Each patient was assigned to the highest class possible, to avoid overlaps [10,12]. This classification included not only bacterial but also mycotic sinonasal complications, which occurred in all three groups [10,16].

All patients underwent surgery, with the choice of approach driven by the classification. A combined FESS and oral approach [17-19] was required for class 1A, 2A, 2B and 3A patients. Endoscopic surgery with removal of the implant was needed for cases in class 2C; the patients in class 3B were treated only with FESS. Finally, in cases of displaced implants without sinusitis (class 2D), the treatment choice was limited to implant removal, either transnasally or transorally according to the surgeon's preference. In most cases, FESS and oral treatment of the underlying dental pathology were managed at the same surgical time.

FESS was performed under general anaesthesia, using a rigid 0° endoscope. Before the surgery, intranasal vasoconstriction with nasal cottonoids soaked in mepivacaine and epinephrine 1% was essential to reduce intraoperative bleeding. The first step was the surgical correction of any significant anatomical variations (septoplasty, removal of the lateral portion of conchae bullosae, or selective bipolar cautery of hypertrophic inferior

Table I. The classification. The table shows the surgical treatment protocol according to type of complication and presents the patient numerosity in the study accordingly. In case a patient fulfils the criteria for two or more classes, he/she is assigned to the uppermost class shown in the table (designed to have on top the most difficult-to-treat scenarios and at the bottom the most easily manageable conditions, thus defining a classification priority).

Groups	Classes	SCDDT patients	Treatment	N° of patients	Rate (%)
I Preimplant treatment complications	1A	Sinusitis following preimplant surgery	FESS + material removal + OAC closure	48	10%
II Implant treatment complications	2A	Sinusitis with perimplantitis and OAC	FESS + implant removal + OAC closure	50	10.4%
	2B	Sinusitis due to implant dislocation with OAC	FESS + implant removal + OAC closure	7	1.4%
	2C	Sinusitis due to implant dislocation	FESS + implant removal	27	5.7%
	2D	Implant dislocation	Implant removal (either endoscopic or transoral)	23	4.8%
III Classic dental disease or treatment complications	3A	OS with OAC	FESS + OAC closure	119	24.8%
	3B	OS	FESS	213	44.4%

G: group; C: class; OS: odontogenic sinusitis; FESS: functional endoscopic sinus surgery; OAC: repair oro-antral communication repair.

turbinates), to eliminate possible obstacles to endoscopic instrument access. Uncinectomy followed to identify the natural ostium of the maxillary sinus. After that, antrostomy was performed, enlarging the natural ostium. The maxillary sinus was then evaluated using 45°or 70° endoscopes to visualise the alveolar recess. Inflammation of the frontal, ethmoid and sphenoid sinuses was treated during the same endoscopic procedure to restore the normal ventilation of the paranasal cavities. When the FESS was completed, the intraoral approach promoted the closure of the OAC and the removal of grafting materials, infected implants or necrotic teeth, not easily reachable using endoscopic access.

Patients were usually discharged the day after surgery. After surgical treatment, antibiotic therapy was recommended. Oral administration of a quinolone, such as levofloxacin 500 mg, once a day for 10 days, is effective to prevent any recurrence of symptoms. Patients were invited to continue nasal washes with saline three times a day for around 30 days after surgery. Topical antibiotic creams and local steroids were indicated in all patients. Mouth rinses, such as chlorhexidine 0.2%, were recommended after dental surgery to maintain oral hygiene. To rule out recurrence of infection, patients were followed up with endoscopic controls at 7, 30 and 90 days after surgery. Treatment success was defined as endoscopic absence of signs of sinusitis and subjective symptom resolution reported by patients.

Results

A total of 480 patients, diagnosed with sinusitis and treated with surgery from 2002 to 2018, were included in our retrospective study. Of these, 212 were men (44%) and 268 were women (56%), a male to female ratio of 8:10. The mean age was 52.36 years, with the youngest patient 16 years and the oldest 86 years. A history of previous oral surgery or dental disease was reported by all patients. The dental origin was confirmed by analysing the patients' medical history, oral examination and imaging. The most commonly reported symptoms were unilateral purulent rhinorrhoea (64%) and unilateral (71%) or bilateral (29%) nasal obstruction, followed by maxillary pain and postnasal drip. A CT scan was performed in all cases before surgical treatment [20]. The maxillary sinus was predominantly involved: 454 patients (94.5%) had unilateral maxillary opacification, while only 26 cases (5.4%) began as bilateral inflammation. Nine of these latter cases (34.6%) presented a bilateral odontogenic focus, while the remaining 17 (65.4%) had a history of unilateral dental pathology. Overall, extra-maxillary extension was observed in 305 patients (63.5%). In group 1, 33 patients showed extra-maxillary involvement (69%), along with 57 (53%) in group 2, and 215 (65%) in group 3. Unilateral interest of ethmoidal cells was found in 294 cases (61.25%), and bilateral in 34 cases (7%); spread of infection to the frontal and sphenoid sinuses was reported in 75 (15.6%) and 19 (4%) patients respectively. In 11 cases, infection was detected in all paranasal sinuses, resulting in pansinusitis (Tab. II).

All patients underwent careful presurgical evaluation with a flexible endoscope to detect concomitant anatomical anomalies, such as nasal septal deviation (37 cases), inferior turbinate hypertrophy and/or concha bullosa (50 cases), or nasal polyps (46 cases). The patients were grouped according to the Felisati et al. classification of SCDDT [8], with 43 patients (9%) in group 1 (class A), 105 (21%) in group 2 (50, 2A; 5, 2B; 27, 2C; 23, 2D) and 332 (70%) in group 3 (119, 3A; 213, 3B). Concerning aetiology of dental diseases and routine dental procedures, exclusive sinus infection without OAC (3B) was the most common cause of SCDDT (213 out of 480, 44%). Pre-implant treatment complications (group 1) were the basis of these problems, including 45 cases (9.4%) of complicated sinus floor elevation procedures and three cases (0.6%) of Le Fort I osteotomies. Analysis of the oral cavity by a dentist identified that OAC alone was present and the cause of OS in 224 patients (45.8%), distributed among classes 1A, 2A, 2B and 3A. A further 50 cases (10.4%) of peri-implant osteitis with OAC (class 2A) were detected. Finally, we diagnosed 57 cases (11.9%) of OS for implant displacement: seven (1.5%) with sinusitis and OAC (2B), 27 (5.6%) with sinusitis without OAC (2C) and 23 (4.8%) without sinusitis (2D).

The main therapeutic approach consisted of FESS, with or without the need for dental treatments. Our endoscopic protocol followed different steps: an uncinectomy, a middle antrostomy and, when the infection was extended to the ethmoidal cells or frontal sinuses, an ethmoidectomy or frontal ostium opening. Anterior and/or posterior ethmoidectomy was performed in 294 patients (61.2%), while the patency of frontal sinuses was restored in 75 patients (15.6%). A combination of endoscopic endonasal access with an intraoral approach was performed in 311 patients (64.8%), while FESS alone was preferred in 169 cases (35.2%). No patient underwent an exclusive intraoral approach. A total of 171 (35.6%) had to be treated for persistent OAC, surgically closed with local flaps (Rehrmann or Bichat's fat pad flap). Classic Caldwell-Luc surgery (removal of part of the anterior lateral wall of the maxillary sinus) was performed in only one case, belonging to class 2B. For this patient, the sinusitis was related to a foreign body (implant dislocated) and treatment required an external approach with the collaboration of a maxillofacial surgeon. Concerning dental approaches, 478 patients

Table II. The sinus involvement. The table shows the involvement of the maxillary, the ethmoid, the frontal and the sphenoid sinuses, both unilaterally and bilaterally.

Sinus involved	Unilateral	%	Bilateral	%	Total
Maxillary	454	94.5%	26	5.5%	480
Ethmoid	260	54%	34	7%	294
Frontal	68	14%	7	1.5%	75
Sphenoid	16	3%	3	0,6%	19

underwent preoperative dental care, not resolving the sinusitis, and only two underwent postoperative dental treatment.

The rate of general complications was low, and no major intraoperative complications were observed. The failure of treatment was described in only eight cases (1.7%): three belonging to class 3A, two to class 3B, two to class 1A and one to class 2A. Five of them (1.1%) reported a recurrence of inflammation, some months after the surgery. In three cases (0.6%), antibiotic management was therapeutic, while the two others (0.4%) underwent new endoscopic surgery. Two patients (0.4%) required a revision under general anaesthesia to repair an oroantral fistula, within two months after the initial surgery. One case (0.2%) of bleeding occurred one hour after the surgical procedure, requiring a revision of haemostasis under general anaesthesia.

The follow-up period was between one and two years, with an average of almost 18 months. Endoscopic examination during follow-up was performed seven and 30 days after surgery and then every three months, with excellent long-term results in terms of endoscopic findings and subjective symptom resolution.

Discussion

The importance of odontogenic foci as a cause of chronic sinusitis has frequently been reported in the literature. Although rhinogenic aetiology remains the main cause of sinusitis, OS has recently increased, likely due to the increase in dental treatments and the consequent increase in sinonasal complications.

In this wide panorama of studies and data, our group has always stood out for its positive contributions to detecting and treating pathological and functional nasal conditions [14]. With this study, we present our experience and propose a protocol of treatment centred on FESS. Although other studies have been published concerning the endoscopic approach to sinusitis [13], the case series have often been limited and the data restricted [21]. Instead, this review includes the largest number of surgical cases ever reported (480 patients), obtained over more than 16 years of research, and examines a variegated population of patients affected by SCDDT. As we have noted, the term OS should be considered superseded, since in 2013 we coined the name SCDDT, which best describes its vastness. Other studies have referred to the Felisati et al. classification, so it is of interest to compare the different results [6,15]. Furthermore, we would like to critically evaluate its applicability in everyday practice.

Fadda et al. [15] showed that, in most patients, conventional dental disease or treatment complications (group 3) were the main factors driving sinonasal complications (45% of their patients). In our cohort, these data are even more clear, with 332 patients (70%) belonging to group 3 (A, B; Fig. 1). Examining numerous cases, we can see how the percentage of patients in group 3 is drastically increasing over time.

Some studies have reported a gradual increase in the incidence of sinusitis as a complication of dental implants and, for some authors [6], dental implant-related complications must even be considered as the main cause of SCDDT. In our experience, complications related to implant dentistry affected 107 of 480 cases (22.3%; group 2). The subclassification included 50 patients (10.5%) in class 2A with peri-implant infections, while the other three classes comprised all the cases of dislocated implants (2B, 1.5%; 2C, 5.7%; 2D, 4.8%). As group 3 was the largest, with 332 patients (70%), we still consider classical dental diseases and complications of dental treatments the main cause of SCDDT.

Whether the main cause of SCDDT or not, dental implants pose important issues in OS, particularly concerning its management. Due to the important healthcare and economic burden imposed on patients by implantology, carefully evaluating the possibility to maintain the implants is clearly important. Nevertheless, we are firmly convinced that in cases of suspected peri-implant osteitis

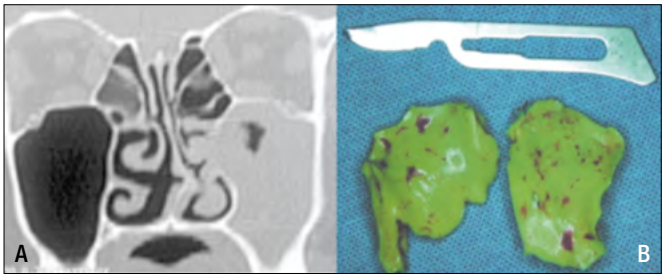

Figure 1. (**A**) CT and aspect of a foreign body unilateral maxillary sinusitis, due to the penetration of moulding material used for the prosthetic rehabilitation right after dental extraction - class 3A; (**B**) the extracted moulding material.

or dubious complete osseointegration, the implant should be removed, in order to minimise the risk of relapse of sinusitis [14]. Implant removal often reveals underlying OAC, usually derived from a pre-existing communication, caused by iatrogenic manoeuvres. OAC is a cause of sinonasal infection because it favours the migration of bacteria from the oral cavity [3]. In our cohort, 224 patients, belonging to classes 1A, 2A, 2B and 3A, had developed an OAC after dental surgical procedures. The closure of OAC was performed with local flaps as Rehrmann flap, formed from the mucoperiosteum of the maxillary bone, or with a buccal fat pad flap [1,3]. In particular, the latter was often our first choice, due to its low morbidity and high resistance. No episodes of wound dehiscence or other significant complications were reported. While some authors propose that small OACs might heal spontaneously after correct endoscopic treatment of the sinusitis, we chose to perform OAC closure no matter the size of the defect, to maximise chances of healing after a single procedure, and because dislocated implants in the absence of sinusitis can be successfully retrieved transnasally or transorally. The latter approach has been accomplished with a number of different techniques worth mentioning: canine fossa puncture [22,23], which evolved into the use of antral retrievers [18] and the elevation of osteoplastic flaps [24].

To perform implant dentistry, a sufficient bone amount is necessary [25,26]. If this condition is unsatisfied, it is possible to perform a sinus floor elevation or sinus lift, a bone augmentation procedure that inserts bone graft material into a newly created space between the maxillary bone and Schneiderian membrane through a lateral or crestal access [12,27,28]. Sinus floor elevation is now considered a routine treatment and widespread, so more complications are arising from its use [27]. When the integrity of the sinus membrane is damaged and grafting material migrates into the cavity, bacterial contamination is favoured, resulting in infection of the sinus. Our group treated 48 cases of SCDDT that occurred after sinus lift surgery (class 1). All patients underwent endoscopic widening of the maxillary natural ostium with closure of the OAC [29].

Due to the complexity of SCDDT, diagnostic workup is fundamental to select the best multidisciplinary team for each case [30]. The first step is examination of the patient and their medical history and symptoms, usually performed by an ENT surgeon. After that, almost all our patients underwent presurgical nasal and upper airway endoscopy, to examine possible anatomical variations or evaluate the extent of the pathology, as well as radiological evaluation. A maxillofacial CT scan constituted a confirmatory diagnostic tool in all our patients, and this should be considered essential, even when the diagnosis is almost self-evident. It can also help quickly locate a foreign body or an implant within the maxillary sinus [31]. Further, CT is fundamental to evaluate the involvement of other paranasal sinuses. Previous studies have described ethmoidal cell involvement, reporting a limited number of cases [21,32]. Our study evaluated not only the prevalence of ethmoid engagement but also that of the frontal and sphenoid sinuses (Tab. II): a total of 305 patients (63.5%) presented extra-maxillary spread of infection. The sinus most affected by pathogenic dissemination was the ethmoid, in 294 cases out of 305, followed by the frontal (n = 75) and sphenoid sinuses (n = 19). In cases of bilateral spread of OS, 26 of 480 patients (5.5%) showed isolated maxillary contralateral diffusion, which in 34 patients (7%) expanded further to ethmoidal cells, in three (0.6%) to the sphenoid sinus and in another seven (1.5%) to the frontal sinus (Tab. II). From this data, it appears that once the infection exits the maxillary sinus it fills firstly the closest and most vulnerable ethmoidal cells, then the frontal and only finally the sphenoid sinuses.

Concerning diagnosis of OS, usually physical exam, endoscopy and triplanar or 3D CT slices provide all the information needed for adequate surgical planning, but complementary cone beam CT (CBCT) could be also prescribed by dentists in selected cases due to the greater bone resolution of CBCT than normal CT (Fig. 2) [15,33]. Another test that can help dentists in the diagnostic pathway is orthopantomogram (OPG), which may help assess the correct surgical approach for treating dental conditions behind sinus inflammation (Fig. 3). A combined approach is useful to recover the natural sinus homeostasis, eliminate dental pathologies and prevent possible complications or recurrence.

In our experience, FESS, combined if necessary with an external approach, seems to be the most appropriate treatment to resolve sinus inflammation. Furthermore, FESS allows

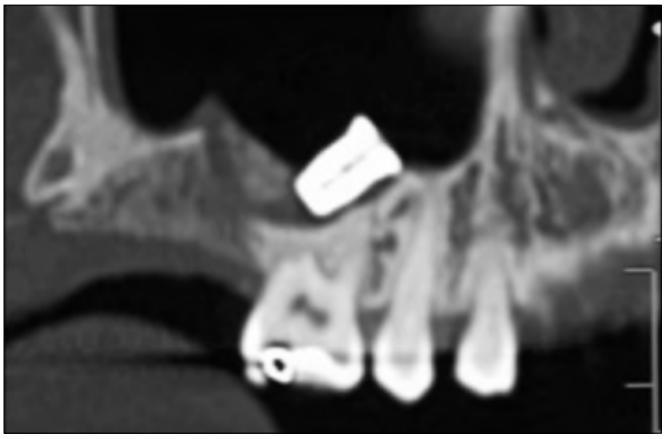

Figure 2. A Cone Beam Computed Tomography of a dental implant displaced into the maxillary sinus, without any signs of sinusitis - class 2D.

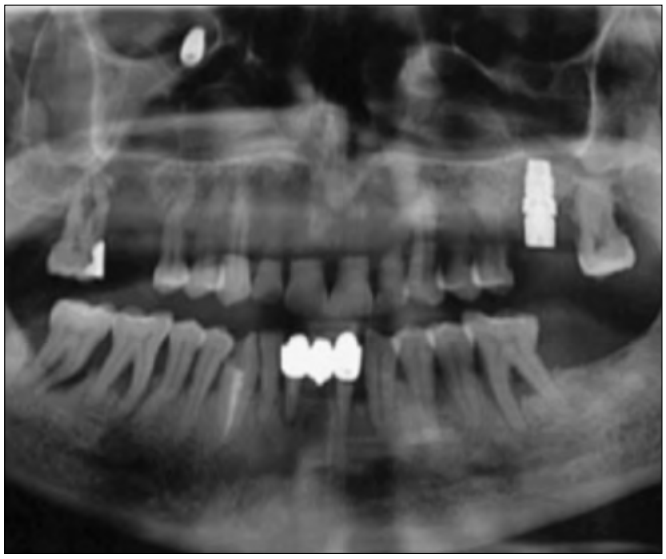

Figure 3. An orthopantomogram of a maxillary sinusitis following implant displacement into maxillary sinus - class 2C.

the management of all the other sinuses and treatment of anatomic alterations that can worsen normal sinus clearance and drainage. Therefore, in one surgical stage, it is possible to resolve the acute inflammation, prevent exacerbations and promote functional recovery of the sinus.

The intraoral access makes it possible to reach the sinus parts that are not easy to manage with nasal endoscopic view only, such as the alveolar recess [21,31]. Additionally, it allows the treatment of external sources of infection, and it is evident that treating the infected teeth plays a fundamental role in the prevention of recidivism.

The percentage of postoperative complications we reported was less than 1%, made up of 62.5% sinusitis recurrence, 25% OAC recurrence and 12.5% postsurgical bleeding. Moreover, FESS results are more effective in respecting the physiological sinus functions and correcting the cofactors of infection, including anatomical anomalies that can worsen the sinus drainage, such as concha bullosa, inferior turbinate hypertrophy or septal deviation. These findings suggest that, when pharmacological and conservative treatments fail, an endoscopic approach is not only valid but also safe.

One limitation of the present study lies in the lack of microbiological examination, except for patients with radiological findings of fungus ball (iron-like signal), in which mucosal biopsy is performed routinely in our centre. Other studies have been published concerning the microbiological and biochemical characterisation of OS, and its antibiotic susceptibility, but this was not the aim of our study [3,10,34,35].

After completing the review of our past cases, we decided to focus attention on the classification itself and its applicability, and the results were conflicting. Certainly, it is complete and, being based on SCDDT aetiology, makes it easy to allocate every patient to the corresponding group and class. However, the number of groups and classes (respectively three and eight) can easily lead to confusion and misleading analysis of data. As a consequence, the choice of correct therapeutic approach can be difficult. Considering these issues, the present classification seems to many colleagues impractical and not suitable for everyday application. Moreover, we realised that, although it was developed to describe a multidisciplinary medical condition (SCDDT), it was mainly directed to otorhinolaryngologists, not considering, for example, SCDDT only requiring an isolated oral approach. Certainly, we could have simply added another group or class to the existing ones, but this would only lead to further complication. Apart from these considerations, the classification has not encountered widespread use for these pathologies, and therefore a newly devised classification, possibly approach-based and not aetiology-based, could be implemented to streamline case categorisation and comparison of surgical results between different rhinologic groups.

Conclusions

According to our experience and to the data reported herein, SCDDT is not always limited to a unilateral maxillary cavity but often reaches other paranasal sinuses. As a consequence, a careful diagnostic approach based on CT scans and presurgical endoscopy must be considered fundamental. It is our opinion that a combined surgical approach, developed through multidisciplinary collaboration between ENT and oral surgeons, represents the best treatment option to achieve solid success rates. On the other hand, our analysis has also shown some weak points of the current classification, highlighting the need to produce a new one that is more practical and suitable.

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Rhinology

A comparison of two endoscopic techniques for the treatment of antrochoanal polyps

Trattamento chirurgico dei polipi antrocoanali: due tecniche endoscopiche a confronto

Hasan Ibrahim Al-Balas[1], Paolo Farneti[2], Andrea Bellusci[2], Francesco Maria Crocetta[2], Giacomo Sollini[3], Ernesto Pasquini[3]

[1] Faculty of Medicine, Yarmouk University, Irbid, Jordan; [2] Bologna University Medical School - Sant'Orsola-Malpighi Hospital, Bologna, Italy; [3] Azienda Unità Sanitaria Locale di Bologna, ENT Department Bologna, Italy

SUMMARY

An antrochoanal polyp (ACP) is a benign sinonasal lesion that originates from the mucosa of the maxillary sinus. In order to avoid any recurrence of disease, it is important to choose the best surgical approach for removal of ACP with respect to the site of attachment within the maxillary sinus walls. A retrospective cohort study was carried out by analysing a database of 82 patients who were operated on for ACPs in the Ear, Nose and Throat (ENT) clinics of both Sant'Orsola-Malpighi Polyclinic Hospital and Bellaria Hospital in Bologna, Italy from January 2001 to November 2017 to compare the rate of recurrence of ACPs after surgical removal using two different approaches. The first technique was endoscopic antrochoanal polypectomy with middle meatal antrostomy and the second was endoscopic antrochoanal polypectomy combined with both middle meatal antrostomy and a minimal access through the inferior meatus. A total of 49 patients were operated on with an endoscopic polypectomy with middle meatal antrostomy and 18.4% experienced a recurrence. The remaining 33 patients underwent endoscopic polypectomy with combined middle meatal antrostomy and access through the inferior meatus with a recurrence rate of 3%. The difference between the two groups was statistically significant (p = 0.0441). The strategy of the authors, namely combining medial antrostomy with a small inferior meatus access, was associated with a lower rate of recurrence and no increased morbidity in the short- or long-term.

KEY WORDS: antrochoanal polyp, endoscopic sinus surgery, middle meatus antrostomy, recurrence

RIASSUNTO

Il polipo antrocoanale (ACP) è una lesione benigna che origina dalla mucosa del seno mascellare. Al fine di evitare la recidiva chirurgica della patologia è importante scegliere il miglior approccio chirurgico per la rimozione del ACP a seconda del suo sito di attacco all'interno del seno mascellare. Uno studio retrospettivo è stato condotto analizzando il database di 82 pazienti operati per ACP presso le cliniche Otorinolaringoiatriche dell'Ospedale Sant'Orsola-Malpighi e dell'Ospedale Bellaria di Bologna, da gennaio 2001 a novembre 2017 al fine di confrontare il tasso di recidiva dopo la rimozione chirurgica utilizzando due differenti tipi di approccio. Il primo tipo prevede una polipectomia endoscopica attraverso un'antrostomia media mentre il secondo approccio è stato eseguito attraverso una rimozione endoscopica combinata con meatotomia media e un accesso di minima attraverso il meato inferiore. Quarantanove pazienti sono stati operati con il primo tipo di approccio con un tasso di recidiva del 18,4% mentre i rimanenti 33 sono stati sottoposti a un approccio combinato con un tasso di recidiva del 3%. La differenza fra i due gruppi è risultata essere statisticamente significativa (p = 0,0441). La strategia di combinare un accesso tradizionale con un accesso di minima attraverso il meato inferiore ha mostrato un minor tasso di recidiva senza un incremento della morbilità post-operatoria a breve e a lungo termine.

PAROLE CHIAVE: *polipo antrocoanale, chirurgia endoscopica nasosinusale, antrostomia media, recidiva*

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Correspondence
Paolo Farneti
via Pancaldi 1, 40138 Bologna, Italy
Tel. +39 051 391017
E-mail: farnetipaolo@gmail.com

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Conflict of interest
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Introduction

Antrochoanal polyps (ACPs) are benign polypoid lesions that originate from the mucosa of the maxillary sinus, extending into the nasal cavity through the natural sinus ostium or through its accessory ostium to reach the choana posteriorly [1]. Although Killian described the lesion in detail in 1906 [2], it was reported for the first time by Palfijn in 1753 [3].

Clinically, an ACP appears as a bright, grey or pinkish mass in the middle meatus and nasal cavity protruding posteriorly to the choana. Computed tomography (CT) can help to assess its nature, showing a soft tissue mass filling the maxillary sinus and growing through the accessory ostium into the middle meatus and the posterior choana [4].

No studies on the efficacy of medical therapy for ACP have been reported [5,6], and the mainstay of treatment is still considered surgery as already proposed by Stammberger in his "Polyposis Nasi" classification [7]. In particular, the endoscopic technique has become the most widely accepted approach [8,9], even in children [10]. To prevent recurrence of the disease, it is important to avoid a simple polypectomy and to remove the underlying mucosa at the site of origin of the ACP with minimal interruption of the normal sinus physiology [6]. However, it is not always possible to determine the point of attachment preoperatively due to the presence of coexistent sinonasal mucosal disease [4,6] and, consequently, to precisely plan the most suitable surgical approach.

In the past, the Caldwell-Luc procedure was used as the primary modality of treatment; however, the risk of damaging tooth development and the growth centres of the maxilla in children together with frequent post-operative cheek anaesthesia and cheek swelling affected its popularity [11].

The role of endoscopic sinus surgery (ESS) has been enhanced by the introduction of angled optics and powered instrumentation, with particular regard to angled micro-debrider blades, which provide a good surgical field by shaving and removing the soft tissue, allowing the intact mucosa to be spared during dissection around the point of attachment [12]. Nevertheless, it is not always possible to locate and reach the maxillary stalk of the ACP purely endoscopically, especially when it is on the anterior or inferior wall of the maxillary sinus. For this reason, different surgical approaches have been proposed in association with the endoscopic technique in order to avoid recurrence due to incomplete removal of the polyp by providing less morbidity and a lower rate of complications compared to a Caldwell-Luc procedure. Better visualisation and access to the maxillary sinus can be obtained by combining ESS with a mini-Caldwell-Luc procedure [13], canine fossa puncture [6,14,15], inferior meatal antrostomy [16,17], to a transnasal prelacrimal recess approach (suggested for revision surgery) [18] or ESS with wide middle meatal antrostomy [8].

The aim of the present study was to compare the rate of recurrence of two different approaches for treatment of ACP. The first technique was endoscopic antrochoanal polypectomy with middle meatal antrostomy and the second was an endoscopic antrochoanal polypectomy combined with both middle meatal antrostomy and a minimal access through the inferior meatus. As for secondary aims, symptoms, age, gender, time of follow up, association with atopy and postoperative complications were assessed in the patients treated.

Materials and methods

This retrospective study was carried out by analysing the database of 82 patients who were operated on for ACPs in the Ear, Nose and Throat (ENT) clinics of both Sant'Orsola-Malpighi Polyclinic Hospital and Bellaria Hospital in Bologna, Italy from January 2001 to November 2017. Factors including age, gender, atopy, associated symptoms, physical findings, imaging findings, surgical techniques, follow-up and management of recurrence were retrospectively studied.

An endoscopic examination was carried out in all patients, revealing the presence of a polypoid mass extending from the middle meatus to the choana. In all cases, radiological evaluation by CT of the paranasal sinuses was carried out. CT confirmed the features of the ACPs, which appeared as unilateral soft-tissue masses without evidence of bony erosion or soft tissue extension (Fig. 1). The concomitant presence of a septal deviation, ethmoidal sinusitis and/or concha bullosa of the middle turbinate were identified (Tab. I).

In the present study, there were no preoperative selection criteria to determine the type of surgery. When the ACPs originated from the posterior or lateral wall of the maxillary sinus, a middle meatal antrostomy was usually satisfactory to reach the site of origin. Otherwise, in patients in whom it was not possible to precisely locate the site of origin of the ACP, association with a minimal inferior meatal access was preferred. However, the inferior access was frequently not feasible in young children because the maxillary sinus was not perfectly pneumatised. In these cases, it was impossible to reach the sinus through the inferior meatus because of the projection of the alveolar bone at this level. Moreover, in these cases, the inferior access would not have been useful because a small maxillary sinus can be completely dominated using a traditional middle meatal antrostomy. Postoperatively, all patients were followed up in an outpatient setting, with nasal endoscopy after 1 month, 3 months and 6 months, and then every year.

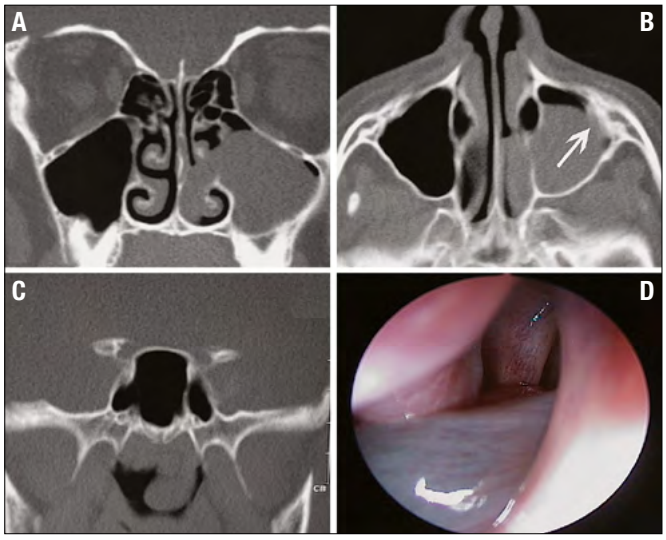

Figure 1. (**A**) Coronal computed tomography (CT) scan illustrating an opacified left maxillary sinus with antrochoanal polyp extending into the nasal cavity; (**B**) axial CT scan showing that the origin is from the lateral wall of the maxillary sinus (white arrow); (**C**) posterior view of the CT scan showing the extension into the choana; (**D**) endoscopic view showing a whitish mass originating from the maxillary sinus, exiting from the accessory ostium and extending into the nasal cavity.

Table I. Preoperative CT findings.

Preoperative findings	Patients	% of patients
SD	10	12.2%
CB	6	7.3%
Ethmoidal sinusitis	10	12.2%
SD and CB	4	4.9%
SD and ethmoidal sinusitis	2	2.4%
CB and ethmoidal sinusitis	4	4.9%
No associated pathology	46	56.1%

CT: computed tomography; SD: septal deviation; CB: concha bullosa.

Surgical procedure

In this study, two techniques for the removal of ACPs were compared with regards to recurrence rates. The first technique consisted of an endoscopic polypectomy with middle meatal antrostomy (standard approach); the second technique consisted of an endoscopic polypectomy with middle meatal antrostomy plus minimal access through the inferior meatus (combined approach). All surgical procedures were performed by two experienced surgeons.

A hypotensive general anaesthesia technique was used for all patients, with supine position and the head was slightly elevated. Cotton mixed with decongestant agents was inserted into the nose for 10 minutes before surgery. Different angled rigid (30º, 70º) 4 mm endoscopes were used to inspect the nose and determine the extent of the polyp. In both techniques, removal of the nasal part of the ACP was followed by retrograde uncinectomy and a large middle meatal antrostomy to access the maxillary portion and extract the antral part using angled instruments or a curved microdebrider. The difference between the two techniques consisted of how the site of origin was approached.

With the first technique, once the antral part of the ACP was removed, the point of attachment was localised using angled endoscopes (30º, 70º), and the underlying mucosa was then removed using an angled instrument or curved microdebrider (120°) (Fig. 2). In cases where it was impossible to adequately localise the point of attachment with the standard approach, the combined approach was performed. In addition to middle meatus antrostomy, a small opening to the inferior meatus was also made with this technique (Fig. 3). After medialising the inferior turbinate, the Hasner's valve was localised to avoid any injury to the lacrimal pathway. A mucosal flap was elevated with a vertical incision on the medial wall of the maxillary sinus laterally to the inferior turbinate and a small opening was created with a "curette" through the medial bony wall of the maxillary sinus. An angled microdebrider or a Weil forceps was inserted through this opening under direct vision with the endoscopes (30º or 70º) introduced through the middle antrostomy to remove the point of attachment of the ACP. The endoscope could also be introduced through the inferior access for a better view of the walls of the maxillary sinus after ACP removal to handle any possible residue. At the end of the procedure, the inferior antrostomy

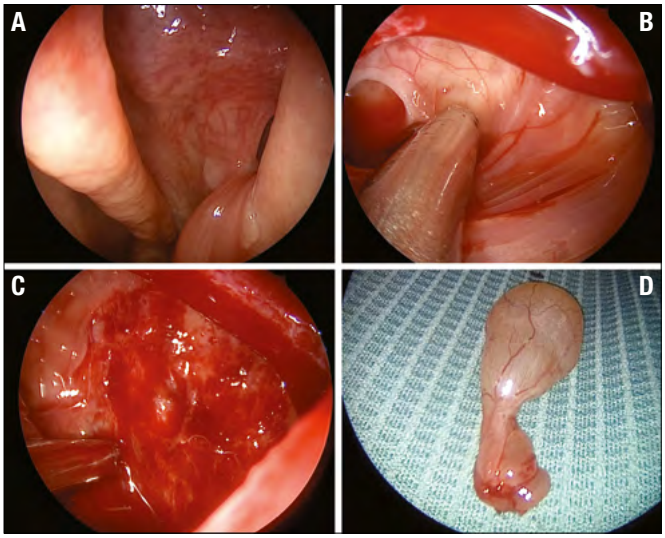

Figure 2. Removal of an antrochoanal polyp (ACP) using the standard approach. (**A**) ACP exiting from the accessory ostium of the left maxillary sinus; (**B**) localisation of the point of attachment on the lateral wall before dissection with a curved debrider blade; (**C**) complete removal of the mucosa at the point of attachment; (**D**) external view of the ACP.

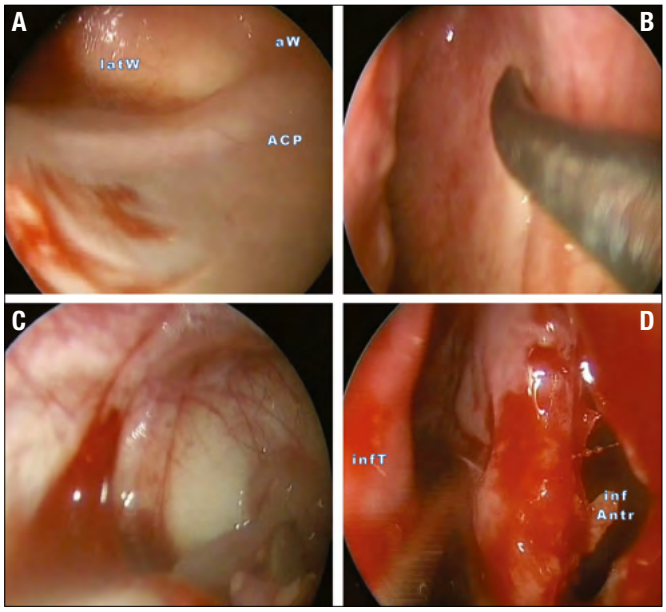

Figure 3. Endoscopic removal of an antrochoanal polyp (ACP) originating from the anterior wall of the maxillary sinus using a combined approach. (**A**) endoscopic view with a 70° endoscope through the middle meatus to show the point of attachment of the ACP on the anterior wall; LatW (lateral wall), aW (anterior wall), ACP (antrochoanal polyp point of attachment); (**B**) point of incision on the lateral wall of the inferior meatus to carry out the inferior minimal access; (**C**) endoscopic view with a 70° endoscope through the middle meatus showing the tip of the microdebrider inserted through the small antrostomy from the inferior meatus while drilling the site of attachment of the ACP; (**D**) endoscopic view with 0° endoscope showing the inferior meatus access in the inferior meatus at the end of the procedure; infT (inferior turbinate), inf antr (inferior antrostomy).

access was covered with a previously prepared mucosal flap, and the inferior turbinate was lateralised, ensuring complete haemostasis and avoiding any recirculation from the inferior access. In both techniques, nasal packing with one short Merocel® was performed.

The nasal packing was removed on the first postoperative day and patients were discharged; daily nasal douching was also prescribed. They were also prescribed topical or systemic steroid therapy if oedema of the maxillary sinus mucosa was detected at the first follow-up visit one month after surgery.

Statistical analysis

Data were recorded in a Microsoft Excel (Redmond, WA, USA) spreadsheet and analysed using SPSS version 16.0. Statistical significance was assessed using a two-tailed Fisher's exact test ($p < 0.05$ were considered significant).

This study was approved by the Local Institutional Review Board of Sant'Orsola-Malpighi Hospital in Bologna (194/2016/O/OssN), and informed consent was obtained from each patient.

Results

Of the 82 patients, 50 (61%) were male and 32 (39%) were female. Ages ranged from 6 to 87 years with a mean age of 32 years. Twenty-eight patients were 16 years old or younger. Of the 82 patients, 16 with recurrent ACPs were referred to us from other centres. In 61% of patients, the ACP was located on the right side and, in 39% of patients, it was located on the left side.

Nasal obstruction was the most common symptom in 86.6% of the patients, followed by rhinorrhea (39%), snoring (12.2%), headache (9.8%), epistaxis (3.7%), anosmia (2.4%) and dysphagia (1.2%). However, the most frequent presenting complaint was a combination of nasal obstruction with one or more other symptoms, followed by nasal obstruction alone; 48% of patients in the study suffered from atopic rhinitis and/or asthma. Of the 82 patients, 49 patients were operated on using a standard approach, and the other 33 underwent a combined approach. Of the 49 patients, 9 had a recurrence of ACPs while, of the 33 patients, only one had a recurrence. At endoscopic follow-up, recurrence was identified as a polypoid mass originating from the maxillary sinus not responding to medical therapy. The difference between the two groups was statistically significant ($p = 0.0441$) (Tab. II).

The study involved 28 patients who were 16 years old or younger. Of these 28 patients, a total of 14 were operated on using the standard approach and, of these, 5 developed a recurrence. On the other hand, 14 patients underwent endoscopic polypectomy with the combined approach, and none developed a recurrence. The difference between the two groups was statistically significant ($p = 0.0407$).

Table II. Comparison of recurrences between the standard and combined approaches.

	No. of patients operated on using a standard approach	No. of patients operated on using a combined approach	Total No. of patients
No recurrence	40	32	72
Recurrence	9	1	10
Total	49	33	82
% of recurrence	18.4%	3%	12.2%

The ACPs in the maxillary sinus were divided into five groups depending on the origin and attachment sites determined intraoperatively as reported in Table III. In 34 patients, the exact origin was missing in the patient's chart. There were no significant associations between the type of surgery for each attachment site and the recurrence rate.

Follow-up ranged from 19 to 106 months (average 41 months, median 37 and standard deviation 19.7). Ten patients had a follow-up of less than 24 months; of these, 3 had undergone a combined approach.

The earliest case of recurrence was documented at 11 months postoperatively. Of the 10 patients with recurrence; 5 underwent revision surgery with a standard approach, 4 patients underwent a combined approach (including the patient who had already been operated on with this approach) and 1 patient refused revision surgery. None of these patients had a second recurrence after a follow-up ranging from 26 to 84 months (average 46 months).

Sixty-six of the 82 patients received topical nasal steroid therapy, and 7 received combined topical and systemic steroid therapy.

No major complications were reported after surgery or at follow-up. Two patients operated on with the combined approach had an anterior synechia between the nasal septum and the inferior turbinate which was treated with an office procedure. None had a recurrence of the ACP. In all cases operated on using the combined approach, access through the inferior meatus was found to be closed at follow-up. None of the patients in either group presented epiphora postoperatively due to the preservation of the lacrimal sac and Hasner's valve.

Discussion

An antrochoanal polyp is a benign sinonasal lesion that originates from the mucosa of maxillary sinus. Although ACPs can occur at any age [9,19,20], they occur more frequently in children and young adults [20,21]. In the present series, 34.1% were 16 years old or younger. The majority of authors have observed that ACPs are more common in males [22]. Cook et al. reported rates of 70% in males and 30% in females [19]. In the present study, 61% of cases were male and 39% were female. However, other authors, such as Gendeh et al. [17] and Kaushalt et al. [23] found ACPs to be more prevalent in females with a male/female ratio of 1:1.5.

Nasal obstruction is the most common symptom of ACPs as was confirmed by Franche et al. who found that 83% of patients had nasal obstruction [24] and also in the present study (86.6% of patients had nasal obstruction). Although Cook et al. found a significant relationship with allergy and asthma among the 33 cases studied [19], the majority of other researchers did not find any association with allergic disease or atopy [25,26]. Of the patients in the present study, 47.6% suffered from atopic rhinitis and/or asthma.

One of the unusual manifestations of ACPs is epistaxis. Patients presenting with this symptom should undergo additional examinations to exclude other possible causes, such as juvenile nasopharyngeal angiofibroma or sinonasal malignancies. In the present study, magnetic resonance imaging was performed in three patients who had epistaxis in order to rule out other differential diagnoses.

ACPs can be subdivided depending on the site of attachment within the maxillary sinus wall. Berg et al, concluded that the 15 cases of ACP which they studied had the site of origin on the inferolateral wall of the maxillary sinus [27]. Deka found that 45% of his cases had an attachment to the posterior medial wall of the antrum adjoining the posterior fontanelle, 40% of the polyps originated from the anteroinferior aspect of the antrum and, in 15%, the site of origin could not be precisely evaluated [28]. In the present study, in 41.4% of cases, information regarding the site of origin was missing in the patient chart, 31.7% originated from the inferior wall, 12.2% from the anterior wall, 9.8% from the lateral wall and just 4.9% originated from the posterior wall.

Many surgical options for treating ACPs have been proposed to decrease the incidence of postoperative recurrence with minimal postoperative complications. All of these surgical options concentrate on a general principle

Table III. Comparison of recurrences considering the site of attachment of the ACP for each surgical approach.

Site of attachment	Total No. of patients	Standard approach	Recurrence (%)	Combined approach	Recurrence	P value
Not reported	34	19	3 (15.8%)	15	1 (6.7%)	0.6128
Anterior wall	10	5	1 (20%)	5	0	1.0000
Posterior wall	4	4	0	0	0	1.0000
Lateral wall	8	6	2 (33%)	2	0	1.0000
Inferior wall	26	15	3 (20%)	11	0	0.2385
Total	82	49	9 (18.4%)	33	1 (3%)	0.0441

ACP: atrochoanal polyp.

which is how to reach the site of origin. One of the surgical options is simple polypectomy (removing the polyp using angled forceps from the maxillary cavity without concern for the site of origin). However, ACP recurrence is reported to be 25% after this type of procedure [29]. On the other hand, in the past, the Caldwell Luc procedure was considered to be the primary modality of treatment, but the significant risks to developing teeth and the bone growth centres of the maxilla in children was considered to be a substantial drawback of this type of surgery [11]. The endoscopic approach avoids swelling of the cheeks, decreases adverse effects on teeth and facial growth in children, and has a shorter hospitalisation time compared with the Caldwell-Luc procedure [21]. Overall, many authors agree with the effectiveness and safety of the endoscopic approach for the removal of ACPs [8,9]. In a study carried out by Franche et al., a recurrence rate of 6.9% was observed in 29 patients operated on using an endoscopic transnasal approach [24]. Freitas et al. managed 16 cases of ACPs with the same approach and reported recurrence in 12.5% [30], while Ozdek et al. recorded up to 22% of recurrences after middle meatal antrostomy alone [21]. In a series of paediatric patients operated on in three ENT Italian Departments, Pagella et al. reported 22% of recurrences on those operated on using a standard approach (12/42 patients) and 0% of recurrence in 4 cases treated with a combined endoscopic and canine fossa approach [6]. In the present study, the recurrence rate after endoscopic polypectomy with middle meatal antrostomy was 18.4%, which is consistent with the majority of published reports.

Few authors used only inferior antrostomy to remove the antral portion of ACPs. In a study carried out by Gendeh et al., two of three patients operated on with an endoscopic intranasal polypectomy using an inferior antrostomy approach developed a recurrence after 1 year of follow-up [17]. Sato and Nakashima also used the same approach to remove the antral portion of ACPs; of the 10 patients enrolled in this study, none had a recurrence after a follow-up of 10 to 46 months [16]. In the present study, the recurrence rate after a combined approach was only 3% with complete closure of the medial wall of the maxillary sinus in the inferior meatus, thanks to the minimally invasive access carried out.

The main advantage of the present technique was to diminish the recurrence rate of ACPs with minimal perioperative complications; a statistically significant decrease from 18.4% with the standard to 3% with the new combined approach was reported with no significant major complications in either case. The advantage of this new approach was evident in situations where the origin of the ACPs was undetermined or was difficult to reach using traditional middle meatus antrostomy (anterior wall or inferior wall). Lee et al. performed endoscopic sinus surgery for ACPs originating posteriorly and inferiorly; on the other hand, for those originating from the lateral wall of the maxillary sinus, a combined (endoscopic and transcanine) approach was carried out. They reported a 76.9 % success rate for those treated with endoscopic sinus surgery alone, and a 100% success rate with the combined approach [14]. In the present study, the success rate for ACPs originating inferiorly and posteriorly was 84.2% with the standard approach and 100% with the combined approach; for those originating from the lateral wall, the success rate was 66.6% with the standard approach and 100% with the combined approach.

Comoglu et al. have recently suggested a transnasal prelacrimal recess approach in patients with recurrent antrochoanal polyps with an 83% success rate (10/12); according to the authors, this method of treatment ensured good exploration of the sinus and easy access to the origin of the polyp [18] despite a higher risk of damaging the lacrimal pathway.

Even if endoscopic polypectomy with inferior meatal antrostomy could be associated with the risk of developing synechia [17] or epiphora in the present study, only two patients operated on with the combined approach had an anterior synechia which was treated with an office procedure.

Limitations of the study

The present study has some limitations, such as a heterogeneous age range and its retrospective nature which did not permit having a random selection of the surgical approach. An additional limitation was due to 10 patients having a follow-up period of less than 24 months. According to Chaiyasate, patients should be followed up for at least 2 years postoperatively in order to detect 95% of recurrences [31]. Multivariate analysis was not carried out due to the limited number of recurrences.

Conclusions

An antrochoanal polyp is a benign expansive inflammatory lesion with a high recurrence rate if not completely excised by removing the underlying mucosa at the site of origin. Therefore, the best surgical strategies should combine radical removal with low morbidity. Either the Caldwell-Luc procedure or a medial maxillectomy are effective in lesion removal, but with higher morbidity. The strategy in the present study, namely combining medial antrostomy with a minimal access through the inferior meatus, showed a low rate of recurrence and no postoperative mid-term morbidity.

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OSAHS

Evaluation of factors that influence the success rate of OSA treatment with a customised adjustable MAD device - a retrospective study

Analisi dei fattori che influenzano il successo della terapia delle OSA con dispositivi MAD individualizzabili - studio retrospettivo

Giuseppe Burlon[1], Michele Tepedino[2], Michele Laurenziello[1], Giuseppe Troiano[1], Michele Cassano[1], Luigi Romano[3], Raffaella Rinaldi[4], Domenico Ciavarella[1]

[1] Department of Clinical and Experimental Medicine, University of Foggia, Italy; [2] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy; [3] Department of Otolaryngology Head and Neck Surgery, San Bassiano Hospital, Bassano del Grappa (VI), Italy; [4] Department of Anatomical, Istological, Forensic and Locomotor System Sciences, Sapienza University of Rome, Italy

SUMMARY

The aim of the present study was to evaluate how the features of obstructive sleep apnoea (OSA) and the degree of mandibular advancement influence the outcomes of oral appliance therapy with a fully-customised mandibular advancement device (MAD) in an adult population. A total of 85 adult patients with mild to severe OSA were retrospectively selected. Polysomnography was taken before treatment and after 2 months treatment with overnight MAD. Treatment success was defined as a > 50% reduction in the Apnoea/Hypopnoea Index (AHI) with a residual AHI < 10. Binary logistic regression was used to evaluate the effects of AHI, oxygen desaturation index (ODI), gender and age on the success rate of MAD therapy. MAD therapy was successful in 77.7% of patients, and the ODI was a significant predictor of treatment success. OSA treatment with the MAD was successful in reducing the AHI in adult patients. An ODI value smaller than 33.3 was a significant predictor of treatment success.

KEY WORDS: obstructive sleep apnoea, OSA, mandibular advancement, sleep parameters, oxygen desaturation index

RIASSUNTO

Lo scopo del presente lavoro è stato quello di valutare in che modo le caratteristiche della sindrome delle Apnee Ostruttive del Sonno (OSA) ed il grado di avanzamento mandibolare influenzano i risultati della terapia con dispositivi di avanzamento mandibolare (MAD) individualizzabili in una popolazione adulta. Sono stati selezionati retrospettivamente 85 pazienti adulti con OSA da lieve a severa. È stata eseguita una polisonnografia pre-trattamento e dopo 2 mesi di terapia notturna con MAD. La terapia è stata definita di successo se ha comportato una riduzione dell'Indice di Apnea/Ipopnea (AHI) > 50% con un AHI residuo < 10. Una regressione logistica binaria è stata usata per valutare l'effetto di AHI, indice di desaturazione dell'ossigeno (ODI), sesso ed età sul tasso di successo della terapia con MAD. Tale trattamento ha avuto successo nel 77,7% dei pazienti, e l'ODI è risultato essere un predittore significativo della probabilità di successo della terapia. Il trattamento delle OSA con il dispositivo MAD utilizzato si è rivelato efficace nel ridurre l'AHI nei pazienti adulti. Un valore di ODI inferiore a 33,3 è indicativo della possibilità di successo del trattamento.

PAROLE CHIAVE: *apnea ostruttiva del sonno, OSA, avanzamento mandibolare, parametri del sonno, indice di desaturazione dell'ossigeno*

Introduction

Obstructive sleep apnoea (OSA) is defined as a syndrome characterised by repeated collapse of the upper airways during sleep, resulting in airflow suspension that requires arousal to recover patency of the airways and

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Correspondence
Michele Tepedino
V.le San Salvatore, Edificio Delta 6, 67100 L'Aquila, Italy
Tel. +39 0862434794. Fax +39 0862434782
E-mail: m.tepedino@hotmail.it

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Conflict of interest
Giuseppe Burlon is the owner of the patent and the registered trademarks for Occlusion®, nonrusso+®, and Protrusor®. All other Authors declare no conflict of interest.

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normal breathing [1]. A diagnosis of OSA is confirmed after overnight polysomnography, when an Apnoea-Hypopnoea Index (AHI, number of apnoea/hypopnoea events per hour of sleep) greater than 5 and a complaint of daytime sleepiness are observed [2]. Hypoxaemia/hypercapnia derived from the reduced airflow, fragmented sleep caused by frequent arousals, exaggerated fluctuations in heart rhythm, blood pressure and intrathoracic pressure are responsible for severe sequelae like cardiovascular morbidity and mortality, neurocognitive impairment, systemic inflammation, increased risk of driving accidents and poorer quality of life [3]. It is a significant health-related problem that affects 5.9% of women and 12.5% of men in the general population over 40 years [4]. A study on an Italian population reported a prevalence of 2.7% in a range between 30 to 69 years of age [5].

The treatment options for this kind of patients comprise behavioural changes (e.g., weight loss and reduced consumption of alcohol), sleep position training, continuous positive airway pressure (CPAP), mandibular advancement devices (MAD) and upper airway surgery. According to the Practice Parameters of Care of the American Academy of Sleep Medicine (AASM), CPAP is the gold standard for treatment of OSA in adult patients, particularly for moderate to severe cases [6]. CPAP therapy is currently provided by the Italian National Health Service, being introduced among the Essential Levels of Care since 2017. This welfare policy is based on a concept of health that has evolved considerably: it is no longer about being healthy and disease-free, but rather about thorough well-being from physical, psychological and social perspectives [7]. Thus, the Italian healthcare system guarantees potentially universal access to care, without any distinction of personal and social conditions. However, nonadherence to CPAP treatment is high [8], and therefore MAD therapy is recommended by the AASM as a first-line treatment in mild to moderate OSA cases or as an alternative therapy for severe cases, non-compliant with CPAP [6]. A MAD acts by forcing the mandible to a forward position, thus increasing the upper airway's volume by widening the velopharynx, stabilising the soft palate and hyoid bone, stretching the tongue muscles and preventing the posterior rotation of the mandible [9]. Although CPAP is more effective in reducing the AHI, this difference is overcome by greater compliance and acceptance of MAD therapy [10,11].

The results of a systematic review demonstrated that different types of MADs have different efficacy in terms of mandibular protrusion and reduction of OSA events [12], with fully customisable devices showing superior performance [10]. While there is consensus on a comparable efficacy in AHI reduction between CPAP and MAD in mild to moderate OSA patients, there is still some uncertainty regarding severe OSA patients: while some authors reported promising results for severe OSA patients [10], a systematic review of the relevant literature was unable to perform a subgroup analysis to evaluate the efficacy of MAD therapy related to OSA severity [11]. In addition, the current literature provides only a limited number of studies that describe the amount of mandibular advancement, considered as an important factor for both treatment outcomes and side effects [13].

The aim of the present retrospective study was to evaluate how OSA features and the degree of mandibular advancement influence the outcomes of oral appliance therapy with a fully-customised MAD in an Italian adult population.

Materials and methods

This retrospective study was carried according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The records of OSA patients treated at a University Dental Clinic, from January 2011 to January 2018, were screened for the following inclusion criteria:

- Epworth Sleepiness Scale > 10;
- diagnosis of OSA confirmed by an overnight polysomnography;
- results of drug-induced sleep endoscopy (DISE) confirming the positive effect of mandibular advancement on airway obstruction;
- overnight MAD therapy with a fully-customisable device (Protrusor®, nonrusso+®, Dr Giuseppe Burlon, Belluno, Italy);
- age > 20 years old;
- a follow-up of 2 months with polysomnographic evaluation;
- completeness of diagnostic records.

Exclusion criteria were: smoking habit, BMI greater than 34 kg/m^2, previous surgical treatment of the maxillo-facial complex or the upper airway, presence of fixed oral appliance or mobile prosthetic rehabilitation, patients in treatment with CPAP or nCPAP, patients with severe cardiovascular disease, presence of temporomandibular joint disorder.

The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. The records were retrieved retrospectively, analysed anonymously and patients signed written informed consent to participate to future research at the time that the records were taken. The Protocol was approved by the Ethics Committee of the University of L'Aquila, Italy (protocol no. 9032).

To detect a moderate to small effect size (0.3) having a I type error of 0.05 and a power of 0.8, 64 subjects were needed [13].

For all patients, data on AHI and the 3% Oxygen Desaturation Index (3% ODI, number of desaturation events greater than 3% of the baseline value per hour of sleep) were retrieved from pre-treatment (T0) polysomnography. According to AASM guidelines, patients with an AHI between 5 and 15 were defined as mild OSA, patients with an AHI ranging between 15 and 30 were defined as moderate OSA, while those with an AHI greater than 30 were considered to have severe OSA [2]. For mild to moderate OSA patients, MAD therapy was the first-choice of treatment, while severe OSA patients started MAD therapy after non-adherence to CPAP therapy.

Instrumental evaluation

Each patient received complete overnight polysomnography (PSG). All subjects were evaluated for one night in a sleep laboratory using a portable device, the Embletta system (Flaga, Reykjavik, Iceland). The recording was performed after one night of adaptation to the hospital setting. The airflow was monitored by a nasal cannula and by an oral thermistor. The thoracic-abdominal movements of all subjects were detected through two piezoelectric belts. Overnight continuous recordings of oxygen saturation were obtained by finger pulse oximetry. Snoring was recorded by a microphone placed at the neck, and note was taken of ECG findings and sleep position.

Apnoea was defined as the cessation of airflow lasting 10 sec; and hypopnoea was defined as a discrete reduction (two-thirds) of airflow and/or abdominal rib-cage movements lasting 10 sec associated with a > 3% decrease in oxygen saturation. The number of events per hour was obtained by dividing the total number of events by the total sleep time (TST) and was defined as the AHI. The oxygen desaturation index (ODI) was also measured, as were the number of arterial oxyhemoglobin saturation dips ≥ 3%. Nocturnal hypoxaemia was evaluated in terms of percentage of total sleep time with oxyhaemoglobin saturation < 90%. Sleep apnoea was defined using AHI ≥ 10 per hour. The test was repeated with oral appliance three months later in all patients.

Patient enrolled in the present study had previously had a DISE to evaluate the collapse area. In the operating room, electrocardiography, pulse oximetry, non-invasive blood pressure and bispectral index (BIS) were monitored. Propofol was used during DISE. Propofol 2 mg/kg was intravenously administrated at DISE start; 1 mg/kg was given for maintenance. The maximum dosage of propofol was 3 mg/kg. A flexible fiberoptic endoscope (Type ENF-GP, Olympus Europe GmbH, Hamburg, Germany) was introduced by one experienced ENT surgeon in the awake patient to evaluate the awake upper airway state.

When target sedation was reached, a soft mandibular protrusion was produced by use of a protrusor appliance.

The device

The MAD used for the present study is a customisable and adjustable device. It is composed of two resin splints connected by two threaded titanium bars with two titanium screw each, which constitutes the protrusive component of the device (Figs. 1, 2). The head of the titanium screws allows for lateral movements of the mandible, while keeping the mandible in a forward and lower position. The titanium bars have laser marks every 2 mm to facilitate the titration of the degree of mandibular advancement.

Treatment protocol

All patients were instructed to wear the MAD: an initial mandibular advancement of 70% of the total possible

Figure 1. The Protrusor® MAD device. It is made of two resin splints connected by two threaded titanium bars, which can be regulated to reach the desired amount of mandibular advancement. A chip for compliance monitoring is embedded in the lower resin splint.

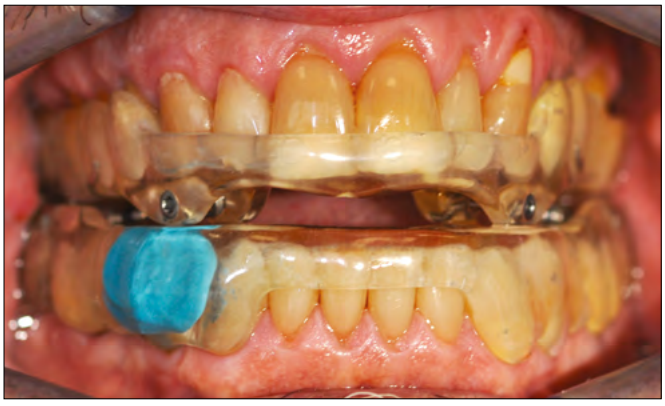

Figure 2. The Protrusor® MAD device in place after individual titration.

protrusive movement was set using and intraoral gauge (Occlusion®, nonrusso+®, Dr Giuseppe Burlon, Belluno, Italy) (Fig. 3). During the following visits every 15 days, the therapeutic mandibular protrusion was adjusted on an individual basis with 1 or 2 mm increments, until the most comfortable position that allowed improvement of symptoms was reached: this position was established based on the symptoms reported by patients and their bed partner. The amount of the final mandibular advancement was recorded for each patient as a percentage of the maximal protrusive movement achievable.

Post-treatment (T1) AHI and 3% ODI values were retrieved from another polysomnography after a period of 2 months of treatment.

The therapy was considered successful based on the residual AHI value: patients showing ≥ 50% AHI reduction compared to baseline and a T1 AHI ≤ 10 were considered good responders. On the other hand, patients showing a reduction < 50% of AHI, but with a residual AHI > 10 were considered bad responders and unsuccessful cases.

Statistical analysis

For AHI and 3% ODI values, the T1-T0 difference was also calculated and reported both as a raw value and a percentage of the T0 value. Descriptive statistics and overall success rate were calculated. A Shapiro-Wilk normality test was used to evaluate the distribution of all variables. Binary logistic regression was performed to study the effects of age, gender, AHI value at T0, ODI 3% at T0, and mandibular advancement on being classified as a good or a bad responder. The predictors were included in the model with a forward stepwise method. The first type error was set as $P < 0.05$.

Results

Complete records for 85 patients were available out of the 150 initially screened; the remaining incomplete diagnostic records of the other subjects were excluded from further study. The study sample was composed of 72 males (mean age 55.3 ± 12.3) and 13 females (mean age 65.5 ± 7.9); other demographic characteristics are reported in Table I. Based on the T0 AHI value, 26 patients were classified as mild OSA, 36 patients as moderate OSA, and 23 patients as severe OSA.

Descriptive statistics are reported in Table I. According to the criteria reported in the Materials and methods, 66 patients were considered good responders and 19 patients poor responders. Therefore, the treatment was considered successful in 77.7% of patients. All patients showed good compliance with MAD therapy. Some of the severe OSA patients who initially refused CPAP, but whose MAD therapy was unsuccessful, returned to CPAP therapy after the period considered for the present study. No side effects on the temporo-mandibular joint (TMJ) were reported by any patient.

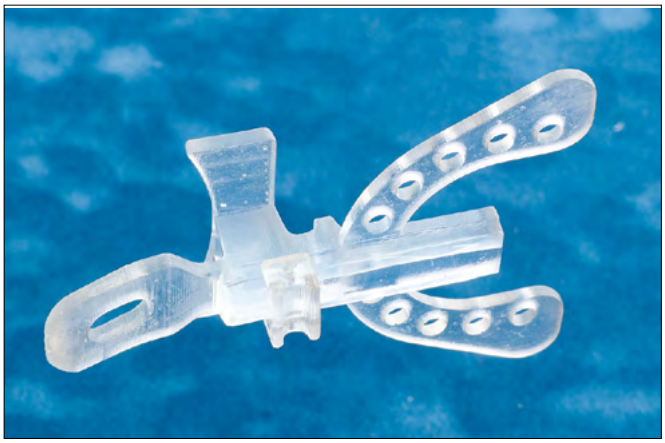

Figure 3. The Occlusion® device used to register the ideal mandibular protrusion, and to transfer the desired mandibular position to the dental laboratory for manufacturing the MAD device.

The logistic model was able to correctly predict 81.2% of cases. The regression model included only the variables ODI 3% at T0 and the Constant (Tab. II), whereas the other predictors were not significant and were excluded by the forward stepwise method (Tab. III). The odds ratio for the ODI 3% variable was 0.92, meaning that a 1-point decrease of ODI multiplies the odds of being a good responder by 0.92. The calculated critical value for ODI 3% was ODI < intercept/coefficient < 3.36/0.09 < 33.3. Therefore, an ODI value smaller than 33.3 was needed to be classified as a good responder.

Discussion

MADs are a valuable treatment modality for patients with OSA: several reports have confirmed they are associated with improvement in the quality of life, daytime sleepiness, cardiac autonomic function [14], and functional and cognitive outcomes that are comparable to CPAP therapy [11]. The results of the present study showed that MAD therapy with the customised adjustable device studied can successfully treat 77.7% of adult patients. Comparing our data with the existing literature is not simple because there is large heterogeneity in the parameters used to consider a treatment successful or not [3]. Some authors reported a success (defined as post-treatment AHI < 10) rate of 72% when using a customised non-adjustable MAD [15]. Other authors observed clinical success (defined as post-treatment AHI < 10) in 54% of adult patients [16]. Fernandez-Julian et al. reported

Table I. Descriptive statistics for good responders and bad responders.

	Good responders (n = 66)		Poor responders (n = 19)	
	Mean ± SD	P value*	Mean ± SD	P value*
Age (y)	55.9 ± 12.4	0.012	59.9 ± 11.3	0.108
AHI T0	19.9 ± 12.3	< 0.001	31.2 ± 11.1	0.900
AHI T1	3.7 ± 3.4	< 0.001	18.1 ± 10.2	< 0.001
AHI T1-T0	-16.1 ± 11.9	< 0.001	-13.1 ± 10.9	0.661
AHI T1-T0 %	69.6 ± 24.4	< 0.001	63.6 ± 28.7	0.012
3%ODI T0	18.8 ± 10.6	0.011	30.6 ± 12.1	0.713
3%ODI T1	5.1 ± 3.9	< 0.001	20.8 ± 12.3	0.293
3%ODI T1-T0	-13.2 ± 10.9	0.002	-9.8 ± 13.5	0.168
3%ODI T1-T0 %	66.5 ± 22.9	0.006	54.1 ± 30.3	0.075
Advancement (%)	80.1 ± 14.9	< 0.001	77.9 ± 15.6	0.105

**: P value from the Shapiro-Wilk normality test.*

Table II. Stepwise binary logistic regression (n = 85).

	B	S.E.	Wald	df	P	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
3% ODI T0	-0.09	0.03	11.24	1	0.001	0.92	0.87	0.96
Constant	3.36	0.74	20.62	1	< 0.001	28.8		

Table III. Variables excluded from the binary logistic regression model (n = 85).

	Score	Df	P value
Age	3.079	1	0.079
Gender	0.085	1	0.770
AHI T0	0.155	1	0.694
Advancement %	1.384	1	0.239
Overall statistics	4.935	4	0.294

successful (AHI< 10 and Epworth Sleepiness Score < 10) treatment in 50% of adult patients with moderate to severe OSA [3]. Mints et al. showed a higher success (defined as post-treatment AHI < 10) rate of 80% using a customised adjustable appliance in a sample of 510 patients comprising mild, moderate and severe OSA [10], and concluded that treatment success is not dependent on the baseline degree of severity of OSA. This finding is in contrast with our results: a significant (P = 0.001) effect of baseline 3% ODI value on treatment success was found (Tab. II). Higher values of 3% ODI predicted an unsuccessful treatment outcome, with a calculated threshold value of 33.3 oxygen desaturation events per hour of sleep. The 3% ODI value was a stronger predictor than the AHI value, the latter being excluded from the regression model due to collinearity (0.792) with the 3% ODI variable.

These results appear to confirm current guidelines suggesting MAD treatment as the first choice therapy for mild to moderate OSA patients, and as an alternative to CPAP for severe OSA [11]. The main advantage of MADs, even in severe OSA patients, is its significantly higher compliance and self-reported usage compared to CPAP [11]. On the other hand, OSA treatment with MAD is also associated with some side effects. In the short term, muscular and articular tenderness, gingival irritation, mouth dryness and excessive salivation can occur: these side effects can be easily managed and even prevented [17]. Regarding TMJ pain, it has been reported in the literature in 12.5% of patients, and usually manifests in the early phases of treatment [18]. A study on FEM models revealed that the TMJ does not experience significant stress, regardless of the amount of mandibular advancement, suggesting that the TMJ discomfort referred by patients could be due to altered muscle dynamics, since the forward posturing of the mandible increases muscular activity [19,20].

On the other hand, long-term side effects are more complex and involve skeletal and dental modifications. The mechanism behind these changes is the same as those described for orthodontic functional appliances: when the muscles are stretched by the device due to the forward posturing of the mandible, forces are transmitted to the bones and the teeth, and the long duration of these forces produces changes in skeletal morphology and teeth position [21]. The dental and skeletal changes are progressive, and thus patients should be monitored over time, and are also dependent on the duration of the MAD therapy [13]. In the present study, no relevant short-term side-effects were reported, while long-term effects could not be evaluated.

Regarding the amount of mandibular advancement, the

present study demonstrated that this is not a parameter that influences clinical outcomes of therapy (Tab. III). On the contrary, some authors reported that greater mandibular advancements were more effective in improving polysomnographic parameters [22,23]. However, Lamont et al. observed that for some OSA patients, excessive mandibular advancement causes an increase in airway obstruction [24]. Other authors recommended MAD treatment with an advancement of no more than 50% of the maximum protrusive movement, because greater advancements did not produce further improvements in AHI reduction [25]. The results of the present study seem to confirm that titration of mandibular advancement through subsequent steps is important, because each patient has their own therapeutic mandibular position that should be recognised, a position that does not necessarily coincide with the maximum achievable protrusion [12].

Other factors like the patient's age and gender were not significant predictors of the success of MAD treatment, confirming the findings of other studies [3].

The main limitation of the present study is its retrospective nature. We took care to avoid any selection bias, and all patients with incomplete records were excluded. Another limitation is the short follow-up, which precludes us from making statements on the long-term success of MAD therapy with the proposed device. Possible future improvements of the present protocol could be evaluation of other patient related parameters such as body mass and neck circumference [26], and assessment of quality of life, since other parameters in addition to AHI can explain the clinical success of therapy [3,27]. Further studies could also take into account skeletal features [28,29] and volumetric assessment of the upper airway [30,31].

Conclusions

The MAD studied was effective in reducing the AHI value below 10 in 77.7% of patients in a population of adults with mild to severe OSA. The main predictor of the success of MAD treatment was a 3% ODI value below 33.3.

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Audiology

Are smartphone applications (App) useful to improve hearing?

Le App per smartphone possono essere utili per migliorare l'udito?

Paz Martinez-Beneyto[1,2], Sebastiano Franchella[3,4], Fabio Alonso Rodriguez[1], Rafael Navarro-Velasquez[1], Miguel A. Martinez-Beneito[5,6], Alessandro Martini[3], Jaime Marco Algarra[1,2]

[1] Servicio de Otorrinolaringologia, Hospital Clinico-Universitario, Valencia, Spain; [2] Departamento de Cirugía, Facultad de Medicina, Universidad de Valencia, Spain; [3] Otorinolaringoiatria, Dipartimento di Neuroscienze DNS, Università degli Studi di Padova, Italy; [4] Dipartimento di Salute della Donna e del Bambino SDB, Università degli Studi di Padova, Italy; [5] FISABIO, Fundacion para el fomento de la investigacion sanitaria y biomedica de la Comunidad Valenciana, Valencia, Spain; [6] CIBER Epidemiologia y Salud Publica (CIBERESP), Madrid, Spain

SUMMARY

The objective of the study is to assess whether a smartphone application (App) designed to improve hearing can improve audiological performance in patients with normal hearing and with varying grades of hearing loss (HL). This is a multicentre prospective analytical study. We performed a battery of audiological tests consisting of pure tone audiometry (PTA) and a word recognition test (WRT) in quiet and in noise at different signal-to-noise ratio (SNR) using or not a smartphone App. Intra-subject results under both conditions were compared to determine the App's effect on hearing. A survey was also carried out to obtain data on subjective hearing experience with the App. We recruited 55 HL patients and 13 normal-hearing controls between June to December 2017. The results show that use of the App in HL patients improved WRT scores by a mean of 30.3% in quiet, 24.3% in noise + 10 dB SNR, and 20.8% in + 5 dB SNR. App use was identified as a factor that increased word recognition (odds ratio = 1.812, $p < 0.05$) and 61% of subjects rated sound quality when using the App as good or excellent. The use of a smartphone hearing App improved scores in both PTA and WRT in most cases. Patients with binaural hearing impairment < 60% obtained the best results. Subjective user satisfaction was good in both conditions.

KEY WORDS: hearing aids, hearing loss, mobile applications

RIASSUNTO

L'obiettivo dello studio è quello valutare l'efficacia di un'App per smartphone creata con lo scopo di migliorare le performance uditive sia in soggetti normoudenti che in pazienti affetti da ipoacusia da lieve a severa. Si tratta di uno studio analitico multicentrico, eseguito tra giugno e dicembre 2017, che ha analizzato un campione di 68 pazienti di cui 55 ipoacusici e 13 normoudenti; a tutti i pazienti sono stati somministrati test audiologici specifici sia durante l'utilizzo della suddetta App che in assenza di ausili uditivi. Il protocollo di valutazione audiologica prevedeva l'esecuzione di un'audiometria tonale liminare e del WRT (word recognition test) sia nel silenzio che in competizione a differenti livelli di rapporto segnale/rumore; la batteria di test è stata eseguita sia in assenza di amplificazione uditiva che utilizzando l'App per smartphone. I pazienti sono stati sottoposti ad un sondaggio relativo all'esperienza uditiva con un questionario sviluppato ad hoc. I dati preliminari sono piuttosto incoraggianti in quanto dimostrano che l'utilizzo dell'App migliora le performance del WRT nei pazienti ipoacusici. Il test ha evidenziato un miglioramento medio del 30,3% nel silenzio, del 24,3% nel rumore con SNR (signal to noise ratio) + 10 dB e del 20,8% nel rumore con SNR+5dB. L'utilizzo dell'app è stato identificato come un fattore che migliora il riconoscimento verbale (Odds Ratio = 1,812, $p < 0,05$) e il 61% dei soggetti ha valutato come buono o eccellente la qualità del suono utilizzando l'App. L'utilizzo dell'App per smartphone ha migliorato nella maggior parte dei casi i punteggi sia all'audiometria tonale che al WRT e i pazienti con un'ipoacusia bilaterale < 60% hanno ottenuto i risultati migliori; tutti i pazienti sono stati soddisfatti dell'App durante l'utilizzo in cabina silente.

PAROLE CHIAVE: *protesi acustiche, ipoacusia, applicazioni per smartphone*

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Correspondence
Paz Martinez-Beneyto
Hospital Clinico Universitario de Valencia, Avenida Blasco Ibanez 17, 46010 Valencia, Spain
Tel. 961973500. Fax 963 862 600
E-mail: pazmabe@gmail.com

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Introduction

Millions of people suffer from disabling hearing loss (HL) that requires some kind of treatment, and hearing aids are the standard recommendation. At the same time, smartphones are now fully integrated in our lives, and these high processing capacity devices can be used to run applications (Apps) with diverse functions. Some have medical uses, under the umbrella term "e-health", as healthcare practices supported by electronic processes and communication, and among these, some Apps can amplify sound with the objective of improving listening. These Apps work by receiving sound through the smartphone microphone, and then processing the signal using algorithms for sound amplification, frequency modulation, background noise elimination, etc. The resulting signal is sent through headphones to the user, who potentially receives a more intense sound with noise reduction.

Information about these Apps is of importance to hearing professionals. Are they really useful? Can we recommend them to our patients? What kind of improvement can we expect? Do they cause sound distortion? To date few studies on Apps for audiological purposes have been published, and most are related to HL screening and diagnosis [1-5], with no published data about the efficacy of Apps designed to improve hearing.

The purpose of this study is to investigate the benefits to hearing provided by an App. A prospective study was designed in which a group of hearing impaired patients and normal-hearing volunteers performed a battery of hearing tests with and without use of the App to objectively quantify the possible benefits to hearing.

Materials and methods

This is a multicentre prospective analytical study, based on an intrasubject comparison and approved by the local Research Ethics Committee. The project was conducted in two tertiary referral hospitals: the Otolaryngology division of the Hospital Clinico Universitario of Valencia (Spain) and the Otolaryngology division of the University Hospital of Padua (Italy).

Subjects

We recruited adult subjects with HL treated at the two centres in the period from June to December 2017 who met the following inclusion criteria:

1. bilateral and symmetrical HL (interaural mean threshold difference < 10 dB);
2. HL onset > 6 months;
3. native in the language of the Word Recognition Test (WRT);
4. > 18 years old;
5. agreed inclusion in the study by signing informed consent.

Exclusion criteria were:

1. mental disorder that could prevent a successful test outcome;
2. acute ear infection.

We recruited a second group of normal hearing adult subjects.

Smartphone and earphones

The smartphone used for the experiment was an Apple iPhone 6S, iOS version 10.1.1. The sound output was connected to Sony MDR-EX15LP in-ear headphones (power handling capacity: 100 mW, impedance: 16 Ω at 1 kHz, sensitivity: 100 dB/mW and frequency response: 8-22,000 Hz).

Mobile application (App)

Several Google searches with the terms [hearing aid App], [deafness App], and [hearing amplification App] were performed. The App selected was Petralex®, version 1.5.3 (developer: IT For You), as it met the following criteria: easy to use, no need for training, free of charge, and available for both Android and iOS.

Although the App allows some parameter settings, the following default settings were established for all patients: volume was set to maximum, compression was turned off, amplification mode was "NAL" [5], low and high frequencies were set to medium, environmental noise reduction was activated, and the main hearing profile was set to normal hearing amplification.

Hearing tests

All participants were tested in a sound-treated booth with an ISO standard calibrated audiometer and headphones. In Hospital Clinico Universitario of Valencia the Interacoustic AC40 audiometer was used, while in the University Hospital of Padova the Otometrics Mercury Madsen Astera was used, with the GN Otometrics OTOsuite, version 4.75.01 software. The tests were performed in both centres by the same operator using the same smartphone and earphones.

The testing sequence is represented in Figure 1. All participants underwent pure tone audiometry (PTA) and word recognition test (WRT), as follows:

- PTA with air-conduction headphones (testing the octave points from 250 to 8,000 Hz) and with bone-conduction oscillator (testing the octave points from 250 to 4,000 Hz);
- Free field (FF) testing was performed under two conditions, first without aid and second using the smartphone

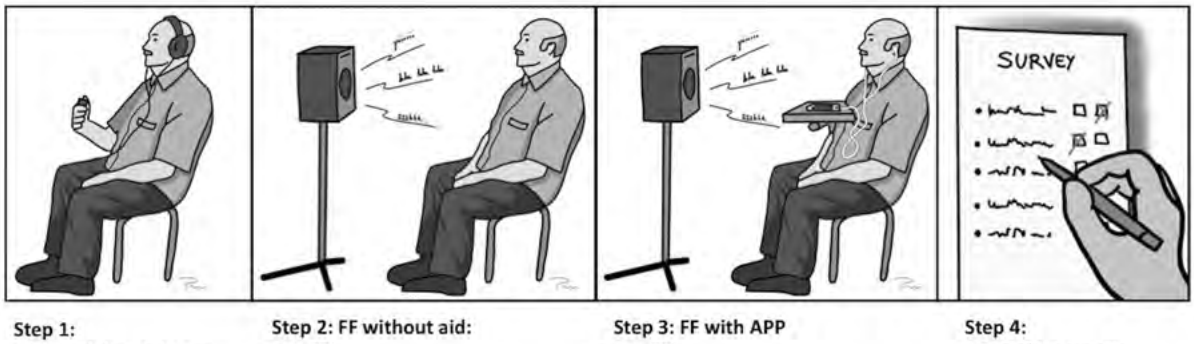

Figure 1. Subject testing steps.

connected to the earphones and using the smartphone with the Petralex® App at one metre from the speaker.

The following tests were performed:

- FF PTA (testing the frequencies 250-500-1,000-2,000-3,000-4,000 Hz);
- FF-WRT at 65 dB HL in quiet;
- FF-WRT at 65 dB HL in noise at + 10 dB SNR (signal-to-noise ratio);
- FF-WRT at 65 dB HL in noise at + 5 dB SNR.

For the WRT, 10 disyllabic words in the official language of the country were delivered and correct answers expressed in percentages. Noise was a narrow-band sound stimulus delivered from the same speaker.

Survey

All participants were asked to complete a brief survey providing subjective assessment of the hearing experience after the testing. The questions were:

1. Did you notice an improvement in your hearing when using the App? Yes/No.
2. Did you notice any sound delay? Yes/No.
3. Did you feel any kind of discomfort during App use? Yes/No.
4. Did you notice annoying noises when using the App? Yes/No.
5. Rate hearing quality when using the App. (1) Very poor; (2) Poor; (3) Appropriate; (4) Good; or (5) Excellent.

Database and statistics

A database was compiled with hearing test and survey data, and other data such as age, sex, deafness type and aetiology. Several hearing parameters were calculated using the raw data from the hearing test, as follows [6,7]:

- Pure tone average: average air conduction thresholds at 500-1,000-2,000-3,000 Hz of the PTA with headphones.
- Percentage of HL $= 1{,}5\left(\frac{0{,}5kHz+1kHz+2kHz+3kHz}{4}-25\right)\%$

  If the value is a negative number a value of 0% is assigned so that normal-hearing subjects have 0%.
- Binaural hearing impairment (BHI) percentage =

$$\frac{5*(\text{percentage of HL best ear})+\text{percentage of HL worst ear}}{6}$$

App benefit was established as the difference between the results obtained using the App and the results without its use. In order to obtain positive values when the use of the App gave improved results, and negative values when the APP impaired the results, the following formulas were devised:

- benefit obtained with App in PTA: [PTA without App] - [PTA with App];
- benefit obtained with App in WRT: [WRT% with App] - [WRT% without App].

A statistical logistic regression model was performed to analyse the effect of each variable on the audiometric test results. This model considers the interaction of each variable analysed during App use to determine which factor effects are modified by its presence.

Results

68 subjects were recruited, 51% male and 49% female, average age 54 years [range, 20-84]. Based on a cut-off hearing threshold of 20 dB of PTA in FF, in order to consider binaural hearing, we studied 55 subjects (80.8%) with HL and 13 subjects (19.1%) with normal hearing. The relevant pathologies in the hearing-impaired subjects

were: 25 (45.4%) presbycusis, 18 (32.7%) chronic otitis media and 12 (21.8%) other ear pathologies (Ménière disease, otosclerosis, or mixed ear pathologies). Regarding hypoacusia type, 36 (52.9%) patients had sensorineural HL, 10 (14.7%) conductive HL, 9 (13.2%) mixed HL and 13 (19.1%) normal hearing. Table I shows the main parameters of the entire sample, normal hearing subjects and patients with HL.

BHI distribution was split into the following ranges: BHI = 0% in 13 subjects; 1-20% in 29 subjects; 21-40% in 10 subjects; 41-60% in 10 subjects; and 61-83% in 6 subjects.

The different hearing test outcomes were analysed with and without App use.

Table II shows the averages of these results and the benefit obtained when the subject was using the App. A positive benefit value means that listening performance improved with App use, while a negative value means that App use provided worse results.

The benefit values varied significantly across patients. Benefit distribution for each hearing test is represented graphically in Figure 2. Calculating the percentage of subjects obtaining better results, 31% of the subjects in quiet, 43% in +10 SNR, and 38% in +5 SNR scored >10% higher on the WRT with the App than without; and 20% of subjects in quiet, 22% in +10 SNR, and 26% in +5 SNR scored > 20% higher when using the App. Results with the App were worse in 11% of the subjects in quiet, 5% in +10 SNR, and 7% in +5 SNR.

A statistical logistic regression model was adjusted to estimate the effect of each main variable (noise, grade and type of HL), and the subject as a random effect, on hearing test results. This regression model considers the interaction of each variable with App use to determine which of these factor's effects are modified by the App.

Table III shows the odds ratio (OR) obtained in relation to the WRT result in a normal-hearing person. An OR = 1 means that the expected results are like a normal-hearing subject; an OR < 1 indicates that the probability of understanding and repeating the words of the verbal audiometry is lower than in normal-hearing condition and an OR > 1 indicates that the probability of understanding and repeating the words is higher than normal. As seen, the presence of noise, the magnitude of BHI, decreases the probability of getting the words correct in WRT, and overall, use of the App increased it (OR = 1.812, $p < 0.05$). The statistical model provides an estimation of the WRT score in both conditions (with and without App use) for different levels of BHI. Figure 3 shows the estimation for sensorineural and conductive HL in silence and in different noise levels. In many cases, App use improved word recognition over a certain range of hearing loss. Cases with more than 10% improvement are shaded in grey.

Finally, the results of the satisfaction survey completed by the participants showed that 43 (63%) subjects noticed an improvement in hearing, 60 (88%) did not notice sound delay, 66 (97%) did not feel discomfort and 63 (93%) did not hear annoying noises. Self-assessment of hearing quality, represented in Figure 4, shows 61% as good or excellent.

Table I. Age, sex and PTA in free field (FF) for the global sample, for the normal hearing and patients with hearing loss groups.

	All	Normal hearing	Patients with HL
N	68	13	55
Age average [range]	53.6 [21-84]	29.1 [21-57]	66 [21-84]
Sex [male/female]	33/35	6/7	27/28
PTA [dB] average [range]	38.7 [5-79.4]	13.6 [5-19.3]	44.6 [21.8-79.4]

HL: hearing loss; PTA: pure tone average in FF.

Discussion

The use of a smartphone + App set to improve hearing is part of the "eHealth" concept [8], which is defined as Information and Communication Technologies used in the Health areas of prevention, diagnosis, treatment, monitoring and management. As health professionals, we must be open to the emergence and increasing importance of eHealth Applications and device use. These new solutions have to be tested prior to their recommendation and use, however, in order to advise patients based on scientific

Table II. Average and [range] of the hearing tests with and without App in the population analysed. Benefit is the difference between the two conditions.

	Normal hearing			Patients with HL		
	No App	With App	Benefit	No App	With App	Benefit
PTA (dB)	13.6 [5-19.3]	8.26 [2.5-13.7]	5.3	44.6 [21.8-79.4]	38.3 [15-71.2]	6,2
WRT - quiet (%)	100	97.7 [90-100]	-2.3	34.3 [0-100]	67.2 [0-100]	30,3
WRT + 10 dB SNR (%)	97.7 [90-100]	99.2 [90-100]	1.5	23.1 [0-100]	50.4 [0-100]	27,3
WRT + 5 dB SNR (%)	86.1 [60-100]	93.8 [80-100]	7.7	16 [0-100]	39 [0-100]	23

HL: hearing loss; PTA: pure tone average in FF; WRT: word recognition test; SNR: signal-to-noise ratio.

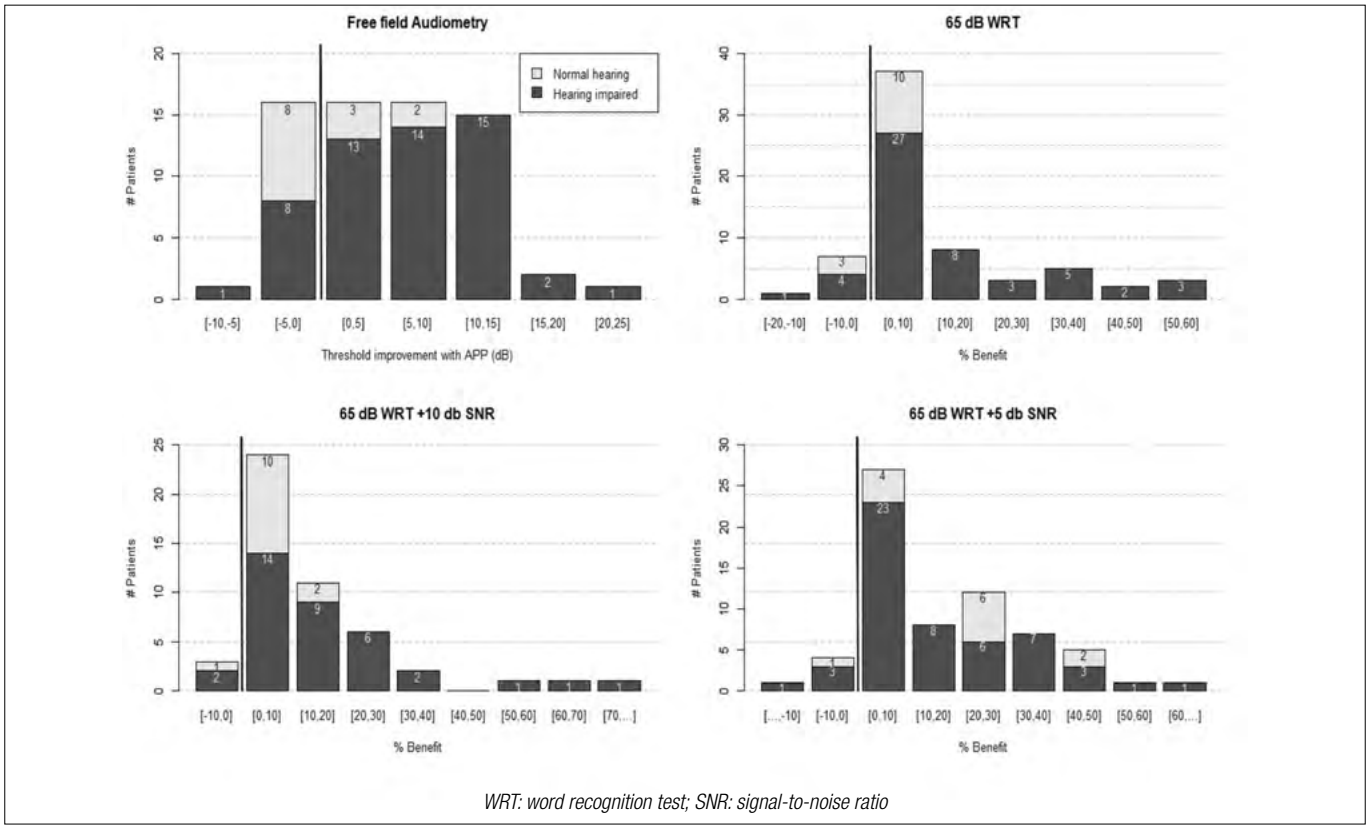

Figure 2. Distribution of benefit percentage when using the App for each hearing test. Subjects with HL are represented in dark grey, and normal-hearing subjects in light grey. Vertical lines split cases of no benefit from App use (left) from cases of better performance when using the App (right).

Table III. Odds ratio (OR) and p-value for each of variables analysed compared with the normal-hearing group for WRT.

	OR	P value
Normal hearing	1	-
Conductive HL	0.323	0.114
Sensory neural HL	0.129	0.1190
Mixed HL	0.026	0.0181
+ 5 dB SNR	0.065	< 0.0001
+ 10 dB SNR	0.227	< 0.0001
Binaural hearing loss	0.880	< 0.0001
Use of the App	1.812	0.0417

OR: odds ratio; HL: hearing loss; SNR: signal-to-noise ratio.

evidence. This study is the first to attempt to validate a Smartphone App as a hearing aid and objectively assess the benefits obtained in order to establish the target groups that could make use of this technology. Though the use of smartphone-connected hearing aid is increasing due to the wide possibility of customising hearing aid amplification in different situations [9,10], few studies consider its use specifically for hearing improvement. Moreover, these studies just consider the users' satisfaction without taking into account the auditory gain [11].

Herein, we observed a moderate improvement in tonal audiometry thresholds (average 6.2 dB) in the HL population. However, a remarkable gain in WRT was obtained both in silence and with competing noise at + 10 dB and + 5 dB SNR, showing a word recognition improvement of 30%, 24% and 20%, respectively. The results in normal-hearing subjects were lower, between 0.8% and 8.4% for WRT, which can be attributed in part to the ceiling effect of the test we used, since the near 100% basal levels in this population were difficult to improve on. The logistic regression statistical model convincingly demonstrates that use of the App improves word recognition (OR = 1.812, $p < 0.05$) regardless of its interaction with any other variable.

Testing different patients in different centres with different audiometers and test material could be considered a bias, but a negligible one due to the fact that each subject acts as their own control, as all comparisons are intra-subject.

In line with the predictions of the statistical model, and choosing > 10% improvement in WRT results as an arbitrary and acceptable benefit with the App, we observed that in silence, this benefit could be obtained in cases of BHI < 55% for conductive HL, and < 60% for sensorineural

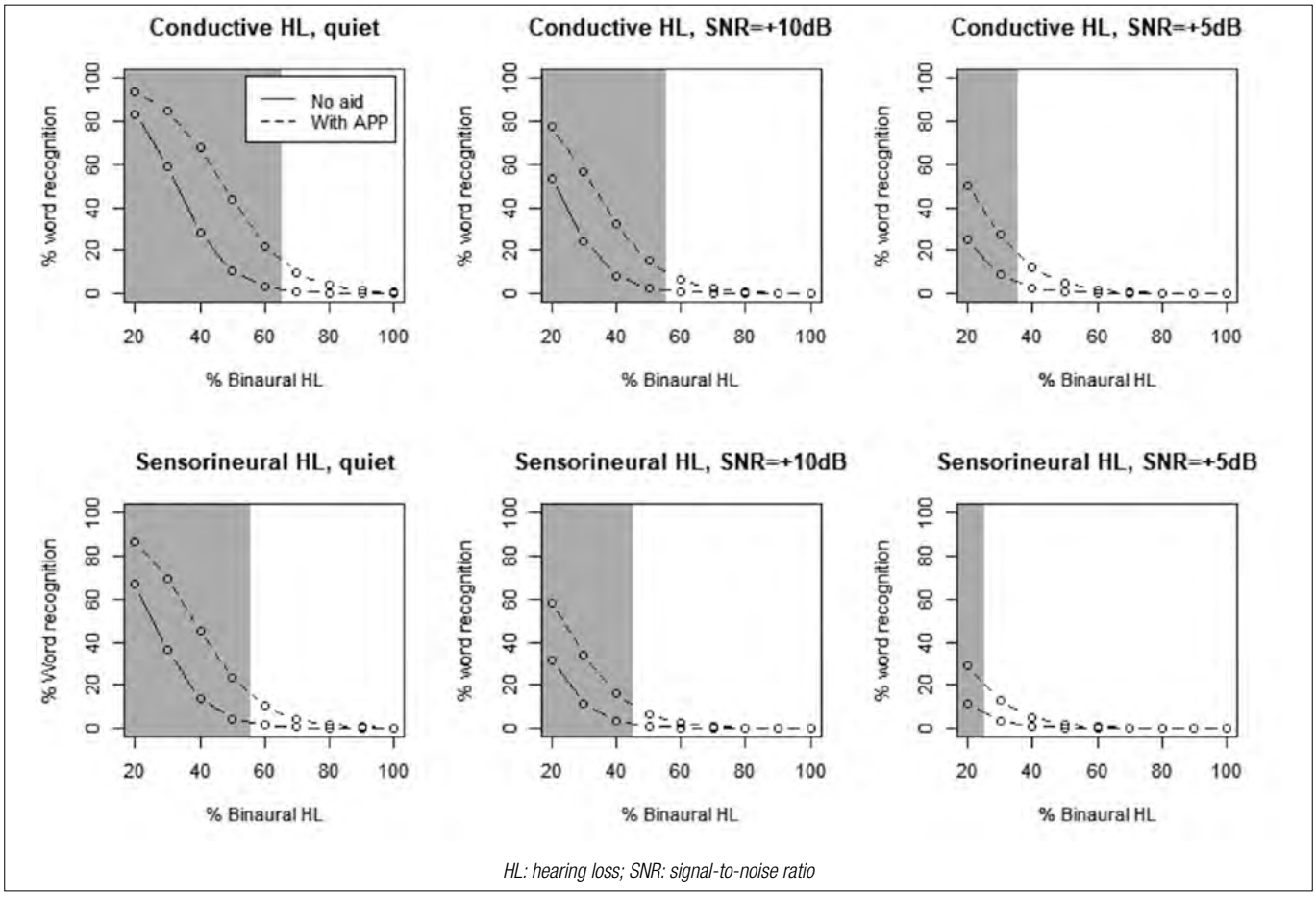

Figure 3. Prediction of verbal comprehension with no aid (solid lines), and using the App (dashed lines). The range of binaural loss with > 10% of improvement in WRT is shaded in grey.

HL, a potential limit for recommending the App to obtain improvement. Hearing under noise conditions are more challenging and the BHI to get > 10% in WRT improvement is logically lower.

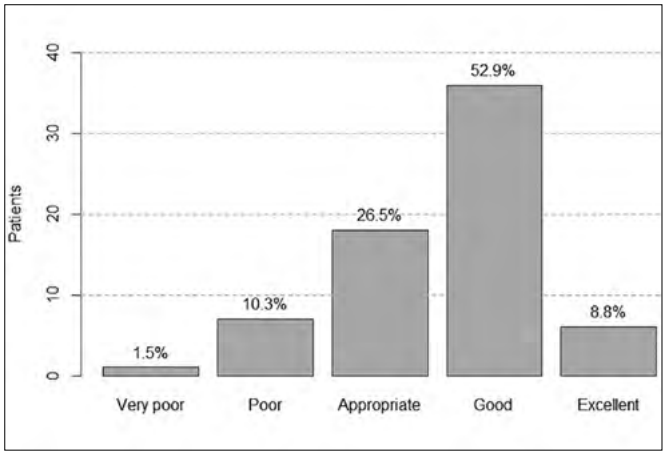

Figure 4. Self-assessment of hearing quality. Answers to the question "Rate hearing quality when using the App".

Admittedly, some participants obtained worse results with the use of the App, which should be taken into account, although they were not significantly worse (< 10% for WRT), which can be explained by the distortion effect that the device can have on natural sound, or by poor headset placement. However, participants gave very good evaluations in the questionnaire, expressing minimal perception of discomfort or annoying noises and a high level of overall satisfaction.

In light of our results, use of this App provides some benefit in most cases, especially under silence conditions, for patients suffering mild and medium hearing loss (audiometric thresholds < 60 dB). The benefit is lower with the presence of background noise and poorer audiometric values.

Beyond purely audiometric aspects, other factors, such as ergonomics or ease of use, are also of importance in mobile phone use for sound amplification. Although this study has not addressed these aspects, it seems obvious that conventional hearing aids are more user-friendly. Using

the App as a hearing aid means: 1) wearing the earphones continuously, although wireless models could be more wearable; 2) holding the smartphone rather than carrying it in the pocket, if the earphones do not include a built-in microphone; and 3) possibly preventing the simultaneous use of other tasks on the device. Issues in everyday use define the Smartphone + App set as a rather cumbersome hearing aid, implying that its use could be limited to specific situations such as meetings, conferences, watching TV, etc… rather than habitual use. Nonetheless, an additional advantage of the Smartphone + App set is the possibility of focusing the microphone and moving it closer to the sound source, thus improving the SNR when listening in noisy environments. Another advantage is the fact that mobile phones are widely distribuited, also in the elderly population, for whom several studies have found association between aided hearing outcomes and cognitive skills [12].

The present study breaks new ground in analysing the use of a smartphone App as a hearing aid, with demonstrated benefits. However, some limitations should be pointed out as proposals for future research. This research was carried out with a specific set of headphones, a single App (of the many available on the market) and one Smartphone device, to provide homogeneity to the sample. In addition, for this study we used only one amplification profile, which amplified all frequencies equally, while the app has the possibility to amplify the different frequencies according to the needs of the patient. However, more research is needed using other software and hardware combinations, which should be taken into account when interpreting our results. Additionally, future system testing should be extended beyond the audiometric booth to real-life situations. Another limitation of the study is that we did not measure the output of the device when using the App, so that the actual amplification could not be estimated. However, this evaluation was not part of our study because our goal was to assess the effectiveness of this product in order to offer advice to our patients.

Nevertheless, this first approach indicates a promising future for smartphones as a hearing aid in particular hearing impairments and circumstances.

Conclusions

In most cases, use of a smartphone hearing App provides better scores in both PTA and WRT. Greatest benefit is obtained by patients with BHI < 60%. App use in background noise situations improves performance, although the benefit is lesser. Subjective user satisfaction was good in booth conditions.

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Letter to the Editor

Depressed ventilatory drive for respiratory muscle weakness and chemo-responsiveness as a pathophysiological mechanism of CSA after surgery for obstructive sleep apnoea

Apnea notturna centrale da transitoria depressione ventilatoria polmonare e risposta chemo-recettoriale periferica causata da debolezza dei muscoli respiratori nei pazienti operati per l'apnea ostruttiva del sonno

Domenico Maurizio Toraldo[1], Michele Arigliani[2], Michele De Benedetto[3]

[1] Department of Rehabilitation "V. Fazzi" Hospital, Cardio-Respiratory Unit Care, ASL/Lecce, San Cesario di Lecce, Lecce, Italy; [2] ENT Unit, Vito Fazzi Hospital, ASL Lecce, Italy; [3] ENT Unit, Vito Fazzi Hospital, ASL Lecce, Italy

KEY WORDS: central sleep apnoea, complex sleep apnoea, loop gain

PAROLE CHIAVE: apnea notturna centrale, apnea notturna complessa, ciclo di guadagno

This Letter is in reply to the Case Series and Reports published in Acta Otorhinolaryngologica Italica 2018;38:476-479. Some reflections on the description of the clinical case presented in the paper entitled "Treatment-emergent central sleep apnoea after surgery for obstructive sleep apnoea" are reported by E. Testani, E. De Corso, A. Losurdo, A. Fiorita, C. Vollono, G. Della Marca, E. Scarano. The description offers some insights into the pathophysiological aspects of OSA (Obstructive Sleep Apnoea) patients during the post-surgical phase: the Loop gain mechanism and the interpretation of complex apneoas in the post-surgery phase and the relative hypotheses of possible therapeutic solutions.

Dear Editor,

In order to avoid any possible misunderstandings, we would first like to point out that the case of CSA (Central Sleep Apnoea), resulting from the OSA surgery described, cannot be considered a complication of OSA surgery and may occur as a temporary resetting of the respiratory system. CSA can also occur in 5% of patients affected by OSA during CPAP treatment: this phenomenon is called *complex sleep apnoea* and occurs when the air flow generated by the CPAP device restores patency of the pharyngeal airways [1]. CSA is defined by the absence of air flow accompanied by cessation of ventilation during sleep. In most forms, CSA manifests cyclically and alternately. It can have cyclic and/or periodic forms characterised by a regular oscillating ventilatory movement: a phase of respiratory hypoventilation, characterised by breathing cessation, is followed in turn, as compensation, by a hyperventilation phase or apnoea phenomena. It can also have other more irregular forms [2]. CSA is of clinical interest because it causes arterial desaturation of oxygen and hypoxaemia, hypercapnia, post-apneic arousal, nocturnal hyperventilation, compensatory responses and increase of negative intrathoracic pressure, feeling of dyspnoea, fluctuations in blood pressure and consequent sympathetic stimulation [3]. CSA can lead to cardiac arrhythmia, reduced cardiac function and is strongly associated with mortality from sudden cardiac events [4].

The Loop gain, one of the pathophysiological phenomena which may explain the

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Correspondence
Domenico Maurizio Toraldo
via A.C. Casetti 2, 73100 Lecce, Italy
E-mail: d.torald@tin.it

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OSA, expresses an alteration/exaggeration of the compensatory response to nocturnal hypoventilation. The nocturnal ventilatory disorder, which generates the Loop gain, is achieved through compensatory tachypnoea that reduces the expiratory minute ventilation (alveolar hypoventilation), which, in turn, produces a reduction of $PACO_2$ (alveolar).The magnitude of changes in alveolar $PACO_2$ depends on the responsiveness of the PLANT (the integrated system of lungs, blood and body tissues where CO_2 is stored). In addition, changes in the alveolar $PACO_2$ also induce a variation in the sensitivity of the central respiratory drive (ventilatory controller system).The Loop gain expresses the extent of the corrective response in logarithmic terms: the corrective ventilatory disorder will be amplified according to the logarithmic scale and will cause disproportionately large fluctuations.

A large mutability of the ventilatory/receptor response system indicates an unstable system leading to pathological oscillations [5].

The cyclic Loop gain model, detectable through polygraphic recording performed during HSAT (Home Sleep Apnoea Testing), represents an exclusion criteria for surgical treatment. A high Loop gain indicates an unstable ventilatory system. The mechanisms of the CSA are not known, but various theories have been proposed, such as temporary absence of respiratory effort, and can be seen in a variety of forms in different pathophysiological situations. The reduction of respiratory effort is a consequence of the hypersensitivity of ventilatory responses to changes in the partial $PaCO_2/PaO_2$ pressures detected by carotid peripheral chemoreceptors, i.e. high gain or low gain (overshoot/undershoot). CSA treatment can be explained in terms of positive effects on the Loop gain phenomenon [6]. The following interventions on the CSA are considered therapeutic regarding respiratory mechanisms and ventilatory control: a) treatment with CPAP/Bi-Level or Auto Bi-level improves lung volumes (with consequent hypoventilation improvement) and reduces partial pressure of $PaCO_2$ in peripheral blood (reduction of the ventilatory gain); b) additional therapeutic oxygen therapy has a profound positive impact on CSA, particularly in obese children with respiratory failure and with sleep apnoea, and improves CSA in some patients with heart failure. The increased partial pressure PaO_2 reduces chemosensitivity of the peripheral vascular carotid body. Oxygen therapy is expected to increase the gain of the ventilatory response with a consequent decrease in the need for peripheric hypoxaemia compensation; c) respiratory stimulant drugs (e.g. carbon dioxide, rebreathing, acetazolamide and theophylline) work to increase the reduction of the partial pressure of $PaCO_2$, making alveolar $PaCO_2$ less sensitive to changes in ventilation. This drive effect causes a reduction in the difference between alveolar and inspired $PaCO_2$; d) the position of the body during sleep can have a therapeutic impact on CSA. Sleeping sideways or with an overhead lift can improve CSA and can partially lead to a lung volume increase [7]. What happens in post-surgical in OSA patients is a different mechanism than the one previously described. In these patients, central apnoea may be the consequence of a depressive/absent ventilatory effort, with very low Loop gain. In the operated pharyngeal site, the increase in compensatory muscle ventilatory response may be inefficient and produce a low air flow due to poor muscle tone of the airways with increased partial pressure of $PaCO_2$ mmHg in peripheral blood [8]. This underlines the importance of having an intact or well-functioning carotid chemoreflex control system to obtain a compensatory corrective response [9]. In patients with transient neuromuscular weakness, as may occur in the first post-surgical phase of OSA, central apnoea may be recorded particularly during REM sleep due to a combination of low peripheral chemosensitivity to hypoxaemia, atony or muscle respiratory inefficiency. The absence of effort during these events determines the central apnoea which have been defined "*diaphragmatic*" to underline the primary role of respiratory muscle weakness in the post-operative phase [10].

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Letter to the Editor

Late relapse in the neck: considerations from a case of seminoma and review of the literature

Recidiva linfonodale cervicale tardiva: spunti di riflessione da un caso di seminoma e revisione della letteratura

Virginia Corazzi[1], Remo Accorona[2], Rosa Negro[3], Luca Calabrese[4]

[1] ENT Department, University Hospital of Ferrara, Ferrara, Italy; [2] Department of Otorhinolaryngology - Head and Neck Surgery, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy; [3] Department of Pathology, "San Maurizio" Hospital, Bolzano, Italy; [4] Division of Otorhinolaryngology, "San Maurizio" Hospital, Bolzano, Italy

KEY WORDS: seminoma, testicular neoplasm, lymphatic metastasis, cancer of unknown primary, neck dissection

PAROLE CHIAVE: *seminoma, neoplasia testicolare, metastasi linfatica, carcinoma a primitività ignota, svuotamento laterocervicale*

Dear Editor,

Differential diagnosis of neck lumps is a routine issue in daily ENT practice. However, in case of adenopathy from cancer of unknown primary it may be very challenging, and integration between medical history and clinical, radiological, and cytological findings becomes fundamental.

We present a case of a very late recurrence of a seminoma in cervical nodes, occurring more than 20 years after the primary treatment, together with a review of the scientific literature.

A 59-year-old man presented to our attention with left indolent neck swelling, which had increased progressively over 6 months. It was a huge mass at level VB, fixed to underlying tissues, with intact overlying skin. In the patient's clinical history, a left testicular seminoma treated with surgery and adjuvant chemotherapy 20 years earlier was reported. No lesions of the upper aerodigestive tract (UADT) were found after pan-endoscopic examination in white light and narrow band imaging.

Neck ultrasound (US) and contrast-enhanced neck-chest computed tomography (CT) showed a 5 cm left colliquated adenopathy in level VB, and other adenopathies in left level III and VA (Fig. 1A), without radiological signs of extracapsular nodal extension.

Total-body fluorodeoxyglucose positron emission tomography (PET) highlighted the presence of the multiple hypermetabolic adenopathies, from level II to V without other findings.

Fine needle aspiration cytology (FNAC) of the largest adenopathy showed necrotic material mixed with poorly differentiated large-sized cells, positive for cytokeratin (CK) CAM 5.2 and CK7, and negative for CK20, TTF1, p40, SOX10, p16 and EBV, which was therefore consistent with neck metastasis from a poorly differentiated carcinoma.

The tumour was staged as cTxN2bM0 (according to TNM staging system 8th edition), and consequently, under general anaesthesia, pan-endoscopy of the UADT (resulted macroscopically negative for disease) and left level II to V dissection were performed.

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Correspondence
Virginia Corazzi
ENT Department, University Hospital of Ferrara,
via Aldo Moro 8, 44124 Ferrara (Cona), Italy
Tel. +39 0532 236317
E-mail: virginia.corazzi@unife.it

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Definitive histologic features showed epithelioid round cells with round ovular nuclei and scarce cytoplasm, and necrotic material interposed (Fig. 1B). The neoplasia showed intense nuclear positivity for the SALL-4 gene (Fig. 1C), nuclear and cytoplasmic positivity for OCT-3/4 (Fig. 1D), both markers for germ cells tumours; it was therefore consistent with metastasis from seminoma in 6 of 24 excised nodes.

The patient underwent to adjuvant second-line cisplatin-based chemotherapy. Follow-up at 6 months showed no evidence of disease.

The patient agreed to the publication of clinical data.

In differential diagnosis of neck masses in adults, malignant tumours represent the most common cause, and neck involvement may frequently be the initial or unique clinical manifestation. Work up includes patient's oncologic history, clinical and endoscopic head and neck (H&N) examination, UADT, US with FNAC, contrast enhanced CT and/or magnetic resonance imaging (MRI), and PET.

CUP cervical node metastases account for almost 3% of all H&N malignancies [1]. About 65-70% of cases are due to squamous cell carcinoma (SCC) metastases from the H&N district, especially when level II and, less frequently, I and III are involved. Tonsil and tongue base HPV-related SCC are reported to be the most common primaries responsible for CUP neck metastases [2]. Papillary thyroid carcinoma should also be considered, since it may present level II to IV metastases as primary and/or unique clinical manifestations [1].

CUP metastases in the low cervical nodes are rarer, and, among H&N subsites, commonly derived from nasopharyngeal and skin cancers, particularly when level V is involved [1].

Besides H&N cancers, levels IV and V are occasionally affected by metastases from tumours originating below the clavicle, such as breast, lung, gastrointestinal tract, kidney and genitourinary tract cancers [1,3].

Remote primary tumours are responsible for about 1% of all cervical node metastases. Breast cancer is the most frequent distant primary, even if only 2.3-4.3% of cases metastasise to the neck [4]. Trans-pectoral, internal mammary, and axillary routes are described as principal lymphatic drainage pathways from breast to low cervical nodes [5]. Among lung cancers, large cell carcinomas and adenocarcinomas are reported to be the most affecting cervical nodes, with lymphatic metastases that can reach the neck along the mediastinal chains.

Oesophageal carcinomas, both SCC and adenocarcinoma, and gastric cancers, predominantly adenocarcinomas, may metastasise to the neck, with predilection for left levels IV and V. The submucosal lymphatic plexus of the oesophagus

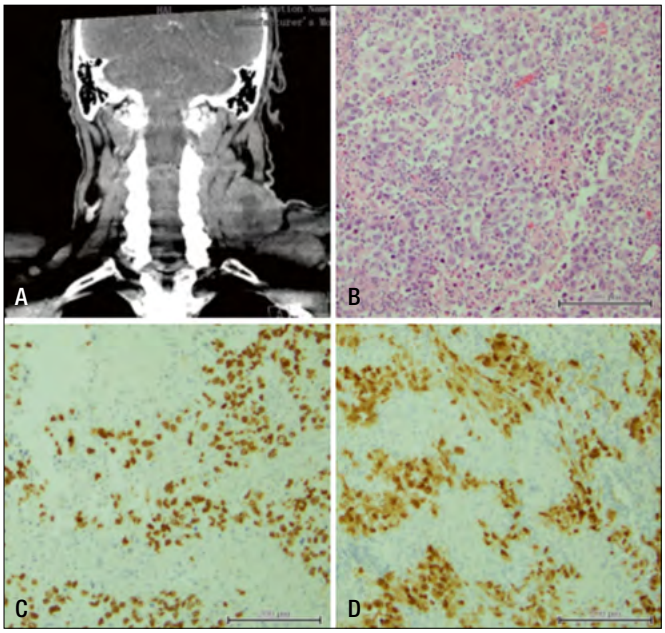

Figure 1. (**A**) Coronal contrast enhanced CT showing a colliquated adenopathy in the left level VB; (**B**) definitive histologic features showing epithelioid round cells with round ovular nuclei and scarce cytoplasm, and necrotic material interposed; (**C**) intense nuclear immunohistochemical expression of SALL-4; (**D**) immunohistochemical staining of nuclear and cytoplasmic OCT-3/4.

seems to be linked to the thoracic duct; indeed, up to 20-30% of oesophageal carcinomas show neck metastases. The lymphatic pathway from the stomach passes through hepatic and splenic chains, celiac plexus, and porta hepatis up to the thoracic duct, with a tendency to involve the left supraclavicular area. This peculiar adenopathy is known as Virchow's node [4]. Moreover, supraclavicular metastases have been reported only rarely in hepatocellular cancer and, anecdotally, in gastrinomas [4].

From the genitourinary tract, renal cancer is the third distant primary tumour responsible for neck metastases in frequency; cervical involvement may occur in 8% of patients at initial presentation or many years after primary treatment. The haematogenous pathway through Batson's venous plexus directed to neck nodes, without lung involvement, is reported to be more common compared to lymphatic spread [4].

With low and uneven frequency, neck metastases from uterine, ovarian, prostate and testicular cancers have been reported. Ovarian cancers may determine cervical metastases at initial presentation and during recurrence, but generally after long time, with up to 20 years reported. In males, supraclavicular metastases may occur during progression of a prostate and testicular cancer, or as the first presentation of disease mainly in younger patients [4].

With regards to our case, seminoma is a malignant germ cells tumour that accounts for about 60% of germ cells tumours

of the testicle and for 30% of all testicular tumours [6]. Involvement of mediastinal and/or supraclavicular nodes is a manifestation of advanced systemic disease; lymphatic spread follows the abdominal retroperitoneal chains above the diaphragm along the thoracic duct, up to the left supraclavicular and scalene nodes [7].

Late relapses of seminoma have been described as recurrences more than 2 years after complete response to initial therapy, in the absence of a contralateral tumour [8]. Sharp reported 75 patients who were affected by late relapse of testicular germ cell tumours, mostly in the retroperitoneum; only 9 presented relapse at more than 15 years after initial treatment, and only 5 cases in the entire sample were seminoma, showing the low prevalence of the disease [8]. To the best of our knowledge, late relapse of seminoma to cervical nodes after more than 20 years from the primary treatment is a unique finding in the literature.

FNAC represents the foremost exam for a cervical mass, and immunochemistry helps to confirm clinical suspicion [9], even if correct diagnostic definition of a cervical cystic mass may be hampered by the high rate of false negatives with FNAC. Distinguishing a cystic metastasis from branchial cyst or infectious disease (such as tuberculosis or abscess) may not be easy. Differential diagnosis of neck masses should always consider inflammatory, infectious and congenital disorders. Additional tests such as complete blood count, autoantibodies, thyroid and parathyroid function tests, Mantoux test and Bartonella titre may also be useful [10].

In conclusion, late neck lymph node metastasis is a rare occurrence in the natural history of distant cancers. The work up of cancer of unknown primary remains challenging; nonetheless, in case of positive clinical data, cancers of remote sites should always be considered in the differential diagnosis of low neck adenopathies with unknown primary, even many years after the primary treatment.

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Author Correction

In the version of this article originally published in **ACTA OTORHINOLARYNGOLOGICA ITALICA 2020;40:204-210; https://doi.org/10.14639/0392-100X-N0477,** there was an error in the given name of the author Mandiello.

Errata

Laryngology

Upper dysphagia in patients affected by systemic sclerosis: prevalence and features

La disfagia orale e faringea in pazienti affetti da sclerosi sistemica: prevalenza e caratteristiche

Jacopo Galli[1], Maria Raffaella Marchese[2], Claudia De Canio[3], Mariachiara Mandiello[3], Giuseppe Michele Mangone[3], Angela Anna Padula[4], Giuseppina Abignano[4], Lorenzo Santandrea[3], Gaetano Paludetti[1]

[1] Department of Aging, Neuroscience, Orthopedics and Head and Neck Sciences, UOC of Otorhinolaryngology, Istituto di Otorinolaringoiatria "Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore", Roma, Italy; [2] Department of Aging, Neuroscience, Orthopedics and Head and Neck Sciences, UOC of Otorhinolaryngology, "Fondazione Policlinico Universitario A. Gemelli IRCCS", Roma, Italy; [3] ENT Department, San Carlo Hospital, Potenza, Italy; [4] Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy

Corrige

Laryngology

Upper dysphagia in patients affected by systemic sclerosis: prevalence and features

La disfagia orale e faringea in pazienti affetti da sclerosi sistemica: prevalenza e caratteristiche

Jacopo Galli[1], Maria Raffaella Marchese[2], Claudia De Canio[3], Marzia Mandiello[3], Giuseppe Michele Mangone[3], Angela Anna Padula[4], Giuseppina Abignano[4], Lorenzo Santandrea[3], Gaetano Paludetti[1]

[1] Department of Aging, Neuroscience, Orthopedics and Head and Neck Sciences, UOC of Otorhinolaryngology, Istituto di Otorinolaringoiatria "Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore", Roma, Italy; [2] Department of Aging, Neuroscience, Orthopedics and Head and Neck Sciences, UOC of Otorhinolaryngology, "Fondazione Policlinico Universitario A. Gemelli IRCCS", Roma, Italy; [3] ENT Department, San Carlo Hospital, Potenza, Italy; [4] Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy