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Information for authors including editorial standards for the preparation of manuscripts available on-line: www.actaitalica.it

Editorial

Editoriale

Acta Otorhinolaryngol Ital 2017;37:173-174

Dear colleagues,

First of all, I would like to express my deepest gratitude to the Italian Society of Otorhinolaryngology which gave me the honour to be the Editor-in-Chief of its official journal, *Acta Otorhinolaryngologica Italica*, for the last 6 years. To be honest, it was a priceless privilege and an exciting experience because in these years the journal has evolved to become an indexed, frequently-cited journal with quite outstanding impact factor. I hope we have succeeded in preserving all the different aims of our diverse specialties and in publishing manuscripts dealing with all the various subareas of ENT.

For many years, this journal has been a vehicle for the delivery of timely and thoughtful information without any cost for authors, while guaranteeing open access to their manuscripts, leading to a free and maximal diffusion of its contents. We have to thank all the editorial staff who offered their service without any compensation and once again the Italian ENT society which sustained the costs of the journal in recent years, despite the economic difficulties that every member is familiar with.

Thanks to the great effort of authors, reviewers and my co-workers, in 2015 we reached the highest impact factor (1.640) in the journal's history, corresponding to a Journal Ranking of Q2 for ISI Web of Science and Q1 for Scimago. In particular, I would also like to thank our reviewers for their service to the journal and for providing the support and feedback necessary to find, develop and publish high-quality material. I think they deserve special acknowledgment because the number of manuscripts submitted was increased significantly: in 2016, we received 433 manuscripts and published 88, corresponding to a rejection rate of 75%. For this reason, the number of accepted and published manuscripts is now higher compared with past years.

In the last years, we have made some significant editorial/organisational changes together with our publisher (Pacini Editore) who we deeply thank for sustaining us in every step of our technological improvements. Our aim, in fact, was to follow the process that had already begun with previous editors in taking the journal from its infancy to maturity. In 2011, we have refined our Author Guidelines to meet the standards set out by the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (*http://www.icmje.org*), and we also provided a template for authors to give them detailed information to make our publications as uniform as possible (please visit the journal's guide for authors *www.actaitalica/journal*). Since the beginning of our experience, we strongly encouraged special guests to submit well prepared review articles in all areas of clinical otorhinolaryngology and head and neck surgery, and giving them high priority in publication and which were frequently cited in the last 5 years. In 2013, we introduced our "Editorial Manager" which has helped us to manage the increasing number of submitted manuscripts and to assist communication with authors, reviewers and the publisher. We observed a very rapid uptake by authors to our web platform; in fact, after 18 months at least 700 authors have registered. In 2014, we introduced for the first time a digital object identifier (DOI) number for each manuscript submitted. The DOI is a unique alphanumeric string assigned by a registration agency (the International DOI Foundation) to identify content and provide a persistent link to its location on the Internet. The publisher assigns a DOI when the article is published and made available electronically. In 2016, according to the request of the executive board of the Italian Society of Otorhinolaryngology, we gave our support to modify the actual official report of the annual meeting of the society that has now become a supplement of the journal and published annually. In the last years, we also modified our editing system by trying to drive it towards the possibility to put our accepted manuscripts as soon as possible in an e-pub format. Accepted manuscripts can be now downloaded early from PubMed with an important advantage in term of rates of citation.

Now that we've begun to change, we will also hope that authors, reviewers and readers will continue to follow our journal and to sustain the new editorial office and the new Editor-in-Chief in their difficult job to manage such a large volume of manuscripts. We also suggest all authors who are publishing in biomedical journals to remember to cite our high-quality manuscripts in all fields of otorhinolaryngology.

I truthfully hope that both scientists and physicians working in the field of ENT and Head and Neck surgery will continue to follow our journal, and that you will enjoy and benefit from reading the publication at least as much I have in the past. At the same time, my best wishes to the incoming Editor-in-Chief and to the editorial staff as I am convinced that they will further increase the quality of the journal and its dissemination on an international level.

Sincerely,

Prof. Gaetano Paludetti
Editor-in-Chief - Acta Otorhinolaryngologica Italica

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Review

Adaptive psychological structure in childhood hearing impairment: audiological correlations

Struttura psicologica adattiva nel deficit uditivo infantile: correlazioni audiologiche

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SUMMARY

The present research deals with the clinical and social problems present during linguistic and cognitive development of deaf children. Currently, the development of Theory of Mind represents an important research field in deafness studies. These international studies highlighted a significant alteration in the development of Theory of Mind in deaf children compared to normal hearing children, especially in cases of congenital or preverbal hearing loss. In particular, the research focuses on the skills of deaf children in recognising emotions and desires, through both perceptive and cognitive methods, by evaluation of psycho-cognitive skills of children with severe hearing loss using a set of questions to be administered to hearing loss patients. The experiment was performed on a group composed of 10 children (5 males and 5 females) aged 4 to 9 years and 54 to 108 months, affected by bilateral congenital hearing loss (severe to total), or hearing loss that developed in preverbal children the year before entering elementary school, or during the fourth year of elementary school. The selection criteria were based on: audiologic evaluation, neuro-psychological tests administered to assess general, cognitive as well as praxis and perceptive abilities, and clinical observations performed to assess psychopathology using tests that assess development of both visual perceptive (Coloured Progressive Matrices) and graphic representational abilities (Test of Human Figure Drawings and the Family Drawing Test). The instrument "cognitive" was the "Deaf Children Series", arranged by us, that consists of a mental status examination (MSE) that evaluates: level of cognitive (knowledge-related) ability, emotional mood, and speech and thought patterns at the time of evaluation. Deaf children show a reduced responsiveness to the expressions of sadness on the perceptive side. Through the test, we observed a psychodynamic defense mechanism considering perceptive understanding performance. On the contrary, in normal hearing children, the emotion 'fear' is the most difficult to identify. Deaf children seem to be more susceptible to recognition of visual emotions. Furthermore, deaf children present significant problem-solving skills and emotional recognition skills, possibly as a result of their hearing impairment.

KEY WORDS: Infant hearing loss • Hearing impairment • Cognitive-relational development • Theory of mind • Emotional recognition

RIASSUNTO

La presente ricerca affronta i problemi clinici e sociali che riguardano lo sviluppo linguistico e cognitivo nei bambini sordi. Attualmente, lo sviluppo della "Teoria della mente" rappresenta un importante campo di ricerca nello studio della sordità. Questi studi internazionali hanno evidenziato nei bambini sordi una significativa alterazione nello sviluppo della "Teoria della Mente", soprattutto in caso di perdita congenita o preverbale dell'udito. In particolare, la ricerca si concentra sulle competenze dei bambini sordi nel riconoscere emozioni e desideri, attraverso metodi sia cognitivi che percettivi, per la valutazione delle capacità psico-cognitiva attraverso una serie di domande composte da alcuni test adeguati, da somministrare ai pazienti con perdita uditiva. L'esperimento è stato condotto su un gruppo composto da 10 bambini (5 maschi e 5 femmine), di età compresa tra 4 e 9 anni e tra 54 e 108 mesi), affetti da perdita uditiva congenita bilaterale (da grave a cofosi), o da perdita uditiva preverbale sviluppata sia in bambini che attendono l'ultimo anno prima di frequentare la scuola elementare, sia in quelli che frequentano il quarto anno di scuola elementare. I criteri di selezione sono stati basati su: valutazione audiologica, somministrazione di test neuropsicologici al fine di valutare, in generale, le capacità cognitive e percettive e osservazioni cliniche effettuate, al fine di valutare la psicopatologia del campione, attraverso dei test che valutano più facilmente lo sviluppo sia della percettività visiva (Coloured Progressive Matrices), sia della rappresentazione grafica (Test di disegno sulla figura umana e il Test di disegno sulla famiglia). Lo strumento di misurazione "cognitiva" è stato il "Deaf Children Series", test strutturato da noi, che consiste in un esame dello stato mentale (MSE), capace di valutare: il livello di capacità cognitiva (conoscenza-correlato), l'umore e modelli di discorso e di pensiero di un paziente al momento della valutazione. I bambini sordi mostrano sul lato percettivo una sensibilità ridotta alle espressioni di tristezza. Nel test possiamo osservare un meccanismo di difesa psicodinamico per quanto riguarda la prestazione percettiva. Al contrario, per quanto riguarda i bambini normoudenti, la paura è l'emozione più difficile da identificare. I bambini sordi sembrano essere maggiormente predisposti al riconoscimento di emozioni visive. Inoltre, i bambini sordi presentano notevoli capacità di "problem solving", capacità di riconoscimento emotivo, probabilmente a causa del loro problema.

PAROLE CHIAVE: *Ipoacusia infantile • Disabilità uditiva • Sviluppo cognitivo-relazionale • Teoria della mente • Riconoscimento delle emozioni*

Introduction

The clinical relevance of the different types of hearing loss in childhood depends on the its impact on psychological and audio communicative aspects of children.
As far as the psychological area is concerned, it is important to understand the different clinical consequences caused by hearing loss affecting children, such as concerns with affection and intelligence, as well as memory and social attitude.
These consequences, which seem not to be related to deafness but to a lack of a good communicative context, can involve serious psychopathological consequences.
The most common developmental problems linked to deafness are:

- attention deficit;
- hyperactivity disorder;
- abnormal behaviour;
- mood disorder.

For this reason, language development skills in deaf children, represents a sub-factor of communicative competence, that should be assessed according to the classification of different types of hearing loss, as well as the specific characteristics of people affected by hearing loss.
In particular, disease evaluation depends on several aspects:

- age;
- severity;
- syndromicity;
- therapy;
- rehabilitation method;
- communication characteristics of parents;
- psychiatric comorbidity;
- association with neuropsychological deficits;
- level of education obtained.

International studies recently conducted on Theory of Mind (ToM) in deaf children, showed a remarkable alteration in the development of mentalisation, empathetic and representational skills [1], compared to normal hearing children, especially in cases of congenital or preverbal hearing loss. The ToM approach specifically deals with the study of specific socio-communicative strategies used for acquiring mentalisation skills, providing the child with pragmatic skills for easing the orientation within the context of daily life.
Identification of sub-factor pragmatic skills, which is a component of the key factor linguistic communicative skills, is the key variable of linguistic development in children. The study focused on the child and the conditions leading to the awareness of the ways of thinking of others. ToM was defined, as a communicative, affective and cognitive special skill, to be understood as a pragmatic ability to recognise the existence of mental representations, both in ourselves and others, not necessarily coinciding with the real world events [2-5].
Actually, the study on ToM overlaps with mirror neurons theory research [6]. The research program investigating "mirror neurons" demonstrated the presence of an observation-execution matching system in humans. Studies carried out on the development of ToM in deaf children investigated the most crucial features of this phenomenon, such as deafness severity and age at onset of symptoms. The discriminant variable concerning the age at onset of symptoms is represented by the fundamental difference between prelinguistic and postlinguistic deafness. Another important feature consists of the family context of deaf children, such as family size, order of geniture and the language spoken at home.
For this reason, the presence of deaf or hearing loss parents and their speech or gestures, as well as the sign language, or the oral language, constitutes an important variable that is necessarily linked to therapeutic and educational approaches.
The variables regarding the educational approach are the following: deaf education [7-9], oral education [6 10 11] and, finally, the investigation including the two previous studies on total communication education [12-15].
The variables regarding the therapeutic approach comprise auxiliary audio enhancement devices versus the impossibility of using hearing aids.
Recently, a better definition of this factor has been provided after comparing children wearing conventional hearing aids with children who received a cochlear implant with an interior ear module [15 16].
Considering the last factors, we can easily make a distinction amongst the samples generated by different investigations, such as native signers, those who learned sign language at an early age as a first language [17]; late signers, those who lost their hearing after childhood and have to learn the sign language as a second language [12-15 16]; and oral deaf, those who are able to communicate orally, learning with or without a prosthetic aid, in most cases, with hearing parents [10-11 18].
The goal of this study is to increase the clinical and social awareness of cognitive and linguistic development of individuals with hearing loss. The study focuses on the perceptive and cognitive ability developed by deaf children in order to identify emotions (happiness, sadness, rage, fear) and desires (fulfilled and failed).

Materials and methods

The experiment was performed on a group composed by 10 children. The group was matched for gender (5 males and 5 females), and age (54 to 108 months), affected by bilateral congenital hearing loss (severe to total), or hearing loss that developed in preverbal children the year before entering elementary school, or during the fourth year of elementary school. The selection criteria of 10 subjects were based on:

- audiologic evaluation;
- neuro-psychological tests administered to assess general cognitive as well as praxis and perceptive abilities;

- oral exams and clinical observations to assess psychopathology.

The set of questions was composed of suitable tests to be administered to hearing loss patients.

The tests facilitate assessment of development of both visual perceptive and graphic representational abilities:

- Coloured Progressive Matrices 19, for visual perceptive abilities;
- the test of Human Figure Drawings 20, and the Family Drawing Test 21, for graphic and representational abilities.

The average age was 75.33 months (73.00 in girls and 76.66 in boys).

Over the course of a year, all patients were given the same set of tests in the presence of a parent silently sitting behind him/her. If required, a sign language interpreter could translate for the patient. Children's answers can be easily translated into words, signs, or gestures.

The findings of the experimental group were compared to those obtained from a normal hearing control group, composed of 30 healthy subjects investigated to implement the "Deaf Children Series". The control group sample was selected from 6 elementary school classes attending the first or second year in a public school.

Subjects were selected by their teachers according to the following criteria: 5 children without disabilities or behavioural problems, but not excellent in a particular subject, always matched for gender (2-3) and age (54-74 months). Five subjects were selected from each class, so the result was a group composed of 16 females and 14 males, aged between 54 and 74 months. The average age was 64.83 months (65.38 for girls and 64.21 for boys). Each individual was given the same set of tests over the space of a month.

The Deaf Children Series was implemented on the basis of two steps:

- processing answers;
- measuring the correlation between the age and mistakes, for each level of answer.

In order to avoid misinterpretation of findings, four children were not considered, since they failed the test investigating the cognitive capacity of attributing mental states. Thus, the statistical sample is composed of 26 subjects: 13 average underage subjects (64.8 months) and 13 average overage subjects.

The measurement instrument is the "Deaf Children Series", which is a test implemented by us. It consists of a mental status examination (MSE) which assesses the level of cognitive (knowledge-related) ability, appearance, emotional mood, and speech and thought patterns at the time of evaluation in the curriculum for educating individuals on ToM [22]. The Deaf Children Series is composed of 10 tables, and its structure is based on 4 development levels of capabilities to recognise desires and emotions (Table I).

Table I. Characteristics of tables.

Level 1 1 table	Understanding photos and facial expressions	Perceptive understanding
Level 2 1 table	Drawing and facial expression understanding	
Level 3 4 tables	Understanding emotions (situations-based)	Cognitive understanding
Level 4 4 tables	Understanding emotions (desires-based)	

Results

As far as deaf children are concerned, the average score in the total sample was 36.00/48.00 (SD: 4.76); in hearing children, the values were 39.97/48.00 (SD: 4.78) (Table II).

As far as cognitive recognition of desire and emotion are concerned, the total score in deaf children (level 3 + level 4) was 28.25/36 (SD: 2.87).

In hearing children, the average score in the total sample was 30.93/36.00 (SD: 3.60); in deaf children, for questions (E) (perceptive and cognitive understanding of emotions) the total score was 25.00/36.00 (SD: 4.32), while in hearing children the score was 28.23/36.00 (SD: 4.46).

In deaf children, for questions (D), the total score was 11.00/12.00 (SD: 115), while in earing children the score was 11.73/12.00 (SD: 0.82).

For the first level, in deaf children, the total score was 3.50/4.00 (SD: 0.58), while in hearing children it was 2.83/4.00 (SD: 1.26) (Table III).

Table II. Average score of the responses in the different levels.

Answers	Maximum score	Deaf children	Hearing children
Level 1	4	3.50	2.83
Level 2	8	4.25	6.20
Level 3	12	9.50	9.67
Level 4	24	18.75	21.27
Levels 1+2	12	7.75	9.03
Levels 3+4	36	28.25	30.93
Question E	36	25.00	28.23
Question E (level 4)	12	7.75	9,53
Question D	12	11.00	11.73
Total	**48**	**36.00**	**39.97**

Table III. Average score of the responses to different emotional states at level 1.

Answers level 1	Maximum score	Deaf children	Hearing children
Happiness	1	1.00	0.83
Sadness	1	0.50	0.73
Rage	1	1.00	0.70
Fear	1	1.00	0.57
Total	**4**	**3.50**	**2.83**

Table IV. Average score of the responses to different emotional states at level 2.

Answers level 2	Maximum score	Deaf children	Hearing children
Happiness	2	1.75	1.87
Sadness	2	0.25	1.23
Rage	2	1.75	1.83
Fear	2	0.50	1.27
Total	**8**	**4.25**	**6.20**

Table V. Average score of the responses to different emotional states at level 3.

Answers level 3	Maximum score	Deaf children	Hearing children
Happiness	3	3.00	2.70
Sadness	3	1.50	2.37
Rage	3	2.75	1.73
Fear	3	2.25	2.87
Total	**12**	**9.50**	**9.67**

For the second level, in deaf children the total score was 4.25/8.00 (SD: 1.71), while hearing children it was 6.20/8.00 (SD: 1.99) (Table IV).
For the third level, in deaf children the total score was 9.50/12.00 (SD: 1.73), while in normal hearing children it was 9.67/12.00 (SD: 1.89) (Table V).
In the fourth level, in deaf children the total score was 18.75/24.00 (SD: 2.50), while in normal hearing children it was 21.27/24.00 (SD: 2.91)
Since there was a substantial average age difference between the two groups, there was a significant decrease in the average score in deaf children for levels 2 and 4.
On the contrary, for level 1 is concerned, deaf children performed better than hearing children.
Deaf children show a reduced responsiveness to the expressions of sadness on the perceptive side. With regards to this specific age range, in the test a psychodynamic defense mechanism regarding perceptive understanding performance was observed. On the contrary, in hearing children, fear was the most difficult emotion to identify (see level 1+2). With regards to level 2, for both samples, fear can be easily mistaken for sadness and vice versa. Paul Harris described his theory in his work on evolution, development and simulation [23]. He embeds the emotion recognition capability into the affective development, as a process much more articulated than the cognitive process. We can easily make a distinction between two specific competences: emotion understanding and emotion control.
Both emotional and cognitive processes are implicated in the successful regulation of thought and behaviour, so the functional relation between these areas provides a biological mechanism for behavioural integration of emotive and cognitive processes in early childhood.
As far as emotional control is concerned, deaf children can easily understand a scared expression, unlike hearing children. Emotional tasks, such as facing sadness involve a defence mechanism among deaf children, rather than facing fear.
As far as level 3 is concerned, the performance on emotion recognition and cognitive understanding was almost the same for both groups, except for sadness, which remains the most difficult emotion to perceptively identify for deaf children, as well as rage for hearing children (unlike fear compared to perceptive understanding). The effects of desires and satisfactions on emotions are investigated in level 4. The unique difference is that deaf children show a reduced responsiveness to the expressions of sadness, so the thesis asserting this difficulty on the cognitive as well as perceptive side, is further bolstered. On the other hand, both samples reveal similarity in the cognitive recognition of desires.

Discussion

According to the our results, deaf children seem to be better at recognising visual emotions (level 1). Furthermore, deaf children present significant problem-solving and emotional recognition skills, perhaps as a result of their innate problem solving attitude towards peers, or because of the oversimplified contexts of interaction, artificially created in order to facilitate their relational approach. The deaf children, when evaluated in conventional language recognition, showed poor perceptive and cognitive ability in identifying emotions in socio-communicative contexts (level 2). This could be due to a lack of socialisation experiences in various contexts compared to hearing counterparts .
Finally, according to the results of the psychological test, deaf children showed a reduced responsiveness to the expressions of sadness on both the cognitive and the perceptive side.
This could be due to their difficulty in controlling negative emotions such as sadness, unlike fear and rage. As easily observed, the latter are manifested in situations characterised by a high rhythmic and sonorous intensity, unlike sadness [24-27].

Conclusions

This study identifies a set of variables that can affect development of psycho-emotional hearing impaired children, distinguishing them from that of the normal hearing child.

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Head and neck

Clinicopathologic idiosyncrasies of nasopharyngeal cancer in a moderate-risk Mediterranean region

Caratteristiche clinicopatologiche del carcinoma rinofaringeo in una regione dell'area mediterranea a rischio moderato

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SUMMARY

Cancer of the nasopharynx displays an unparalleled skewness of its epidemiologic, pathogenic and clinico-prognostic characteristics depending on the geographic location. Between the endemic and sporadic forms, which occur in Southeastern Asia and Northern America, respectively, intermediate incidence is noted around the Mediterranean. This study describes the patterns of the disease affecting the population of Western Greece. The records of 70 patients with nasopharyngeal cancer diagnosed in a single institution between 1994-2014 were retrospectively reviewed. Primary treatment involved irradiation with or without concurrent chemotherapy. Demographic data, patient risk factors, tumour parameters, clinical presentation and treatment outcomes were assessed for potential intercorrelations. Overall (OS) and disease-specific (DSS) 5-year survival rates were determined. Possible predictors of survival were tested on univariate and multivariate analysis. WHO-type 3 histopathology was diagnosed predominantly (74.3%) and associated significantly with nasal symptomatology upon presentation (p = 0.050), metastatic lymphadenopathy (p = 0.028), advanced clinical stage (p = 0.009) and complete response to initial treatment (p = 0.018). Univariate analysis revealed a negative prognostic significance for older age (OS, p = 0.029 DSS, p = 0.041), poor response to treatment (OS & DSS p < 0.001) and cancer recurrence (OS, p = 0.003 DSS, p = 0.001). On multivariate analysis, disease relapse maintained its adverse effect (HR 7.442, 95% CI 2.199-25.187, p = 0.001). In conclusion, among nasopharyngeal carcinomas arising in western Greece, lymphoepitheliomas manifest a distinct clinical behaviour, so that their latest grouping along with WHO-type 2 tumours into the "non-keratinising" category may not apply. Regardless of pathology, cancer recurrence after initial remission is a severe event.

KEY WORDS: Epidemiology • Nasopharyngeal neoplasms • Pathology • Prognosis

RIASSUNTO

Il carcinoma del rinofaringe presenta una notevole eterogeneità per quanto riguarda le caratteristiche epidemiologiche, patogenetiche, cliniche e prognostiche sulla base dell'area geografica considerata. L'incidenza registrata nel Mediterraneo per tale patologia si colloca fra quella delle forme epidemiche e sporadiche registrate rispettivamente nel Sud Est Asiatico e nel Nord America. Il presente studio descrive le caratteristiche di questa patologia per quanto riguarda l'ovest della Grecia. Sono stati analizzati i dati relativi a 70 pazienti affetti da carcinoma del rinofaringe la cui diagnosi è stata posta presso un singolo centro fra il 1994 e il 2014. Il trattamento primario si è basato sulla radioterapia con o senza chemioterapia associata. Sono stati raccolti ai fini dell'analisi statistica i dati demografici, i fattori di rischio, le caratteristiche della neoplasia, la presentazione clinica e l'outcome. Sono state calcolate sia la sopravvivenza globale (OS) che la sopravvivenza specifica per malattia (DSS) a 5 anni. Tutti i fattori potenzialmente predittori di sopravvivenza sono stati testati a un'analisi univariata e multivariata. La variante maggiormente diagnosticata all'analisi istopatologica è stato il tipo 3 secondo la WHO (74,3%) che si è associato in modo significativo con sintomatologia nasale alla presentazione (p = 0,050), linfoadenopatie metastatiche (p = 0,028), stage clinico avanzato (p = 0,009) e risposta completa al trattamento iniziale (p = 0,018). L'analisi univariata ha evidenziato un impatto negativo in termini prognostici per l'età avanzata (OS p = 0,029, DSS p = 0,041), la mancata risposta ai trattamenti (OS & DSS p < 0,001) e la recidiva di malattia (OS p = 0,003, DSS p = 0,001). A un'analisi multivariata la recidiva di malattia ha mantenuto un impatto prognostico negativo (HR 7,442, 95% IC 2,199-25,187, p = 0,001). In conclusione, fra i carcinomi nasofaringei diagnosticati nell'ovest della Grecia, il linfoepitelioma mostra caratteristiche peculiari sotto il profilo clinico, tali per cui la sua inclusione assieme alle neoplasie tipo 2 secondo la WHO nel gruppo di carcinomi rinofaringei "non cheratinizzanti" potrebbe risultare inappropriata. Infine, la recidiva di malattia, indipendentemente dagli altri fattori in gioco, appare essere un evento gravemente avverso.

PAROLE CHIAVE: *Epidemiologia • Neoplasie del rinofaringe • Patologia • Prognosi*

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Introduction

Of all head and neck epithelial malignancies, nasopharyngeal cancer historically holds a unique position, being different essentially in every aspect of its clinic-biologic profile. Tumours of the nasopharynx share the privilege of silent growth, as they expand inside a hidden cavity and do not impinge on nerves unless substantial enlargement has occurred. Not only that, but due to its core location, this head and neck region is not amenable to radical surgery [1]. Notably, the micro-anatomy of the area is as distinct as its macro-anatomy: the nasopharyngeal lumen is lined with transitional epithelium, instead of the stratified squamous cell layer which gives rise to more than 90% of head and neck carcinomas. Moreover, subepithelial tissues are heavily infiltrated with lymphocytes. Collectively, such a histological arrangement explains the diversity of tumour pathology originating in the same area. For the last four decades, nasopharyngeal carcinomas have been traditionally grouped into three types: (a)-WHO type 1, identical to the common form of keratinising head and neck squamous cell carcinoma, (b)-WHO type 2, the poorly differentiated, non-keratinising squamous cell variant, and (c)-WHO type 3, a.k.a. lymphoepithelioma, which lacks any cellular differentiation [2]. The heterogeneity in histopathology reflects the variety of clinical patterns, that is, WHO type 1 neoplasms predominate in the older population and tend to advance locally, whereas WHO types 2 and 3 carry a higher risk of distant spread. Lymphoepitheliomas in particular, though histologically undifferentiated and frequently metastatic, present with the paradox of a more favourable prognosis, owing to their enhanced radio- and chemo-sensitivity [3].

As is the case in virtually all kinds of malignancy, the aetiology of nasopharyngeal cancer is multifactorial. Genetic predisposition, dietary carcinogens, smoking, occupational exposure and latent Epstein-Barr virus (EBV) infection have all been implicated, if not documented. Interestingly, it seems that each WHO histological type is associated with a distinct pathogenesis and combination of inducing factors. In detail, WHO type 1 carcinomas demonstrate a robust correlation with alcohol and tobacco, in resemblance with the classic head and neck cancer, while types 2 and 3 share a stronger relationship with EBV infection [4].

The histologic, clinical and aetiologic diversity of epithelial nasopharyngeal tumours is not distributed uniformly around the globe, but exhibits geographic differences. In that regard, cancers of the nasopharynx belong to an enigmatic group of neoplasias such as Kaposi's sarcoma and Burkitt's lymphoma, which occur either in a sporadic or endemic form in specific regions of the planet, maintaining a clear-cut distinction between the clinico-pathophysiologic features of the two disease types. The "endemic" areas of nasopharyngeal cancer extend across most of Southeastern Asia, where at specific locations, e.g. Hong Kong, the incidence is 30 times higher than that observed in the "sporadic" regions, typically USA and Western Europe. Focusing on Europe, the incidence across the Mediterranean countries(1.4 cases/100,000 men), including Greece, is higher than the northern part (< 1/100,000) [5]. As stated above, the endemic and sporadic forms differ in terms of pathogenesis and clinical aggression. Roughly speaking, tumours of WHO 3 and 2 histological class are associated with the former type, whereas the keratinising carcinomas tend to occur in the sporadic fashion [2]. However, there is little knowledge of the clinicopathologic profile of nasopharyngeal cancer diagnosed in "grey" regions, such as Mediterranean countries. In an attempt to fill in a piece of the geographic puzzle, this study aims to record the individual characteristics of the disease affecting the population of Western Greece.

Materials and methods

This retrospective study was approved by our institution's Research Ethics Committee. Patras University hospital receives the majority of cancer patients from Western Greece, with a population of 2,500,000. The records of 70 consecutive nasopharyngeal cancer patients diagnosed from 1994 to 2014 were reviewed. For all cases, diagnostic work-up, histologic confirmation and treatment were provided in our institution. Social history was also documented. Smokers' classification was based on the number of pack years, as moderate (≤ 20) or heavy (> 20). Alcohol drinking was graded as social (up to three drinks/week), moderate (3-7 drinks) and heavy (> 7 drinks). The management plan entailed conventional irradiation of the primary tumour with a total dose of 6600-7000 cGy, along with therapeutic (6600-7000 cGy) or prophylactic (5000 cGy) targeting of the neck. Concurrent chemotherapy with cis-platinum and 5-fluouracil was offered to patients of stage II or higher. A salvage neck dissection was performed in case of regional recurrence. Patients were followed-up every 2 months for the first post-treatment year, every 3 months for the next two years, twice annually for the 4th and 5th years and yearly afterwards. The follow-up period stretched between 1 and 176 months. Complete clinical response was defined as the documentation of pure scarred tissue along the nasopharyngeal walls, without evidence of deep invasion, or regional or distant disease. Patients with complete response and new evidence of disease at least 6 months after completion of treatment were classified as recurrences. Because relapsing patients would often seek a second opinion before showing to follow-up in our institution, unfortunately our data regarding the exact time and sort of recurrence were scant, and thus omitted from

subsequent processing. The collected information included demographics, initial manifestation, TNM classification, histology, response to treatment, tumour recurrence within 3 years from the completion of treatment and are summarised in Table I.

The correlations between categorical values were investigated by either Chi-square or Fisher's exact test. The Kaplan-Meier method produced all survival analyses, and the log-rank test was employed to determine the statistical significance of differences among the survival rates of various patient subgroups. To eliminate censoring, living patients with duration of follow-up shorter than 60 months were not considered for calculation of 5-year cumulative survival. Prognostic factors exhibiting a p value < 0.2 on univariate testing, were next submitted to a multivariate Cox-regression model to assess their independent influence. A two-sided p value ≤ 0.05 was considered significant. All tests were performed using SPSS 17.0 statistical software.

Results

Chi-square, or Fisher's exact test in the case of binomial variables, were utilised to determine the effect of our sample's demographics, smoking and alcohol consumption data on tumour characteristics, as well as on clinical course. None of the correlations produced statistically significant results. In the second set of analyses, the association of the WHO histologic type with the locoregional and distant extent of disease was explored. We also examined the impact of histopathology and TNM classification on the original manifestation and the pattern of clinical progression, the latter defined by the responsiveness to initial treatment and the risk of recurrence. At first, we failed to establish any statistically significant differences among the clinicoprognostic variables of the three WHO histologic subgroups. It is likely that the small number of WHO type 1 carcinomas limited the statistical power of the analyses. Next, we merged cases with WHO types 1 and 2 into a single group, the so-called "squamous cell differentiated" type, as opposed to the undifferentiated WHO type 3. Furthermore, aiming to focus exclusively on those cases presenting with local symptomatology as the primary manifestation, we investigated only patients complaining initially either of hearing loss or of a nasal symptom, i.e. epistaxis or nasal obstruction.

Subsequent to our data regrouping, Chi-square testing yielded several significant relationships (Table II). To begin with, WHO type 3 histology was significantly associated with an increased rate of neck metastases at diagnosis. Of note, 80.8% (42/52) of lymphoepitheliomas manifested regional spread, whereas in only half (9/18) of WHO type 1 and 2 carcinomas was lymph node involvement detected. No relationship could be established between the state of differentiation and N staging,

Table I. Characteristics of the study population.

Description	N	%
Gender		
Male	54	77.1
Female	16	22.9
Age		
Mean (range)	56.3(16-85)	
Smoking		
No	26	37.2
Moderate	8	11.4
Heavy	36	51.4
Alcohol		
No	40	57.1
Social	11	15.7
Moderate	10	14.3
Heavy	9	12.9
Initial manifestation		
Otitis media with effusion	15	21.4
Epistaxis	12	17.1
Nasal obstruction	3	4.3
Facial numbness/pain	2	2.9
Neck mass	38	54.3
WHO histologic type		
I	3	4.3
II	15	21.4
III	52	74.3
T		
1	57	81.4
2	10	14.3
4	3	4.3
N		
0	19	27.1
1	7	10.0
2	31	44.3
3	13	18.6
M		
0	69	98.6
1	1	1.4
Stage		
I	17	24.3
II	7	10.0
III	29	41.4
IV	17	24.2
Radiation		
Yes	70	100
No	0	0
Chemotherapy		
Yes	22	31.4
No	48	68.6
Neck dissection		
Yes	7	10.0
No	63	90.0
Complete response		
Yes	63	90.0
No	3	4.3
No available data	4	5.7
Recurrence		
Yes	21	33.3
No	36	57.1
No available data	6	9.6

Table II. Comparison between the differentiated and undifferentiated nasopharyngeal cancer subgroups.

Patient variable	N (%)		P
	WHO 1 and 2	WHO 3	
Gender			0.536
Male	13 (24.1)	41 (75.9)	
Female	5 (31.3)	11 (68.8)	
Age			0.259
≤ 50	4 (16.7)	20 (83.3)	
> 50	14 (30.4)	32 (69.6)	
Smoking			0.540
No	5 (19.2)	21 (80.8)	
Moderate	3 (37.5)	5 (62.5)	
Heavy	10 (27.8)	26 (72.2)	
Alcohol			0.958
No	11 (27.5)	29 (72.5)	
Social	3 (27.3)	8 (72.7)	
Moderate	2 (20.0)	8 (80.0)	
Heavy	2 (22.2)	7 (77.8)	
Initial manifestation			0.414
Local	10 (31.3)	22 (68.8)	
Neck mass	8 (21.1)	30 (78.9)	
Initial local manifestation			0.050
Aural	8 (53.3)	7 (46.7)	
Nasal	2 (13.3)	13 (86.7)	
T			0.564
1	15 (26.3)	42 (73.7)	
2	3 (30.0)	7 (70.0)	
4	0	3 (100.0)	
N			0.028
0	9 (47.4)	10 (52.6)	
+	9 (17.6)	42 (82.4)	
M			1.000
0	18 (26.1)	51 (73.9)	
1	0	1 (100.0)	
Stage			0.009
I-II	11 (45.8)	13 (54.2)	
III-IV	7 (15.2)	39 (84.8)	
Complete response to treatment			0.018
No	3 (100.0)	0 (0.0)	
Yes	15 (23.8)	48 (76.2)	
Recurrence			0.059
No	6 (16.7)	30 (83.3)	
Yes	9 (42.9)	12 (57.1)	

however. Nonetheless, a clear-cut correlation between advanced clinical stage (III-IV) and WHO type 3 histologic diagnosis was revealed. Moreover, in the subgroup of patients presenting with a local symptom, either aural or nasal, differentiated nasopharyngeal cancer showed a significant relationship with the former [80% (8/10)], in contrast with the WHO-type 3 neoplasms, which were more likely to cause epistaxis or nasal obstruction [65% (13/20)]. Obviously, due to the limited size of this particular subgroup, the above mentioned results need to be approached with caution. With reference to its prognostic significance, undifferentiated cancer manifested absolute response [100% (48/48)] to initial treatment, while for WHO types 1 and 2 the remission rate was 83.3% (15/18). Not only, but the recurrence rate after successful response to treatment was lower in WHO type 3 cases [28.6% (12/42)] than in patients with other pathologies [60% (9/15)], although the latest association was marginally non-significant.

The overall (OS) and disease-specific (DSS) 5-year survival rates of our patients were 46.9% and 48.9%, respectively. Univariate comparison of the 5-year OS and DSS curves among the various patient subgroups revealed a negative prognostic significance of older age, poor response to treatment and cancer recurrence. Those parameters, along with neck status and clinical stage, which achieved a p value< 0.2, were included in the multivariate model. Nevertheless, owing to the limited number of unsuccessful therapies, the treatment response variable was rejected from the final equation. Finally, logistic regression analysis established that in our study population disease recurrence was the sole independent prognostic factor affecting negatively both OS and DSS (Table III). Relapsing patients faced a 7-fold higher risk of dying from nasopharyngeal cancer. Of note, the differentiation state of carcinomas exerted no effect on survival (Fig. 1).

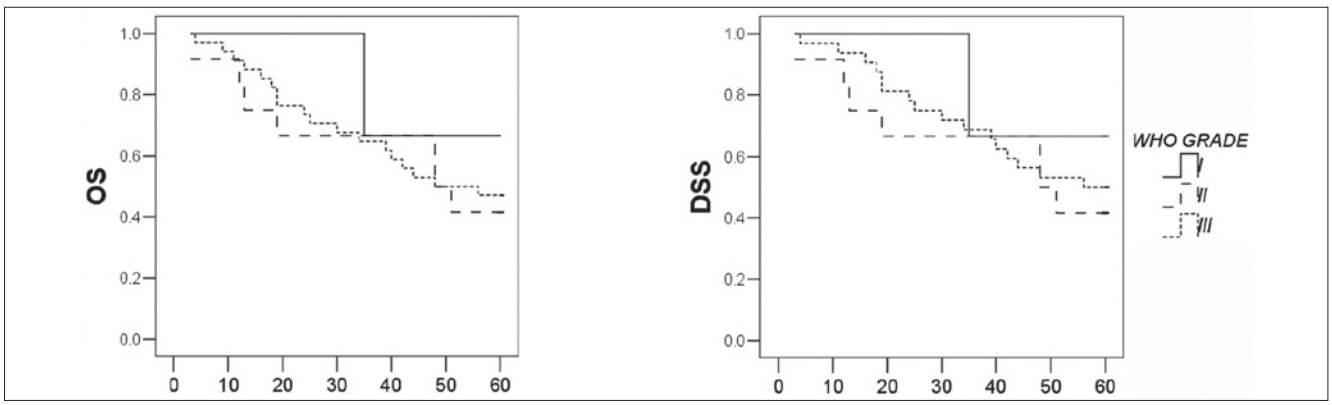

Fig. 1. Kaplan-Meier 5-year OS (p = 0.770) and DSS (p = 0.744) survival curves for patients with nasopharyngeal cancer of various histopathological grades. x-axis represents months elapsed since the diagnosis.

Table III. Univariate and multivariate analyses testing the prognostic effect of various patient and disease parameters on overall and disease-specific 5-year survival.

Factor	OS			DSS		
	Univariate	Multivariate		Univariate	Multivariate	
	P	HR (95%CI)	P	P	HR (95%CI)	P
Gender						
Male						
Female	0.981			0.879		
Age						
≤ 50		Referent value			Referent value	
> 50	0.029	2.477 (0.707-8.677)	0.156	0.041	2.162 (0.605-7.773)	0.236
Smoking						
No					Referent value	
Moderate					2.785 (0.471-16.466)	0.259
Heavy	0.242			0.189	3.048 (0.944-9.845)	0.062
Alcohol						
No						
Social						
Moderate						
Heavy	0.678			0.509		
Initial manifestation						
Local						
Neck mass	0.970			0.683		
Initial local manifestation						
Aural						
Nasal	0.595			0.595		
WHO type						
1 and 2						
3	0.949			0.861		
T						
1						
2						
4	0.269			0.261		
N						
0		Referent value			Referent value	
+	0.076	5.470 (0.559-53.525)	0.144	0.112	7.804 (0.708-86.050)	0.093
M	Not enough data			Not enough data		
0						
1						
Stage						
I-II		Referent value			Referent value	
III-IV	0.129	1.469 (0.220-9.821)	0.692	0.190	1.305 (0.178-9.554)	0.793
Complete response to treatment						
No		Rejected			Rejected	
Yes	< 0.001			< 0.001		
Recurrence						
No		Referent value			Referent value	
Yes	0.003	4.820 (1.669-13.915)	0.004	0.001	7.442 (2.199-25.187)	0.001

** HR, hazard ratio; CI, confidence interval.*

Discussion

The epidemiology of nasopharyngeal cancer varies enormously with geographic latitude and longitude, so that it may be unsafe to generalise conclusions pertaining to risk factors, pathogenetic events, or prognostic markers based upon evidence from a single regional tumour registry. Rather, a more comprehensive approach would entail the combination of data from various parts of the world in order to shed light onto the fundamental principles governing the clinical behaviour of such a diverse neoplastic disease. Four decades after the sole publication on the incidence and clinical course of nasopharyngeal cancer in the region of Greece [6], this study reports the current trends in the local disease pattern. Despite the prolonged accumulation of cases from nearly one-quarter of the Greek population, the size of our study sample, due to the scarce occurrence of nasopharyngeal malignancies, might be still considered insufficient for certain statistical analyses.

Firstly, the male-to-female ratio (3:1) and mean age at diagnosis (56 years) of our patient sample were similar to those reported in the literature, both for the sporadic and endemic forms of nasopharyngeal cancer [5], with the exception of Northern Africa, where a secondary peak incidence is spotted during the second and third decades of life [7]. Apart from that, being an intermediate zone between the sporadic and endemic provinces from a cancer incidence standpoint, Greece also exhibits an average ratio of the histologic subtypes. While in Northern America the WH -types 1, 2 and 3 represent 25%, 12% and 63%, respectively, in the high-risk countries of Southeastern Asia the relative proportions are reported as 2%, 3% and 95% [8]. In our study population, the documented ratio was 4%, 22% and 74%, showing, in comparison with the endemic variant, a rise of the type 2 non-keratinising squamous cell carcinoma, at the expense of lymphoepithelioma. So far, it has been strongly suggested that the nasopharyngeal carcinomas of different histopathologic subtypes correspond to dissimilar pathogenetic processes and predisposing factors. In specific, WHO type 1 tumours share a causal relationship with smoking, as well as a sporadic occurrence, with the classic squamous cell carcinoma arising from the other head and neck subsites, whereas the tumourigenesis of WHO type 3 neoplasms is likely dominated by chronic subclinical EBV infection and thus takes place in the form of an epidemic [2]. Since EBV carrier state is a ubiquitous condition, involving nearly 95% of the human population, carcinogenic cofactors have been considered in endemic regions, with the primary focus on consumption of salted fish [9]. As the Mediterranean diet does not usually include a substantial amount of preserved fish, our study investigated the role of more "traditional" carcinogenic factors, i.e. smoking and alcohol drinking. None of those demonstrated an association with a distinct WHO type of cancer, although the keratinising tumour was poorly represented in our sample. A multitude of studies from both "hot" and "cold" areas has excluded tobacco and alcohol as risk factors for WHO types 2 and 3 [10]. Notably, these particular subtypes constitute together 96% of all our cases, hence suggesting that a different set of carcinogenic factors is possibly responsible for the "Greek variety" of nasopharyngeal cancer. Obviously, the lack of information regarding the presence and severity of EBV-infection in our patients poses a limitation to the conclusions of this study.

The histopathologic identity of nasopharyngeal tumours relates not only to specific aetiopathogenetic factors, but also to distinct clinical patterns. According to our data, a growing neck mass was the commonest symptom that led patients, regardless of histology, to seek medical advice. This finding is in agreement with reports both from sporadic [11] and endemic [12] regions. Still, 19% of our patients, despite having noticeable cervical metastases, did not present for examination until a local manifestation eventually occurred. It appears that functional compromise, such as hearing loss or nasal obstruction, is more alarming to the patient than a painless lump in the neck. Since the latter unfortunately is a sign of advanced disease, proper education of the population is vital. Among those cases of our study presenting because of a local manifestation, WHO type 3 tumours were associated with nasal symptomatology, either obstruction or epistaxis, in contrast to aural complaints. To date, no relationship has been reported between histological type and initial symptoms. We can only hypothesise that undifferentiated carcinomas, at least during the early stage of their development, tend to grow exophytically into the nasal cavities, whereas the differentiated squamous cell neoplasms exhibit a more lateral, submucosal extension, thus disrupting the function of the eustachian tube [13]. A second finding of our analysis was the increased risk of neck metastases in the lymphoepithelioma subgroup. Due to the higher frequency of regional spread, WHO type 3 tumours of our sample were diagnosed at a relatively advanced clinical stage. Metastatic lymphadenopathy of the neck is a well-established clinical feature of nasopharyngeal cancer of both WHO types 2 and 3 [7]. However, in our regional patient population, we documented a definite distinction between the two histologic variants, i.e., only the undifferentiated carcinomas displayed a clear propensity for lymph node dissemination. Accordingly, advanced clinical stage upon consultation, a hallmark of all forms of nasopharyngeal cancer [11], was in our study heavily pronounced in WHO type 3 cases, as they most often presented with positive lymph nodes. Certainly the silent tumour growth in such a concealed anatomic location, the vague symptomatology that does not alarm either the patient or even sometimes the physician, as well as the dependence on nasopharyngoscopy to identify the primary lesion, are all contributing factors to considerable disease progression prior to diagnosis [14].

Besides their distinctive tumour parameters, undifferentiated carcinomas included in our study were further distinguished in terms of their response to treatment. Impressively, lymphoepitheliomas responded in toto to the initial therapeutic approach. In addition, they displayed a much lower risk of locoregional or distant recurrence, in comparison with differentiated squamous cell cancer, though this discrepancy was found to be marginally non-significant. In the head and neck family of malignancies, cancer of the nasopharynx has traditionally been managed therapeutically by oncologists, instead of surgeons, due to its remarkable radio- and chemo-sensitivity [1]. However, the effect of histopathology on treatment outcome is an issue of controversy. In agreement with our results, more effective disease control for WHO type 3 tumours has been reported in Western populations [15]. Yet in endemic areas, where undifferentiated carcinomas prevail, lymphoepitheliomatous histology is not a clear-cut

determinant of treatment success, though it confers a survival benefit [16], even if not evident in our study.

On the basis of our univariate survival analysis, older age, non-response to treatment and cancer recurrence were found to be ominous predictors, although only disease relapse was demonstrated in multivariate testing as an independent adverse indicator. The overall 5-year survival rate in our study (46.9%) is within the globally reported range (32-62%) [17]. However, the survival determinants vary remarkably throughout the literature, reflecting the geographic heterogeneity of the disease. Negative prognostic factors well-established worldwide include older age, advanced TNM stage, cranial nerve involvement and skull-base erosion [15 18]. Excluding distant metastasis, which was diagnosed in only one case on initial evaluation, tumour size and status of the cervical lymph nodes had no impact on survival in our patient group, suggesting that cancer aggressiveness may not be associated with the locoregional extent of disease, as for other carcinomas of the head and neck. Paradoxically, the histologic identity of nasopharyngeal neoplasia, which, as supported by our data, exerted an influence on several clinical parameters, did not produce, as would be expected, an effect on survival, possibly indicating that the entire clinicopathologic cancer profile might not be a reliable marker of the course of disease. Failure to produce a long-term therapeutic outcome was, in our sample, the critical factor that shortened survival. For that reason, highly aggressive but infrequently implemented therapeutic techniques such as intracavitary brachytherapy [19] and surgical resection [7] might be applied on a larger scale, particularly in cases of strictly localised recurrent tumours. Not only, but newer treatment modalities, namely intensity-modulated radiation therapy, adjuvant or neo-adjuvant chemotherapy, as well as up-to-date targeted molecular approaches against epidermal growth factor receptor or vascular endothelial growth factor, may be of enormous benefit to nasopharyngeal cancer patients [1]. Admittedly, recurrences in our institution were managed exclusively with salvage neck dissection, when this was applicable, to control of regional spread only. The role of re-irradiation to the primary site merits careful investigation [20].

Conclusions

On the whole, the present report documents the epidemiologic and clinicoprognostic traits of nasopharyngeal cancer in Western Greece, an area with intermediate incidence between the endemic and sporadic regions. Perhaps in the era of proteomics and cell signaling modification, purely observational studies might seem outdated. Nevertheless, the comprehensive understanding of a malignancy with such striking differences across the globe requires a piece-by-piece description of its geography. Our findings support a distinct place for WHO type 3 tumours, comparatively to the squamous cell group comprising WHO types 1 and 2 together. Accordingly, the categorisation of carcinomas into "undifferentiated" vs. "differentiated" may apply more precisely to our regional variant of the disease, rather than the latest classification by WHO into "non-keratinising"(WHO types 2 and 3) vs. "keratinising"(WHO type 1), proposed in 2005 [21]. Further exploration of the clinicopathologic diversity of this unpredictable neoplasia might hopefully lead to an accurate universal classification scheme that could facilitate the study of the natural history of the disease and the design of improved treatment strategies.

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HEAD AND NECK

Supracricoid partial laryngectomy with crico-hyoido-epiglottopexy for glottic carcinoma with anterior commissure involvement

La laringectomia parziale sopracricoidea con crico-ioido-pessia per il carcinoma della glottide coinvolgente la commissura anteriore

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SUMMARY

Glottic cancers discovered at an early stage (T1-T2) can be treated with either radiotherapy or surgery. The aim of our study is to analyse survival and functional results of supra-cricoid partial laryngectomy (SCPL) with crico-hyoido-epiglottopexy (CHEP) as surgical treatment for glottic carcinoma with anterior commissure involvement. We performed a retrospective study (1996-2013) which included patients who underwent SCPL-CHEP for glottic squamous cell carcinoma with involvement of the anterior commissure. Before surgery, all patients underwent staging including head, neck and chest CT-scan with contrast injection as well as suspension laryngoscopy under general anaesthesia. A total of 53 patients were included. The median follow-up period was 124 months. Tumour resection was complete in 96.2% of cases. The overall, specific and recurrence-free survival rates at 5 years were, respectively, 93.7%, 95.6% and 87.7%. The average period of hospitalisation was 18 days. The average time elapsed before decannulation and before restoration of oral feeding were 15 and 18 days, respectively. SCPL-CHEP is an important option for laryngeal surgical preservation. It allows adequate disease control as well as good functional results as long as the indications are well respected and the surgical techniques are mastered.

KEY WORDS: Glottic cancer • Anterior commissure • Partial laryngectomy • Survival • Functional results

RIASSUNTO

I tumori della glottide scoperti in fase precoce (T1-T2) possono essere trattati sia con la radioterapia, sia mediante un intervento chirurgico. Lo scopo del nostro studio è stato quello di analizzare la sopravvivenza ed i risultati funzionali della laringectomia parziale sopracricoidea con crico-ioido-epiglotto-pessia per trattare il carcinoma della glottide con coinvolgimento della commissura anteriore. Abbiamo condotto uno studio retrospettivo (1996-2013), che includeva pazienti sottoposti a laringectomia parziale sopracricoidea con crico-ioido-epiglotto-pessia per un carcinoma a cellule squamose della glottide coinvolgente la commissura anteriore. Prima dell'intervento è stato inoltre effettuato uno staging completo con TC del collo e del torace, nonché una laringoscopia diretta in sospensione in anestesia generale. 53 pazienti sono stati inclusi nel nostro studio. Il periodo mediano di follow-up è stato di 124 mesi. La resezione tumorale è stata completa nel 96,2% dei casi. I tassi di sopravvivenza, specifica e senza recidiva, a 5 anni sono stati rispettivamente 93,7%, 95,6 e 87,7%. Il periodo medio di ricovero è stato di 18 giorni. I tempi medi trascorsi prima del decannulamento e prima della ripresa dell'alimentazione per os sono stati rispettivamente 15 e 18 giorni. La laringectomia parziale sopracricoidea con crico-ioido-epiglotto-pessia è un'opzione importante per la conservazione chirurgica della laringe. Tale approccio consente un adeguato controllo della malattia e buoni risultati funzionali, purchè le indicazioni siano seguite pedissequamente e la tecnica chirurgica sia perfetta.

PAROLE CHIAVE: *Carcinoma della glottide • Commissura anteriore • Laringectomia parziale • Sopravvivenza • Risultati funzionali*

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Introduction

Glottic cancers discovered at an early stage (T1-T2) can be treated with either radiotherapy or surgery. Whatever the treatment, the aim is to eradicate the tumour and to maintain laryngeal functions which include phonation, breathing and swallowing to allow the best possible quality of life for patients.

Total laryngectomy is considered as an excessive treatment for T1-T2 tumours of the vocal folds, hence the development of partial surgical techniques of the larynx. Horizontal partial surgery of the larynx for glottic carcinoma was developed in the 1970s. Supra-cricoid partial laryngectomy (SCPL) or open partial horizontal laryngectomy (OPHL) type II, with crico-hyoido-epiglottopexy

(CHEP) is one of most widely used surgical techniques [1]. Compared to vertical partial laryngectomy (VPL), it has a low local failure rate for T1 and T2 glottic tumours with anterior commissure involvement [2].

The SCPL with CHEP was first introduced in 1959 by Majer and Rieder [3]. The first functional results of this surgical technique were reported by Piquet et al. in 1974 [4]. In this technique, in addition to total resection of the thyroid cartilage, both vocal folds, the paraglottic space, both ventricular folds and the infrahyoid part of the epiglottis are removed. In SCPL, at least one functional cricoarytenoid unit must be preserved [5].

Since the first publications describing SCPL with CHEP, additional studies were performed to improve this surgical technique, and broadened its indication to include selected advanced stages of glottic carcinoma. Despite this, there are some reported local failures with SCPL-CHEP, which raises concern about the relevance and indication of this technique.

The present retrospective study reports our experience with SCPL-CHEP in 53 cases. Our objectives were to analyse the oncologic and functional results of this technique and to compare our results with those in the literature.

Materials and methods

We carried out a retrospective monocentric study (1995 2013) in our tertiary referral hospital. All patients were treated at the same centre.

Inclusion criteria were:

1) glottic squamous cell carcinoma discovered at an early stage (T1-T2) involving the anterior commissure;
2) no prior treatment for the glottic lesion;
3) a minimum of 24 months follow-up after the end of treatment.

All patients underwent staging comprising:

1) head and neck as well as chest CT-scan with contrast injection;
2) suspension laryngoscopy under general anaesthesia with laryngeal examination using 30° and 70° rigid endoscopes;
3) biopsies were performed during laryngoscopy;
4) pan-endoscopy was done under anaesthesia at the same time of the laryngoscopy to rule out synchronous lesions. A careful in-office examination of the vocal folds and arytenoid mobility was performed using transnasal flexible laryngoscopy. Extension of the lesion to the preepiglottic, paraglottic and subglottic spaces was evaluated by CT scan. All patients underwent pulmonary function tests (PFTs). In case of history of pulmonary disease and/or age > 70 years, in addition to the PFTs, patients were examined by a pulmonologist to rule out respiratory insufficiency that could contraindicate surgery.

All cases were discussed at our local head and neck cancer multidisciplinary meetings. Tumours were classified according to the TNM classification of glottic carcinomas (UICC 2002). All patients were treated by SCPL-CHEP according to Majer and Piquet [3 4] technique or Guerrier technique [6]. All patients underwent tracheostomy during surgery. A bilateral neck dissection was performed in 43 cases.

Functional results were defined according to the following data:

1) time of decannulation;
2) time of nasogastric tube removal after ensuring through videofluoroscopy that patients recovered swallowing without inhalation with a daily oral caloric intake ≥ 1500 kcal;
3) time of discharge from the hospital.

Statistical analysis was performed using Kaplan Meier survival curves and Log-Rank comparison test with GraphPad Prism 5 software (GraphPad Software). The comparison of categorical variables and the mean ranks between different subgroups were calculated, respectively, by Fisher's exact test and Wilcoxon signed-rank test. The Kaplan Meier method was used to study survival. The log-rank test was used to compare survival curves between T1 (T1a and T1b) and T2 tumours.

Results

Between 1996 and 2013, 53 patients underwent SCPL with CHEP (Table I). All patients presented a tumour of the vocal folds, with extension and invasion of the anterior commissure. Histological analysis of all cases showed invasive squamous cell carcinoma that was more or less differentiated. No synchronous lesion was discovered during endoscopy and no metastases were detected at initial assessment. Among patients treated using the technique of Majer and Piquet, resection of the anterior arch of the cricoid cartilage was performed in one case due to anterior subglottic extension. All patients underwent neck dissection except in 8 cases with a T1a tumour and in 2 cases with a T1b tumour (Table II).

The rate of local complications was 5.6%. Two cases of cervical abscess and one case of haematoma required drainage in the 24-72 hours postoperatively. Six patients (11.3%) presented general complications in the form of pulmonary infection (n = 5) and pulmonary embolism (n = 1). These patients showed recovery after medical treatment. No patient died during the postoperative period.

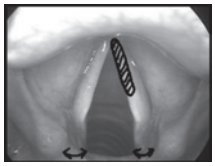
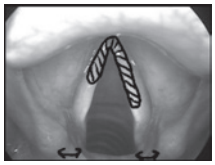
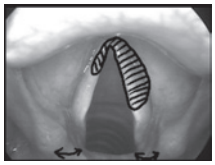
Complete tumour resection was achieved in 51 cases (96.2%). Two cases showed incomplete resection and presented 5 mm anterior subglottic extension confirmed on CT. For this reason, resection of the anterior part of the cricoid cartilage was performed in one case. Pathological examination showed massive invasion at that level and the patient underwent total laryngectomy in the two weeks following SCPL-CHEP. Surgery was followed by radiation therapy (58 Gy) targeting the surgical bed and the

Table I. Characteristics of the population.

	n	%
Male [a]	53	100
Smoking [b]	46	86.7
Alcohol consumption [c]	21	39.6
Classification (T)		
-T1a	10	20.7
-T1b	22	43.3
-T2	21	35.8
Classification (N) [d]		
N0	53	100
Surgical Technique		
Surgical resection		
-Majer-Piquet [*]	46	86.7
-Guerrier	7	13.2
Number of preserved arytenoid cartilages		
-Two arytenoid cartilages	28	52.8
-One arytenoid cartilage	25	47.1
Neck dissection [e] [**]	43	81.1

*a) Mean age 66 (38-78); b) Mean tobacco use 27 PY; c) Mean alcohol consumption 40 gr/day; d) Clinical and radiological classification; e) functional neck dissection; * partial resection of the anterior cricoid in 1 case; ** Neck dissection was not performed in 8 cases with T1a tumour and 2 cases with T1b tumour*

Table II. Tumour extension.

Classification (T)	Tumour extension	Endoscopic view
T1a	Anterior 1/3 of the vocal fold with anterior commissure involvement	
T1b	Tumour is limited to the anterior commissure or Tumour involves the 2 vocal folds with at least one vocal fold presenting an intact posterior 1/3	
T2	Tumour extends to the supraglottis and/or subglottis < 5mm Normal mobility of the vocal folds No extension to the paraglottic or pre-epiglottic space	

↔*: normal vocal fold mobility*

level VIb lymph nodes bilaterally. For the second case, the mucoperichondrium of the anterior part of the cricoid cartilage was resected. Pathological analysis showed close surgical margins less than 2 mm. The patient received postoperative radiotherapy with 60 Gy for the surgical bed and level VIb lymph nodes bilaterally. In both cases, the remainder of lymph node levels were not irradiated given the absence of lymph node metastasis on pathological examination. Among the 43 patients who underwent neck dissection, 3 cases (6.9%) presented lymph node metastasis without capsular rupture at level III. T classification for these 3 patients was: T2 (n = 2) and T1b (n = 1). No patient was lost to follow-up. The mean follow-up period was 124 months (median = 96 months). Six cases presented local recurrence (11.3%), 12 months on average after SCPL-CHEP. Initially, 5 of these patients had a T2 tumour and 1 patient had a T1b tumour. All of these patients were treated by salvage total laryngectomy followed by radiation therapy with no local recurrence. Following laryngectomy, one of these patients presented an inoperable cervical lymph node recurrence that was treated by chemotherapy. The rest of cases (n = 52) did not show any cervical lymph node recurrence during follow-up.

During follow-up, one case showed pulmonary metastasis (1.8%), 22 months following surgery. Seven patients presented a metachronous lesion (13.2%) in the lung (n = 3), oral cavity and oropharynx (n = 2), hypopharynx (n = 1) and oesophagus (n = 1). The overall survival rate, specific survival rate and recurrence-free survival rate at 5 years, were, respectively, 93.7%, 95.6% and 87.7% (Fig. 1). We did not find any difference in survival between T1 and T2 tumours.

The mean period of hospitalisation was 17.8 days (15-54) with a median of 16 days. The length of hospital stay was significantly shorter for the group of patients whose age was less than the median age (p = 0.05). 98% of patients (n = 52) were able to restore oral feeding without aspiration. The average time to achieve caloric intake ≥ 1500 kcal/24 h was 21 days (8-45) with a median of 14 days. This period was independent of the number of cricoarytenoid units preserved during SCPL-CHEP, but it was significantly shorter in younger patients (p = 0.04). One patient underwent gastrostomy tube placement due to local recurrence that was treated by total laryngectomy and radiotherapy. The patient maintained gastrostomy tube feeding for 12 months after laryngectomy because he presented delayed surgical wound healing, followed by pharyngeal stenosis.

All patients were decannulated. The mean time elapsed before decannulation was 15 days (8-53) with a median of 13 days. One patient underwent endoscopic resection of a mucous flap on the side of the resected arytenoid cartilage to allow decannulation. As for restoration of oral feeding, the time elapsed before decannulation was independent of the number of preserved cricoarytenoid units, but it was also significantly shorter in the group of younger patients (p = 0.05).

Long-term functional results showed that two patients presented with repeated aspiration pneumonia due to impaired swallowing and frequent choking episodes. One case showed improvement on speech therapy. Thickened liquids were also used to improve bolus control and helped prevent aspiration. The second case did not improve on

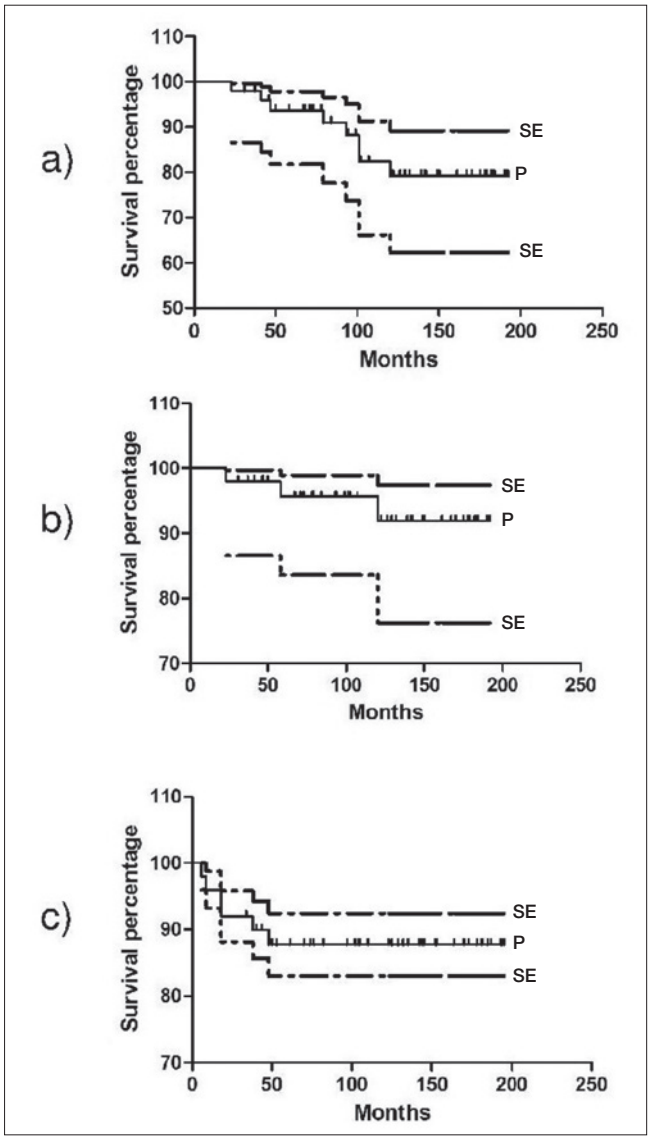


Fig. 1 Kaplan Meier survival curves. a) overall survival rate. b) specific survival rate. c) recurrence-free survival rate. P: percentage, SE: standard error.

speech therapy and required gastrostomy feeding tube placement. All patients were able to phonate audibly after SCPL-CHEP. No voice handicap index questionnaire was filled out by patients.

Discussion

T1 and T2 glottic carcinomas can be treated by radiotherapy or surgery [7]. The advantages of radiation therapy are that it preserves the anatomical structures of the larynx and thus better voice quality is maintained [8]. In the literature, for T1 tumours, the local control rate is 89.5% at 5 years with radiotherapy alone [9]. After salvage surgery which is usually not conservative, the final local control rate is between 90% and 95%. In our series, we did not observe any local recurrence in patients with T1a tumours involving the anterior commissure. On the other hand, one patient with a T1b tumour presented local recurrence, for a local failure rate of 4.5%, which is slightly lower than that reported in the literature [6]. For T2 tumours, the local failure rate of radiotherapy is between 25% and 30% and the local control rate reaches 90% after non-conservative salvage surgery [9 10]. In our series, the local failure rate for T2 tumours is 23.8% and the local control rate reaches 100% after salvage surgery followed by radiotherapy. Our results show better local control rates than those of radiotherapy alone or salvage surgery after radiotherapy [11 12]. Several factors affect the local control rate in case of exclusive treatment by radiotherapy of glottic tumours: male patients, low level of haemoglobin, radiotherapy dose-time fractionation, tumour volume, differentiation degree of the tumour and extension to the anterior commissure and/or to the subglottis [7 13 14]. The local control rate of T2 tumours extending to the anterior commissure treated by radiotherapy is between 15% and 40% [15 16]. These unsatisfactory results of local control rate of tumours involving the anterior commissure treated exclusively by radiotherapy can be explained by two factors: the difficulty to evaluate clinically and radiologically the extension depth of the tumour to the cricothyroid membrane as well as to the thyroid cartilage, and the technical difficulties to irradiate this part of the larynx [17]. However, with the emergence of intensity modulated radiation therapy (IMRT), one could ask if there is better disease local control in tumours extending to the anterior commissure. In addition, there are many concerns that IMRT under-doses the anterior commissure, but it has been shown that with careful treatment planning this can be avoided. Moreover, some studies showed that IMRT provides at least equal overall coverage of the entire larynx compared to 2D techniques [18]. These data as well as the impact of IMRT on local control rate need to be confirmed by further studies.

For many years, VPL represented the only conservative surgical treatment for T1and T2 glottic tumours. VPL, is called this because of the vertical thyrotomy carried out for tumour excision. It involves three type of resections: cordectomy, hemiglottectomy and fronto-lateral hemilaryngectomy. These resections are not well adapted in case of massive involvement of the anterior commissure. In fact, they do not allow adequate excision of the cricothyroid membrane, the thyroid cartilage or the anterior part of the paraglottic space even if a fronto-lateral hemilaryngectomy is performed, which results in a high local recurrence rate at the level of the thyroid cartilage and prelaryngeal tissue. The local recurrence rates following VPL are, respectively, 13.1% and 22.3% for T1b and T2 glottic lesions [19]. SCPL with CHEP according to the technique of Majer and Piquet or Guerrier allows optimal resection of glottic tumours. It enables adequate tumour resection in case of massive involvement of the anterior commissure and/or less than 5 mm extension to the subglottis. The near total laryngectomy with epiglottic reconstruc-

tion according to the Tucker technique [20] is an alternative to SCPL-CHEP. It has a common point with the SCPL according to the Guerrier technique, of preserving the posterior part of the thyroid cartilage and not to dissect the pyriform sinus mucosa. These two techniques differ by the reconstruction procedure; the first uses the epiglottis to reconstruct the anterior part of the resected thyroid cartilage, and the second performs a CHEP for anterior laryngeal reconstruction [6]. Local control rates for T1 and T2 carcinoma of the vocal folds treated by the Tucker technique and SCPL are equivalent. They vary between 90% and 95% for T1 tumours and from 80% to 90% for T2 tumours. These rates exceed 95% if we take into consideration salvage surgery by total laryngectomy [6 21].

The recurrence-free survival rate at 5 years that we achieved in our study (87.7%) is consistent with literature data on SCPL-CHEP (80% to 86.8%) [6 22 23]. The lack of a significant survival difference between the group of patients with T1 and T2 tumours has also been reported in the literature [6]. Disease control failure can be local, regional (lymph nodes) and general (metastasis). In our study, when we analysed the 6 cases in whom we performed total laryngectomy salvage surgery, 4 patients (66.6 %) had a subglottic extension more than 5 mm. Tumour extension to the subglottis is considered as a limitation for the indication of SCPL and any extension to the subglottis more than 5 mm is considered as a contraindication for this type of surgery; otherwise, a supratracheal partial laryngectomy should be performed with different functional and oncologic outcomes [6 24]. The regional recurrence rate is very low in our experience (1.8%) which is concordant with the literature (1.2% to 5.7%) [6 25]. Metastatic lesions are also rare in our series (1.8%), which is consistent with the experience of other teams [6]. On the other hand, our cohort had 13.2% of metachronous lesions which is higher than the mean rate reported in the literature (9.8%) [6 25 26]. This relatively high rate is probably due the high life expectancy of patients treated for T1-T2 glottic carcinomas. Currently, endoscopic laser surgery and transoral robotic surgery represents an alternative to open surgery [27 28]. For transoral robotic surgery, we do not have enough hindsight to determine the effectiveness of this treatment, especially in T1 and T2 tumours with anterior commissure involvement. Concerning laser surgery, it should be done by an experienced surgeon. One of the limiting factors of laser surgery is the quality of exposure of the larynx and in particular the anterior commissure [28]. In many cases, in order to facilitate laryngeal exposure, neck hyperextension and the use of curare may be necessary [28]. For patients with poor endoscopic laryngeal exposure, SCPL should be considered as an alternative to endoscopic laser resection of lesions extending to the anterior commissure to ensure the best possible resection quality. Laser resection represents a type IV cordectomy extended to one or both vocal folds. Treatment of T2 tumours by laser resection shows a local control rate of 85% [29 30]. This rate reaches 90% after taking into account salvage surgery or radiotherapy performed to treat local recurrence after endoscopic laser resection [29-31]. The two main factors influencing local control are involvement of the anterior commissure and extension to the laryngeal ventricle. It appears that local disease control is better with surgery, without any difference between endoscopic and open surgery, in contrast to radiotherapy that shows a lower local control rate, especially when the tumour extends to the anterior commissure and/or to the subglottis. Salvage surgery following radiotherapy allows local control optimisation, but unfortunately it is usually non-conservative surgery. The very low rate of histological lymph node metastasis allows considering not to perform neck dissection in patients with no clinical and radiological adenopathy, but adequate clinical and radiological (CT-scan) follow-up should be done.

In our study, we analysed the early functional results of SCPL-CHEP. The results that we obtained are satisfactory and concordant with literature data [32]. All patients were decannulated and 98% of patients restored oral feeding with adequate daily caloric intake. In the literature, the average time for nasogastric feeding tube removal is 15 to 19 days [6 25] in comparison to 21 days (median=14 days) in our series. One patient had a gastrostomy feeding tube (1.8%) for a local recurrence with delayed surgical wound healing after salvage laryngectomy and radiotherapy. In the literature, the rate of permanent gastrostomy feeding tube placement is 1.2% [6]. In all published series, the authors emphasise the risk of postoperative aspiration pneumonia and swallowing difficulties especially in elderly patients. This point is consistent with our results and we think that PFTs should be systematic for all patients. Moreover, we insist that patients older than 70 years should be referred to pulmonary consultation before making the decision whether to perform partial laryngeal surgery. Our results showed that the number of preserved cricoarytenoid units does not affect the time or quality of swallowing restoration. In our series, the average time of decannulation was 15 days, which is quite consistent with the literature [6 12]. As for restoration of oral feeding, the time elapsed before decannulation was significantly shorter in the group of younger patients. We found no series that discusses the need to maintain a tracheotomy tube in the setting of SCPL-CHEP. In contrast, the percentage of patients with a tracheotomy after radiotherapy is between 0.5% and 2.2% [9 10]. Moreover, when performing partial laryngeal surgeries with an external approach, complete tumour resection should be a main goal in order to avoid adjuvant radiotherapy toxicity, which is usually considered a relevant issue and can be associated with delayed decannulation due to the development of supraglottic stenosis [33]. The short period of hospitalisation (17.8 days) in our study is explained by the fact that young patients

show a rapid decannulation and restoration of oral feeding periods. In the literature, the functional outcomes in case of endoscopic laser resection seem to be better whatever the size of the tumour (T1-T2), with a low percentage of tracheotomy and swallowing disorders and shorter hospital stay [31 33]. Nevertheless, the number of published series for T1 and T2 tumours with anterior commissure involvement treated by endoscopic laser resection is still low with selected cases and restricted cohorts of patients.

Conclusions

SCPL with CHEP is an important option for laryngeal surgical preservation, especially for tumours with anterior commissure involvement and/or subglottic extension less than 5 mm. It allows adequate disease control and good functional results as long as the indications are well respected and the surgical techniques are mastered.

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HEAD AND NECK

Design of a customised bridging mandibular prosthesis for complex reconstruction: a pilot study

Realizzazione di una protesi personalizzata per le ricostruzioni complesse della mandibola: studio pilota

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SUMMARY

The gold standard for mandibular reconstruction is universally recognised and consists of the replacement of the bony part of the mandible with a bony microvascular free flap supported by a reconstructive plate. Although this procedure is feasible and reproducible in most patients, at times poor oncological prognosis or poor performance status force surgeons to consider other reconstructive solutions. In these cases, the main alternative in reconstructing a mandibular defect is represented by bridging plates combined with soft tissue flaps. However, repairing a mandibular defect with a reconstructive plate only can lead to a series of diverse complications. The most frequent complications reported are rupture and oral exposure of the plate. In this paper, we describe a new method for mandibular reconstruction using a customised bridging mandibular prosthesis (CBMP) without bone free flap.

KEY WORDS: Computer-aided design • Computer-aided manufacturing • Mandibular reconstruction • Reconstructive surgery • Bridging plate • Prosthesis

RIASSUNTO

La ricostruzione mandibolare è attualmente effettuata mediante il trasferimento di lembi liberi rivascolarizzati di tessuto osseo, supportati da placche di osteosintesi. Sebbene questa procedura sia generalmente efficace e riproducibile, talvolta la scarsa prognosi oncologica o le condizioni cliniche scadenti del paziente costringono il chirurgo a considerare alternative ricostruttive. In tali casi, la principale possibilità è rappresentata dall'utilizzo di placche ricostruttive 'a ponte', associate a lembi liberi di tessuti molli. Comunque la ricostruzione così concepita espone a un significativo rischio di sviluppare complicanze di vario genere. Le più frequenti complicanze sono rappresentate dalla rottura e dall'esposizione della placca. In questo articolo descriviamo un nuovo metodo ricostruttivo mandibolare, che si avvale di una protesi mandibolare customizzata, senza lembo libero osseo.

PAROLE CHIAVE: *Progettazione computer-assistita • Costruzione computer-assistita • Ricostruzione mandibolare • Chirurgia ricostruttiva • Placca a ponte • Protesi*

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Introduction

Mandibular reconstruction after wide bone resections is a well-standardised procedure. The gold standard for mandibular reconstruction is universally recognised and consists of the replacement of the bony part of the mandible with a bony microvascular free flap supported by a reconstructive plate [1-3].

Although this procedure is feasible and reproducible in most patients, at times poor oncological prognosis or poor performance status together with other relative or absolute vascular contraindications force surgeons to consider other reconstructive solutions [4-6]. In these cases, the main alternative in reconstructing a mandibular defect is represented by bridging plates combined with soft tissue flaps, especially when the condyles are bilaterally preserved [7-9]. Considering biomechanical and structural results, this procedure guarantees a reasonable alternative to a bony free flap reconstruction [4].

However, repairing a mandibular defect with a reconstructive plate only can lead to a series of diverse complications. The most frequent complications are rupture and oral exposure of the plate [10 11]. The latter complication is mostly due to the misplacement of plate positioning during the surgical reconstructive procedure. In both cases, the plate has to be removed, creating a challenging surgical scenario for the surgeon. In fact, after the removal of a mandibular plate, a secondary approach and mandibular reconstruction is always difficult due to the lack of healthy bone on which to fix the new plate.

In this paper, we describe a new method for mandibular reconstruction using a customised bridging mandibular prosthesis (CBMP) without bone free flap.

Clinical techniques and technologies

A 70-year-old patient had the following clinical history: onset of mandibular pain and swelling since 2011. The symptoms persisted after therapy with antibiotics and painkillers. Four years earlier the patient had been surgically treated for prostate adenocarcinoma.

Afterwards, he developed multiple bone metastases. These were treated with chemotherapy associated with zolendronic acid. The patient clinically presented multiple skin and oral fistulas of the anterior region of the mandible and a large bisphosphonate-related osteonecrosis of the mandibular bone.

Since he was affected by multiple bone metastases (lower leg, ankle, spine), fibular and DCIA free flaps reconstruction was not appropriate. Therefore, the procedure chosen for the correction of the defect, after mandibular segmental resection, was the use of a reconstructive plate and a soft tissue microvascular free flap (anterolateral thigh flap, ALTF).

Ten days after surgery, plate exposure appeared in the anterior vestibular oral region of the mouth. The exposure became larger, exposing all the anterior sector of the plate (Fig. 1). Furthermore, the lack of soft tissue anchors allowed the mouth to posteriorly and inferiorly collapse.

When the patient came to our Department, four months after the previous surgery, we identified bilateral rami anti-version and rotation without condyle displacement (Fig. 2). This was probably caused by an intra-operative misplacement of the reconstructive plate, which was partially responsible for its oral exposure.

Therefore, 5 months after the first surgery, we decided to replace the reconstructive plate with a customised bridging mandibular prosthesis (CBMP).

Virtual planning began by processing Digital Imaging and Communications in Medicine (DICOM) files from CT scan data of the patient, using Rhino software, version 4.0 (Robert McNeel & Associates, Seattle, WA, USA).

Superimposition of pre-resection CT scan and post-resection CT scan of the mandible was performed according to a best-fit algorithm using 3-Matic software (Materialise, Leuven, Belgium). This demonstrated the displacement of both of the mandible rami (Fig. 3). The virtual project was carried out with a biomedical engineer (SINTAC s.r.l. Biomedical Engineering, Trento, Italy), realising a CBMP to reach our surgical goal.

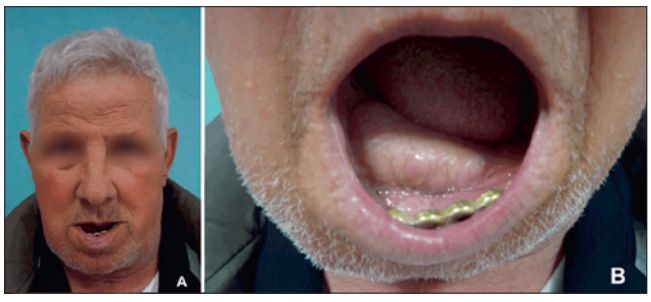

Fig. 1. Clinical view of reconstructive plate exposure. A: facial appearance. B: intra-oral exposure.

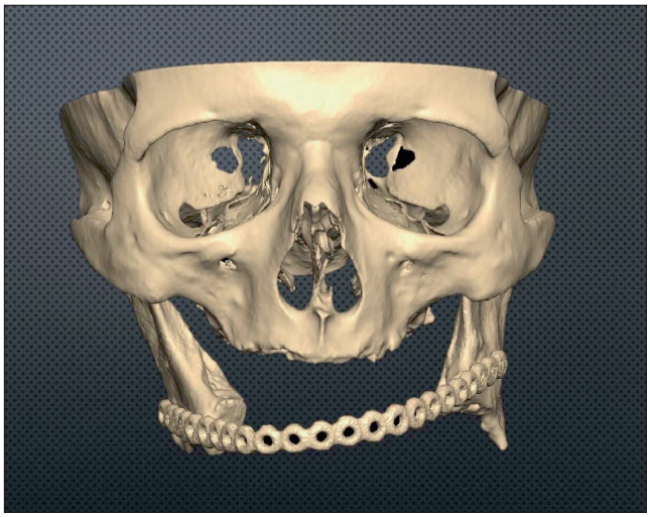

Fig. 2. 3D model of CT showing bilateral rami anti-version and rotation without condyle displacement.

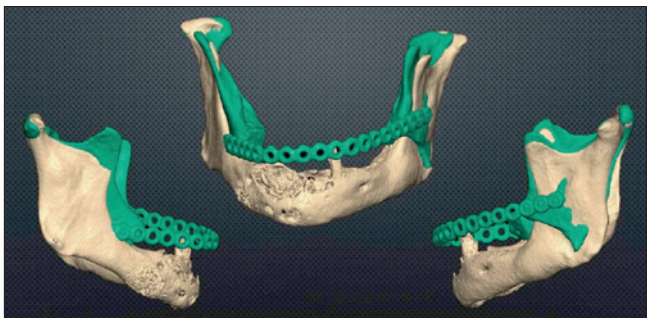

Fig. 3. Superimposition of native mandible (yellow) and post-resection (green) CT-scan data showing mandibular rami displacement.

The virtual planning consists in the mandibular rami repositioning as well as in the pre-resection situation. Afterwards, a CBMP was designed in order to reconstruct the anterior part of the mandible and restore mandibular continuity. CBMP was designed on the internal (lingual) cortical bone surface of the native mandible in order to reduce the tension on soft tissues of the chin region (Fig. 4). CBMP was designed as a mandible-like bridging prosthesis, with a rounded three-dimensional surface in order to reduce the damage at prosthesis/soft tissues interface. The height of the CBMP was 1 cm and the minimum thickness was 3 mm. Two retention titanium structures were designed on each plate-end side to increase hardware stability (Fig. 5).

Twelve holes were provided on the anterior part, corresponding to the chin. These should allow the surgeon to position the anterior digastric and genioglossus muscles on the prosthetic chin. The part of the prosthesis corresponding to the mandibular body has some grooves in order to fix the mylohyoid muscles (Fig. 5). Repositioning

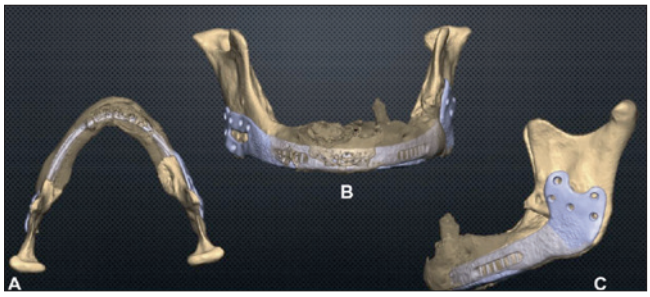

Fig. 4. Computer-assisted design of CBMP. CBMP is designed on the internal (lingual) bone surface of the native mandible. A: inferior view. B: anterior view. C: left view.

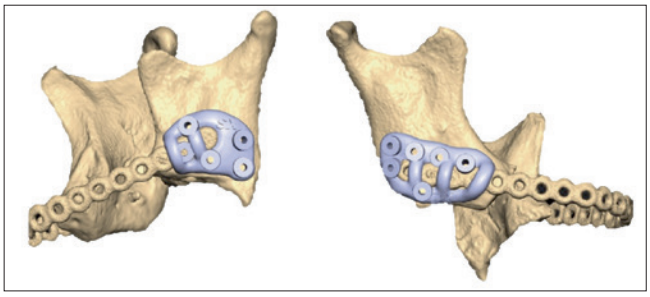

Fig. 6. Computer-assisted design of drilling guides: they were designed to fit on the previously placed reconstructive plate.

the suprahyoid muscles on the CBMP should both avoid the antero-rotation of the mandibular rami and restore more physiological mandibular movements.

To achieve accurate CBMP positioning, we designed two drilling guides (Fig. 6). Their design was made to fit on the previously placed reconstructive plate. This allowed the reduction of potential errors during intra-operative positioning. Drilling guides were used to perform the new screw holes and, since the holes for the fixing screws of the guides were the same as those in the CBMP, to obtain the correct positioning of CBMP and, consequently, of the mandibular rami. The guides were of polyamide and manufactured using a 3-D Printer.

The CBMP was manufactured by a direct metal laser sintering method: titanium Ti64 was fused into a solid component and melted locally using a focused laser beam [12]. The solid-to-layer files of the guide and plate were then manufactured through direct metal laser sintering (DMLS) using an EOSINT M270 system (Electro-Optical Systems, GmbH, Munich, Germany). DMLS was used to fuse the titanium powder into a solid form and then melt it locally with a focused laser beam. As with other additive manufacturing technologies, the components were built up additively in layers.

Cervical surgical access was performed. Oral access was avoided in order to reduce the risk of further future plate exposure, since the oral mucosa and the soft tissue of the ALTF conditions were in good healing status.

Drilling guides were positioned on the pre-planned sites and fixed with screws (Fig. 7).

Then, the reconstructive plate was removed and substituted with the CBMP. Mandibular prosthesis was placed

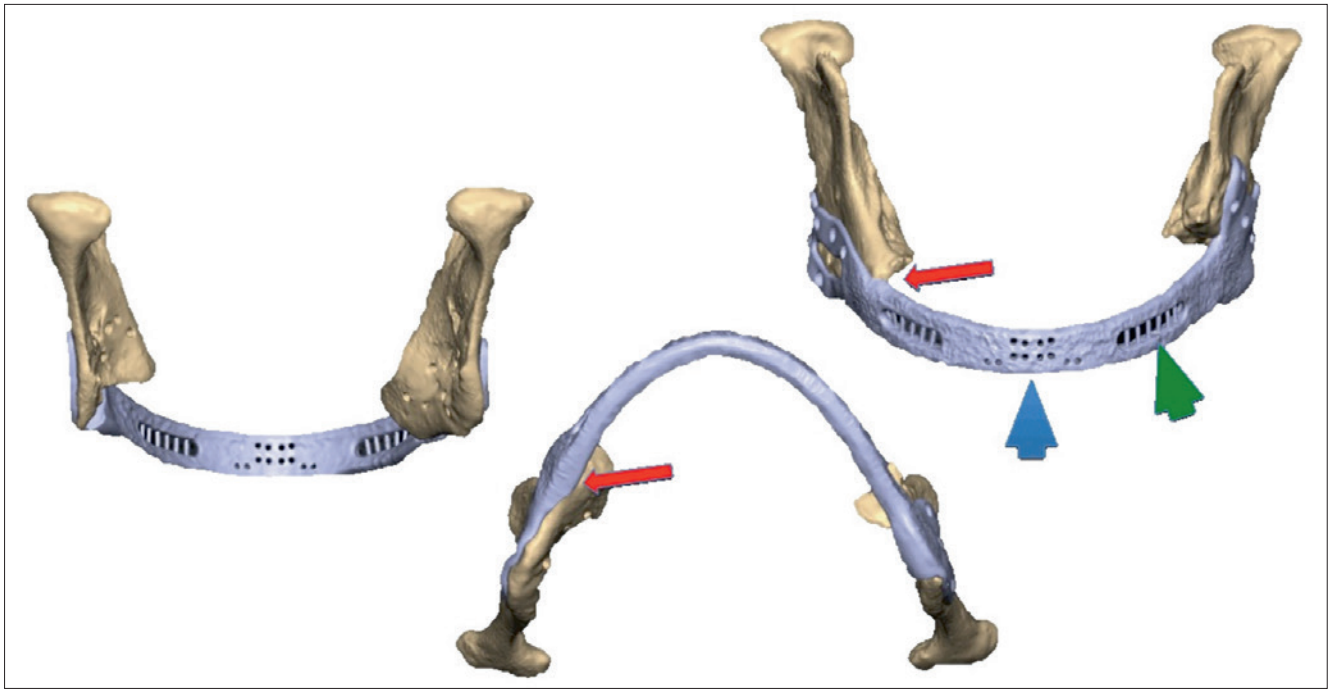

Fig. 5. Computer-assisted design of CBMP. Two retention titanium structures were designed on each plate-end side in order to increase hardware stability (red arrow). Twelve holes were provided on the anterior part (blue arrow). These should allow the surgeon to position the anterior digastric and genioglossus muscles on the prosthetic chin. The part of the prosthesis corresponding to the mandibular body has some grooves in order to fix the mylohyoid muscles (green arrow).

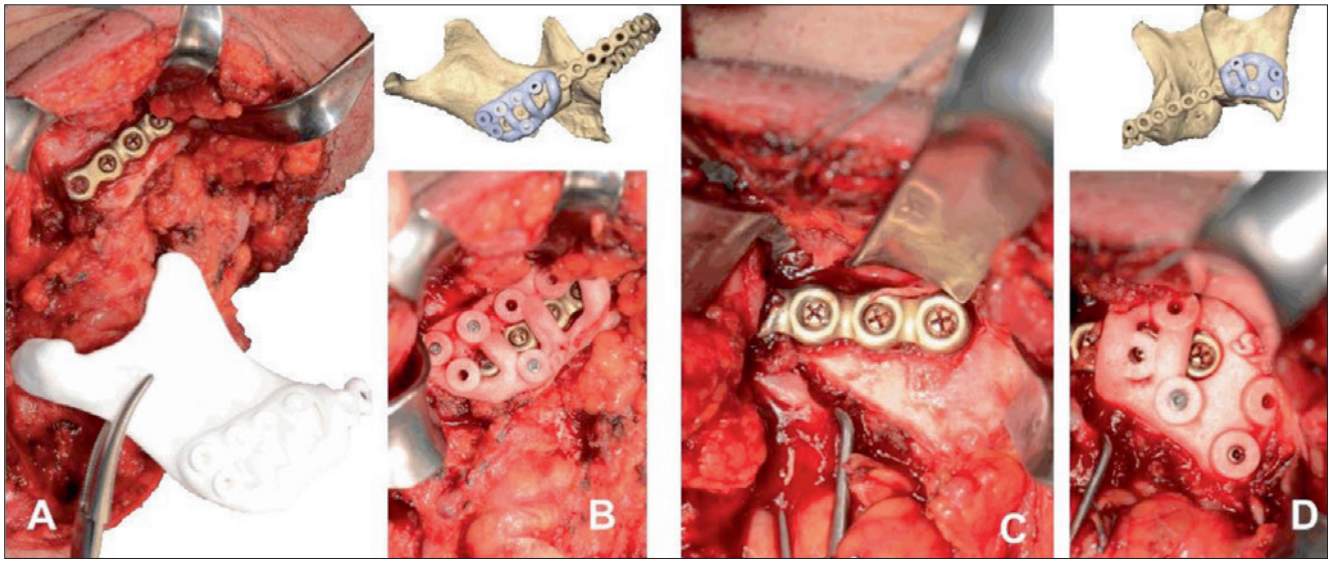

Fig. 7. Intra-operative image showing drilling guides positioning. A: right plate side exposition; B: right drilling guide positioning on the plate; C: left plate side exposition; D: left drilling guide positioning on the plate.

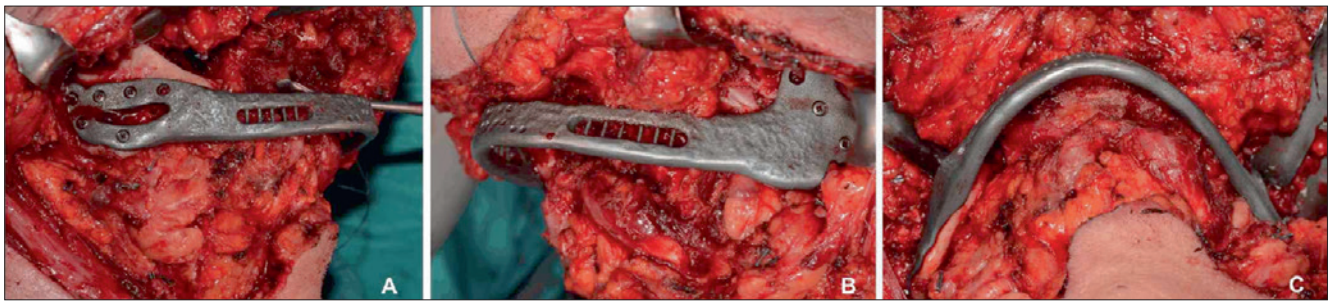

Fig. 8. Intra-operative images showing CBMP positioning. Note the nice fitting of the customised implant to the mandible. A: right view; B: left view; C: inferior view.

by using holes performed following drilling guides and fixed to the bone with 2.4 bicortical screws. The CBMP perfectly fit in the planned position (Fig. 8).

Suprahyoid muscles were anchored to the anterior part of the CBMP using non-resorbable sutures, as well as mylohyoid muscles in the lateral portion of the prosthesis.

The post-operative course was uneventful and the patient was discharged without complications. No radiological signs of CBMP dislocation were identified in post-operative CT scan.

At 3 months follow-up, no oral exposure of CBMP was detected (Fig. 9).

A post-operative CT scan was performed 1 week after surgery to confirm the accuracy of the reconstruction. Morphological results were evaluated using SimPlant O&O software (Dentsply Implants, Mölndal, Sweden). The difference between the virtually-planned and post-operative position of the CBMP was then calculated. The pre-operative CT data set used for virtual planning was superimposed onto the postoperative CT scan, while the "best fit" algorithm of the GOM (GOM mbH, Braunschweig, Germany) 3D software enabled overlapping of the skull to provide the exact points of deviation. These were obtained by determining the deviation between the pre-operative design and post-operative outcome. First, 3D rendering of the bone contour was reconstructed from the post-operative CT scan and exported into the STL

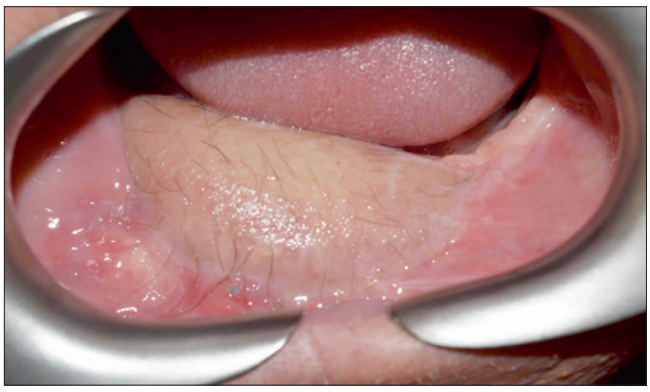

Fig. 9. Intra-oral image showing good soft tissue healing without signs of implant exposure.

files. Second, the pre- and post-operative data were imported into the software using manual and global registration functions to match the non-surgical parts of the two models. A 3D comparison was then performed and the deviation from the pre-operative design was reflected in a deviation spectrum. The program is able to recognise corresponding points from two images and highlight them on the superimposed image using different colours according to the distance between corresponding points. The resulting error grade colour map provides a direct impression of the concordance between the pre-operative design and the post-operative outcome (Fig. 10).

The error grade colour map revealed that good reproducibility was obtained with an average error of 0.4 mm.

In particular, the area of the condyle presented an average error between 0 and 0.4 mm, compared to pre-resection CT-scan; the mandible angle presented an average error ranging between 0 and 0.8 mm and the coronoid a mean error of 1.30 mm (Fig. 10).

Discussion

The state-of-the-art treatment for anterior mandibular defects is primary bone reconstruction, which prevents major facial deformities, provides the lip support that is essential for labial competence, and restores bone for osteointegrated implants [4].

In fact, anterior mandibular arch resections always cause major aesthetic and functional problems: loss of the anterior tongue attachments causes retroposition of the oral cavity soft tissues and suprahyoid muscles, which gives rise to a reduction of airway volume and the loss of oral competence with continuous drooling. Whereas loss of the symphysis and segments of the mandibular body may be so detrimental that the patient becomes a social recluse, determining an Andy-Gump deformity. Consequently, there is an absolute need for reconstruction techniques that not only restore mandibular continuity, but also replace suprahyoid muscles. Reconstruction with bridging plates is an alternative surgical option if microvascular reconstruction using bone free flap is not possible [4]. Although reconstructive plates fixed to the mandibular stumps restore bone continuity and maintain residual occlusion and TMJ function, many complications can occur [5]. The literature has reported plate exposure as the most frequent complication [5]. The possible factors involved are both contracture and a tenuous vascular supply of soft tissues overlying the plate. Scar contracture produces a retraction toward the side of the dead space created under the plate. Consequently, the plate continues to exercise pressure on the overlying tissues and results in necrosis and exposure over time [5]. Furthermore, the disconnection of the masticatory muscles can be the cause of intraoral plate exposure, especially in patients who underwent anterior mandibulectomy [7]. For this reason, anterior mandibular defects are usually more complex to reconstruct without bone free flaps, compared to lateral defects [4].

The surgical algorithm and procedure described in the present study consisted in the creation of a customised bridging mandibular prosthesis, based on patient's specific mandibular prototyping of the native mandible. Computer-assisted design and computer-assisted manufacturing have recently become a significant improvement in mandibular reconstructions [13 14]. This approach is very useful when secondary reconstruction is performed. In fact, in these cases the local clinical conditions and the quality of the remaining bone are usually not adequate to perform a new plate fixation. Printing titanium CAD/CAM prosthesis helped us to have larger anchorage surface on the bone and larger bone contact. This can reduce the problem relative to plate fracture for inadequate biomechanical forces on the hardware surface.

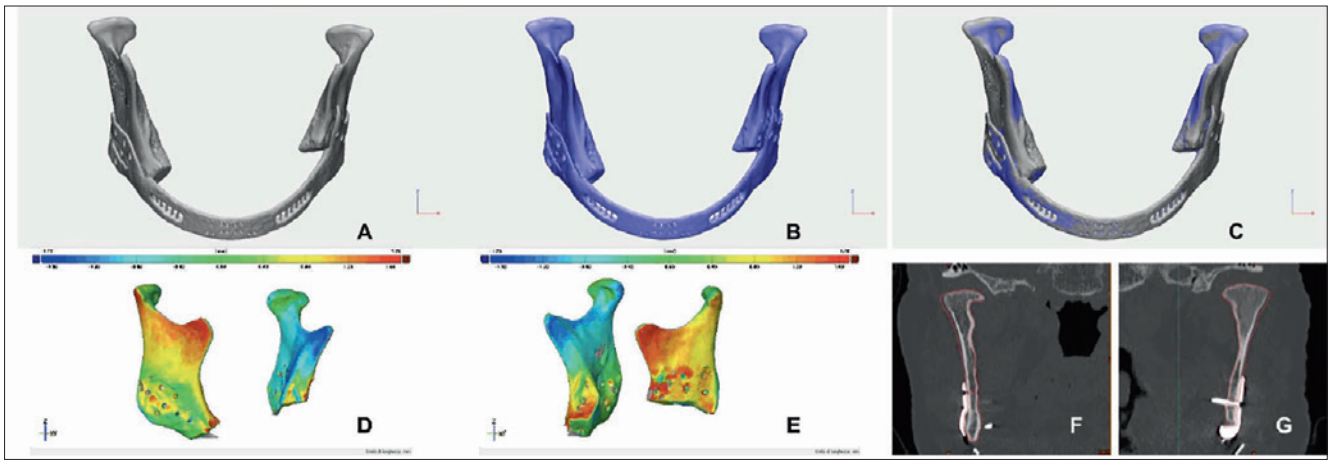

Fig. 10. Post-operative accuracy evaluation. A: virtual planning; B: post-operative 3D CT-scan; C: superimposition of the virtual planning with the post-operative CT scan. D-E: error grade colour map. It provides a direct impression of the concordance between the pre-operative design and the post-operative position of the mandibular rami. F-G: CT-scan concordance between virtual planning (red line) and post-operative situation (coronal view).

Furthermore, virtual planning is of crucial importance for the setting of the new screw holes in the right points of the bone, making this procedure surgically safer. Moreover, this planning permits to have at least 3 points of screw fixation to achieve the best obtainable stability [15].

Biomechanically, the load is efficiently and largely distributed on the new plate, since it has a larger surface than a standard reconstructive plate. In addition, bone-titanium surface contact was realised in order to achieve the best fitting of the CBMP on the mandible.

To reduce the risk of oral exposure, the prosthesis was designed to be more likely positioned along the lingual cortex of the native mandibular bone, thus reducing tension on soft tissues.

Another new feature that we added on the CBMP were the holes for muscle insertion. This way we guaranteed both a better recovery of mandibular movements and the physiological balance between elevator and depressor muscles.

By printing the prosthesis based on the native mandible, we had good aesthetic results for the patient, giving a natural contouring to the inferior mandibular region.

Potential disadvantages of this technique include the cost of designing and prototyping the device. This aspect should be considered in the following way: the effective cost of CBMP should be considered as a tool that can reduce the needing for secondary or tertiary revision procedures for plate dislocation or exposure.

Another disadvantage of the proposed protocol is that it is impossible to obtain dental rehabilitation: due to lack of bone graft, it is not possible to perform implant-supported rehabilitation. In the described case, the patient was edentulous before surgery.

In conclusion, although longer follow-up is needed to evaluate long-term results, CBMP may be a viable method for mandibular reconstruction in patients who cannot undergo microvascular reconstruction with bony free flap.

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Dysphagia

The endoscopic evaluation of the oral phase of swallowing (Oral-FEES, O-FEES): a pilot study of the clinical use of a new procedure

La valutazione endoscopica della fase orale della deglutizione (Oral-FEES, O-FEES): studio pilota sull'uso clinico di una nuova procedura

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SUMMARY

Oral FEES (O-FEES) is an endoscopic procedure conceived to directly visualise the oral phase of swallowing. In the perspective of clinical use, the feasibility, safety and acceptability of O-FEES has been evaluated. Subsequently, the procedure was compared with the radiological gold standard. The acceptability of O-FEES was compared to that of FEES using a 10 point questionnaire submitted to a sample of 52 outpatients complaining of swallowing disorders. Repeated measure analysis of variance (rm-ANOVA) models were used to test the mean difference of acceptability in the same subjects after FEES and O-FEES. Subsequently, another sample of 8 male outpatients underwent a simultaneous O-FEES and videofluoroscopic study (VFSS). The inter-rater reliability using 10 radiological landmarks, compared to O-FEES, was blindly determined between two raters. Inter-rater agreement between the two judges for O-FEES and VFSS scores was assessed with the single score intra-class correlation coefficient (ICC). Differences between FEES and O-FEES answers for each question and among all the items considered overall were statistically significant (rm-ANOVA; F-statistic $p < 0.001$). The inter-rater agreement concerning endoscopic and radiological evaluations between the two raters showed strong values of intra-class correlation coefficient (ICC) (95% confidence interval): 0.875 (0.373-0.979) and 0.921 (0.542-0.986), respectively. The Bland-Altman test showed a bias of -0.24 (95% limits of agreement; -1.77 to +1.19), which suggests that both methods produced almost identical results. In clinical practice and compared with FEES, O-FEES is a well tolerated and safe procedure. Compared with the radiological gold standard, O-FEES offers reliable information about oral preparation and oral propulsion of the bolus.

KEY WORDS: Instrumental examination • Endoscopy • Fluoroscopy • FEES • O-FEES • VFSS • MBS

RIASSUNTO

O-FEES (O-FEES) è una procedura endoscopica, concepita per visualizzare direttamente la fase orale della deglutizione. Nella prospettiva di un utilizzo clinico, la fattibilità, la sicurezza e l'accettabilità dell'O-FEES è stata inizialmente valutata. Successivamente, la procedura è stata confrontata con il gold standard radiologico. L'accettabilità dell'O-FEES è stata confrontata con quello della FEES per mezzo di un questionario a dieci punti, sottoposto ad un campione di 52 pazienti ambulatoriali che lamentavano di disturbi della deglutizione. Il modello Repeated measure analysis of variance (rm-ANOVA) è stato utilizzato per testare la differenza media di accettabilità delle due procedure nello stesso soggetto. Successivamente un altro campione di 8 pazienti ambulatoriali di sesso maschile, è stato sottoposto alla registrazione simultanea di O-FEES e videfluoroscopia (VFSS). L'affidabilità inter-individuale, utilizzando 10 parametri radiologici di riferimento, fra O-FEES e VFSS, è stata determinata alla cieca tra due giudici. La concordanza inter-individuale tra i due giudici, per i punteggi di O-FEES e della VFSS è stata determinata con il Single score intra-class correlation coefficient (ICC). Le differenze FEES e O-FEES tra le risposte per ogni domanda e tra tutte le domande considerate, sono risultate statisticamente significative (rm-ANOVA; F-statistica $p < 0,001$). La concordanza inter-individuale fra la valutazione endoscopica e radiologiche tra i due valutatori, ha mostrato una forte correlazione intra-classe (ICC) (intervallo di confidenza al 95%): 0,875 (0,373-0,979) e 0,921 (0,542-0,986) rispettivamente. Il test di Bland-Altman suggerisce che le due metodiche producono risultati analoghi. Nella pratica clinica e confrontata con la FEES, l'O-FEES è una procedura tollerata e sicura. Rispetto al gold standard radiologico, l'O-FEES offre informazioni affidabili sulla preparazione e propulsione orale del bolo.

PAROLE CHIAVE: *Valutazione strumentale • Endoscopia • Fluoroscopia • FEES • O-FEES • VFSS • MBS*

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Introduction

The oral phase of swallowing has not yet been assessed by endoscopy [1 2]: this seems a limitation of different endoscopic procedures using this tool [1-3]. FEES (Fiberoptic Endoscopic Evaluation of Swallowing) was the first protocol to be proposed [1]. In endoscopy, information about the oral phase of swallowing can be inferred. Base of tongue movements during preparation and propulsion of the bolus and all the events that occur before swallowing can be seen in endoscopy as well as the bolus entering the pharynx and the subsequent motor events before the white-out onset [4]. Moreover, the events that occur after the white-out are better seen in endoscopy. What happens during white-out may be a concern that occurs less frequently compared to the previous conditions [5], and easily confirmed by residues invading the larynx and the cervical trachea. Paradoxically, the ability of endoscopy to rate false routes seems better than fluoroscopy [6]. Nonetheless, there is agreement that fluoroscopy is ideal for viewing the oral phase of swallowing [7].

The oral phase of swallowing is a complex miscellany of events: oral preparatory and oral propulsive are the main stages that occur in the oral cavity and their sequence is strictly joined with the other events of the pharyngeal stage of swallowing. The possibility of direct viewing of the oral events allows a better interpretation of the pharyngeal events with a more precise reconstruction of the entire swallowing act. For this reason, to date, VFSS is considered the instrumental gold standard. However, endoscopy offers a direct view of the anatomical features of the pharynx and larynx, and a direct view of their movement characteristics: speed, precision and range. Endoscopy offers an exceptional view of material pooling or bolus residues, and test sensation. Considering these advantages, during endoscopic evaluation the possibility of direct viewing of the oral events might offer a more comprehensive interpretation of the swallowing sequence, similarly to radiological study [8].

Oral-FEES (O-FEES) is an extension of the FEES procedure conceived to directly observe the oral phase of swallowing [8]. O-FEES offers the clinician a direct view of the oral cavity and its content: in a dynamic perspective, all the events that occur inside the mouth can be seen, except bolus passage through the fauces, due to the white-out.

The aims of this study are to evaluate the: 1) tolerability of O-FEES and 2) inter-rater reliability and concurrent validity by comparing O-FEES with VFSS, limited to predefined radiographical symptoms. The use of O-FEES in clinical practice should allow more comprehensive evaluation of swallowing disorders and provide more useful information for the therapeutic plan.

The preliminary data about pilot experiences in this field are reported below.

Materials and methods

Using a Storz endoscope with a reversible tip of 180° (model 11101RP2, 30 cm long, 3.5 mm in diameter, tip mobility: up 180°, down 90°), starting from a position intermediate between high and low, it is possible to introduce the tip of the instrument into the back of the oral cavity (*anterior position or retrograde position*). From this position, it is possible to see an inverted image of the oral cavity and its content, up to the teeth and lips (Fig. 1a; in Fig. 1b the radiological visualisation of the endoscope in place).

In the experiences described, all evaluations were performed in the usual fashion scheduled in our institution [8 9], completed with bolus tests and recorded with a workstation (Xion medical products GmbH, Berlin Buchholz). Regarding the tests with bolus, it should be specified that there is no general consensus regarding the specifics of the tests nor is there a validated procedure regarding the sequences of

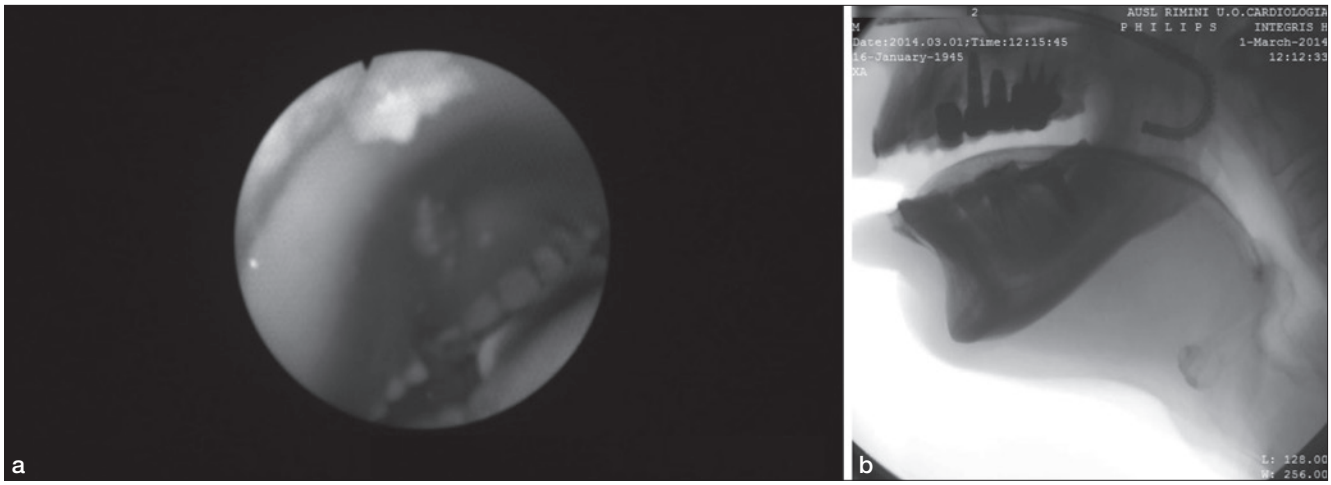

Fig. 1. a) Anterior or retrograde position: the oral cavity is directly visible; b) radiological lateral view. [The a) photographs have been rotated 180° to obtain viewing equal to the real one and make the images more easily interpretable.].

consistencies, volumes and number of trials for each bolus [8]. An average of three boluses for each consistency has been proposed [1-4], although it has been documented that in neurological and in post-surgical head and neck patients, 7 and 2 trials, respectively, are an adequate number to better document, with FEES, aspiration of thin liquids [10].

Tolerability analysis

Both FEES and O-FEES were proposed respectively to a sample of 52 consecutive out-patients (29M/21F, mean age 66.96 yrs ± 15.46, range 22-88) (Table I) complaining of swallowing disorders of different aetiology seen in our swallowing centre from January to March 2014.

After the procedures, each patient was requested to complete a 10-point questionnaire for FEES and O-FEES. Pain, gagging, choking, anxiety and overall tolerability were measured on a 1 to 10 scale, with 1 being well-tolerated and 10 being poorly tolerated (Table II) [11]. Repeated measure analysis of variance (rm-ANOVA) model was used to test mean difference of tolerability in the same subjects after FEES and O-FEES. Cronbach's alpha reliability coefficient was calculated to assess the internal consistency of the tolerability questionnaire, with values above 0.7 indicating desirable levels [12]. Finally, an independent t-test was performed to compare the O-FEES tolerability score between males and females.

Reliability & validity analysis

Eight consecutive male outpatients (mean age 76.00 years ± 10.81, range 56-89) were submitted to a simultaneous O-FEES and VFSS. Patients were complaining of swallowing disorders of different aetiology (Table III). O-FEES was performed with the instrumentation previously described and the endoscope in the anterior position. VFSS was performed with a Philips Poly Diagnostic C and recorded with a cardiac imaging digital recorder, 25 fps, with the samples being recorded on CD support. All patients were firstly submitted to VFSS to clarify the clinical complaint and the physiopathology of the swallowing disorder. Subsequently, they were submitted to simultaneous O-FEES and VFSS. Considering the aim of the study (identification of radiographic symptoms) and to reduce exposure to ionising radiation, during O-FEES it was decided to test only one bolus for each consistency. Thus, during O-FEES, and with the endoscope in place, one bolus of different consistency was given to each patient: creamy, solid and liquid (5 cc for creamy and liquid and ¼ of a cracker). Barium powder (Prontobario HD, Bario Solfato Ph.Eur. 98.45% p/p, BRACCO S.p.A. Milan) was added to the foods and sprinkled on the surface of the crackers, without changing their consistency or palatability. The patients prepared the bolus and swallowed without any command. Some patients were not able to test all three consistencies, owing to the severity of their complaint.

Table I. Tolerability analysis: case series.

No. pts	Main pathology	Mean age (years) Range: 22-88 yrs	Gender
5	Dementia		
3	Radiotherapy sequelae		
1	Myastenia gravis		
2	Post-head and neck surgery		
7	Parkinson's disease		
10	Cerebrovascular disease sequelae		
1	Multiple sclerosis		
2	Steinert syndrome	66.96	29 M 21 F
1	Syringomyelia		
2	Traumatic brain injury		
1	Corea major		
7	Internistic disease		
2	Laryngeal paralysis		
6	Oesophago-gastric disease		
2	Failed O-FEES (GERD, dementia)		
52	TOTAL		

Table II.

10-question assessment of procedure acceptability (anxiety, pain, gagging, or choking with insertion of the endoscope or during the procedure)	
Items	
1	The level of pain that you experienced during insertion of the endoscope *0 = no pain, 10 = severe pain*
2	The level of pain that you experienced during the procedure *0 = no pain, 10 = severe pain*
3	The level of gagging or retching that you experienced during insertion of the endoscope *0 = no gagging, 10 = worst gagging*
4	The level of gagging or retching that you experienced during the procedure *0 = no gagging, 10 = worst gagging*
5	The level of choking that you experienced during insertion of the endoscope *0 = no choking, 10 = worst choking*
6	The level of choking that you experienced during the procedure *0 = no choking, 10 = worst choking*
7	The level of anxiety, nervousness or worried feelings that you experienced during insertion of the endoscope *0 = no worries, 10 = I was terrified*
8	The level of anxiety, nervousness or worried feelings that you experienced during the procedure *0 = no worries, 10 = I was terrified*
9	The level of anxiety, nervousness or worried feelings that you experienced before having endoscopy *0 = no worries, 10 = I was terrified*
10	Overall, how well did you tolerate the procedure? *0 = well-tolerated, 10 = poorly tolerated*

Table III. Reliability & Validity analysis: case series.

Patient #	Main pathology	Gender	Age
1	Arnol-Chiari malformation	M	56
2	MSA-P	M	85
3	Myastenia gravis	M	73
4	Vascular dementia	M	74
5	Parkinson's disease	M	75
6	Supraglottic laryngectomy	M	85
7	Cervical hyperostosis	M	89
8	Steinert syndrome	M	71

Table IV. VFSS parameters considered.

Oral phase parameters	
Preparation	
	Cannot form a bolus
	Cannot hold a bolus
	Abnormal hold position
Propulsion	
	Tongue moves forwards to start the swallow
	Stasis of food on the tongue
	Disturbed lingual peristalsis
	Incomplete tongue to palatal contact
	Adherence of food to the hard palate
	Uncontrolled bolus or premature loss of food into the pharynx
	Piecemeal deglutition

Table V. Differences among the pairs of answers of 10-question assessment of procedure acceptability (F= FEES OF= O-FEES).

Questions	Obs	Mean	Std. Dev	Min	Max	F-statistic p < 0.01
F1	50	3.46	1.232386	1	8	0.000
OF1	50	5.06	1.300078	1	8	
F2	50	2.52	0.762380	2	5	0.000
OF2	50	3.86	1.178203	2	7	
F3	50	2.52	0.862838	1	5	0.000
OF3	50	5.54	1.631451	1	8	
F4	50	1.56	0.674915	1	4	0.000
OF4	50	4.0	1.498298	1	9	
F5	50	2.0	0.968904	0	5	0.000
OF5	50	4.82	1.637444	1	8	
F6	50	1.38	0.966584	0	6	0.000
OF6	50	3.6	1.678191	1	9	
F7	50	3.84	1.283490	0	6	0.000
OF7	50	5.5	1.488048	2	10	
F8	50	2.78	0.840068	2	5	0.000
OF8	50	4.54	1.541401	2	8	
F9	50	4.48	1.216217	2	7	0.0015
OF9	50	4.86	1.178203	2	8	
F10	50	3.28	0.729551	2	5	0.000
OF10	50	5.2	1.525297	2	9	
Total F	50	27.82	6.76332	15	47	0.000
Total OF	50	46.98	11.9223	15	77	

For each patient, short videos were obtained for each oral transit. The videos, collected in pairs for each patient, were seen blindly by two raters.

According to Logemann [13], 10 of 15 parameters (Table IV) were considered for each consistency tested (creamy, solid, liquid). Each rater scored every symptom for VFSS and O-FEES in a binary way, the parameter being present or absent (yes/no response where yes = 1 and no = 0). The scores, for each consistency, were globally considered in relation to the reduced sample. Thus, in this way, the O-FEES and the VFSS scores were calculated as the sum of every score, realised for each symptom, and considered as a single ordinal number ranging from 0 to 10 (arithmetic mean ± standard deviation). This final score expresses the severity of oral impairment of swallowing, stating the 19 symptoms. Timing was not considered.

Inter-rater agreement between the two judges for the O-FEES and VFSS scores was assessed with the single score intra-class correlation coefficient (ICC), which was interpreted as follows: 0-0.2, poor agreement; 0.3-0.4, fair agreement; 0.5-0.6, moderate agreement; 0.7-0.8, strong agreement; > 0.8, almost perfect agreement. To validate O-FEES with VFSS (used as "gold standard") the Bland-Altman test was used.

All statistical analyses were performed with SPSS 21 software.

All patients were over 18 years old and gave written consent to the procedures, according to the Declaration of Helsinki.

Results

Regarding the tolerability analysis, of the 52 participants who were enrolled in the study, 50 (96%) completed both procedures: 2 patients discontinued O-FEES secondary to excessive gag. No participant experienced any adverse event or complication. The mean and standard deviation for each answer to the 10 questions are reported in Table V. The major differences between the pairs of answers was noted for answer 3 (gagging during insertion), answer 4 (gagging and retching during the procedure), answer 5 (choking during insertion) and answer 8 (anxiety during procedure). The difference between the means for overall tolerability (question 10) was 1.92. Differences between FEES answers and O-FEES answers for each question and among all the items considered overall were statistically significant (rm-ANOVA; F-statistic $p < 0.01$). For FEES and O-FEES answers, Cronbach's alpha reliability coefficient was, respectively, 0.88 (CI, 83-92) and 0.94 (CI, 91-96) and can be considered to be highly consistent. The total O-FESS tolerability score (mean males 45.6; mean females 47.7) did not document any difference between male and female, with a t-test p value of 0.76.

Considering the reliability and validity analysis, the inter-rater agreement concerning endoscopic and radiological

evaluations between the two raters showed a good value of intra-class correlation coefficient considering the parameters evaluated by O-FEES and the parameters evaluated by VFSS. In the first case, the intra-class correlation coefficient (ICC) (95% CI) was 0.875 (0.373-0.979), and in the second case it was 0.921 (0.542-0.986). The Bland-Altman test showed a bias of -0.24 (95% limits of agreement; -1.77 to +1.19), which suggests that both methods produced almost identical results.

Discussion

The events that occur in the oral cavity during mastication and propulsion are a complex sequence of neuro-muscular acts, linked with the pharyngeal bio-mechanical events that coordinate breathing and the passage of the bolus through the pharyngeal cavity. Mastication, in particular, requires the coordination of lips, cheeks, tongue, floor of mouth muscles and saliva to chew food until obtaining the bolus. VFSS is the best instrumental examination for a complete view of the oral phase of swallowing. Logeman [13] listed the main topics to consider during evaluation and reporting of this phase.

O-FEES, a procedure conceived to directly view the oral cavity during swallowing, gives information about oral preparation and propulsion of the bolus, as well as residue after swallowing.

According to the experience reported, O-FEES, although accepted and safe, (only 2 of 52 patients did not tolerate it, without any complication during the study) seems to be more uncomfortable compared to FEES. Table V shows a large variability in the scores of the pairs of answers, which were all statistically significant. Insertion of the endoscope and feeling of gagging during the procedure seemed to be the major concerns of patients. The difference between the means for anxiety and overall tolerability was nonetheless quite low. In addition, the sum of the final total scores was significant. The overall tolerability of O-FEES is probably decreased if the oral cavity is smaller and more sensitive compared to the pharygeal cavity. Furthermore, with an equal volume and consistency of the bolus, the oral phase takes a comparably longer time to be concluded compared with the pharyngeal phase of swallowing: during this time, the contact of the endoscope with the mucosa may be perceived as disturbing by the patient, if not outright painful. Although the male's pharynx is larger than the females, gender differences in tolerability were not documented in our experience. Probably the relationship between FEES and O-FEES tolerability could be mainly influenced by individual anatomical variations (surface/volume) rather than variations due to gender. In addition, the dexterity of the clinician in carrying out such a delicate procedure must be taken into account.

Regarding comparison with the gold standard, it was decided to consider a simple rate expressing the status for each parameter (radiographical symptom) selected by Logeman [13] to be present or absent (yes/no response). No other diagnostic considerations about preparation, propulsion and timing were made, considering that at this stage, in this preliminary study, only the ability of O-FEES to evaluate oral events (yes/no events) was tested, without any other more sophisticated considerations.

With these premises, it can be noted that the agreement between the scores attributed by the two raters to both O-FEES and VFSS was strong, and the results of O-FEES and VFSS scores are correlated to each other, that is O-FEES can be considered valid compared with the radiological gold standard relatively to the parameters selected. It can be disputed that only approximate radiological parameters have been considered, despite the complexity of the oral phase: this is true but the research, at this stage, does not allow further detailed considerations.

Conclusions

A new procedure to directly evaluate the oral phase of swallowing with endoscopes has been proposed. The procedure is a variation of FEES and has been called oral-FEES (O-FEES). The procedure is feasible without any further technological implementation, but only by reversing the tip of the endoscope back in the oral cavity or just behind the soft palate. In this way, the anatomical boundaries of the oral cavity and all the events that occur inside the cavity (mainly the tongue movements as in verbal articulation, maneuvers, mastication, bolus formation) are visible. Considerations can also be made about the efficiency of the oral phase, evaluating the residues after swallowing.

Compared with the radiological gold standard, O-FEES offers reliable information about oral preparation (bolus formation, holding the bolus, abnormal bolus position) and oral propulsion (residues, disturbed lingual peristalsis, incomplete lingual contact, piecemeal deglutition, spillage). For these reasons, O-FEES may offer further clinical information for evaluation of patients with conditions that considerably alter the oral phase of swallowing, such as ALS, Parkinson, chorea, ictus acute/sequelae, radiotherapy: in general, conditions affecting the muscular activities in terms of speed, range of motion, precision and symmetry. Additionally, anatomo-functional alterations due to malformations or surgery sequelae of the lips, tongue, gums and palate, for example, might be directly evaluated. Bearing in mind the previous considerations about the volume and sensation of the surfaces, O-FEES seems to be unsuitable for use in children or in other uncooperative patients, unless otherwise proven by a simple attempt.

In clinical practice and compared with FEES, O-FEES is a feasible and safe procedure. During O-FEES, patients experienced higher levels of pain, gagging, choking and anxiety, although the procedure was accepted and well

tolerated. Differences in tolerance may be due, among other factors**,** to a lack of dexterity on the part of the clinician in performing the procedure.
Attempts are in progress to routinely use O-FEES in clinical practice by involving patients with different aetiologies.

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Rhinology

An "ex vivo model" contributing to the diagnosis and evaluation of new drugs in cystic fibrosis

Un "modello ex vivo" per contribuire alla diagnosi ed alla valutazione di nuovi farmaci per la fibrosi cistica

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SUMMARY

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene. About 2000 mutations have been described so far. We setup an *ex vivo* model of human nasal epithelial cells (HNECs) to study CF patients testing the effect of novel mutations and molecular therapies. We performed sampling (by brushing), followed by culture and analysis of HNECs using a series of molecular techniques. We performed 50 brushings from CF patients and controls. Using cultured cells, we: i) demonstrated the widely heterogeneous *CFTR* expression in patients and in controls; ii) defined the splicing effect of a *CFTR* mutation; iii) assessed the CFTR gating activity in patients bearing different mutations; iv) demonstrated that butyrate significantly enhances *CFTR* expression. Based on our data, we can conclude: 1) HNEC brushing is performed without anaesthesia and is well tolerated in all CF patients (children and adults); 2) HNECs can be preserved for up to 48 hours before culture allowings multicentre studies; 3) HNECs culture can be considered a suitable model to study the molecular effects of new CFTR gene mutations and/or uncertain meaning specific mutations of carriers; 4) an ex vivo model of HNECs may be used to evaluate, before human use, the effect of new drugs on patients' cells bearing specific CFTR mutations; 5) the methodology is adequate for a quantitative measurement, by fluorescence, of the CFTR gating activity of the HNECs from patients with different genotypes identifying: a) CF patients bearing two severe mutations with an activity < 10% (compared to controls – 100%); b) CF patients bearing at least a mild mutation with an activity of 10-20%; c) CF carriers (heterozygous subjects) with an activity between 40-70%.

KEY WORDS: CFTR • Nasal brushing • Cystic Fibrosis • CF • Mutations

RIASSUNTO

La fibrosi cistica (FC) è una malattia autosomica recessiva causata da mutazioni nel gene CFTR (Cystic Fibrosis Transmembrane conductance Regulator). Finora sono state descritte circa 2000 mutazioni, ma per la maggior parte di esse è difficile definirne l'effetto senza complesse procedure in vitro. Abbiamo effettuato il campionamento (mediante brushing), la cultura e l'analisi di cellule epiteliali nasali umane (HNEC) utilizzando una serie di tecniche che possono aiutare a testare l'effetto delle mutazioni CFTR. Abbiamo eseguito 50 brushing da pazienti FC e controlli, e in 45 casi si è ottenuta una coltura positiva. Utilizzando cellule in coltura: i) abbiamo dimostrato l'espressione ampiamente eterogenea del CFTR nei pazienti e nei controlli; ii) abbiamo definito l'effetto di splicing di una mutazione sul gene CFTR; iii) abbiamo valutato l'attività di gating di CFTR in pazienti portatori di differenti mutazioni; iv) abbiamo dimostrato che il butirrato migliora in modo significativo l'espressione di CFTR. I dati provenienti dal nostro studio sperimentale dimostrano che l'uso del modello ex-vivo di cellule epiteliali nasali è un importante e valido strumento di ricerca e di diagnosi nella studio della FC e può anche essere mirato alla sperimentazione ed alla verifica di nuovi farmaci. In definitiva, in base ai nostri dati è possibile esprimere le seguenti conclusioni: 1) il prelievo delle cellule epiteliali nasali mediante brushing è applicabile senza alcuna anestesia ed è ben tollerato da tutti i pazienti affetti da FC (bambini e adulti), è scarsamente invasivo e facilmente ripetibile, è anche in grado di ottenere una sufficiente quantità di HNECs rappresentative, ben conservate, idonee allo studio della funzionalità di CFTR; 2) la conservazione delle cellule prelevate è possibile fino a 48 ore prima che si provveda all'allestimento della coltura e ciò permette di avviare studi multicentrici con prelievi in ogni sede e quindi di ottenere una ampia numerosità campionaria; 3) la coltura di cellule epiteliali nasali può essere considerata un modello adatto a studiare l'effetto molecolare di nuove mutazioni del gene CFTR e/o mutazioni specifiche di pazienti "carriers" dal significato incerto; 4) il modello ex-vivo delle HNECs consente inoltre di valutare, prima dell'impiego nell'uomo, l'effetto di farmaci (potenziatori e/o correttori) sulle cellule di pazienti portatori di mutazioni specifiche di CFTR; tali farmaci possono modulare l'espressione genica del canale CFTR aprendo così nuove frontiere terapeutiche e migliori prospettive di vita per pazienti affetti da una patologia cronica come la Fibrosi Cistica; 5) la metodologia da noi istituita risulta essere idonea alla misura quantitativa, mediante fluorescenza, dell'attività di gating del canale CFTR presente nelle membrane delle cellule epiteliali nasali prelevate da pazienti portatori di differenti genotipi; in tal modo è possibile individuare: a) pazienti FC portatori di 2 mutazioni gravi con un'attività < 10% (in rapporto ai controlli -100%), b) soggetti FC portatori contemporaneamente di una mutazione grave e di una lieve con un'attività tra 10-30%, c) i cosiddetti portatori "carriers"- eterozigoti - con un'attività tra 40-70%.

In conclusione la possibilità di misurare l'attività del canale CFTR in HNECs fornisce un importante contributo alla diagnosi di FC, mediante individuazione di un "cut-off diagnostico", ed anche alla previsione della gravità fenotipica della malattia; quindi quanto rilevabile dalla misura del suddetto canale permette di prospettare per il futuro la possibilità di valutare meglio i pazienti per i quali il test del sudore ha dato risultati ambigui (borderline o negativi).
La metodica da noi sperimentata consente anche di monitorare i pazienti durante il trattamento farmacologico, valutando in tal modo i reali effetti delle nuove terapie.

PAROLE CHIAVE: *CFTR • Brushing nasale • Fibrosi cistica • FC • Mutazioni*

Acta Otorhinolaryngol Ital 2017;37:207-213

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene that encodes the CFTR membrane cAMP-activated chloride (Cl-) channel. To date, about 2000 mutations have been reported in the disease gene in patients with classic CF and in those with milder, atypical CF that are sometimes difficult to diagnose, particularly in adults [1]. However, only for a few *CFTR* mutations has a molecular effect been defined. Molecular analysis contributes to confirm diagnosis, identify asymptomatic carriers and perform prenatal diagnosis in high risk couples [2]. It is based on the analysis of a panel of the most frequent mutations that identifies about 80% of CF alleles using commercial kits [3]. The subsequent sequencing of the entire coding regions of the *CFTR* gene [4] that includes the study of large rearrangements [5] is available. However, these procedures frequently identify novel mutations for which it is difficult to define the effect and pathogenicity without complex *in vitro* procedures [6].
Furthermore, only symptomatic therapies are available for CF patients, even if, recently, novel drugs that may potentiate the CFTR protein activity or may correct mislocalisation of the mutated protein have become available [7]. Such therapies have an effect only in patients bearing mutations with specific effects, so it is difficult to select patients that may benefit from novel molecular drugs.
We established the sampling, culture and analysis of human nasal epithelial cells (HNEC) using a series of techniques that may help to test the effect of *CFTR* mutations. This *ex vivo* model may contribute either to study the effect of novel mutations and to assess the effect of novel molecular therapies on cells from patients bearing specific mutations.

Materials and methods

Nasal brushing

Informed consent was obtained from patients (legal guardians for minors) before sampling, after a complete description of the aims of the study. All subjects underwent complete ear-nose-throat evaluation. Freshly-isolated HNECs were collected by nasal brushing. After nasal washings with physiological saline to remove mucus (two washings per day in the week before and one washing immediately before sampling), nasal brushing was performed by a soft sterile interdental brush with 2.5 to 3 mm bristles (Paro-Isola, Switzerland) by scraping (Fig. 1a) along the middle portion of the inferior turbinate using gentle backward–forward and rotatory movements (circular movement) in each nostril, under direct visualisation, using a headlamp without decongestant or local anaesthesia (Fig. 1b). Patients were carefully monitored for vital and minor signs, comfort and pain. They were discharged on the same day.

Culture of nasal cells

The sample obtained from each nostril was immediately conserved in a 15 mL tube containing 2.5 mL of RPMI 1640 medium, with 3% antibiotics. Cells were placed on an Eppendorf Thermomixer and agitated at 700 rpm for one hour to remove all cells from the bristles. Once the brush was removed, cells were centrifuged at 2000 rpm for 20 minutes, the supernatant were discarded and cells were resuspended in serum-free bronchial epithelial cell growth medium BEGM (Clonetics, MD). Next, cells were placed in CELL T 25 flasks (Sarstedt Ltd, UK). At confluence of 60%, cells were passed in new flasks after counting using Invitrogen (Italy) Cell Countess. A trypan blue exclusion test was used to establish the total number of viable cells and percentage of viability. Nasal cells can be stored at 4°C

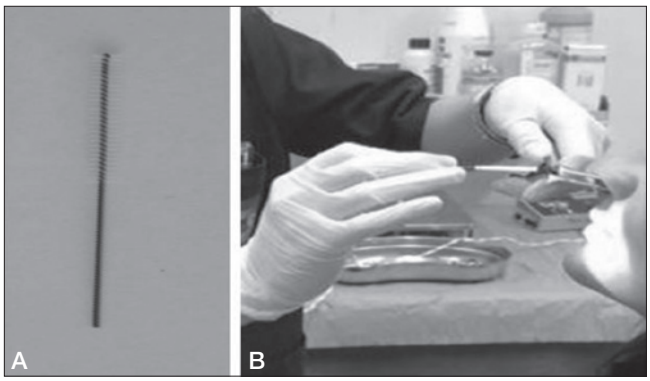

Fig. 1. A) an example of scraping using a soft sterile interdental brush with 2.5 to 3 mm bristles (Paro-Isola, Switzerland); B) ENT specialist during execution of nasal brushing in a patient.

up to 48 h before culturing (using the RPMI 1640 medium), and this permits collecting samples from patients followed in other centres. At a confluence of > 80%, cells were treated with 5 mM sodium butyrate for 24 hours.

Nasal cytology

Epithelial cells were classified into three major categories (ciliated, non-ciliated, striated and basal) on the basis of described criteria [8]. Ciliated cells (target of our study) represent more than 80% of cells obtained from nasal brushing; they have tall columnar shapes with distinct cilia; no ciliated cells, including secretory goblet cells, have similar shape but no cilia; striated and basal cells are smaller with dense, round nuclei, strongly stained cytoplasms, and a high nuclear-to-cytoplasmic ratio. In addition, leukocytes or inflammatory cells may be found in the brushing sample if the patient had an inflammatory condition.

We used May-Grunwald-Giemsa staining of freshly obtained nasal cells to verify the presence of an adequate amount of ciliated cells, and the possible presence of inflammatory cells. The freshly isolated human cells recovered from nasal brushings and spread on silane glass slides were stained with May-Grunwald-Giemsa. After 5 minutes of fixation in methanol, slides were immersed for 5 min in May-Grunwald's standard stain (Fluka Chemie, Switzerland), freshly diluted with an equal volume of phosphate buffer pH 6.8, and then, without washing, immersed for 10 to 15 min in Giemsa stain (Merck, Germany) diluted with 9 volumes of phosphate buffer pH 6.8. After 3-4 rapid washes in phosphate buffer pH 6.8 and 2 to 5 min in water, slides were mounted with Entellan (Merck), covered with glass coverslips and dried for at least 1 hour before analysis. Samples on slides were evaluated for cell differential count and morphology on a conventional light microscope (Zeiss, Germany).

Furthermore, the culture of nasal epithelial cells helps to selectively expand epithelial ciliate cells. To verify that such cells maintain their phenotype after prolonged culture (> 20 days) we used cytokeratin staining. Anti- KRT18/ cytokeratin-18 (CK- 18; Abcam, Italy, ab52948) antibody was used to confirm epithelial cell purity, and that with anti-CD3 +, (Abcam, ab5690), CD4 + (Abcam, ab51312), or CD19 + (Abcam, ab25232) 1:500 antibodies was used to exclude the presence of lymphocytes or inflammatory cells. Moreover, cells were treated with anti-Pan-cytokeratin (C5992, Sigma Aldrich, Italy) 1:500 and MUC5AC (Abcam, ab3649) or MUC3B (Abcam, ab85006) 1:200 antibodies to exclude mucipar differentiation.

Real-time PCR for quantitative analysis of CFTR mRNA

Total RNA was isolated from nasal epithelial cells using TRIzol reagent (Invitrogen, Italy) as previously described [9]. RNA concentration and purity was determined with a NanoDrop ND-1000 spectrophotometer; reverse transcription was carried out on 1 µg of total RNA resuspended in DEPC-treated nano-pure water using a QuantiTect Rev Transcription Kit (Qiagen, CA) using the protocol supplied by the manufacturer. To evaluate levels of *CFTR* transcript in nasal epithelial cells, relative quantification by real-time PCR was performed in duplicates using LightCycler 480 Probes Master containing *CFTR* primers (Roche, Italy) and a TaqMan CFTR probe (ID. Assay 102716). Amplification was carried out with a LightCycler 480 System for real-time PCR (Roche) with a two-step PCR protocol (preincubation for 10 min at + 95° C followed by 45 cycles of amplification: 95°C for 10 sec, 60°C for 25 sec, 72°C for 1 sec). mRNA quantification results were normalised using glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) gene (Roche, ID. Assay 101128) as an endogenous control.

RT-PCR analysis to assess the effect of splicing mutations

All mutations that are located in the exon-intron boundary were, first of all, analysed by prediction software such as Alamut or NetGene2. Next, if *in silico* analysis predicted an alteration of the splicing pattern, we performed an electrophoretic analysis on cDNA obtained by RT-PCR from *CFTR* mRNA extracted from cultured nasal cells. We used different pairs of primers complementary to two (or more) subsequent exonic sequences. Using these primers, intronic DNA sequences retained in the mRNA due to the altered splicing (if present) were amplified, giving rise to one or more bands of greater size compared to wild type.

Quantitative analysis of CFTR channel activity

To test the functionality of the CFTR protein, we used the halide-sensitive fluorescent system. The iodide-sensitive fluorescent indicator, SPQ (Molecular Probes, Invitrogen, M440), was introduced into cells in a hypotonic solution of iodide buffer (130 mM NaI, 4 mM KNO_3, 1 mM $Ca(NO_3)_2$, 1 mM $Mg(NO_3)_2$, 10 mM glucose and 20 mM HEPES, pH 7.4) diluted 1:1 with water and containing a final concentration of 10 µm SPQ. Nasal cells were loaded for 20 min at 37°C in a humidified chamber with 5% CO_2. SPQ-loaded cells were then mounted on a LSM510 meta-confocal microscope with a 37°C heated stage and perfused with iodide buffer. Changes in CFTR-mediated SPQ fluorescence were monitored at 445 nm in response to excitation at 340 nm. Fluorescent was constantly measured by the passage between different solutions containing halide anions. Cells were initially perfused with iodide buffer followed by perfusion with nitrate buffer (NaI replaced with 130 mM $NaNO_3$) with the addition of specific activators of CFTR channel as forskolin (20 µM) (Sigma Aldrich) and genistein (50 µM) (Sigma Aldrich). The peak iodide efflux rate was calculated in accordance with the Stern-Volmer relationship as follows:

$$(F_o/F) - 1 = KC_Q$$

where F is the observed fluorescence, F_o is the fluorescence in the absence of a quenching anion, C_Q is the concentration

of the quenching anion, and K is the Stern-Volmer quench constant. The rates were calculated using SigmaPlot Version 7.1 for each mean fluorescence trace generated from the 50 cells examined per population per coverslip.

Statistical analysis

For real-time PCR, the values of CFTR mRNA are reported as means +/- SD ratio to GAPDH housekeeping mRNA. Rate of chloride efflux was measured in at least 50 cells for experiment. Mean ± SD are those of three experiments. Statistical significance was defined as a p value of < 0.05 vs control subjects.

Results

We collected samples of nasal epithelial cells from 20 healthy volunteers and from 30 CF patients (or carriers) with different *CFTR* mutations. In all 50 cases, the sampling was obtained successfully, with any complication or discomfort for subjects; May-Grunwald-Giemsa staining (performed in 20 cases) confirmed the presence of adequate amounts of ciliated epithelial cells. In all cases we cultured cells and in 45/50 (90.0%) cases we obtained a positive culture. Figure 2 shows an example of the culture of nasal epithelial cells at different days. In 5/50 cases the cells did not expand due to the low number of cells obtained by sampling because of the strong contamination of cells with mucus or with a high number of keratinocytes. In fact, we modified our original protocol, and before sampling we now: i) carefully verify the absence of any clinical condition potentially associated with high mucus production; ii) perform washings with physiological solutions (see Materials and methods).

In order to verify that the culture did not modify the phenotype of cultured cells, we used a panel of anti-cytokeratin antibodies, specific for epithelial cells; furthermore, we assessed, by quantitative RT-PCR, the levels of *CFTR* transcript in cells before culture and at different days of culture until day 20 (in 10 different experiments), and no significant changes were observed (data not shown). Finally, we assessed the effect of storage of cells in transport medium before culture, and in 10 different experiments we demonstrated that cells can be stored at least 48 hr at 4°C before culture.

Next we analysed, by quantitative RT-PCR, the levels of CFTR mRNA as a ratio with the *GAPDH* gene transcript in a control sample from a healthy subject and in CF patients with different mutations (Fig. 3); this analysis can be performed either on RNA from cultured cells or on RNA extracted from fresh sampled nasal cells entrapped in the brush, avoiding culture. The analysis showed a very heterogeneous basal expression of CFTR mRNA. We then treated cultured nasal epithelial cells from 5 controls and 20 patients with sodium butyrate. The treatment caused the enhancement of CFTR mRNA in all cases (see an example in Fig. 4).

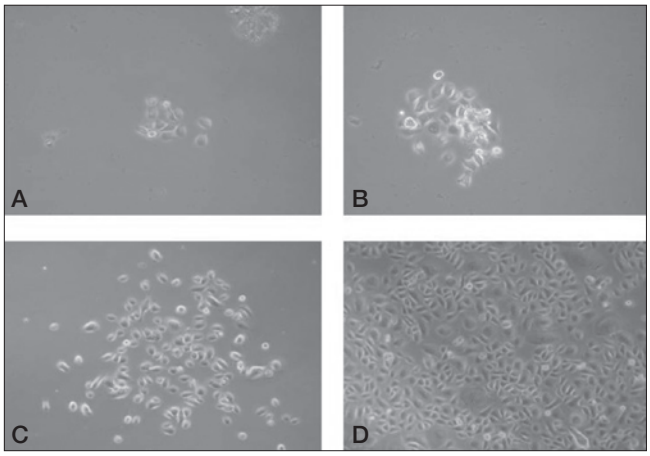

Fig. 2. An example of human nasal epithelial cell expansion at different days of culture. A: 3 days; B: 4 days; C: 7 days; D: 10 days.

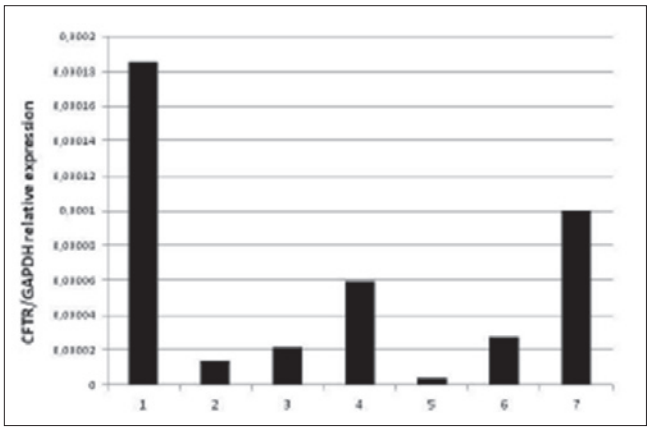

Fig. 3. Quantitative RT-PCR analysis of CFTR mRNA levels expressed as a ratio to the housekeeping GAPDH mRNA. 1: control sample from a healthy subject; 2 to 7: samples obtained from CF patients with different *CFTR* genotypes.

Furthermore, we studied a CF patient heterozygous for the 711 + 1G > A mutation, that was predicted to cause the altered splicing of exon 5. The analysis was performed by RT-PCR, using primers that included *CFTR* exons 4, 5 and 6. Electrophoretic analysis of the cDNA amplicon clearly showed that the 711 + 1G > A mutation caused the retention of intron 5 due to altered splicing (Fig. 5).

Finally, we analysed the quantitative gating activity of *CFTR* in all 30 CF patients or carriers. In all cases, the analysis provided a clear result, and Figure 6 shows several examples: # 1 is a healthy control subject (its activity is considered 100%); # 2 and 3 are two CF patients with two severe mutations each (i.e., F508del/F508del for case # 2 and G542X/4016insT for case # 3): they show an activity of 9.9% and 10.4% compared to the control, respectively; case # 4 is a CF patient with a severe and a mild CF mutation (i.e., W1282X/D1152H), which showed an activity of about 20.3%. Finally, case # 5 is a heterozygous carrier of the severe G542X mutation, which showed an activity of 76.8%.

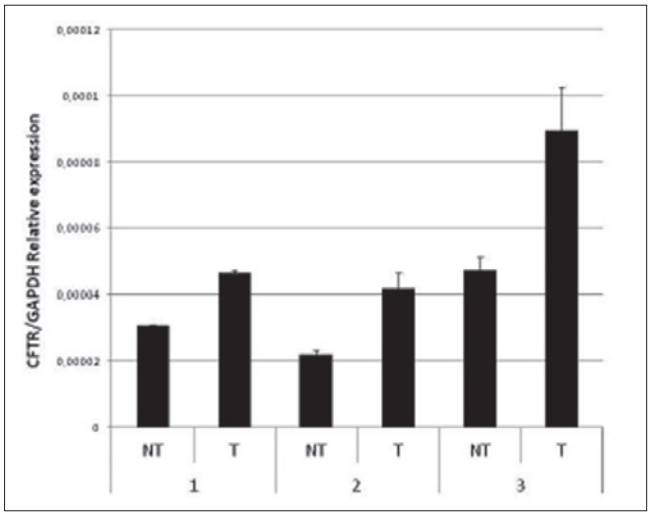

Fig. 4. Effect of butyrate on CFTR mRNA expression. The figure shows the quantitative RT-PCR analysis of CFTR mRNA levels expressed as a ratio to the housekeeping GAPDH mRNA in three samples of nasal epithelial non-treated (NT) and butyrate-treated cells (T).

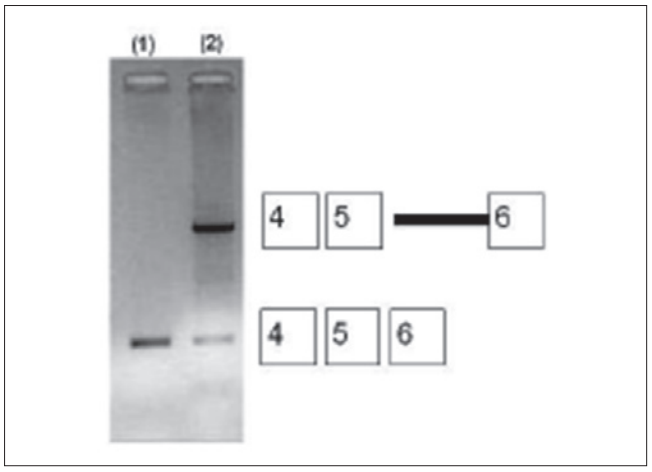

Fig. 5. RT-PCR analysis of CFTR mRNA from a healthy control subject (1) and from a CF patient heterozygous for the 711+1G>A mutation (2). The mutation has a potential effect of altered splicing of the CFTR mRNA causing the retention of an intronic sequence that appears as an electrophoretic band with a higher molecular weight in addition to the normal band also present in the healthy subject.

Discussion

Culture of HNECs is a suitable model to study the molecular effect of *CFTR* mutations and to assess the effects of novel drugs in cells from patients bearing specific *CFTR* mutations. We already used this model to study the effect of butyrate on the expression of the *SLC26A3* gene in patients with congenital chloride diarrhoea [10]. In the present study, we improved and validated the procedures for sampling and culture on a large number of cases, and established procedures for molecular analysis of the *CFTR* gene. The sampling was well tolerated by all 50 subjects studied. Interestingly, the use of the transport medium permits storing sampled cells before culture for up to 48 hours, allowing the analysis of sampled cells from other centres.

Staining with May-Grunwald-Giemsa and anti-cytokeratin antibodies confirmed that we effectively obtained and cultured HNECs without contamination of the culture with inflammatory cells. HNECs can be effectively cultured up to 15 days, as we also demonstrated in a previous study in which we assessed the effect of mannose binding lectin on several types of cells [11]. So far, only a few studies have been performed on the use of human *ex vivo* models for CF. This is mainly because of the invasiveness and the risk of most techniques used to collect human cells, the small number of cells collected, and the limited number, poor quality, and non representative nature of samples resulting from surgery (such as nasal polypectomies or lung transplants). Brushing of the respiratory tract allows easy sampling of numerous, representative, well-preserved and dissociated cells from the superficial mucosa. The group by Garratt et al., recently described the bronchial brushing technique as a possible gold standard model of airway disease in CF, but such sampling requires anaesthesia of patients, and less that 50% of samples could be successfully cultured [12]. Another study examined the use of porcine nasal epithelial cells in culture as a model to study the pathogenesis of sinusitis, but a such model is limited by the possibility to study transgenic pigs with only a single *CFTR* genotype [13].

Other studies used cultured cells from nasal polyps. Recently, for example, a very elegant study carried out proteomic analysis of nasal epithelial cells obtained from nasal polyps [14]. However, the limit of such approach is that only a few percentage of CF patients undergo surgery for rhinosinusitis with nasal polyps [15 16]. The availability of cells from patients bearing specific mutations permits study of the molecular effects of mutations of uncertain significance. For example, mutations within exon-intron boundaries may affect the splicing process (more than two dozen CFTR mutations described so far impair the splicing process), also in addition to silent mutations (i.e., missense mutations that do not change the amino acid) may impair the splicing [17]. The study of the splicing effect of novel mutations would require a complex procedure to express the mutation *in vitro*, followed by the mini-gene assay [17]. This is a rather complex and expensive procedure, and not available for routine use. Conversely, the availability of nasal cells directly from the patient with the mutation to be characterised permits studying the splicing effect with a simple RT-PCR reaction followed by electrophoresis. This analysis can be performed on nasal epithelial cells with no need for culture. Both our group for a mutation [1] and another for two mutations [18] demonstrated that the results obtained with this novel procedure fully match with those obtained with the classic minigene assay.

Quantitative RT-PCR analysis can be performed rapidly on cultured and directly on fresh sampled nasal cells, and can be used to assess the effect of mutations in the promoter region [19] or in other regulatory regions of the gene [20 21] revealing the mutations that may cause a reduced gene expression. Also in this case, a simple quantitative RT-PCR analysis of epithelial nasal cells would avoid the complex and expensive procedure of *in vitro* expression and analysis of mutations in cell lines [19]. However, our study demonstrated that the levels of *CFTR* gene expression are highly heterogeneous in normal subjects and in CF patients, and it would be necessary to study a larger number of healthy subjects to obtain reference values. Quantitative RT-PCR analysis may be used also to assess the effect of potential drugs that may enhance or reduce gene expression, like butyrate, that seems to enhance *CFTR* gene expression.

Finally, we also set up a functional method for the quantitative fluorescence measurement of chloride secretion to assess the gating activity of CFTR protein. Chloride transport across epithelial cell membranes can be assessed using a fluorescent microscopic assay based on the quenching of a water-soluble fluorescent dye, SPQ, by iodide. The possibility to measure the channel activity of CFTR in cells from patients bearing different genotypes is a useful contribution to either CF diagnosis and to the prediction of the phenotypic severity.

In particular, CF patients bearing two severe mutations have an activity < 10%, as in case 2 (Fig. 6; homozygous for the F508del microdeletion) and in case 3 who is heterozygous for the G542X nonsense mutation and for the 4016insT variant, a severe mutation frequently observed in CF alleles from southern Italy [22]. However, CF patients bearing a mild mutation, such as D1152H [23] present in patient 4 shown in Figure 6 shows an activity between 10% and 20%. Of course, quantitative analysis of CFTR in nasal cells can also be used to assess, in the *ex vivo* model from patients bearing specific mutations, the effect of potential drugs like potentiators and/or correctors [7] or molecular therapies [24 25] before their use in humans.

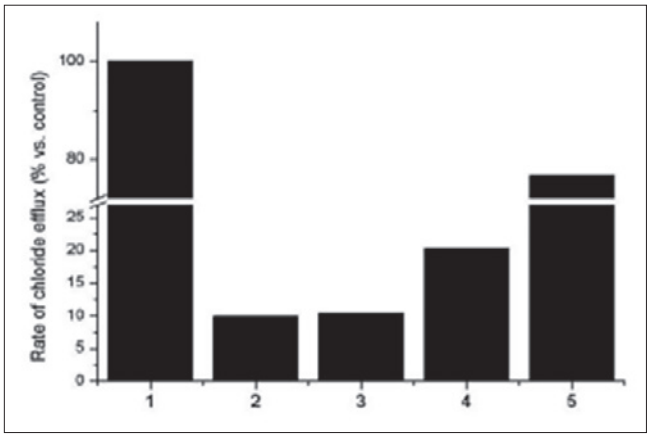

Fig. 6. Quantitative gating activity of *CFTR*. #1 is a healthy control subject (its activity is considered 100%); #2 and #3 are two CF patients compound heterozygous for two severe mutations each (i.e., F508del/F508del for case #2 and G542X/4016insT for case #3): they show an activity of 9.9% and 10.4% compared to the control, respectively; case #4 is a CF patient with a severe and a mild CF mutation (i.e., W1282X/D1152H) with 20.3% of activity. Finally, case #5 is a heterozygous carrier of the severe G542X mutation with an activity of 76.8%.

Conclusions

The *ex vivo* model of cultured HNECs is a very contributory tool to study the pathogenetic mechanism of specific CF mutations directly on cells from the affected patient allowing investigation of the effect of novel mutations and assessment of the effect of novel molecular therapies.

Based on our data, we conclude the following:

1) HNEC brushing can be performed without anaesthesia and is well tolerated in all CF patients (children and adults). It is slightly invasive, easily repeatable, and allows collection of a sufficient amount of representative, well-preserved HNECs, which are suitable for studying respiratory epithelium through a wider range of cell culture techniques;
2) HNEC can be preserved for up to 48 hours before culture, thus allowing multicentre studies with large samples;
3) HNEC culture can be considered a suitable model to study the molecular effects of new CFTR gene mutations and/or uncertain meaning specific mutations in carriers;
4) the ex-vivo model of HNECs may be used to evaluate, before human use, the effect of new drugs (potentiators and/or correctors) on patients' cells bearing specific CFTR mutations; these drugs can modulate CFTR gene expression opening new therapeutic frontiers and better perspectives of life for these patients and others;
5) our methodology is adequate for the quantitative measurement, by fluorescence, of the CFTR gating activity of the HNECs from patients with different genotypes identifying:
   - CF patients bearing two severe mutations with an activity < 10% (compared to controls – 100%);
   - CF patients bearing a mild mutation with an activity of 10-20%;
   - CF carriers (heterozygous patients) with an activity between 40-70%.

In conclusion, the possibility of measuring the activity of the CFTR channel in HNECs provides an important contribution to the diagnosis of CF, by identification of a "diagnostic cut-off", and to the prediction of phenotypic severity of disease. This quantitative channel gating activity measurement improves the ability to evaluate patients with ambiguous results (borderline or negative) at the sweat test.

Moreover, our experimental method allows monitoring patients during drug treatment, and evaluating the real effects of new molecular therapies.

Acknowledgements

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Sleep apnoea

Barbed reposition pharyngoplasty in multilevel robotic surgery for obstructive sleep apnoea

La barbed reposition pharyngoplasty nella chirurgia multilivello robotica per il trattamento delle apnee ostruttive in sonno

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SUMMARY

The surgical treatment of obstructive sleep apnoea in patients who are non-compliant with continuous positive airway pressure therapy still represents a valid alternative. In recent years, the multilevel approach is becoming more diffuse in routine surgical practice, especially since the introduction of transoral robotic surgery. Barbed reposition pharyngoplasty in multilevel robotic surgery for OSA may represent a valid option to surgically approach the soft palate. Herein, we describe the technique and preliminary results of our experience.

KEY WORDS: Obstructive Sleep Apnoea Syndrome • Surgery • Medical failure • Procedure • Robotic

RIASSUNTO

Il trattamento chirurgico delle apnee ostruttive in sonno rappresenta una valida alternativa per i pazienti non complianti al ventilatore CPAP. Negli ultimi anni, l'approccio chirurgico multilivello sta divenendo pratica comune, soprattutto dall'introduzione della chirurgia robotica. La Barbed Reposition Pharyngoplasty nella chirurgia robotica multilivello per OSA potrebbe rappresentare una valida opzione per il trattamento del palato molle. In questo lavoro descriviamo la tecnica e risultati preliminari della nostra esperienza.

PAROLE CHIAVE: *Sindrome di apnea ostruttiva del sonno • Chirurgia • Fallimento medico • Procedure • Chirurgia robotica*

Acta Otorhinolaryngol Ital 2017;37:214-217

Introduction

The surgical treatment of obstructive sleep apnoea (OSA) in patients who are non-compliant with continuous positive airway pressure (CPAP) therapy is still a valid alternative. In recent years, the multilevel approach is becoming more diffuse in routine surgical practice, especially since the introduction of transoral robotic surgery (TORS) [1].

Although in some patients the main site of nocturnal obstruction is the base of tongue (BOT), the soft palate collapse is commonly associated. In the past 2 decades, several surgical techniques have been introduced to manage soft palate collapse [2]. Recently, our group introduced a new surgical approach to soft palate in OSA patients that is promising in terms of efficacy, feasibility and teachability [3]. Herein, we describe the technique in a multilevel robotic surgery setting.

Materials and methods

The study was conducted in compliance with our Institutional Review Board requirements. Between January 2014 and December 2015 at Otolaryngology, Head-Neck and Oral Surgery Unit, Department of Head Neck Surgery, Morgagni Pierantoni Hospital, Azienda USL Romagna, 85 TORS for OSA were carried out. The barbed reposition pharyngoplasty (BRP) was associated in 43 cases. We included all patients who completed a one-year post-operative full overnight sleep study.

All procedures are performed with the patient under general anesthesia who signed an informed consent. Robotic surgery is usually the first procedure to be performed as previously described [4]. Tonsillectomy may be performed robotically or in a traditional approach depending on the surgeon's choice. An important factor is meticulous sparing of the palatoglossus (PGM) and palatopharyngeus (PPM) muscles and as much as possible the mucosal covering both pillars. The centre point closest to the posterior nasal spine (PNS) was marked at the palatal spine, and the pterygomandibular raphe (PMR) in both sides were located by digital palpation and marked (Fig. 1). Next, a partial incision was carried out using a pinpoint bowie monopolar scalpel at the inferior (caudal) part of the PPM.

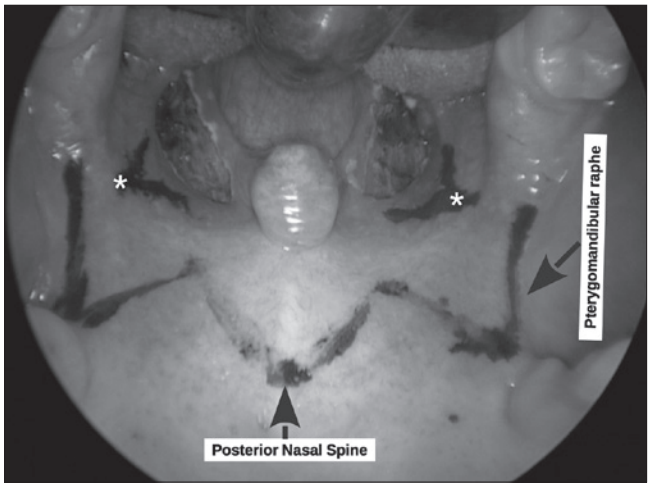

Fig. 1. Marking the landmarks and drawing the suture line including the triangles of superolateral corner of the tonsillar fossa on both sides (*).

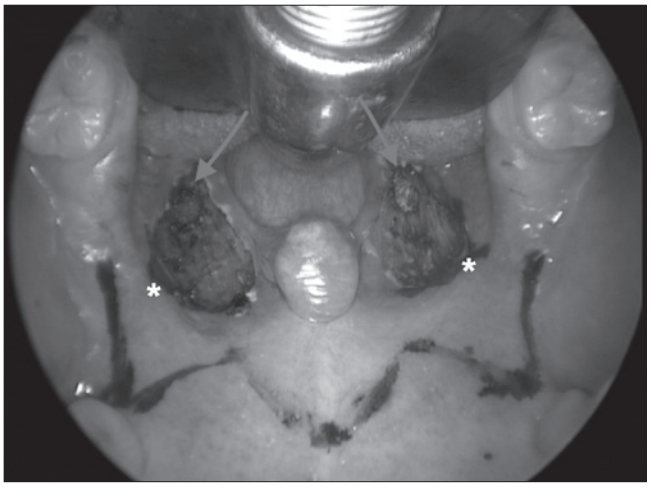

Fig. 2. Incision and releasing of the palatopharyngeal muscle(arrows). Full thickness triangles were removed at the superolateral corner of the tonsillar fossa on both sides (*).

A full thickness triangle was removed at the superolateral corner of the tonsillar fossa to obtain a wider and squared oropharyngeal inlet (Fig. 2). We usually use two needles polydioxanone (PDO) barbed suture (size 0 36 x 36 cm, taper 1/2 circle QUILL Knotless Tissue Closure Device, Surgical Specialities Corp., Vancouver, CA). One needle is introduced at the centre point and then passed laterally within the muscular layer of the soft palate (point 1 to 2 in Fig. 3); the thread is then pulled until it hangs at the central transition zone, which is a free zone between the two directions of the thread. After passing through point 2, the needle is inserted within PMR at the most superior part of the raphe at one side (point 3). The needle again is reintroduced close to point of exit, passing around the PMR, until it exits into the tonsillectomy bed, then through the upper part of the PPM sparing the overlaying mucosa (point 4). The posterior pillar is entered at the junction between the upper third and the lower two-thirds. Then, the needle is again passed back through the tonsillectomy bed and then this suture will be suspended around the PMR (point 5); gentle traction is then applied on the thread only and no knots are made. This leads to stable repositioning of the posterior pillar to more lateral and anterior location without any knot, and then this stitch is repeated at least three times between raphe and muscle till the lower pole of the muscle is reached (point 5 to 7). The opposite side is done by the same way. Finally, each thread comes out at the PMR of the same side, to lock the stitches and prevent looseness; a superficial stitch in the opposite direction is taken, and then the thread is cut while pushing the tissue downward for more traction (point 8). The closure of pillars by single stitches is a surgeon's preference. The final result is widening of the oropharyngeal lateral wall and forward sustaining of the soft palate (Fig. 4). The multilevel surgery is concluded, if required, with a nasal procedure.

Statistical analysis was performed with STATA 12.0 software (Stata Corp., College Station, TX, USA).

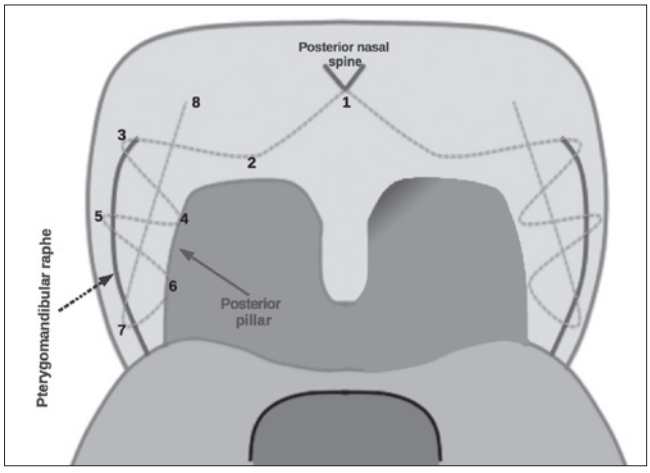

Fig. 3. Scheme of suture points.

Results

Currently, only 10 of 43 patients who underwent BRP associated with TORS completed the follow-up with a full overnight sleep study after one-year post-operatively. The preoperative and post-operative characteristics of patients are shown in Table 1. The median age was 64 years (range 45-74), and the median preoperative apnoea-hpyopnoea index (AHI) and body mass index (BMI) were 32.7 (10-58) and 27.9 (21.7-32.5), respectively. The median preoperative Epworth Sleepiness Scale (ESS) score was 12 (7-15). The usual collapse pattern highlighted by drug-induced sleep endoscopy (DISE) was complete antero-posterior oropharyngeal collapse (O4ap) with involvement of the epiglottis (L+). The median post-opera-

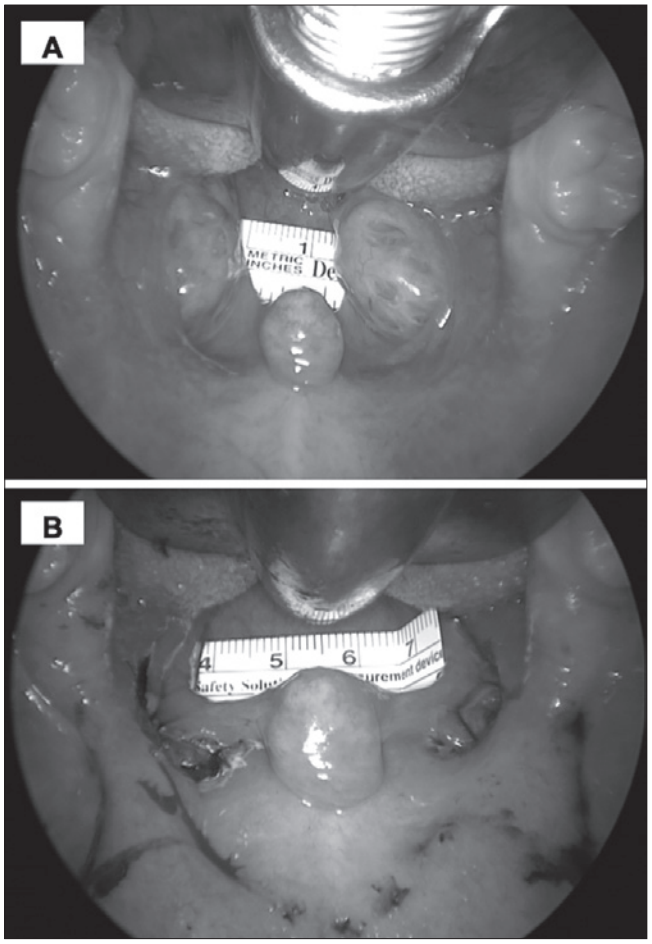

Fig. 4. A) The starting view before the tonsillectomy and the barbed pharyngoplasty. B) Immediate post-operative endoscopic view. Note the increased space between soft palate and posterior pharyngeal wall.

tive values of AHI, BMI and ESS were 16.9 (6.1-45), 28.9 (21.7-31.4) and 4 (0-12) respectively. The mean TORS time was 44.8 ± 22.3 minutes, whilst the mean pharyngoplasty time was 13.5 ± 1.5 minutes. The overall procedure time was 79.3 ± 36 minutes whether nose surgery and/or tracheostomy were done.

The treatment was effective in 7 of 10 patients. Patients #2, #3 and #6 experienced no improvements after surgical treatment. Although further investigation will be required to assess the failure, it is important to note that their BMI increased at the post-operative evaluation and these patients had a severe OSA syndrome. No patients experienced intra-operative, post-operative or delayed complications. Patients #5 and #6 experienced a transient dysphagia that spontaneously resolved within one month.

Discussion

Since 2003, various surgical techniques have been published to address the obstruction caused by the soft palate and lateral pharyngeal wall [2]. However, uvulopalatopharyngoplasty (UPPP) is still the most widely used despite its low success rate and long-term, post-surgical side effects. In 2014, Salamanca et al. [5] described a novel and compelling technique using barbed sutures in anterior pharyngoplasty. The use of this kind of suture showed interesting results in simple snorers or mild OSA-patients with significant fewer complications and reduced operative time. Based on this report, our group developed a new variant of ESP using the barbed sutures [3]. This preliminary study shows promising results in reducing the operative time, efficacy on OSA and a very simple learning curve. Post-operative pain is a common problem in palatal surgery and some patients experience an unacceptable level of intense post-operative pain [6-8]. In BRP, the healing time and post-operative pain is related mostly to tonsillectomy; in fact, in patients who underwent previously tonsillectomy, usually very minimal post-operative pain and rapid oral feeding is reported in our sleep surgery experience. Neither velopharyngeal insuffi-

Table I. Patient characteristics.

Patient	Pre-op BMI	Pre-op AHI	Pre-op DISE classification†	Post-op BMI	Post-op AHI
#1	26.7	42.5	N3O4apH4apL-	26.7	19.4
#2	29.4	20.1	N2O4apH3L+	31.4	33.8
#3	25.7	43	N3O4apH4apL+	29.8	44
#4	29.6	34.6	N3O4cH4apL+	29.6	24
#5	21.7	30.7	N0O3apH4apL-	21.7	14.4
#6	29	58	N0O4apH4apL+	29.2	45
#7	32.5	35.7	N3O3cH3apL+	28.6	11.8
#8	22.6	26	N3O4apH4apL+	22.4	11
#9	22.6	16.6	N0O3tH4cL+	22.6	6.1
#10	30	10	N3O2cH1tL-	29.3	7.5

Pre-op = pre-operative; Post-op = post-operative; BMI = body mass index; AHI = apnea-hypopnea index; DISE = drug-induced sleep endoscopy

† according to Vicini et al. The nose oropharynx hypopharynx and larynx (NOHL) classification: a new system of diagnostic standardised examination for OSAHS patients. Eur Arch Otorhinolaryngol 2012;269:1297-300.

ciency nor nasopharyngeal regurgitation are noted. In this report, we describe our early experience using this technique in multilevel robotic surgery. The technique fits well within the robotic surgery framework because its inherent ease and rapid execution allows reducing surgical times that have a considerable impact on costs.

Conclusions

Barbed reposition pharyngoplasty in multilevel robotic surgery for OSA may represent a valid option to surgically approach the soft palate. Further investigations are needed to evaluate the effectiveness in a large population.

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Audiology

Benefits of active middle ear implants over hearing aids in patients with sloping high tone hearing loss: comparison with hearing aids

Benefici degli impianti attivi dell'orecchio medio rispetto alle protesi acustiche tradizionali nei pazienti con perdita dell'udito per le frequenze acute

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SUMMARY

In this retrospective chart review we compared the subjective and objective benefits of active middle ear implants (AMEIs) with conventional hearing aids (HAs) in patients with sloping high tone hearing loss. Thirty-four patients with sensorineural hearing loss were treated with AMEIs. Of these, six had sloping high tone hearing loss and had worn an HA for more than 6 months. Objective assessments, a pure-tone audiogram, as well as a word recognition test, and the Korean version of the Hearing in Noise Test (K-HINT), and a subjective assessment, the Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire, were performed. Tests were conducted under three circumstances: 1) the unaided state before surgery; 2) the HA-aided state before surgery; and 3) the AMEI-aided state 3 months after surgery. The average high-frequency hearing gain (≥ 2 kHz) was significantly better with AMEIs than with HAs. Although the result had no statistical significance, AMEIs showed a superior word recognition score (WRS) compared to HAs. However, the most comfortable hearing level at which the WRS was tested was significantly decreased with an AMEI compared to an HA. In the K-HINT, patients with an AMEI showed greater recognition than those fitted with an HA under both quiet and noisy conditions. The APAHB scores revealed that patients were more satisfied with an AMEI rather than an HA on all subscales. The use of vibroplasty in patients with sloping high tone loss resulted in positive hearing outcomes when compared to conventional HAs. Based on the data from this study, AMEIs provided better objective and subjective results and could, therefore, be a better alternative for the treatment of sloping hearing loss.

KEY WORDS: Middle ear implant • Hearing loss • High frequency • Hearing impaired rehabilitation • Hearing aids

RIASSUNTO

In questo studio retrospettivo, abbiamo confrontato i benefici oggettivi e soggettivi degli impianti attivi dell'orecchio medio (AMEI) rispetto alle tradizionali protesi acustiche (HA) nei pazienti con perdita dell'udito per le frequenze acute. Trentaquattro pazienti con ipoacusia neurosensoriale sono stati trattati con l'impianto di AMEI. Tra questi, sei avevano un audiogramma "in discesa" con perdita dell'udito per le frequenze acute, ed avevano usato per più di sei mesi HA. È stata quindi eseguita una valutazione oggettiva, tramite l'audiometria tonale e il test di riconoscimento delle parole, una versione coreana del "Hearing in Noise Test" (K-HINT), ed una valutazione soggettiva tramite il seguente questionario: Abbreviated Profile of Hearing Aid Benefit (APHAB). I pazienti sono stati sottoposti ai suddetti test in tre occasioni distinte: 1) prima della chirurgia, senza protesi; 2) prima della chirurgia, con HA; 3) tre mesi dopo l'impianto di AMEI. Il guadagno medio per le alte frequenze (≥ 2 kHz) si è rivelato migliore con AMEI che con HA. Sebbene il risultato non ha raggiunto un livello di significatività statistica, gli impianti attivi dell'orecchio medio hanno mostrato un punteggio di riconoscimento delle parole superiore rispetto a HA. Ad ogni modo, il livello di comoda udibilità al quale il punteggio di riconoscimento delle parole è stato testato si è rivelato significativamente più basso con AMEI rispetto ad HA. Al K-HINT i pazienti con AMEI hanno mostrato un migliore riconoscimento rispetto ai risultati ottenuti con HA, sia in condizione di quiete sia di rumore. Gli score APAHB hanno rivelato che i pazienti erano più soddisfatti con AMEI. L'uso degli impianti attivi dell'orecchio medio in pazienti con perdita dell'udito per le frequenze acute ha permesso di ottenere risultati migliori rispetto all'utilizzo delle protesi tradizionali. Basandoci su questi dati, gli AMEI hanno offerto risultati oggettivi e soggettivi migliori, e pertanto, potrebbero rappresentare una valida alternativa per il trattamento delle ipoacusie con audiogramma in discesa.

PAROLE CHIAVE: *Impianti dell'orecchio medio • Ipoacusia per le frequenze acute • Riabilitazione uditiva • Protesi acustiche*

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Introduction

Sloping high tone hearing loss is defined as relatively intact hearing at frequencies lower than 500 Hz and decreased hearing at frequencies greater than 3 kHz, with thresholds exceeding the low frequencies by more than 30 dB [1]. Sloping high tone loss occurs in up to 31% of patients with hearing loss [2]. Patients with this condition can recognise small sounds, but their speech discrimination ability decreases and they often have difficulty communicating in against a background of daily noise. Most individuals with mild-to-moderate sensorineural hearing loss would benefit from using conventional hearing aids (HAs), but patients with sloping high tone loss do not gain any particular benefit from conventional HAs. It is reported that less than 4 in 10 people use an HA secondary to complaints of occlusion, ear canal discomfort, distortion, feedback, difficulty with background noise, and limited benefit at high frequencies [3].

Open-fitting HAs have recently been developed to overcome these limitations. This type of HA has an open ear mould and the microphone is separate from the receiver, thereby reducing the effects of occlusion and acoustic feedback to some extent. However, because the amplification peak in open-fitting HAs decreases dramatically above 4 kHz, their use in patients with sloping high tone hearing loss remains limited [4]. For this particular population, who fall outside traditional cochlear implant candidacy guidelines and who continue to struggle with HAs, hybrid cochlear implantation has emerged as a potential solution. Its design incorporates a short cochlear implant electrode that is used to electrically stimulate basally located high frequencies, while preserving apically-located low frequencies for acoustic stimulation. Several studies have demonstrated the benefits of this type of implant for speech recognition under both quiet and noisy conditions, as well as for music perception in patients [5 6]. However, hybrid cochlear implantation is not without risk. Patients may lose their residual hearing at low frequencies as a result of surgery, and residual hearing loss following implantation may occur with a shorter electrode that has a reduced capacity to stimulate the apically located low frequencies; therefore, there is always the potential to undergo re-implantation with a standard length electrode design.

Because of these limitations, the role of active middle ear implants (AMEIs) in the treatment of moderate-to-severe sloping high tone loss continues to be explored as an alternative to HAs. The Vibrant Soundbridge® (VSB; Med-El, Innsbruck, Austria) was developed for patients with moderate-to-severe hearing loss and functions by coupling the floating mass transducer (FMT) to the long process of the incus. The VSB comprises an externally worn speech processor and an implanted signal processor (vibrating ossicular replacement prosthesis) with an FMT. Vibroplasty does not occlude the external auditory canal and transmits sound energy to ossicles through direct-drive stimulation; thus, it is not associated with wearing problems and provides adequate and stable functional gain.

Many studies have reported greater hearing performance and satisfaction with vibroplasty than with an HA, as vibroplasty solves the problem of wearing the device in the canal [4 7-12]. The aim of the current study was to evaluate the effect of vibroplasty in patients with sloping high tone hearing loss using both objective and subjective assessments.

Materials and methods

Patients

A total of 34 subjects underwent vibroplasty between October 2011 and October 2013 at our tertiary hospital. Of these, six patients had sloping high tone hearing loss and were included in the study. These patients completed audiological tests and self-assessment questionnaires. Sloping high tone hearing loss was defined as a difference of 30 dB or more between the pure-tone thresholds at 250-500 Hz and 3 kHz in the implanted ear. All patients had worn an HA for more than 6 months before AMEI implantation. The VSB was used for all implanted devices along with the Amade® (Med-EL, Innsbruck, Austria) speech processor. The VSB was switched on at 8 weeks after surgery, and postoperative evaluation was performed after 3 months.

The study was approved by the Institutional Review Board of the Severance Hospital in Seoul, Korea (4-2012-0474).

Surgical procedure

None of the study patients had undergone previous ear surgery. A mastoidectomy and posterior tympanotomy were simultaneously performed. The posterior tympanotomy was performed widely so that the long process of the incus was clearly visible, and was extended anteriorly and superiorly so that the FMT could be safely introduced. The attachment clip of the FMT was firmly attached to the long process of the incus using clippers. An implant bed was drilled into the occipitotemporal bone to fix the implant housing with bone-anchored sutures. Procedures were performed under general anaesthesia in all patients.

Objective assessment

The six selected patients completed a pure-tone audiogram (PTA), word recognition test (the word recognition score; WRS), and the Korean version of the Hearing in Noise Test (K-HINT), both pre- and postoperatively. The PTA was conducted at frequencies of 250-8,000 Hz. The average hearing threshold was defined as the mean of the

following frequencies: 500 Hz, 1 kHz, 2 kHz, and 3 kHz. The WRS was measured at the most comfortable hearing level (MCL) using 50 monosyllabic Korean words that are commonly heard during everyday life.

The K-HINT (HINT pro 7.2; Bio-logic® Systems, Natus Medical Inc., CA, USA) was administered with a commercialised instrument in accordance with previously described methods [13]. The test was performed under both quiet and noisy conditions. The reception threshold for speech (RTS), which is the lowest decibel level at which the patient recognised the presented sentence, was measured under quiet conditions. Noisy conditions were divided into three types – front, right, and left noise conditions – and the noise intensity was fixed at 65 dB. The signal-to-noise ratio (SNR) was calculated as the lowest decibel level at which the patient could correctly repeat around 50% of the presented sentences under noisy conditions with the noise intensity of 65 dB deducted. The composite SNR, which represented hearing under general noisy conditions, was calculated as follows: 2 × (front noise + right noise + left noise) / 4. The gain was calculated as the K-HINT data without the AMEI minus the K-HINT data with the AMEI.

Subjective assessment

The Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire is a reliable tool for quantifying the benefits of various hearing-aided conditions. It consists of four subscales: ease of communication (EC), reverberation, background noise (BN), and aversiveness. Each percentage subscale measures adverse reactions to various environmental sounds. For the APHAB, a lower score indicates a greater level of comfort; for the benefit score, a larger score indicates a greater level of satisfaction. The APHAB score for the HA-aided state was measured preoperatively, and the APHAB score for the VSB-aided state was measured at 3 months postoperatively. The scores were analysed and compared as subscales.

Statistical analysis

An independent *t*-test and a paired *t*-test were used. All statistical analyses were performed with SAS for Windows software (ver. 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics

The mean patient age was 60.8 years (range: 27-76 years) and all patients were male. Four patients wore receiver-in-the-canal (RIC)-type HAs and two wore in-the-canal (ITC)-type HAs. Among these, three patients wore bilateral HAs; two patients stopped wearing contralateral HAs after implantation, and the other patient wished to achieve better hearing ability and decided to receive a hybrid cochlear implant; this patient is now content with using bimodal HAs. Three patients who wore a single HA received the implantation in the same ear, and the contralateral ear was not treated either before or after implantation. Vibroplasty was performed in the right ear in four cases and in the left ear in two cases. Information regarding the patients is given in Table I.

Objective results

The preoperative unaided hearing threshold was 51.9 ± 7.2 dB. The average PTA with an HA and VSB was 44.0 ± 11.9 dB and 40.4 ± 7.0 dB, respectively (Fig. 1A). With the average PTA value, which was defined as the mean of the 500 Hz, 1 kHz, 2 kHz, and 3 kHz frequencies, the difference between the hearing threshold with an HA and that with the VSB was not meaningful. The functional hearing gain (FHG) of each device was then analysed. Again, no significant difference was found between the two devices even though the average FHG was improved with the VSB (11.5 ± 3.1 dB vs. 7.9 ± 8.5 dB, $p > 0.05$). We then analysed the average high-frequency hearing gain, which refers to the mean of frequencies greater than or equal to 2 kHz and is critical for hearing rehabilitation in sloping type hearing loss patients. The high-frequency hearing gain with the VSB was 26.0 ± 3.7 dB, which was significantly better than that with an HA, of 18.1 ± 18.0 dB ($p < 0.05$, Fig. 1B).

The WRS was compared for each device. The WRS improved from 55.7% to 62.3% with an HA, and from 55.7% to 66.3% with the VSB (analysis of variance, $p > 0.05$, Fig. 1B). The WRS was measured at the MCL of each patient, and the initial MCLs, with an HA and the VSB, were compared. The initial MCL, of 77.4 ± 9.5 dB,

Table I. Patient characteristics.

Patient No.	Sex/age (years)	Implant site	Previous usage of HA	HA type	Contralateral ear treatment after implantation
1	M/27	L	Bilateral	RIC	CI hybrid
2	M/76	R	Unilateral	ITC	No treatment
3	M/65	R	Unilateral	RIC	No treatment
4	M/69	R	Bilateral	RIC	HA refusal
5	M/60	L	Bilateral	ITC	HA refusal
6	M/68	R	Unilateral	RIC	No treatment

HA, hearing aid; RIC, receiver-in-the-canal; ITC, in-the-canal; CI, cochlear implant

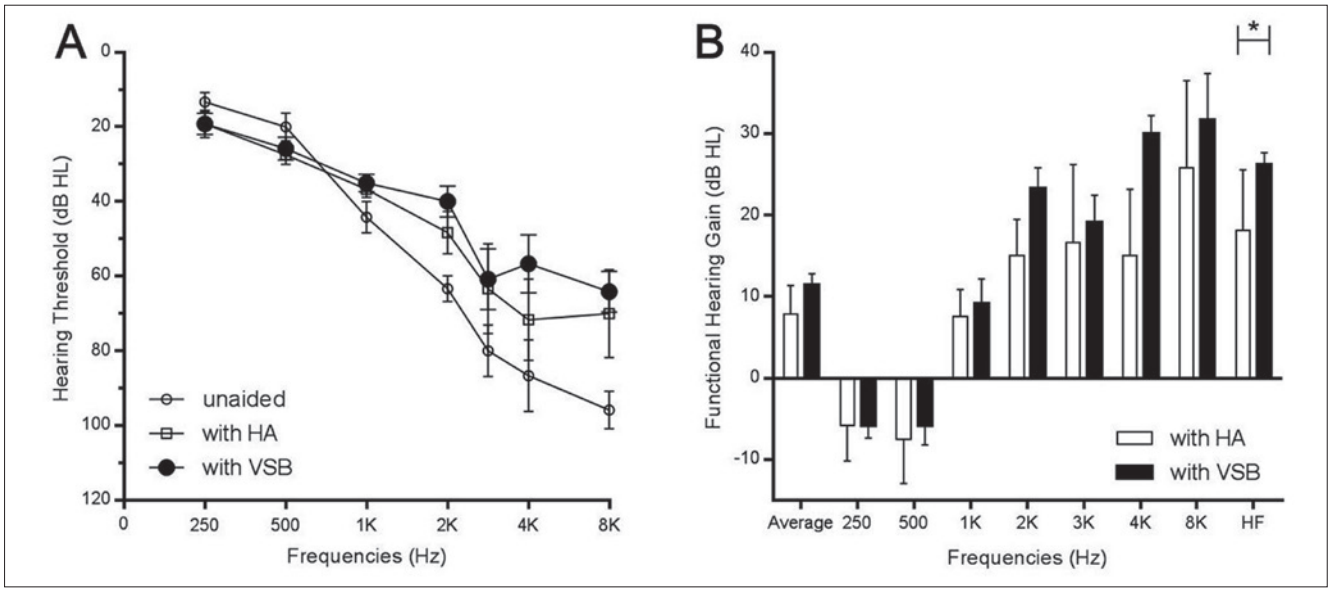

Fig. 1. (A) Summary of the unaided, heading aid (HA)-aided and Vibrant Soundbridge® (VSB)-aided pure-tone thresholds. (B) Functional hearing gain (FHG) as frequencies with HA and VSB. The average FHG did not significantly differ between devices. However, high-frequency hearing gain, which refers to the mean of frequencies ≥ 2 kHz, was prominent with the VSB (26.0 ± 3.7 dB vs. 18.1 ± 18.0 dB, $p < 0.05$).

Table II. Summary of the K-HINT results according to HA and AMEI usage

	Unaided state	With HA	With AMEI
Quiet (RTS)	47.0 ± 10.5 dB	43.2 ± 6.1 dB	35.7 ± 5.3 dB
Frontal noise	4.9 ± 3.7 SNR	4.4 ± 2.9 SNR	2.8 ± 1.7 SNR
Ipsilateral noise	2.9 ± 5.3 SNR	2.3 ± 2.4 SNR	-2.0 ± 3.4 SNR
Contralateral noise	0.6 ± 2.3 SNR	2.0 ± 3.4 SNR	-4.2 ± 1.8 SNR
Composite	3.4 ± 2.9 SNR	2.3 ± 1.8 SNR	-0.3 ± 1.3 SNR

HA, hearing aid; AMEI, active middle ear implant; RTS, reception threshold for speech; SNR, signal-to-noise ratio

decreased to 64.0 ± 7.4 dB with an HA ($p < 0.01$) and to 55.1 ± 6.1 dB with the VSB ($p < 0.01$, Fig. 1B). The MCL with the VSB was also statistically greater than that with an HA ($p < 0.05$).

The K-HINT scores revealed that patients obtained greater benefits from the VSB under both quiet and noisy conditions. The average RTS for the unaided state was 47.0 ± 10.5 dB, improving to 43.2 ± 6.1 dB with an HA and to 35.7 ± 5.3 dB with the VSB. Under the composite noise

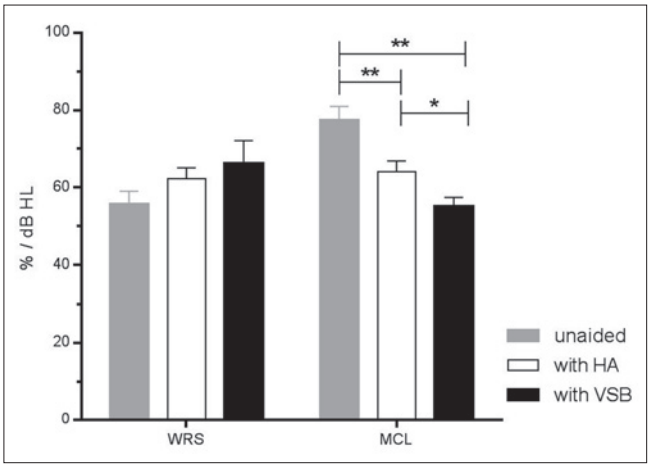

Fig. 2. Improvement in the word recognition score (WRS) and most comfortable level (MCL) at the WRS was measured. Patients benefited most from the VSB, although no significant difference between devices was observed in the comparison of the WRS. The initial MCL decreased from 77.4 ± 9.5 dB to 64 ± 7.4 dB with an HA ($p < 0.01$), and to 55.1 ± 6.1 dB with the VSB ($p < 0.01$). The MCL with the VSB was also statistically greater than that with an HA ($p > 0.05$). * $p < 0.05$; ** $p < 0.01$

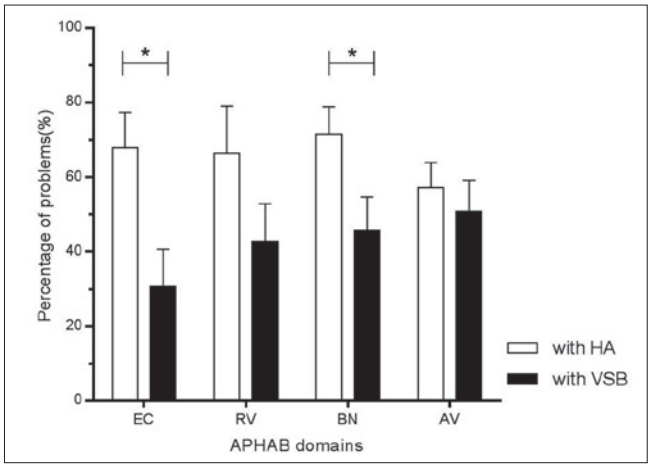

Fig. 3. Comparison of the Abbreviated Profile of Hearing Aid Benefit (APHAB) score with an HA versus the VSB. The APHAB scores were markedly decreased with the VSB. Patients showed greater benefit from the VSB versus the HA on all subscales. EC, ease of communication; RV, reverberation; BN, background noise; AV, aversiveness; * $p < 0.05$; ** $p < 0.01$

condition, the average SNR decreased from 3.4 ± 2.9 dB to 2.3 ± 1.8 dB with an HA, and from to -0.3 ± 1.3 dB with the VSB (Table II). Even though no statistical significance was observed, patients received the most benefit from the VSB under both quiet and noisy conditions.

Subjective results

The APAHB scores decreased markedly with the VSB, with particularly significant improvements in EC and BN ($p < 0.05$, Fig. 3). Even though no statistical difference was found, patients were more satisfied with the VSB compared to an HA in all subscales.

Discussion

This study evaluated the effectiveness of the VSB in patients with sloping high tone hearing loss using both objective and subjective measurements. With the VSB, the average hearing level improved from 51.9 dB to 40.4 dB, and the improvement was notable at mid-to-high frequencies. Similar results have been obtained by previous studies, either in a sensorineural hearing loss group or a mixed/conductive hearing loss group. The VSB system is unable to improve hearing at frequencies of 500, 250, and 125 Hz regardless of whether the FMT is placed on the incus, oval window, or round window [14 15]. Needham et al. explained this phenomenon as being a result of the mass loading effect [16]. A loaded mass (stapes, 3 g; FMT, 25 g) would result in stiffening of the ossicular ligaments, increasing the tension on the joints, and changing the movement pattern of the ossicular chain [17]. This series of processes leads to limited hearing amplification at low frequencies. Moreover, a study that used vibrometry to assess the operating mechanism of middle ear ossicles reported that the stapes shows rotational movement during high-frequency amplification, which is a more energy-efficient movement than simple lever movement [18]. When high frequencies were amplified with the VSB, physiological rotational movement was apparent rather than simple lever energy transmission movement. These results suggest that the VSB amplifies high frequencies sufficiently and effectively. The characteristics of the VSB provide sufficient functional gain to patients with sloping high tone loss up to 65 dB without any side effects [4 8], whereas HAs limit the range of hearing gain due to occlusion effects.

Previous studies have used the WRS to measure speech gain with the VSB, and some studies have reported that the VSB does not provide additional benefits compared to HAs, because the VSB does not lead to a marked improvement in the WRS relative to HAs [1 19]. Similar results were also found in this study. The WRS in the HA- and VSB-aided state hardly differed from each other and it is therefore difficult to demonstrate the benefit of the VSB over HAs. However, in our study the WRS was tested at the MCL, and the level corresponding to the maximum WRS varies considerably between individuals. Although the WRS is one of the critical factors in verifying speech gain, the MCL should be taken into account when determining patients' comfort indices. In our study, the MCL was significantly better with the VSB compared to the unaided or HA-aided states. This could explain patients' preference for the VSB over an HA, even if the hearing gain is comparable between them.

We also used the K-HINT to evaluate speech gain under noisy conditions. Although there was no statistical difference between the unaided, HA-aided, and VSB-aided states, patients with the VSB showed the most improvements in K-HINT scores. They also received the most benefit in contralateral noise conditions. In the K-HINT, a 1-dB change in the SNR generally corresponds to a 9% change in word intelligibility. Thus, theoretically, patients benefit from a maximum word intelligibility rate of 43.2% in the unaided state under the application of contralateral noise [13 20].

We anticipated that the VSB would lead to higher subjective satisfaction than the HA. We measured subjective satisfaction quantitatively using the APHAB score. Patients with the VSB showed obvious improvement in the EC and BN subscales of the APHAB compared to their preoperative scores ($p < 0.05$), and achieved better scores over HAs on all subscales. Several factors are likely to affect subjective satisfaction, of which the first is the problem of wearing the device. The VSB, however, solved the problem of feedback and eliminated the occlusion effect. The other problem concerns the ability to achieve a sufficient level of amplification. In patients with sloping high tone loss, in particular, the amplification of high frequencies consequentially incurs unnecessary amplification of low frequencies that can cause an occlusion effect.

Our study demonstrates the efficiency of the VSB over conventional HAs in patients with sloping high tone loss. A conventional HA showed benefits with fitting; however, the VSB was able to provide much better hearing gain at the mid-to-high frequencies that are essential for conversation. The VSB also provided significant benefits under noisy conditions. Overall, a preference for the VSB, and a good level of satisfaction among patients, were observed in our study.

However, as with all retrospective investigations, this study had some limitations. Firstly, patients were fitted with different types of HAs for different durations, such that it was not possible to guarantee that their device had been fitted optimally. Additionally, a 3-month follow-up period was thought to be sufficient to compare the techniques. However, to enable better comparison, a long-term follow-up is needed. Moreover, further studies should include a greater number of subjects to obtain more accurate results. Nevertheless, to our knowledge, this is the first study to compare unaided, HA-aided, and VSB-aided states in the same subjects.

Conclusions

The use of vibroplasty in patients with sloping high tone loss resulted in positive hearing outcomes when compared to conventional HAs. Based on the data from this study, the VSB provided both better objective and subjective benefits. The VSB could, therefore, be a better treatment option for sloping hearing loss.

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Otology

Expanded transcanal transpromontorial approach to the internal auditory canal and cerebellopontine angle: a cadaveric study

Approccio allargato transcanalare transpromontoriale per il condotto uditivo interno e l'angolo ponto-cerebellare: studio su cadavere

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SUMMARY

The aim of this paper is to describe and evaluate the feasibility of an expanded endoscopic transcanal transpromotorial approach (ExpTTA) to the internal auditory canal and the cerebellopontine angle. To this end, we performed a cadaveric dissection study in September 2015. In total, 2 heads (4 sides) were dissected focusing on anatomical landmarks and surgical feasibility. Data from dissections were reviewed and analysed for further consideration. In all 4 sides of the cadavers the procedure was feasible. In all cadavers, it was necessary to extensively drill the temporo-mandibular joint and to calibrate the external ear canal to allow adequate room to manoeuver the instruments and optics and to comfortably access the cerebellopontine angle. In addition, thorough skeletonisation of the carotid artery and the jugular bulb were necessary for the same purpose. In conclusion, ExpTTA appeared to be successful to access the internal auditory canal and cerebellopontine angle region. Potential extensive and routine application of this type of approach in lateral skull base surgery will depend on the development of technology and surgical refinements and on the diffusion of skull base endoscopic skills among otolaryngologists and neurosurgical community.

KEY WORDS: Cerebellopontine angle • Endoscopic ear surgery • Inner ear • Internal auditory canal • Transcanal approach

RIASSUNTO

Lo scopo dello studio è quello di descrivere e valutare la fattibilità di un approccio allargato transcanalare transpromontoriale al condotto uditivo interno e all'angolo pontocerebellare (ExpTTA). Nel settembre 2015 è stato condotto uno studio di dissezione su cadavere. In totale 2 teste (4 lati) son state dissecate focalizzando l'attenzione sull'anatomia chirurgica. I dati ottenuti dalle dissezioni son stati quindi analizzati. In tutti e quattro i lati è stato possibile eseguire la procedura, e tutti i punti di repere descritti son stati identificati. In tutti i cadaveri si è resa necessaria una ampia fresatura della articolazione temporo-mandibolare e il calibraggio del condotto uditivo esterno per permettere una adeguata esposizione e possibilità di manovra degli strumenti e le ottiche, e per accedere agevolmente all'angolo pontocerebellare. Anche la scheletrizzazione della carotide interna e del golfo della giugulare si sono rese necessarie con la stessa finalità. In conclusione l'ExpTTA si è dimostrata efficace per accedere chirugicamente al condotto uditivo interno e all'angolo pontocerebellare. Il potenziale uso estensivo e routinario di questo tipo di approccio alla pratica clinica dipenderà dallo sviluppo di tecnologie adeguate, dal rifinirsi di questa nuova tecnica, e dalla diffusione delle capacità manuali di chirurgia endoscopica del basicranio tra la comunità otorinolaringoiatrica e neurochirugica internazionale.

PAROLE CHIAVE: *Angolo pontocerebellare • Chirurgia endoscopica dell'orecchio • Orecchio interno • Condotto uditivo interno • Approccio transcanalare*

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Introduction

Surgical approaches to the internal auditory canal (IAC) are widely known and extensively recorded, the most popular being classified as retrosigmoid, transmastoid-translabyrinthine and middle cranial fossa. The clinical indications, advantages, disadvantages and risks in terms of mortality and morbidity have been carefully described [1]. A common factor in all of the methods described to date is that they are all indirect approaches to the inner ear, since the retrosigmoid and translabyrinthine methods approach the pathology posteriorly, while the middle cranial fossa approaches the pathology superiorly. To access the internal auditory canal (IAC) and cerebellopontine angle (CPA), all of these approaches require

wide external incisions and a variable degree of bone removal [1].

The first introduction of the endoscopic technique in IAC surgery was in combination with the retrosigmoid approach [2]. After removal of the CPA portion of the neoplasm, the intracanalicular extension was removed under endoscopic control, trying to avoid extensive drilling of the posterior aspect of the petrous bone. In surgical treatment of the middle ear, the endoscope was introduced in the 1990s[3] as an additive tool to visualise hidden areas [4]. During the last years, technical improvements and growing expertise in the handling of the endoscope allowed introducing an exclusive endoscopic approach to the middle ear [5 6] and lateral skull base [7 8]. The development of these endoscopic techniques required several cadaver dissections [9] to better understand the anatomy and to define appropriate instruments for this purpose. During these dissections, some advances were made in exploring the internal ear, from the labyrinth to the IAC, until an appropriate procedure was recorded, and ready to be applied clinically.

For the first time, an exclusive endoscopic approach to the IAC was described in and used to remove a cochlear schwannoma (CS) involving IAC in March 2012. The operation used a direct transcochlear approach from lateral to medial and from external to internal auditory canal, without any external incision [10]. Other lateral skull base applications were described during the last two years by our team [7 8]. The first case series of the exclusive endoscopic transcanal transpromontorial approach (EndoTTA) to remove vestibular schwannomas involving IAC has been recently published [11].

The aim of this paper is to describe an expanded endoscopic transcanal transpromontorial approach (ExpTTA), derived from the EndoTTA, and to discuss the feasibility, results and findings of this approach on a cadaver model. Since management of intracanalicular vestibular schwannomas (VSs) is complex and strongly debated [12], this kind of therapeutic option in appropriate and selected cases could modify classic concepts of the management of this pathology, even expanding the indications of EndoTTA, which at present are limited to small vestibular schwannomas of the IAC.

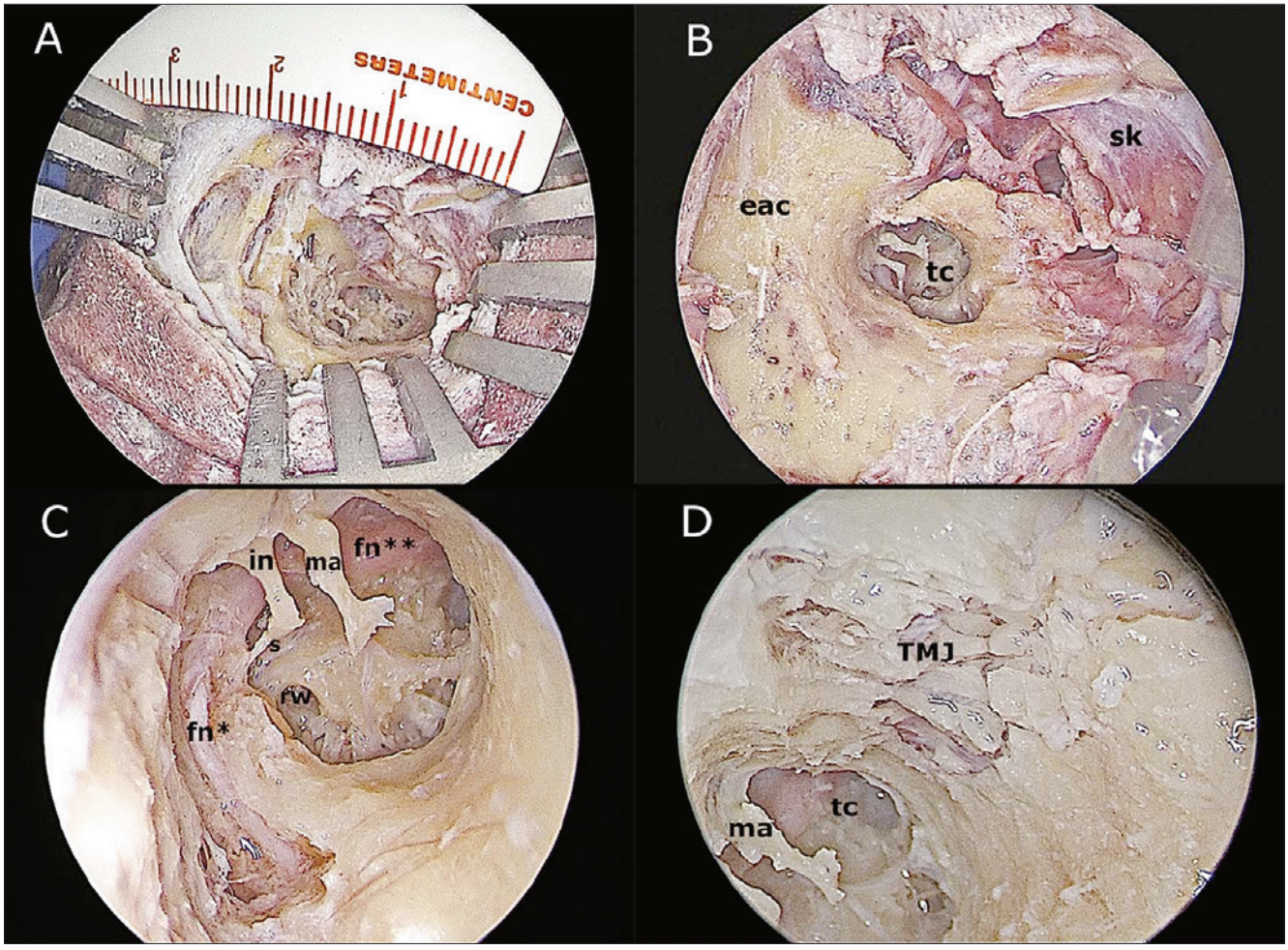

Fig. 1. Shambaugh incision and removal of the tympanic membrane along with the skin of the external auditory canal (A and B); identification of the facial nerve (C) and the temporo-mandibular joint (D). eac, external auditory canal; tc, tympanic cavity; sk, meatal skin; fn*, third tract of the facial nerve; fn**, second tract of the facial nerve; in, incus; ma, malleus; s, stapes; rw, round window niche; TMJ, temporo-mandibular joint.

Techniques and technologies

In September 2015, two fresh cadaver heads (4 sides) were dissected using an endoscopic technique by the first author (LP). An expanded approach was codified and named expanded transcanal transpromontorial approach (ExpTTA). Video and photographic material were collected, and a retrospective review and analyses of data obtained by this dissection was performed in October 2015.

Surgical technique

The head was slightly extended and rotated contra-laterally, just as in the traditional endoscopic middle ear surgery. The surgeon held a 4 mm diameter, 15 cm length, 0° angled endoscope (Karl Storz Tuttlingen Germany) with the left hand, and the operative instruments with the right hand. The endoscope was connected to an AIDA three-chip high-resolution monitor and camera system (Karl Storz, Tuttlingen, Germany).

Approach to the tympanic cavity and identification of the main landmarks

The first step was a circular incision of the external ear canal skin approximately 1.5 cm from the tympanic annulus, under classical traditional endoscopic view, with the endoscope introduced through the external auditory canal (EAC). The skin was then removed "en bloc" with the tympanic membrane. A Shambaugh incision (intercartilaginous skin incision between helix and tragus) was performed to allow the detachment of the lateral portion and the skin of the EAC to expose widely the bony EAC (Fig. 1A). After positioning orthostatic retractors, the EAC was drilled circumferentially to allow a better view of the surgical field and to allow accurate movements of the surgical instruments in the canal (Fig. 1B and 1C).

The next step was the exposition of the temporo-mandibular joint (TMJ) capsule, an important anatomical landmark for this approach representing the superficial anterior limit (Fig. 1D). It was obtained by drilling the anterior

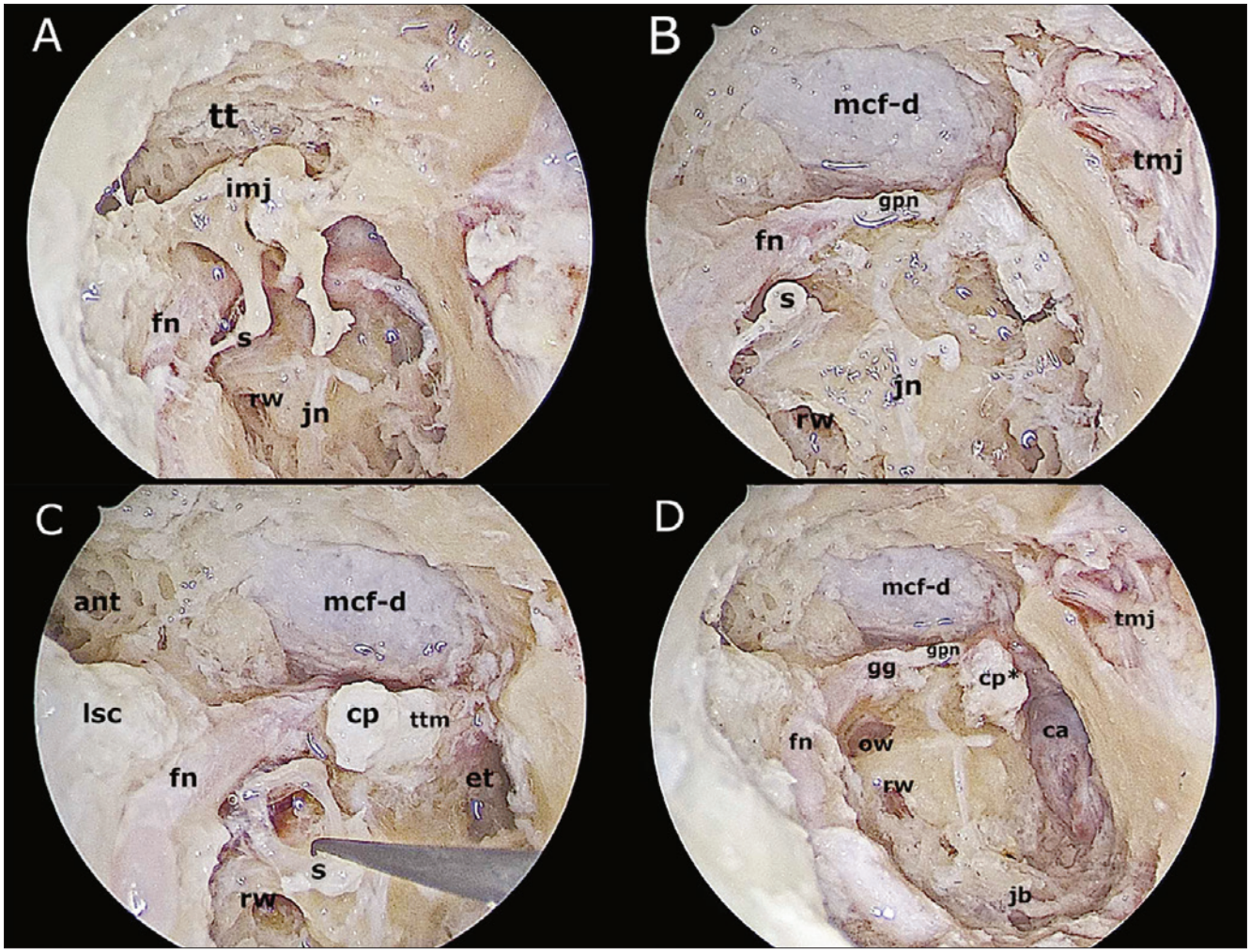

Fig. 2. Removal of the ossicular chain and exposure of the middle cranial fossa dura (A and B); removal of the stapes (C) and skeletonisation of the carotid artery and jugular bulb (D). tt, tegmen tympani; imj, incudo-malleolar joint; fn, facial nerve; s, stapes; rw, round window niche; jn, Jacobson nerve; mcf-d, middle cranial fossa dura; tmj, temporo-mandibular joint; gpn, great petrous nerve; ant, antrum; lsc, lateral semicircular canal; cp, cochleariform process; cp*, cochleariform process overturned; ttm, tensor tympani muscle; et, Eustachian tube; ow, oval window; gg, geniculate ganglion; ca, carotid artery; jb, jugular bulb.

wall of the EAC. A wide atticotomy was made to expose the ossicular chain (Fig. 2A). Consecutively, the incus and the malleus were removed to obtain a clear view of the whole tympanic tract of the facial nerve (Fig. 2B), the geniculate ganglion and its relationship with the cochleariform process. The identification of the main landmarks for this approach continued with the exposition of the middle cranial fossa dura superiorly (by drilling the tympanic tegmen), the carotid artery anteriorly under the tympanic tube orifice (in the protympanic space), the jugular bulb inferiorly and the third tract of the facial nerve posteriorly, drilling the posterior aspect of the EAC and the posterior portion of the bony annulus.

Transpromontorial micro-/endoscopic approach to the IAC

After the clear identification of anatomical landmarks, the dissection proceeded with the removal of the stapes (Fig. 2C) from the oval window and the exposition of the vestibule and the spherical recess in the saccular fossa (Fig. 2D). This structure appears like a thin cribriform plate separating the vestibule from the fundus of the IAC and represents the site of medial termination of the inferior vestibular nerve fibers.

The enlargement of the oval window was made by a microcurette, a burr or by a Piezosurgery® instrument (Mectron, Carasco/Genova, Italy). At this stage, a transpromontorial approach to the IAC was performed (Fig. 3A), drilling the promontorial bone and exposing progressively the basal, middle and apical turns of the cochlea.

Knowledge of the position of the labyrinthine tract of the facial nerve was allowed by previous identification of all the anatomical structures described that were at the same time boundaries of the surgical field and surgical landmarks. An imaginary line passing from the geniculate ganglion to the spherical recess just above the apical turn of the cochlea indicated the facial nerve route through the inner ear.

The progressive drilling of the IAC was performed until the fundus of the IAC was opened, at the level where the

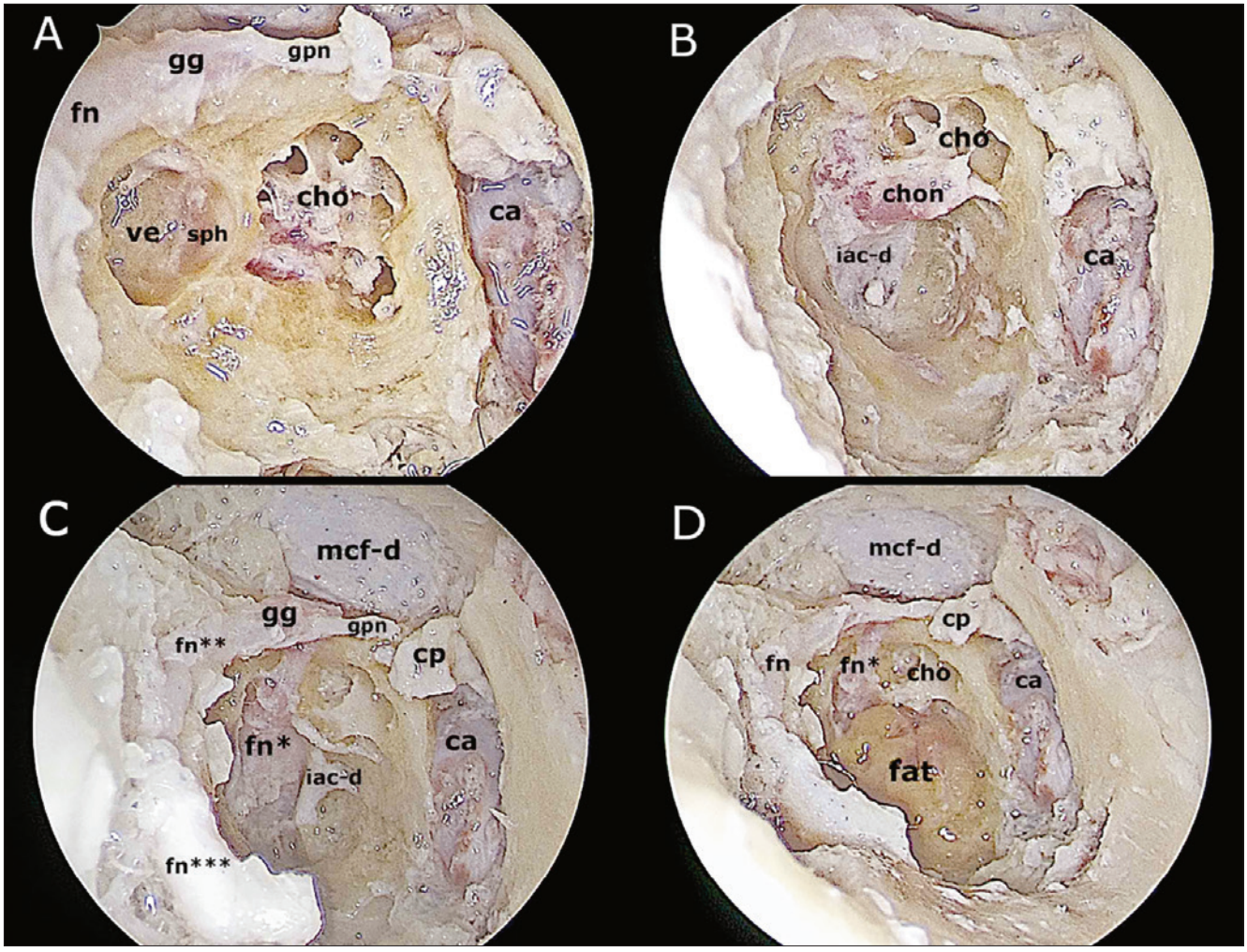

Fig. 3. Approach to the fundus of the IAC and identification of the first tract of the facial nerve. fn, facial nerve; fn*, facial nerve first tract; fn**, facial nerve second tract; fn***, facial nerve third tract; cho, cochlea; gg, geniculate ganglion; gpn, great petrous nerve; sph, spherical recess; ca, carotid artery; chon cochlear nerve; iac-d, internal auditory canal dura; cp, cochleariform process; mcf-d, middle cranial fossa dura; fat, abdominal fat.

cochlear nerve emerges (Fig. 3B). Our limits of dissection at this point were the second tract of the facial nerve superiorly, the vertical tract of the internal carotid artery anteriorly, the jugular bulb inferiorly, the third portion of the facial nerve posteriorly and the middle cranial fossa dura superiorly (Fig. 3C). The dissection kept on until the lateral aspect of the IAC dura was completely exposed. The dura along the IAC was then cut to reach the internal auditory canal.

The cerebellopontine angle was reached with further bone drilling to enlarge the opening of the IAC meatus, always keeping in mind the anatomical boundaries of the dissection to avoid noble structures injuries, and following the acoustic-facial bundle**.** Finally, the obliteration of the internal auditory canal was obtained by abdominal fat (Fig. 3D).

In all 4 sides of the cadavers the procedure was feasible, and all the landmarks reported above were identified (Fig. 4). In all cadavers it was necessary to extensively drill the TMJ and to calibrate the EAC to allow adequate room to maneuver the instruments and optics and to comfortably access the CPA. Additionally, the wide skeletonisation of the carotid artery and the jugular bulb were necessary for the same purpose.

Discussion

Actually, the IAC is a very poor accessible anatomical region despite the different approaches chosen. By a retrosigmoid approach, craniotomy and an extensive drilling of the posterior aspect of the petrous bone are required to fully expose the IAC. In most cases, the use of endo-

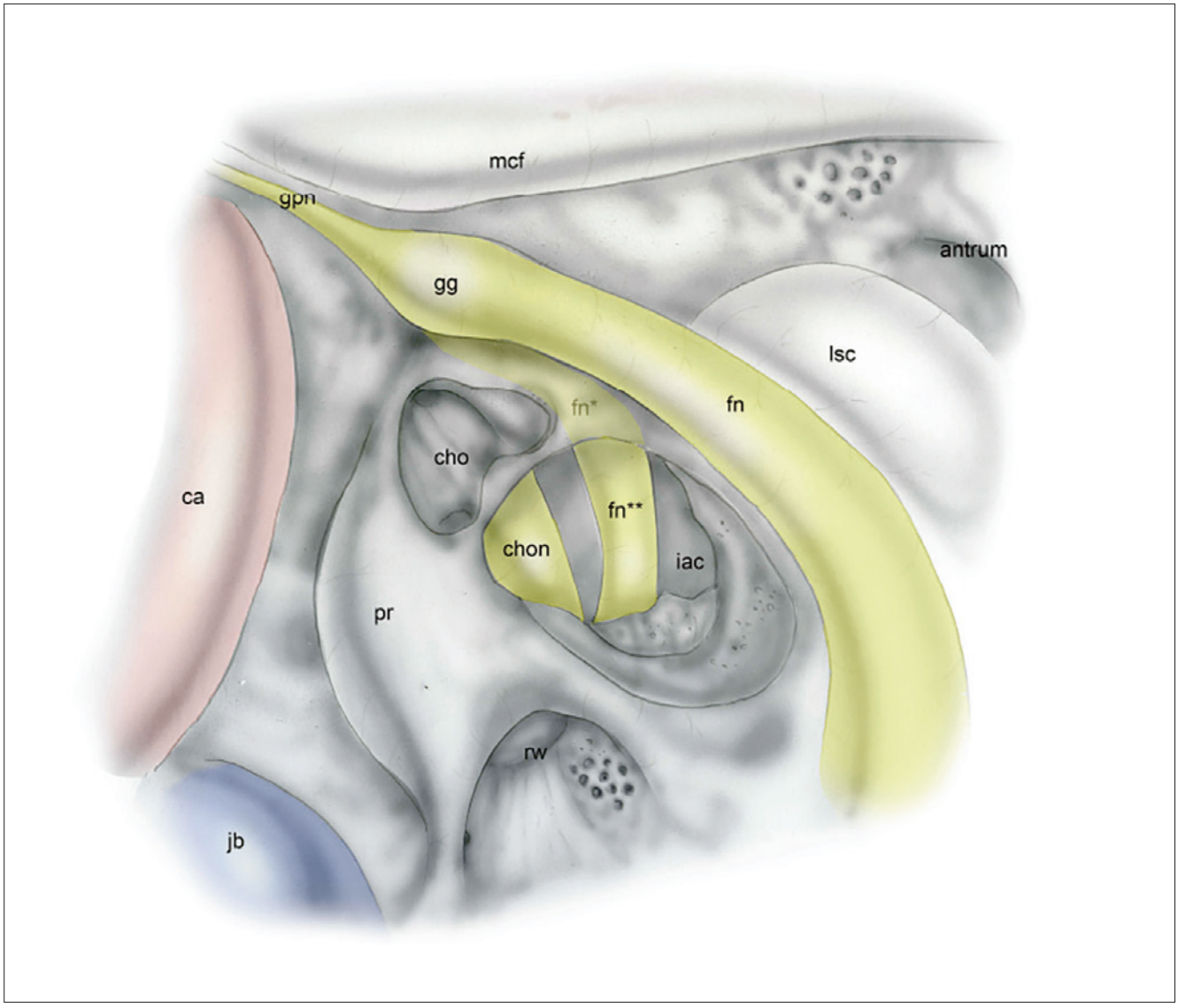

Fig. 4. (Left ear) picture showing the main landmarks of the approach. Jb, jugular bulb; ca, carotid artery; pr, promontory; chon, cochlear nerve; fn, facial nerve; fn*, intralabyrinthine facial nerve; fn**, facial nerve on the internal auditory canal; iac, internal auditory canal; rw, round window; lsc, lateral semicircular canal; mcf, middle cranial fossa; gg, geniculate ganglion; gpn, greater petrosal nerve.

scopes inside the CPA is required to visualise the fundus of the IAC. By a translabyrinthine approach, subtotal petrosectomy is required to identify the IAC and to properly skeletonise it. The middle cranial fossa approach guarantees less bone work to the petrous bone, but requires wide craniotomy and temporal lobe retraction [1]. Independently of the approach, the surgery of this region (e.g. VS surgery) is traditionally considered very delicate overall. Post-operative morbidity can be high, due to intraoperative and post-operative complications. Besides this, facial nerve post-operative results are critical for functional and psychological issues and the patient's quality of life. For these reasons, a general attitude in management is to encourage in most cases wait and see policies, so as to evaluate the growth of the mass over time [13]. In case of documented growth, a therapeutic attempt can be more strongly suggested.

In 2013, our team published the first case of EndoTTA [10]. The approach guaranteed cochlear schwannoma removal, with IAC extension. Since this first clinical application, we have started using the approach more frequently for stage I and II (Koos) VSs and in 2015 the first case series of 10 patients was published [11]. The EndoTTA gives the possibility of lateral to medial control of IAC, with a high magnification of every structure inside and outside the IAC, including the facial nerve. The morbidity, based on our first results, can be compared to those of a tympanoplasty, rather than to an operation to the CPA. Certainly, the sample size is still small, since at present the indication to EndoTTA for VS treatment is considered as follows: growing VS stage I or II (Koos), with class D hearing (AAO-HNS) and whose symptoms does not respond to medical treatment (e.g. intratympanic gentamicin injections in case of debilitating vertigo). Nonetheless, considering these very strict indications, we believe that EndoTTA is very promising, since it potentially differs in terms of morbidity from classic microscopic approaches. Moreover, it guarantees radical removal of the pathology, with a possible very low morbidity to the facial nerve, due to direct control and magnification of the entire nerve path thanks to the endoscope. Of course, hearing preservation is not feasible by this approach, and it is for this reason that the indication to surgery is restricted to patients with unserviceable hearing.

ExpTTA, as shown herein, may potentially expand the anatomical limits of the indication to surgery for two main reasons. The first is an obviously enlarged space for maneuvering surgical instruments, compared to EndoTTA. The second one is, as a direct consequence of the increased space for surgical instruments, the possible use of a microscope in combination with the endoscope for some delicate steps, for example while dissecting vessels in the most medial portion of the pathology, or towards the CPA. The use of a microscope would free one hand during the dissection, facilitating the procedure when necessary.

Morbidity, although this needs to be confirmed in living patients, would be theoretically similar to the EndoTTA, since it involves only a small skin incision between tragus and helix (Shambaugh incision), and only a small increase in bone work.

In summary, this approach can be considered a sort of less-invasive translabyrinthine approach, since it demolishes the labyrinth, but it spares the mastoid, most of the temporal bone and avoids large skin incisions and wide soft tissue dissections. Of course, clinical experience is necessary to confirm its potential benefits and define the feasibility and morbidity of this expanded approach. The risks of the approach must also be highlighted: actually, going medially toward CPA the risk of incontrollable bleeding, possibly from branches of the anterior inferior cerebellar artery (AICA) would increase, and the room created would not be enough to control it. Moreover, drilling of the internal carotid artery could be theoretically associated with a potential risk of carotid artery injury, and drilling the temporomandibular joint could lead to a potential discomfort to the patient. Moreover, although EndoTTA has very low risk of complications such as post-operative cerebrospinal fluid leak, or facial nerve palsy, the ExpTTA could have potential higher rates of unfavourable events. Also, the small number of specimens dissected does not take in consideration the chance of some anatomical variations such as a high jugular bulb, a more medial internal carotid canal in the temporal bone, a temporo-mandibular joint protrusion in the external auditory canal, a very low middle cranial fossa dura tegmen and lastly a more medial course of the third portion of the facial nerve. All these anatomical variations lead to very limited exposure of the surgical area and consequently of the operative field in the CPA by ExpTTA. Finally, all types of endoscopic lateral skull base procedures require preliminary, long training in endoscopic middle ear surgery to acquire enough manual expertise. Additionally, perfect knowledge of endoscopic landmarks is necessary to recognise and dissect in the safest way the neurovascular structures inside the temporal bone.

Conclusions

ExpTTA is a feasible approach to access the IAC and cerebellopontine area. Potential extensive and routine application of this approach in lateral and posterior skull base surgery will depend on the development of technology and surgical refinements, and on the diffusion of skull base endoscopic skills among otolaryngologists and the neurosurgical community.

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VESTIBOLOGY

Body-worn triaxial accelerometer coherence and reliability related to static posturography in unilateral vestibular failure

Impiego degli accelerometri triassiali nel deficit vestibolare unilaterale: affidabilità rispetto alla posturografia statica

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SUMMARY

Since changes in vestibular function may be one cause of disequilibrium, major advances in measuring postural control and sensory integration in vestibular impairments have been achieved by using posturography. However, in order to overcome problems related to this type of technology, body-worn accelerometers (ACC) have been proposed as a portable, low-cost alternative to posturography for measurements of postural sway in a friendly and ecologic environment. Due to the fact that no study to date has shown the experimental validity of ACC-based measures of body sway with respect to posturography for subjects with vestibular deficits, the aim of the present study was: i) to develop and validate a practical tool that can allow clinicians to measure postural sway derangements in an otoneurological setting by ACC, and ii) to provide reliable, sensitive and accurate automatic analysis of sway that could help in discriminating unilateral vestibular failure (UVF) patients. Thus, a group of 13 patients (seven females, 6 males; mean age 48.6 ± 6.4 years) affected for at least 6 months by UVF and 13 matched healthy subjects were instructed to maintain an upright position during a static forceplate-based posturography (FBP) acquisition while wearing a Movit® sensor (by Captiks) with 3-D accelerometers mounted on the posterior trunk near the body centre of mass. Pearson product moment correlation demonstrated a high level of correspondence of four time-domain and three frequency-domain measures extracted by ACC and FBP testing; in addition, t-test demonstrated that two ACC-based time- and frequency-domain parameters were reliable measures in discriminating UVF subjects. These aspects, overall, should further highlight the attention of clinicians and researchers to this kind of sway recording technique in the field of otoneurological disorders by considering the possibility to enrich the amount of quantitative and qualitative information useful for discrimination, diagnosis and treatment of UVF. In conclusion, we believe the present ACC-based measurement of sway offers a patient-friendly, reliable, inexpensive and efficient alternative recording technique that is useful – together with clinical balance and mobility tests – in various circumstances, as well as in outcome studies involving diagnosis, follow-up and rehabilitation of UVF patients.

KEY WORDS: Accelerometer • Unilateral vestibular failure • Static posturography • Video Head Impulse Test

RIASSUNTO

Poichè le alterazioni della funzione vestibolare possono essere causa di disequilibrio, i principali reperti sviluppati ad oggi per misurare il controllo posturale e l'integrazione sensoriale nel danno vestibolare sono stati ottenuti grazie alla posturografia. Tuttavia, al fine di superare i problemi legati a tale genere di tecnologia, sono stati proposti gli accelerometri indossabili (ACC) come un'alternativa portatile e a basso costo per la misurazione dell'oscillazione corporea in ambienti confortevoli. D'altro canto, nessuno studio ad oggi ha dimostrato la validità sperimentale delle misurazioni ottenute con ACC - rispetto a quelle derivanti dalla posturografia - in soggetti affetti da deficit vestibolare. Pertanto, l'obiettivo del presente lavoro è stato quello di i) sviluppare e validare una strumentazione pratica che potesse consentire la misurazione dei disordini dell'oscillazione corporea nell'ambito della valutazione otoneurologica attraverso gli ACC e ii) fornire un'analisi delle oscillazioni affidabile ed automatica, che potesse implementare in modo sensibile ed accurato la possibile discriminazione di pazienti affetti da deficit vestibolare unilaterale (UVF). A tale scopo, un gruppo di 13 pazienti (sette femmine, 6 maschi; età media 48.6 ± 6.4 anni) affetti da UVF da almeno 6 mesi e un altro omogeneo di 13 soggetti sani sono stati invitati a mantenere la posizione eretta durante l'esecuzione della posturografia statica (FBP) mentre indossavano a livello lombare - vicino al centro di massa - un sensore Movit® (by Captiks) costituito da accelerometri 3-D. La correlazione 'product-moment' secondo Pearson ha dimostrato un elevato livello di corrispondenza di quattro misure, estratte da ACC e da FBP, nel dominio del tempo e di tre in quello della frequenza. Inoltre il t-test ha evidenziato che due parametri nel dominio del tempo e due in quello della frequenza si sono dimostrati affidabili nel discriminare i soggetti affetti da UVF. Tali aspetti, nel loro complesso, dovrebbero focalizzare l'attenzione in ambito clinico e di ricerca su tale tecnica di registrazione, considerato l'arricchimento quantitativo e qualitativo di informazioni utili nella discriminazione, diagnosi e trattamento di pazienti affetti da UVF. In conclusione, noi riteniamo che la misurazione basata su ACC offra un'alternativa confortevole, affidabile, economica ed efficiente utile, assieme ai test clinici di equilibrio e mobilità, in molteplici circostanze così come negli studi implicati nella diagnosi, controllo e riabilitazione di pazienti affetti da UVF.

PAROLE CHIAVE: *Accelerometro • Deficit vestibolare unilaterale • Posturografia statica • Video test impulsivo del capo*

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Introduction

Among the general population, 20-30% of individuals experience balance disorders that affect daily activities [1 2] inducing, as a consequence, a higher risk of bodily fall, which is becoming a serious social problem, especially for the elderly [1 2]. As is known, appropriate equilibrium in space depends on the integration of vision, proprioception and vestibular information [1]. These afferent sensory feedback signals play a crucial role in adapting and modulating the operation of the locomotor and stance network in the real environment [1]. Considering also that changes in vestibular function may be one cause of ataxia, major findings in measurement of postural control and sensory integration in vestibular impairments were achieved using static posturography in an ambulatory or forced-experimental setting [3].

This type of technology currently uses force plate analysis of centre of pressure (COP) displacement during quiet stance, the sensitivity of which has been demonstrated to be reliable to measure postural disorders in neurological, systemic and vestibular diseases and in fall risk in the elderly [3 4].

However, forceplate-based posturography (FBP; or stabilometry) is a large and expensive instrumentation that requires proper installation, and as such may not be practical for clinical use [1 4]. Recently, in order to overcome these problems, body-worn accelerometers (ACC) have been proposed as a portable, low-cost alternative to a force plate for measurements of postural sway in a friendly and ecologic environment [1 2 4 5]. Despite the potential advantages of accelerometric systems in clinical practice, they still have several drawbacks, such as the need to pre-process data and the question of how to translate sway measures into clinically-understandable outcomes [4-6]. However, the major limitation is that there is no consensus as to which sway-related measures should be considered [4-6]. In fact, in order to make ACC-based measures useful for clinical applications, it is important to assess their validity, sensitivity and reliability compared to gold standard laboratory and clinical assessments [4 6], such as FBP, in vestibular clinical and research. The relationship between the same postural sway measures calculated from the force plate COP and from ACC that would support the experimental validity of ACC measures has only been reported in few studies, and none have demonstrated the experimental validity of ACC-based and force plate-based measures of postural sway for subjects with vestibular deficits [4 6].

The aim of the present study was to develop and validate a practical tool that could allow clinicians to measure postural sway derangements in an otoneurological setting using body-worn ACC. Our vision is that this tool will provide reliable, automatic analysis of sway that is sensitive, accurate, robust and consistent, without the need for clinical experts to deal with raw data. To determine if the sensitivity and experimental concurrent validity of ACC – compared to FBP measures of postural sway – could be a reliable tool in diagnosing and discriminating vestibular impairments, a group of unilateral vestibular failure (UVF) and age-, body mass index (BMI) and gender- matched healthy subjects (HS) were enrolled.

Materials and methods

Participants

Thirteen subjects (seven females, 6 males; mean age 48.6 ± 6.4 years; body mass index, BMI = 22.3 ± 2.1 kg/m^2) affected for at least 6 months by UVF and 13 BMI-, gender- and age-matched HS (6 females, 7 males; mean age 47.7 ± 6.1 years; BMI = 21.9 ± 2.3 kg/m^2) participated in the study. After thorough clinical otoneurological examination (binocular electrooculography analysis, Head Shaking Test, clinical Head Impulse Test as well as limb coordination, gait observation and Romberg stance Test) all subjects underwent video Head Impulse Test (vHIT) measurements using the EyeSeeCam™ System and the technique proposed by Blodow et al. [7]. The vHIT results were defined as normal if they were within the calculated gain-reference range, mean$_{normal}$ ± 2 standard deviations (SD), incorporating 95% of population and if no refixation saccades occurred. For the HS, the average VOR gain was 0.97 ± 0.12 (mean$_{normal}$ ± SD) on the right side and 0.98 ± 0.14 on the left side. A t-test was performed between both sides VOR gain and no significant difference ($p < 0.05$) was found. Thus, diagnosis of UVF was achieved in case of values under a gain threshold set to 0.73 for the right side and to 0.7 for the left side. Right and left UVF subjects demonstrated an average VOR gain of 0.44 ± 0.18 and 0.42 ± 0.19, respectively.

The protocol adhered to the principles of the Declaration of Helsinki and all participants provided written informed consent after receiving a detailed explanation of the study.

Static posturography testing

Each subject was instructed to maintain an upright position on a standardised platform for static posturography (EDM Euroclinic®). The recording period was 60 sec for each test (eyes closed [CE] or opened [OE] while standing on the stiff platform [SP] or a 6 cm heightened foam carpet [FC]); the sampling frequency was 25 Hz [3]. The COP was monitored while performing the test.

Accelerometer implementation

According to previous studies [4], during all conditions subjects wore an inertial measurement unit termed Movit® (by Captiks Srl, Italy), equipped with 3-D accelerometers (±1.7 g range) mounted on the posterior trunk at the level of L5 by means of an elastic belt, near the body centre of mass (Fig. 1). The sensing axes were oriented along the anatomical anteroposterior (AP), medio-lateral (ML), and vertical directions.

Fig. 1. Experimental setting and body-worn accelerometer position.

The Movit® combines a 3D accelerometer with a 3D gyroscope, a 3D compass and a barometer forming a complete position and orientation tracker. Combination of sensors allows data integration to reduce drift and/or cumulative measurement errors. All sensors were handled by an AT32UC3A4256 microcontroller (by Atmel, San Jose, California, US), with a frequency clock of 40 MHz. The Movit® uses an 802.15.4 protocol to send wireless data to a receiving base station, which feds data to a personal computer at a selectable data rate within 4 Hz-1000 Hz. The power supply has a USB-rechargeable built-in Li-Po battery that can provide up to eight hours of operation.
In particular, we focused on data coming from the 3D accelerometer, which integrates a 16-bit A/D converter, and allows options of ±2 g, ±4 g, ±8 g and ±16 g full scale acceleration range. For our purposes, the choice was the ±16 g option, and the low-power mode of the Movit® was selected. corresponding at an operative current of 140 μA at a 50 Hz updating data rate. For our purposes, we considered two out of three parameters of the accelerometer, namely the AP (or pitch) angle, and the ML (or roll) angle.
The receiving personal computer was equipped with 4 GB of RAM and an i5 processor (by Intel, Santa Clara, California, US), and data were elaborated using ad-hoc written software routines in Matlab (by Matworks, Natick, Massachusetts, US).

Data handling and statistical analysis

After a MATLAB-based automatic check of normality distribution of parameters, a total of 11 ACC measures previously validated in literature [4] were computed from the 2D acceleration time series, similar to COP analysis. Following the same study [4] and details reported in Table I,

Table I. Summary of the extracted measures. Accelerometer, ACC; centre of pressure, COP.

Measure	Description
DIST	Mean distance from centre of COP (ACC) trajectory [mm] ([m/s^2])
RMS	Root mean square of COP (ACC) time series [mm] ([m/s^2])
PATH	Sway path, total length of COP (ACC) trajectory [mm] ([m/s^2])
RANGE	Range of COP displacement (acceleration) [mm] ([m/s^2])
MF	Mean frequency, the number, per second, of loops that have to be run by the COP (ACC), to cover a total trajectory equal to PATH (MF = PATH/(2*π*DIST*trial duration) (Hz)
AREA	Sway area, computed as the area spanned from the COP (ACC) per unit of time [mm2/s] ([m^2/s^5])
PWR	Total power [mm^2] ([m^2/s^4])
F50	Median frequency, frequency below which the 50% of PWR is present (Hz)
F95	95% power frequency, frequency below which the 95% of PWR is present (Hz)
CF	Centroidal frequency (Hz)
FD	Frequency dispersion (–)

for each trial we computed in the time-domain six measures that characterised the ACC trajectory: mean distance from centre of COP trajectory (DIST), root mean square of COP time series (RMS), total length of COP trajectory (PATH), range of COP displacement or acceleration (RANGE), the number of loops that have to be run by the COP to cover a total trajectory equal to PATH (MF) and the sway area computed as the area spanned from the COP per unit of time (AREA). In the frequency-domain, spectral properties were assessed for each trial by five measures: one that quantifies the total power of the signal (PWR), one that estimates the variability of the frequency content of the power spectral density (FD) and three measures of characteristic frequencies in the power spectral density (median frequency, below which the 50% of PWR is present, F50; 95% power frequency, below which the 95% of PWR is present, F95; and the centroidal frequency, CF) (Table I).

Algorithms for signal analysis and statistical evaluation of outcomes were written in MATLAB.

A Pearson product moment correlation was used to assess the relationship between COP and ACC metrics. Differences between UVF and control groups were determined using a t-test. Differences were assumed significant when $p < 0.05$.

Results

The major results of this technical report are represented by a significant correlation both in UVF and HS subjects in PATH, RANGE, MF, AREA, F50, F95 and CF (Table II, Fig. 2). Moreover, a statistically significant difference was found between UVF and HS subjects in AREA, MF, F50 and F95 parameter scores in many of tested conditions (for details see Table II).

Discussion

In the present study we tested, for the first time, validated ACC-based time-domain and frequency-domain measures in a group of UVF patients with the attempt of defining their possible usefulness, with regard to FBP, in discriminating vestibular impairments.

Sensors measures of postural sway were validated by force-plate measures of COP displacement and many, but not all, ACC-based measures were correlated with the gold-standard laboratory measures of sway from a force-plate. In particular, the first interesting finding was represented by the high level of robust correspondence of four time-domain (PATH, RANGE, MF, AREA) and three frequency-domain (F50, F95 and CF) measures extracted by ACC and FBP testing, when recorded in same subjects during same conditions (Table II).

According to previous studies, if the body was thought to be moving like an inverted pendulum, a correlation close to 1 would be expected between trunk acceleration and COP displacement [4]. Thus, highly correlated measures of COP and centre of mass amplitudes have also been reported during quiet stance [4]. However, a possible explanation of the absence of correlation in some measures could be related to the fact that subjects do not sway strictly as inverted pendulums [4]. In fact, even quiet stance in young, healthy subjects includes some hip strategy, and the amount of hip strategy used to control posture have been shown to increase with age [3 4]. Besides this, to the best of our knowledge, in the present work the reliability of important postural sway measures in UVF subjects using an accelerometer-based approach is reported.

Secondly, when comparing parameters extracted in all conditions by ACC-based and COP-based recordings two important time-domain measures – MV and AREA – were further demonstrated to be significant reliable parameters

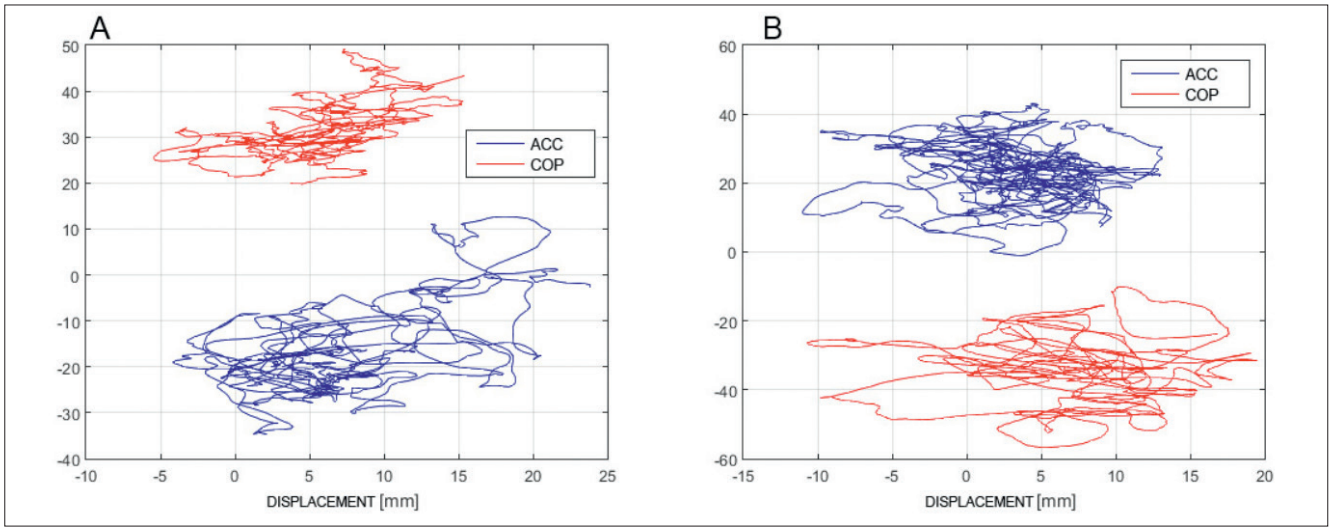

Fig. 2. Accelerometer (ACC) and centre of pressure (COP) traces in the horizontal plane during opened eyes stance on a stiff platform for a representative healthy (A) and unilateral vestibular failure (B) subject.

Table II. Sensitivity of COP and ACC-based measures.

		COP					ACC						
		UVF		HS		T-test	UVF		HS		T-test	Correlation	
		MEAN	SD	MEAN	SD	p values	MEAN	SD	MEAN	SD	p values	r	P
DIST	SP-OE	6.8	1.43	5.4	1.58	0.1046	6.78	2.19	8.72	2.51	0.2297	-0.05	0.32838
	SP-CE	7.72	2.35	6.96	2.17	0.2774	6.72	1.92	9.96	3.09	0.065	0.83	0.60377
	FC-OE	7.69	2.78	6.9	2.59	0.2544	**7.5**	**2.66**	**15.38**	**3.63**	**0.0059**	0.36	0.05575
	FC-CE	**13.52**	**5.5**	**10.71**	**1.34**	**0.0762**	**15.24**	**4.11**	**27.1**	**7.21**	**0.0329**	**0.9**	**0.02532**
RMS	SP-OE	77.42	12.43	55.46	10.81	0.1842	96.75	20.16	221.64	33.45	0.1756	0.66	0.2305
	SP-CE	104.21	14.91	77.7	13.43	0.1864	74.73	12.25	256.27	44.21	0.0874	-0.38	0.40721
	FC-OE	103.34	16.76	79.75	11.67	0.2312	101.26	14.36	494.37	57.17	0.0275	0.59	0.10912
	FC-CE	348.7	73.13	183.41	34.43	0.0626	**739.65**	**173.64**	**1561.53**	**105**	**0.0451**	**-0.35**	**0.04117**
Path	SP-OE	**537.72**	**109.1**	**333.67**	**66.85**	**0.00136**	2315.5	592.94	2283.21	693.8	0.46877	0.42	**0.0000**
	SP-CE	**947.38**	**212.76**	**505.68**	**124.11**	**0.00286**	2727.53	737.13	3264.01	672.93	0.24802	0.8	**0.0000**
	FC-OE	**1012.91**	**316.34**	**515.48**	**107.25**	**0.0001**	3084.45	570.2	3831.15	488.17	0.19274	0.05	**0.0000**
	FC-CE	**2842.47**	**759.51**	**1409.81**	**583.18**	**0.00006**	8252.69	1496.54	7148.73	1276.84	0.31056	0.36	**0.0000**
Range	SP-OE	42.91	9.64	34.24	8.73	0.1085	54.58	13.01	76.59	18.87	0.1425	**0.76**	**0.02559**
	SP-CE	47.96	11.19	41.78	7.9	0.1642	48.15	10.27	110.37	27.05	0.0475	0.78	0.13619
	FC-OE	53.58	12.12	42.22	10.64	0.0745	**55.47**	**14.61**	**147.87**	**20.42**	**0.0066**	**0.79**	**0.02808**
	FC-CE	**101.91**	**22.45**	**68.52**	**7.88**	**0.0156**	181.25	30.6	205.45	44.96	0.4128	0.97	0.05762
MF	SP-OE	0.11	0.04	0.09	0.04	0.1657	0.5	0.14	0.5	0.18	0.4976	**-0.93**	**0.0000**
	SP-CE	**0.17**	**0.04**	**0.1**	**0.03**	**0.0007**	**0.55**	**0.1**	**0.44**	**0.11**	**0.0483**	**0.65**	**0.0000**
	FC-OE	**0.18**	**0.03**	**0.1**	**0.03**	**0.0001**	**0.61**	**0.19**	**0.34**	**0.15**	**0.0012**	**-0.53**	**0.0000**
	FC-CE	**0.29**	**0.07**	**0.17**	**0.08**	**0.0012**	**0.71**	**0.13**	**0.45**	**0.12**	**0.0089**	**-0.12**	**0.0000**
Area	SP-OE	**24236.25**	**5180.33**	**9909.11**	**2260.59**	**0.0045**	**56187.86**	**9376.84**	**154228.5**	**21038.88**	**0.0459**	**0.07**	**0.01874**
	SP-CE	**35693.62**	**7323.77**	**14694.15**	**2405.05**	**0.0103**	**49174.5**	**6898.21**	**455780.41**	**45459.84**	**0.0504**	**0.37**	**0.012886**
	FC-OE	**47539.11**	**6921.1**	**21722.47**	**4405.45**	**0.0025**	**70412.12**	**10142.29**	**776658.33**	**71616.59**	**0.0178**	0.11	0.06251
	FC-CE	**166576**	**23829.34**	**50165.57**	**10159.06**	**0.0006**	**433879.8**	**54227.5**	**1391118.98**	**98335.51**	**0.0411**	**0.36**	**0.0247**
PWR	SP-OE	**19.27**	**6.34**	**9.62**	**5.78**	**0.0149**	**21.24**	**9.48**	**125.51**	**21.94**	**0.0466**	**0.35**	0.11985
	SP-CE	**35.02**	**11.44**	**15.38**	**6.36**	**0.0211**	**28.57**	10.89	703.77	135.01	0.0891	0.31	0.26012
	FC-OE	**42.62**	**15.66**	**19.75**	**8.68**	**0.0249**	**31.92**	**12.75**	**900.58**	**191.91**	**0.0436**	**0.82**	0.1641
	FC-CE	**142.67**	**33.4**	**50.15**	**13.78**	**0.0126**	355.32	73.9	1209.77	144.64	0.0981	0.94	0.06832
F50	SP-OE	0.19	0.01	0.18	0.00	0.0612	0.28	0.05	0.31	0.14	0.2707	**0.27**	**0.00001**
	SP-CE	0.21	0.02	0.2	0.01	0.4553	**0.29**	**0.06**	**0.25**	**0.05**	**0.0465**	**0.93**	**0.00003**
	FC-OE	0.21	0.02	0.2	0.04	0.3923	**0.35**	**0.06**	**0.27**	**0.01**	**0.0161**	**0.25**	**0.0000**
	FC-CE	0.27	0.04	0.27	0.06	0.4073	**0.35**	**0.06**	**0.27**	**0.01**	**0.0161**	**0.62**	**0.04192**
F95	SP-OE	0.99	0.2	0.88	0.21	0.1174	2.19	0.38	1.92	0.42	0.1402	**0.91**	**0.0000**
	SP-CE	0.78	0.22	0.89	0.15	0.1113	1.89	0.42	1.9	0.53	0.4858	**0.93**	**0.0000**
	FC-OE	0.85	0.23	0.93	0.08	0.1772	**2.34**	**0.47**	**1.84**	**0.6**	**0.0391**	**0.94**	**0.0000**
	FC-CE	0.84	0.19	0.76	0.08	0.1324	**2.77**	**0.57**	**1.74**	**0.6**	**0.0421**	**0.43**	**0.0000**
CF	SP-OE	0.32	0.03	0.3	0.03	0.1414	0.53	0.1	0.55	0.15	0.4018	-0.37	**0.0000**
	SP-CE	0.29	0.04	0.31	0.02	0.1464	0.51	0.08	0.49	0.13	0.31	-0.83	**0.0000**
	FC-OE	0.31	0.04	0.33	0.03	0.1205	**0.59**	**0.13**	**0.48**	**0.16**	**0.0394**	**0.54**	**0.0000**
	FC-CE	0.34	0.05	0.34	0.04	0.3525	**0.64**	**0.1**	**0.51**	**0.16**	**0.0213**	**0.86**	**0.0000**
FD	SP-OE	**0.5**	**0.12**	**0.25**	**0.11**	**0.0207**	**0.34**	**0.19**	**2.2**	**0.66**	**0.0411**	-0.01	0.19063
	SP-CE	**0.99**	**0.21**	**0.38**	**0.15**	**0.0187**	0.36	0.17	12.93	3.3	0.09	-0.9	0.30152
	FC-OE	1.28	0.6	0.48	0.1	0.08	**0.36**	**0.19**	**17.25**	**3.29**	**0.0395**	-0.13	0.19055
	FC-CE	3.67	1.11	0.97	0.39	0.0661	2.99	1.04	19.96	6.65	0.058	-0.73	0.17618

In boldface are reported significant different measures between unilateral vestibular failure (UVF) and healthy subjects (HS) and significant correlations between accelerometer (ACC) and centre of pressure (COP) parameters. standard deviation, SD; mean distance from centre of COP (ACC) trajectory, DIST; root mean square of COP (ACC) time series, RMS; total length of COP (ACC) trajectory, PATH; range of COP displacement (acceleration), RANGE; mean frequency, the number, per second, of loops that have to be run by the COP (ACC), to cover a total trajectory equal to PATH, MF; sway area, AREA; total power, PWR; median frequency, F50; 95% power frequency, F95; centroidal frequency, CF; frequency dispersion ,FD; eyes closed, CE; eyes opened, OE; stiff platform , SP; foam carpet, FC.

in discriminating UVF from healthy subjects. Interestingly, on one hand they are in line with the natural history of these kind of vestibular disorders in which length and surface values were addressed to be higher than healthy subjects [3]. On the other, a new interesting ACC-based and length-derived parameter (see Table I), such as MF, could be proposed as a further measure to follow UVF patients during the course of the disease. Finally, two frequency-domain measures (F50 and F95) were also demonstrated to be reliable parameters in discriminating UVF subjects when assessed by ACC recordings, especially in situations in which the balance integration system is involved in more difficult sensory input conditions (i.e. FC and CE; see Table II). This could be of interest for clinicians, and in particular when the vestibular system will be studied – under frequency-domain parameters – to assess its possible relationships with risk of fall.

These overall aspects should further highlight the attention of clinicians and researchers on this type of sway recording technique in the field of otoneurological disorders, considering the possibility to enrich the amount of quantitative and qualitative information useful in discrimination, diagnosis and treatment of UVF. In addition, the ACC body sway recording provides a large number of measures that automatically, fully characterise body sway in amplitude, smoothness and frequency; these measures are relevant for testing any individual with balance deficits. Thus, for future perspectives its potential application should not be limited to testing subjects with UVF.

In fact, it is likely that a different subset of ACC-based measures might be sensitive to different constraints. Further studies are needed to determine the best subset of postural sway parameters that can predict body sway or stance disability during daily activities in many neuro-otological, neurological, systemic, or musculoskeletal disorders.

Finally, the ease distinguishing this kind of technique can supply further information in case of multiple body-worn sensors worn on patients and in those conditions in which the recording trace is investigated during patient-tailored tasks or sensory feedback.

Conclusions

The present accelerometric-based measurement of sway offers a patient-friendly, reliable, inexpensive and efficient alternative recording technique that is useful to quantify and qualify posture control. This method demonstrated – under controlled conditions – a high level of reliability compared to gold-standard FBP measures. Thus, it could be used together with clinical balance and mobility tests in various circumstances, particularly in outcome studies, involving diagnosis, follow-up and rehabilitation of UVF patients.

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Clinical techniques and technologies

Preliminary experience with 4K ultra-high definition endoscope: analysis of pros and cons in skull base surgery

Esperienza preliminare con endoscopio 4K: analisi di pro e contro nella chirurgia del basicranio

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SUMMARY

During the last two decades endoscopic skull base surgery observed a continuous technical and technological development 3D endoscopy and ultra High Definition (HD) endoscopy have provided great advances in terms of visualisation and spatial resolution. Ultra-high definition (UHD) 4K systems, recently introduced in the clinical practice, will shape next steps forward especially in skull base surgery field. Patients were operated on through transnasal transsphenoidal endoscopic approaches performed using Olympus NBI 4K UHD endoscope with a 4 mm 0° Ultra Telescope, 300 W xenon lamp (CLV-S400) predisposed for narrow band imaging (NBI) technology connected through a camera head to a high-quality control unit (OTV-S400 – VISERA 4K UHD) (Olympus Corporation, Tokyo, Japan). Two screens are used, one 31" Monitor – (LMD-X310S) and one main ultra-HD 55" screen optimised for UHD image reproduction (LMD-X550S). In selected cases, we used a navigation system (Stealthstation S7, Medtronic, Minneapolis, MN, US). We evaluated 22 pituitary adenomas (86.3% macroadenomas; 13.7% microadenomas). 50% were not functional (NF), 22.8% GH, 18.2% ACTH, 9% PRL-secreting. Three of 22 were recurrences. In 91% of cases we achieved total removal, while in 9% near total resection. A mean follow-up of 187 days and average length of hospitalisation was 3.09 ± 0.61 days. Surgical duration was 128.18± 30.74 minutes. We experienced only 1 case of intraoperative low flow fistula with no further complications. None of the cases required any post- or intraoperative blood transfusion. The visualisation and high resolution of the operative field provided a very detailed view of all anatomical structures and pathologies allowing an improvement in safety and efficacy of the surgical procedure. The operative time was similar to the standard 2D HD and 3D procedures and the physical strain was also comparable to others in terms of ergonomics and weight.

KEY WORDS: 4K • Ultra-high definition • Endoscopy • Skull base • Endoscopic sinus surgery

RIASSUNTO

Negli ultimi venti anni la chirurgia endoscopica del basicranio ha osservato continui sviluppi tecnici e tecnologici. L'endoscopia 3D e l' alta definizione (HD) 4K hanno fornito grandi vantaggi in termini di visualizzazione e di risoluzione spaziale. L'ultra HD 4K, recentemente introdotta nella pratica clinica, determinerà i prossimi passi soprattutto nella chirurgica endoscopica del basicranio. I pazienti sono stati operati attraverso un approccio transnasale transfenoidale endoscopico, utilizzando un endoscopio Olympus NBI 4K UHD con ottica 4 mm 0 ° Ultra Telescope, lampada allo xeno 300 W (CLV-S400) predisposto per la tecnologia narrow band imaging (NBI) collegato con una videocamera ad un alta qualità unità di controllo (OTV-S400 - VISERA 4K UHD) (Olympus, Tokyo, Giappone). Due schermi, un 31 "Monitor - (LMD-X310S) e quello principale ultra-HD 55" a pollici ottimizzati per la riproduzione immagini UHD (LMD-X550S). In casi selezionati abbiamo usato un sistema di navigazione (Stealthstation S7, Medtronic, Minneapolis, MN, Stati Uniti). Abbiamo valutato 22 adenomi ipofisari (86,3% macroadenomi; 13,7% microadenomi). Il 50% non erano secernenti (NS), 22,8% GH, 18,2% ACTH, 9% PRL-secernenti. 3/22 erano recidive. Nel 91% dei casi abbiamo raggiunto la rimozione totale, mentre nel 9% la resezione subtotale. Un follow-up medio di 187 giorni, durata media del ricovero era 3,09 ± 0,61 giorni. Tempo chirurgico 128,18 ± 30,74 minuti. Abbiamo avuto solo 1 caso di fistola intraoperatoria a basso flusso senza ulteriori complicazioni nel follow up. Il 100% dei casi non ha richiesto emotrasfusione. La visualizzazione e l'alta risoluzione del campo operatorio hanno fornito una vista dettagliata di tutte le strutture anatomiche e patologie e permesso il miglioramento della sicurezza e l'efficacia della procedura chirurgica. Il tempo operatorio è stato simile a quello dell'endoscopio HD standard 2D e 3D, come la fatica fisica era paragonabile ad altri in termini di ergonomicità e peso.

PAROLE CHIAVE: *4K • Endoscopia ultra HD • Chirurgia del basicranio • Chirurgia endoscopica nasosinusale*

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Introduction

Transnasal endoscopic routes, especially for skull base surgery, are costantly evolving field. Nowadays, the introduction of new tools such as neuronavigation, UHD 4K endoscopy, 3D endoscopy together with many surgeon anatomical endevors are establishing the prominent role of transnasal endoscopic surgery [2]. 4K UHD is a new equipment, released in 2015, that has been first used by ENT mainly in laryngoscopy. We report on the first preliminary surgical experience in skull base lesions in which we used a new ultra-high definition (UHD) 4K endoscope.

Clinical techniques and technologies

The UHD endoscopy system (Visera 4K UHD, Olympus) needs the usual set-up of the operating room (OR) for a combined neurosurgical/ENT procedure. The camera head (CH-S400, Olympus) is equipped with a 4 mm 0° ultra telescope (WA96200A, Olympus), and 300 W xenon lamp (CLV-S400, Olympus). A high-quality control unit (OTV-S400, Olympus), which is also predisposed for narrow band imaging (NBI) technology, give us the final images through a dedicated ultra-HD 55'' main screen (LMD-X550S, Olympus) optimised for endoscopic application and allowing correct reproduction of UHD images. A second ultra HD 31" screen is setted on the stand unit and can be useful for the second surgeon. A navigation system Stealthstation S7 (Medtronic, Minneapolis, MN, US). when needed, was setted up in our surgical theater. This surgical set-up was used in 22 patients operated by the same ENT/neurosurgical team performing a conventional bi-nostril transsphenoidal approach [3] (Fig. 1). Once exposed, the adenoma was removed: microadenomas could be taken out utilising the extracapsular dissection technique; macroadenomas, instead, needed first intracapsular debulking and then extracapsular removal by meticulous microdissection from pituitary gland and diaphragm sellae. The dissection was completed without complications in nearly all cases. The nasal part was generally performed without any magnification with wide field, while the opening of the dura and removal of the pituitary pathology was usually performed holding the endoscope in a four hand technique and with 1.4 or 1.6 magnification to focus and gain detail on the sellar and parasellar structures. The bony and dural defect was closed with gelfoam (Johnson & Johnson), autologous bone fragment harvested from the nasal septum and fibrin glue when necessary, the pedicled nasoseptal flap was added. The plasty was stabilised with fibrin glue. Bilateral nasal packs were kept in place for 48 hours. In the post-operative period, patients underwent nasal medications and clinico-radiological follow up at 3, 6 and 12 months. We operated 22 pituitary adenomas, from grade zero to grade IV according to Knosp Classification (Table I). 22.8% grade 0; 40.9% grade I; 18.1% grade II; 4.5% grade IIIA, 9.2% IIIB and 4.5% grade IV. 86.3% were macroadenomas, while 13.7% were microadenomas. Three of 22 were recurrences. 50% of cases were NS, 22.8% GH, 18.2% ACTH and 9% PRL. 31.8% were male, 68.2% female, mean age was 45.8 ± 16.7 years. Mean follow up 187 days and the average length of hospitalisation was 3.09 ± 0.61 days. Surgical duration was 128.18± 30.74 minutes. We only experienced 1 case of intraoperative low flow fistula without sequelae during follow-up. We always

Table I. Demographic details of patients.

Demographic details	
Male	31.8%
Female	68.2%
Age	45.8 y ± 16.7

Table II. Surgical details of patients. Abbreviations: NF, non-functional; GH, growth hormone; PRL, prolactin; ACTH, adrenocorticotropic hormone.

Surgical details	
Size	
Macro	86.3%
Micro	13.70%
Pathology	
NF	50.00%
GH	22.80%
PRL	9.00%
ACTH	18.20%
Type of removal	
Subtotal	9.,00%
Total	91.00%
Knosp	
Grade 0	22.80%
Grade I	40.90%
Grade II	18.10%
Grade IIIA	4.50%
Grade IIIB	9.20%
Grade IV	4.50%
Naso-septal flap	
Yes	9.00%
No	91.00%
CSF leak	
Yes	1 case
No	21 cases
Surgical time	
Mean (min)	129,.18 ± 30.74
Follow-up	
Mean (days)	187.00 ± 10.5
Hospitalisation	
Mean (days)	3.09 ± 0.61

arranged a rescue flap (vascular pedicled naso-septal flap) on one side, but used it in only 9% of cases (Table II). In terms of postoperative outcomes, in 91% of the cases we achieved total removal, while in 9% removal was near total. We observed no post operative CSF leak even if we had a low grade fistula during surgery. None of the cases required post- or intraoperative blood transfusion. The team did not experience any kind of technincal trouble during the procedures listed above; surgical time was the same of the standard 2D procedures. The new technology 4K UHD endoscope showed easy usage process and no complications such as image straining or shape diversion. We noted that it was fundamental to properly set the chromatic configuration, especially with red wavelengths, in order to have a good colour perception during bleeding in surgical procedures. The use of the dedicate rigid optics optimise the chromatic experience even if with a prope setting it is possible to use rigid scope of other brands previously available and routinely used. An ergonomic and low weight camera allowed us to have a reasonable physical stress given by camera holding that was very similar to other endoscopes and compared with the old system, even lighter.

Discussion

The continuous development and constant research of innovative technologies is mandatory in all third leves endoscopic skull base centres. All new and updated visualisation technologies needs to be considered in this ever expanding field.

Obvioulsy good surgery needs good anatomical knowledges and skilled and experienced surgerons to have reasonable safety and good success margins. The visualisation systems play a significant and preeminent role in this context, mostly for endonasal endoscopic skull base surgery. Four thousand pixels on the longer axis give us a satisfactory visual resolution, more anatomical and well detailed information and an higher definition of the pathology under examination than the standard systems currently in use: it is almost 4 times more informations for frame compared to standard HD images. Structures like diaphragm sellae, pituytary gland, pituitary stalk and pathological lesion within the sellar space stood out clearly (Figs. 1, 2).

This new system did not require a learning curve because is not a 3D visualisation of the surgical field so it basically had the same landmarks of the other 2D high resolution devices.

The NBI equipment is a particular visual filter that can highlight the vascular trama of tissues, allowing us to properly distinguish the pituitary gland from the pathological tissue (Fig. 3); this should be taken into account especially for oncologic cases, but in this field need further study and experience.

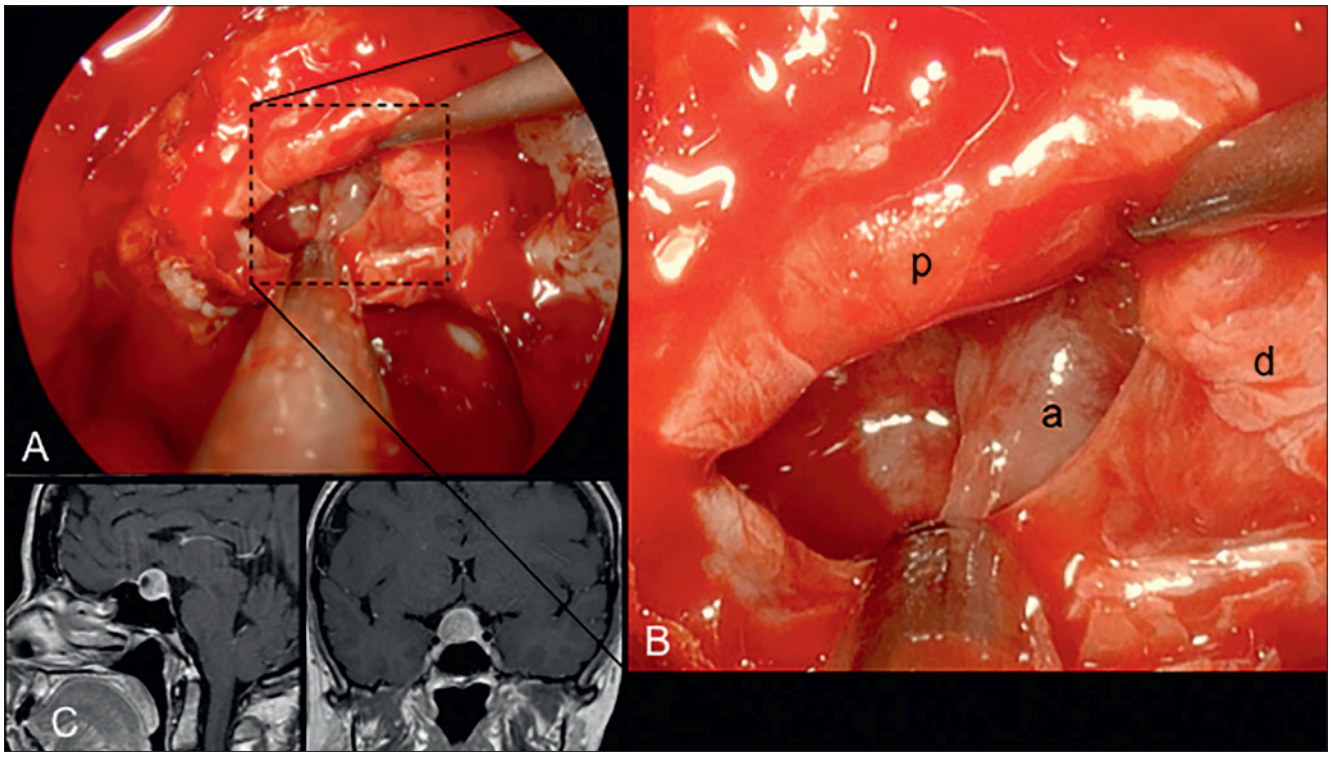

Fig. 1. Endoscopic view (A) of the sellar phase using the 4K Olympus endoscope in a case of not secreting macroadenoma as observed in MRI (C). The magnified view (B) allowed a correct discrimination of the details and chromatic differences between normal pituitary (p) tissue versus adenoma (a) the different layers of dura (d) and the texture of the pathologic tissue.

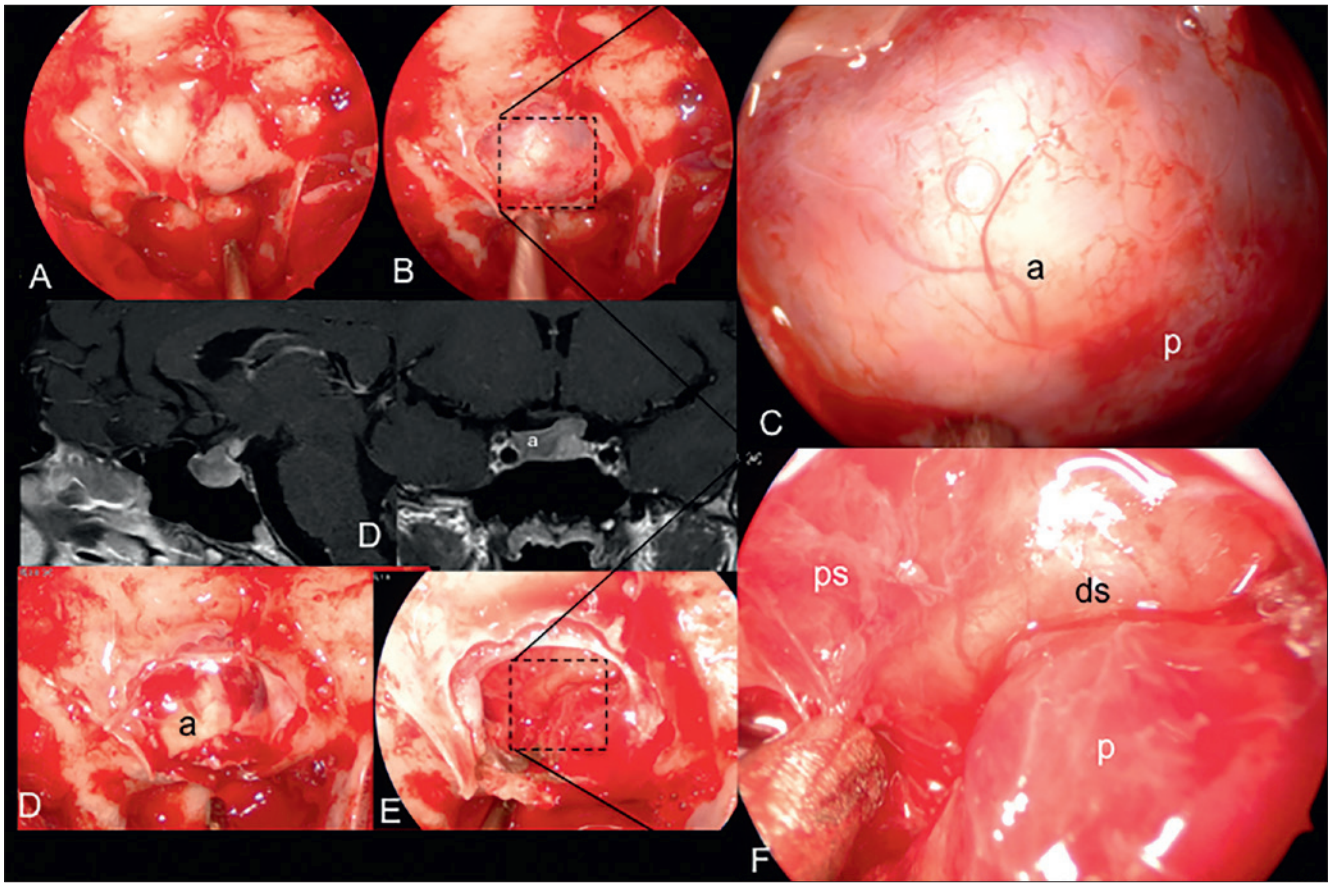

Fig. 2. Endoscopic view (A) of the sellar phase using the 4K Olympus endoscope in a case of GH secreting macroadenoma as showed in the MRI (D). The magnified view allowed a correct discrimination of the details and chromatic differences between normal pituitary tissue versus adenoma, starting from the initial phases before opening the dura (B-C). After tumour removal the great detailed resolution allowed the correct evaluation of the normal pituitary gland (p), the meningohypophiseal arteries and the pituitary stalk (ps) leading to a complete removal of the pathologic tissues and exposure of the dura of the dorsum sellae (ds).

Among the minor disadvantages, important to comment upon, we found during our surgical procedures were: 1) an dedicate colour combination setting that had a very huge role in the red colour discrimination, especially during a bleeding within the sellar space; 2) the 4K video and image storage needs a lot of space to build up a archive and a dedicated storage and registration unit is of paramount importance even if this is not inexpensive; 3) the use of 55' monitor requires a lot of space in the operating room to have a correct distance for good visualisation.

Fortunately, we acquired all the video with this tool but the user will also need a updated computer in order to visualise and mount videos, but the final result is very impressive in terms of resolution. 4K endoscope combined with NBI technology [4] has in our opinion the potential to start a revolution in skull base surgery, even if Akutsu used a flexible scope and standard HD monitor after removal of pituitary adenoma to check if there is still pathology in a series of 25 cases [5].

Further studies using the same NBI technology combined with 4K resolution and rigid scope are necessary to validate this extremely interesting potential. Surgery was successfully completed in all 22 cases and the new device shows promising features. This preliminary experience suggests that UHD endoscopy has a great potential going farther than the mere technical specifications might suggest. The visualisation and high resolution of the operative field provided a very detailed view of all anatomical and pathological structures leading to an improvement of safety and efficacy of the surgical procedure. The operative time was similar to the standard 2D HD and 3D procedures and the physical strain was also comparable to the latter techniques in terms of ergonomics and weight.

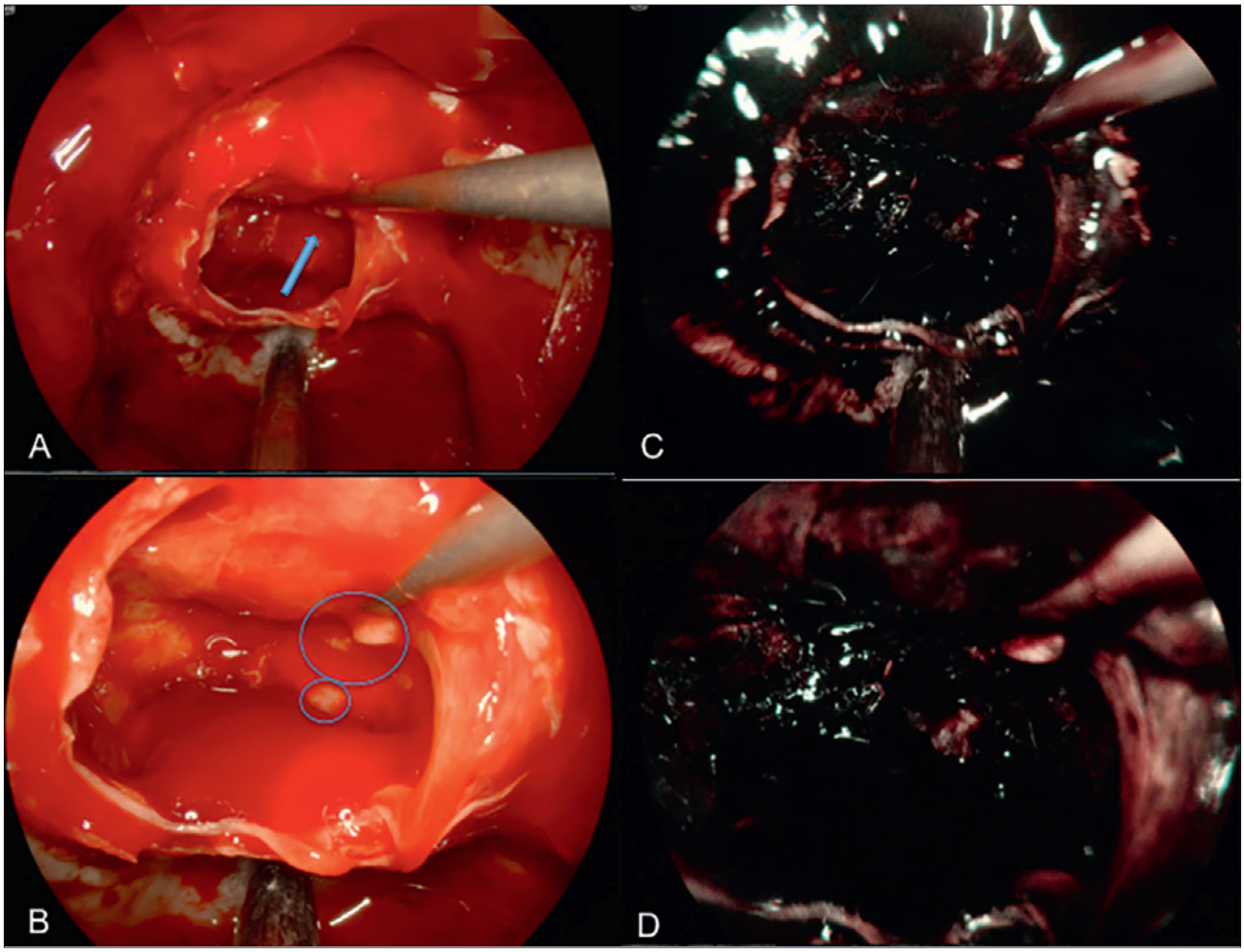

Fig. 3. Endoscopic view of the field after complete removal of the macroadenoma (A) showing the suspect quite small residual disease (arrows and circles) that clearly appears with magnification at high resolution (B) but seems to be confirmed using NBI filter (C,D), even if further experience and studies are necessary.

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CASE SERIES AND REPORTS

Voluminous laryngeal schwannoma excision with a mini-invasive external approach: a case report

Exeresi mediante approccio mini-invasivo di un voluminoso schwannoma laringeo: un case report

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SUMMARY

Laryngeal schwannomas are extremely uncommon. We present a case of bulky supraglottic schwannoma with involvement of the preepiglottic and superior paraglottic spaces. Clinical findings, computed tomography and magnetic resonance images are presented. These characteristics are typical, however not specific to schwannomas. For definitive diagnosis, histology and immunohistochemistry are necessary. We present an external mini-invasive approach that allowed us to both obtain diagnosis and provide definitive treatment for this kind of voluminous laryngeal tumour.

KEY WORDS: Schwannoma • Neurilemmoma • Nerve sheath tumours • Supraglottic larynx • Mini-invasive approach

RIASSUNTO

Gli schwannomi laringei sono una variante estremante rara dei tumori benigni della laringe. Riportiano il caso di un voluminoso schwannoma localizzato nella regione sopraglottica, con coinvolgimento dello spazio pre-epiglottico e paraglottico superiore. I segni e i sintomi di presentazione di tale tumore e le principali caratteristiche radiologiche riscontrabili alla TC e alla RMN sono descritte dettagliatamente. Pur non permettendo una diagnosi certa, tali caratteristiche, tipiche ma non esclusive dello schwannoma, sono importanti per sospettare il tumore in fase preoperatoria. La diagnosi definitiva necessita comunque dell'esame istologico e immunoistochimico, ottenibile mediante biopsia escissionale. Nello specifico descriviamo l'utilizzato nuovo approccio open mini-nvasivo che consente di ottenere la exeresi completa del tumore, con un ottimo outcome funzionale.

PAROLE CHIAVE: *Schwannoma • Neurilemmoma • Tumori della guaina dei nervi • Laringe sopraglottica • Approccio miniinvasivo*

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Introduction

Schwannomas are the most common benign peripheral nerve sheath tumours and originate from Schwann cells of the peripheral nervous system. Laryngeal schwannomas are rare and usually present as insidious, slow-growing, submucosal masses, bringing diagnostic and management challenges for the otolaryngologist. Appropriate therapy requires complete excision with minimal injury to uninvolved areas of the larynx. Both endoscopic and open approaches have been described depending on tumour features [1 2].

We describe a case of bulky laryngeal schwannoma of the preepiglottic space and discuss our management. We present a new possible approach to benign and encapsulated tumours that allowed both mini-invasive radical resection of the tumour and complete recovery with short hospitalisation time.

Case report

A 61-year-old man presented to the otolaryngology clinic with an 18-month history of foreign-body sensation and hoarseness. He denied dyspnoea, dysphagia, otalgia or recent respiratory tract infection. He had quit smoking about 40 years prior to presentation. Family history was negative for remarkable disease, with no case of laryngeal tumours or hereditary diseases.

Flexible fiberoptic laryngoscopy revealed the presence of a bulky submucosal mass in the right aryepiglottic fold with suspected involvement of the pre-epiglottic space. It occupied the ipsilateral piriform sinus and appeared cystic in nature (Fig. 1A). The laryngeal airway was decreased, but sufficient and both vocal folds were mobile. No cervical lymph nodes were palpable. Computed tomography (CT) performed in another hospital identified a paramedian supraglottic mass. It was characterised by a cystic appearance and clear margins with no evidence of cartilage erosion. Magnetic resonance imaging (MRI) identified a round mass that occupied the preepiglottic and superior paraglottic spaces. The mass pushed the epiglottis and right aryepiglottic fold posteriorly and the false vocal cord posteromedially. It had hyperintense signal on T2

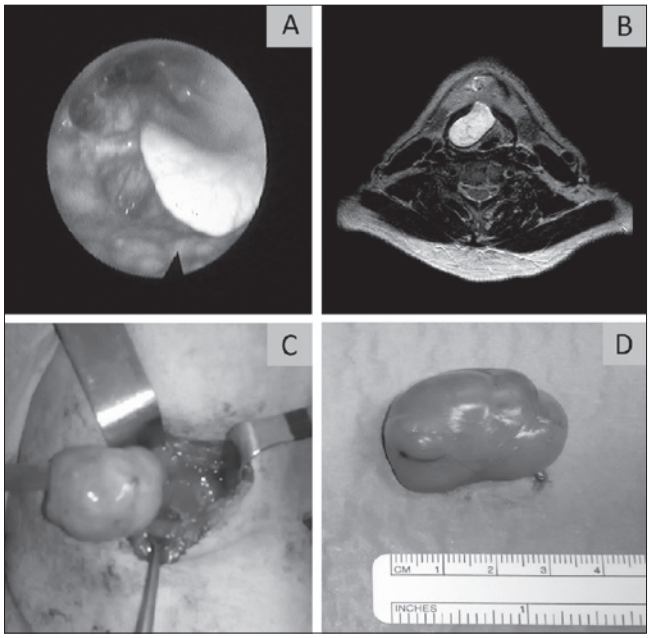

Fig. 1. (A) Endoscopic view of the lesion; (B) T2-weigthed MRI image of the mass; (C) surgical procedure for removal of the tumour; (D) surgical specimen.

weighted imaging and hypointense signal on T1 with wall enhancement after gadolinium (Fig. 1B). The radiological findings were suspicious for benign encapsulated lesions such as minor salivary gland adenoma or schwannoma.

Due to the dimension of the mass, the patient underwent surgery with an external approach. A horizontal median skin incision of 3.5 cm was made above the upper edge of the thyroid cartilage in a skin crease. Subplatysmal flaps were raised and the midline raphe was identified. Proceeding in depth at the midline, the thyroid cartilage and thyrohyoid membrane were exposed. To obtain good exposure of the area, the ipsilateral thyrohyoid muscle was sectioned and the remaining muscles were divaricated. The thyrohyoid membrane was cut with access to the preepiglottic space. Eventually the mass was removed by blunt dissection, taking care to maintain the integrity of the capsule and overlying laryngeal mucosa and preserving the trunk of the internal branch of the superior laryngeal nerve (Fig. 1C). Having achieved satisfactory haemostasis, a drain was placed to prevent supraglottic haematoma. At the end of the procedure, no tracheostomy was necessary and the respiratory space was checked by fibroscopy 20 min later in the recovery room.

The surgical specimen was a solid, oval shape and capsulated mass and measured 3 x 2.5 x 2 cm (Fig. 1D). On microscopic evaluation, the tumour fulfilled Enzinger and Weiss's diagnostic criteria for schwannoma: (1) presence of a capsule, (2) presence of Antoni A and/or Antoni B areas, and (3) positivity of S-100 reaction [2 3]. Furthermore, Verocay bodies were visible and no interspersed axons were present.

In the postoperative period, the patient did not present any vocal fold motility impairment, laryngeal mucosa sensitivity deficit, dyspnea, or dysphagia. The patient was discharged two days after surgery. A 7 months, follow-up examination showed disappearance of the foreign body sensation and an excellent vocal outcome.

Discussion

Schwannomas (also called neurilemmomas) are encapsulated tumours made entirely of benign neoplastic Schwann cells. The vast majority of schwannomas occur sporadically as single lesions, affecting patients of all ages, reaching a peak between 20 and 50 years, without associated lifestyle risk factors [4]. About 25% to 45% of all schwannomas occur in the head and neck region, the majority in the parapharyngeal space.

Laryngeal schwannomas are uncommon lesions and represent 0.1 to 1.5% of all benign laryngeal tumours [2 5 6]. The majority of schwannomas in the larynx originate either from the aryepiglottic fold or the false cords and then grow in the supraglottic compartment. The internal branch of the superior laryngeal nerve seems to be the most frequent nerve of origin. Macroscopically, laryngeal schwannomas appear as submucosal, smooth, well-encapsulated, firm masses and grow eccentrically to the nerve of origin [7]. Histologically the Schwannoma must meet the diagnostic criteria of Enzinger and Weiss mentioned above, as fulfilled by our patient.

The clinical symptoms strictly depend on the location, size and direction of the laryngeal schwannoma growth. Most patients are asymptomatic until the tumour reaches a large size and leads to conflict with surrounding structures. The typical symptomatology is constituted by long-standing history of hoarseness and foreign body sensation in the throat, dysphagia, or inspiratory dyspnea with stridor. On laryngoscopy, a laryngeal schwannoma appears like a submucosal mass. Paralysis or hypomobility of the ipsilateral vocal cord can be present [2 3]. The very slow growth (in the order of years), the absence of pathological lymphadenopathy and the lack of weight loss are characteristics indicating the benignity of this neurogenic tumour. Good family history and complete clinical examination of the patient is required to detect hereditary disease (neurofibromatosis or schwannomatosis).

With regards to diagnostic imaging methods, CT and MRI are most frequently indicated. CT and MRI imaging of schwannomas show the typical features of a benign lesion and can provide a preoperative estimation of the extent and nerve of origin [5]. The clinical and radiological characteristics are typical, but not specific to schwannomas. Definitive diagnosis is provided by histology and immunohistochemistry.

Previous reports indicate that fine needle aspiration cytology (FNAC) is often inconclusive [1 8]. Incisional biopsy has

higher diagnostic efficacy, but (1) exposes the patient to an increased risk of relapse; (2) requires an additional surgery for exeresis of the tumour (increasing the risks and the costs) and (3) leads to formation of a scar on the site of mucosal incision, making subsequent excision more difficult and necessarily wider with a higher risk of early and late complications [1 10].

We believe that when there is an indication to remove a submucosal capsulated laryngeal lesion, that does not present signs of malignancy, the best choice is excisional biopsy. In fact, this procedure allows us to simultaneously obtain a diagnosis and initiate definitive treatment of laryngeal schwannoma or other benign lesions.

The literature shows that the main differential diagnoses for laryngeal schwannomas include benign laryngeal tumours (neurofibroma, lipoma, adenoma, chondroma, papilloma, paraganglioma,) and non-neoplastic lesions (internal laryngocele, ectopic thyroglossal duct cyst, laryngeal cyst). Malignant lesions should, however, also be excluded.

Traditionally the surgical excision of the mass is the treatment of choice [8]. Adjuvant treatment (either radiotherapy or chemotherapy) is not contemplated. Appropriate surgical therapy requires complete excision of the mass with minimal injury to uninvolved areas of the larynx, laryngeal mucosa and healthy structures. The surgical approach may be selected by the size and site of the tumour, and tracheotomy is not always required.

If the tumour is small and superficial or localised in the glottis or peduncolated with good endolaryngeal exposure, the best choice is an endoscopic approach [2 5 9]. The advantages of this approach include a less-invasive procedure, absence of scar in the neck and fewer days of hospitalisation (1-5 days). For voluminous tumours, an external approach may offer the best exposure for complete extra-capsular excision in a single block and allow preservation of the laryngeal mucosa while minimising complications and maximising postoperative voice outcome [1]. The most frequently used open approaches are the median thyrotomy [2 6] and lateral thyrotomy [1 3]. Recently, Ueha et al. proposed a suprathyroid alar cartilage approach (STACA) for submucosal laryngeal tumours that includes sacrifice of the ipsilateral prelaryngeal muscles, a larger lateral incision of thyrohyoid membrane and tracheostomy [9]. In contrast, our mini-invasive approach gives excellent oncological and functional results and at the same time minimises risk, hospital stay and costs. Indeed, only one thyrohyoid muscle was sectioned and repaired and tracheostomy was not necessary. The patient was discharged after 36 hours and voice outcome was good.

We believe that by relying on the characteristics of the tumour and the patient, the treatment must be tailored and, respecting oncological radicality, should be the least invasive as possible. We believe that for bulky submucosal supraglottic tumuors this should be the initial approach. If this approach proves inadequate, it is simple to switch to a more invasive approach (e.g. removing a portion of thyroid lamina). After treatment, long-term follow-up for possible recurrence is appropriate, although to date it is unclear what the appropriate duration should be.

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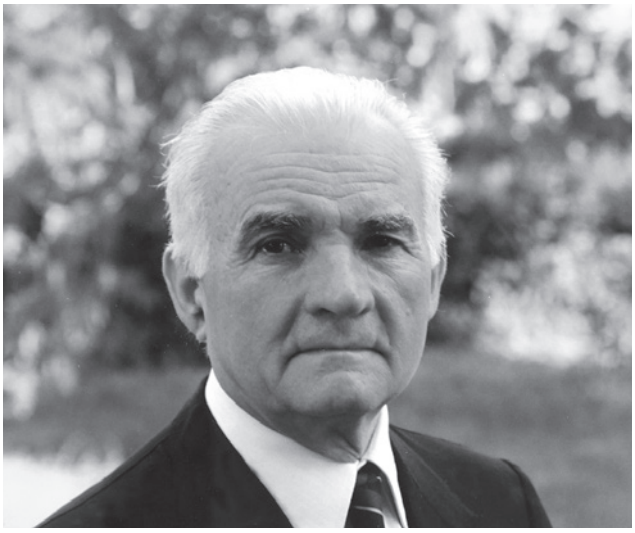
In Memoriam of Dino Felisati

(22/11/1922 - 12/3/2017)



Dino Felisati was born in a small town on the delta of the Po river, a place to which he remained bound throughout his life, a place to which he returned often and whenever possible, and to which he dedicated two volumes of considerations and memories. He was also strongly bound to two cities: Venice, where his family had transferred and where he lived his adolescence, and Milan, where he carried out his intense and gratifying professional life.

His career started in the prestigious school of Luigi Pietrantoni and, in 1960, following Pietrantoni's death, he moved from a hospital to university setting. Since 1961, Felisati was department head at Merate Hospital, and since 1972 at Bassini in Milan, which had become a university centre, at which he, in the 1980s and 1990s, was first Lecturer and later Adjunct Professor. But it was above all the organisation and development of the Italian Society of ENT that Dino Felisati brought fundamental contributions for which we all owe him our gratitude.

First of all, it must be remembered that he, together with other hospitals (De Amicis, Clerici, Tavani, Borasi), contributed significantly to the transformation, in 1976, of SILOR to SIO, and worked hard to give it new life by modifying many statutes and regulations, using knowledge that he had acquired over many years of undisputed expertise. This dedication to the activities and development of our society never wavered, even in old age. I remember, for example, that after reaching the presidency of the SIO and after it ended in 1987 with the organisation of the superb National Congress in Milan, Felisati was always present at the meetings of the Executive Board during which he provided helpful advice dictated by his long experience and good sense. I also remember his collaboration with me, Giuliano Perfumo, Gianni Ralli and Domenico Celestino in setting up and improving the Historical Museum and Library at our office in Rome, further highlighting his commendable spirit of service.

I must lastly remember the 30-year collaboration that has tied me and Dino thanks to our shared passion for historical studies. In truth, at the beginning of this relationship in the early 1980s, it was certainly not ideal because I perceived him as gruff, hard and sometimes unfriendly, but over time I realised that behind this facade lurked a kind soul, openly jovial, available to friendship, and so a great, fraternal friendship established between us and bound us for many years. Our shared passion for the History of Medicine and our mutual esteem cemented this long collaboration, which was witnessed by long series of articles and books published over the years and dedicated to the evolution of otolaryngology over time. I must admit that it was always Dino, despite being the oldest, to always give the right incentives, to kindle enthusiasm for discovering new evidence, so much so that only a few months ago he had proposed some new projects. Now, unfortunately, this dear friend is gone, leaving behind a great void and immense regret.

Giorgio Sperati

Calendar of events – Italian and International Meetings and Courses

Acta Otorhinolaryngol Ital 2017;37:246-247

Information, following the style of the present list, should be submitted to the Editorial Secretariat of Acta Otorhinolaryngologica Italica (actaitalicaorl@rm.unicatt.it).
In accordance with the Regulations of S.I.O. and Ch.C.-F. (Art. 8) Members of the Society organising Courses, Congresses or other scientific events should inform the Secretary of the Association (A.U.O.R.L., A.O.O.I.) within the deadlines set down in the respective Statutes and Regulations.

MAY-DECEMBER 2017

XXV INTERNATIONAL EVOKED RESPONSE AUDIOMETRY STUDY GROUP (IERASG) BIENNIAL SYMPOSIUM • ***May 21-25, 2017 • Warsaw – Poland***

Website: ierasg2017.com/

104° CONGRESSO NAZIONALE SIO – SOCIETA ITALIANA DI OTORINOLARINGOLOGIA E CHIRURGIA CERVICO-FACCIALE • ***May 24-27, 2017 • Sorrento – Italy***

President: Carlo Antonio Leone – Website: www.sioechcf.it

THE 8th MANCHESTER SINUS, RHINOPLASTY AND NASAL PLASTICS DISSECTION COURSE
June 5-8, 2017 • Manchester – United Kingdom

E-mail: rajiv.bhalla@manchester.ac.uk – Website: www. Nose-manchester.co.uk

TINNITUS AND HYPERACUSIS THERAPY INTENSIVE MASTRCLASS
June 7-9, 2017 • Copenhagen – Denmark

Website: www.tinnitustherapy.org.uk

HANDS-ON COURSE, BASIC - SINUS & SKULL BASE SURGERY: ANATOMICAL DISSECTION, DIAGNOSTICS AND OPERATIVE TECHNIQUES • ***June 12-14, 2017 • Varese – Italy***

Website: www.attingo-edu.it

MIDDLE EAR SURGERY COURSE • ***June 12-16, 2017 • Piacenza – Italy***

E- mail: corsi.sanna@gruppootologico.com – Website: www.gruppootologico.com

20th INTERNATIONAL WORKSHOP 2017. LASER VOICE SURGERY AND VOICE CARE
June 22-23, 2017 • Paris – France

E-mail: voice.abitbol@gmail.com – Website: www.laservoicesurgery.com

IFOS PARIS 2017 - ENT WORLD CONGRESS • ***June 24-28, 2017 • Paris – France***

Website: www.ifosparis2017.org

CORSO DI DISSEZIONE DELL'OSSO TEMPORALE 1°LIVELLO (BEGINNERS)
July 3-6, 2017 • Parma – Italy

E-mail: chiara.cammi@promoleader.com; silvia.pirisino@promoleader.com

53rd GRAZ COURSE ON RHINOSURGERY • ***July 12-15, 2017 • Graz – Austria***

E-mail: claire.zwerina@klinikum-graz.at – Website: www.ent-graz.com

28th AND 29th INTERNATIONAL SIALOENDOSCOPY HANDS-ON COURSES
Sialoendoscopy Beginner's Hands-on course: August 28-30, 2017 • Geneva – Switzerland
Sialoendoscopy Advanced course: August 30-September 1, 2017 • Geneva – Switzerland

Website: www.sialendoscopy.com

12th PAN EUROPEAN VOICE CONFERENCE • ***August 30-September 1, 2017 • Ghent – Belgium***

Website: www.pevoc12.be

SWISS ENDOSCOPIC EAR SURGERY COURSE SEES – HANDS-ON ENDOSCOPIC EAR AND LATERAL SKULL BASE SURGERY • ***September 4-5, 2017 • Bern – Switzerland***

Website: http://sees.swiss-meeting.org

ENDOSCOPIC PARANASAL SINUS & SKULL BASE HANDS ON COURSE PSSB
September 7-8, 2017 • Bern – Switzerland

Website: http://paranasal.swiss-meeting.org

VII CORSO TEORICO PRATICO DI AUDIOLOGIA E VESTIBOLOGIA "GIANNI MODUGNO"
September 25-27, 2017 • Benevento – Italy

Direttore: Luigi Califano – E-mail: vertigobn@hotmail.com

XXXVI CONGRESSO NAZIONALE DELLA SOCIETÀ ITALIANA DI AUDIOLOGIA E FONIATRIA
September 27-30, 2017 • Siena – Italy

Website: www.congresso-siaf2017.it/

XVI CONGRESSO NAZIONALE AIOLP • ***October 6-7, 2017 • Venice – Italy***

Website: www.aiolp.it/

4th CONGRESS OF THE EUROPEAN ORL-HNS • ***October 7-11, 2017 • Barcelona – Spain***

Website: www.ceorlhns2017.com/ – E-mail: orl-hns2017@topkon.com – E-mail: scientific_orl-hns2017@top-kon.com

CORSO DI DISSEZIONE DELL'OSSO TEMPORALE 2°LIVELLO (ADVANCED)
October 16-20, 2017 • Parma – Italy

E-mail: chiara.cammi@promoleader.com; silvia.pirisino@promoleader.com

RHINOPLASTY & FACIAL PLASTIC SURGERY • ***October 20-21, 2017 • Porto – Portugal***

Website: www.portofacialplastic.com

AUDIOVESTIBOLOGIA... IN CORSO D'OPERA - III EDIZIONE
October 23-25, 2017 • Benevento – Italy

Direttore: Luigi Califano – E-mail: vertigobn@hotmail.com

CORSI PRATICI DI VIDEOCHIRURGIA ENDOSCOPICA NASO-SINUALE E DEL BASICRANIO
November 13-17, 2017 • Milan – Italy

Direttore: Alberto Dragonetti – Website: http://www.dragonettialberto.it/corsi.html

17th ASEAN ORL HNS CONGRESS • ***November 16-18, 2017 • Myanmar***

Website: www.entnet.org/content/17th-asean-orl-hns-congress

JANUARY-DECEMBER 2018

15th INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS AND OTHER IMPLANTABLE AUDITORY TECHNOLOGIES • ***June 13-16, 2018 • Antwerp – Belgium***

Chairman: Paul Van de Heyning – E-mail: vincent.van.rompaey@uza.be – Website: www.ci2018.org

6th WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF HEAD AND NECK ONCOLOGIC SOCIETIES • ***September 1-5, 2018 • Buenos Aires – Argentina***

Website: http://ifhnos2018.org/

JANUARY-DECEMBER 2019

14th ASIA-OCEANIA ORL-HNS CONGRESS 2019 • ***January 9-13, 2019 • Hyderabad – India***

Email: info@14asiaoceania.com – Website: http://14asiaoceania.com/