POSTE ITALIANE SPA - Spedizione in Abbonamento Postale - D.L. 353/2003 conv. in L. 27/02/2004 n° 46 art. 1, comma 1, DCB PISA - Iscrizione al tribunale di Pisa al n. 10 del 30-07-93 - Finito di stampare presso IGP Pisa - Febbraio 2021 - ISSN: 0392-100X (Print) - ISSN: 1827-675X (Online) - Contiene I.P.

ACTA

Otorhinolaryngologica Italica

Official Journal of the Italian Society of Otorhinolaryngology Head and Neck Surgery

Organo Ufficiale della Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale

S.I.O.e.C.C.F.

PACINI EDITORE MEDICINA

Volume 41
February 2021

1

www.actaitalica.it

Acta Otorhinolaryngologica Italica

Official Journal of the Italian Society of Otorhinolaryngology Head and Neck Surgery

Organo Ufficiale della Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale

Managing Editor
M. Ansarin

Publisher
Pacini Editore Srl
Via Gherardesca, 1 - 56121 Pisa, Italy
Tel. +39 050 313011 -Fax +39 050 3130300
info@pacinieditore.it - www.pacinimedicina.it

Acta Otorhinolaryngologica Italica is cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

2019 Journal Impact Factor, Journal Citation Reports (Source Clarivate, 2020): 1.510
Acta Otorhinolaryngologica Italica is available on Google Scholar

S.I.O.C.C.F.

PACINI EDITORE MEDICINA

Volume 41
February 2021

www.actaitalica.it

Contents

Articles in open access, information for authors including editorial standards for the preparation of manuscripts and submission and Publisher's note available on-line: www.actaitalica.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:1-5; doi: 10.14639/0392-100X-N1002

COVID-19

Acoustic voice analysis in the COVID-19 era

L'analisi acustica della voce in era COVID-19

Giada Cavallaro, Vincenzo Di Nicola, Nicola Quaranta, Maria Luisa Fiorella

Otolaryngology Unit, Department of Biomedical Sciences, Neuroscience and Sensory Organs, University of Bari "Aldo Moro", Italy

SUMMARY

Objective. Among the different procedures used by the ENT, acoustic analysis of voice has become widely used for correct diagnosis of dysphonia. The instrumental measurements of acoustic parameters were limited during the COVID-19 pandemic by the common belief that a face mask affects the results of the analysis. The purpose of our study was to investigate the impact of surgical masks on F0, jitter, shimmer and harmonics-to-noise ratio (HNR) in adults.

Methods. The study was carried out on a selected group of 50 healthy subjects. Voice samples were recorded directly in Praat. All subjects were trained to voice a vocal sample of a sustained /a/, at a conversational voice intensity, with no intensity or frequency variation, for the Maximum Phonation Time (MPT), wearing the surgical mask and then without wearing the surgical mask.

Results. None of the variations in acoustic voice analysis detected wearing a surgical mask and not wearing a surgical mask were statistically significant.

Conclusions. Our study demonstrates that the acoustic voice analysis procedure can continue to be performed with the use of a surgical mask for the patient, even during the COVID-19 pandemic.

KEY WORDS: COVID-19, acoustic voice analysis, Praat, dysphonia, surgical mask

RIASSUNTO

Obiettivo. *Tra le diverse procedure diagnostiche di competenza otorinolaringoiatrica, l'analisi acustica della voce si rivela utile alla valutazione quantitativa della disfonia ma la misurazione strumentale dei parametri acustici è stata limitata durante la pandemia da COVID-19 essendo la mascherina chirurgica considerata comunemente come da ostacolo nella registrazione della voce. Lo scopo del nostro studio è stato quello di analizzare l'impatto della mascherina chirurgica su parametri vocali quali F0, jitter, shimmer e harmonic-to-noise ratio (HNR).*

Metodi. *È stato studiato un campione di 50 soggetti eufonici utilizzando il programma Praat. I soggetti sono stati istruiti a fonare la vocale /a/ tenuta ad intensità di voce di conversazione, senza variazioni di intensità o frequenza, per il Tempo Massimo Fonatorio (TMF), con e senza mascherina chirurgica.*

Risultati. *L'analisi acustica eseguita con le due diverse modalità non ha rivelato differenze statisticamente significative nei parametri vocali considerati.*

Conclusioni. *Il nostro studio dimostra come la procedura diagnostica di analisi acustica della voce può essere eseguita sul paziente che indossa la mascherina chirurgica.*

PAROLE CHIAVE: *COVID-19, analisi acustica della voce, Praat, disfonia*

Introduction

During the ongoing COVID-19 pandemic caused by SARS-CoV-2, the World Health Organization and other public health organisations agree that face masks can limit the spread of respiratory viral diseases [1,2]. Whether masks are useful depends on the mechanisms for transmission for SARS-CoV-2, which are likely an association of contact, droplet and aerosol modes. Surgical face masks have been in use since the early 1900s to help prevent infection of surgical wounds from staff-generated oral and nasal bacteria [3]. Today, appli-

Received: July 19, 2020
Accepted: August 12, 2020
Published online: November 24, 2020

Correspondence
Giada Cavallaro
Otolaryngology Unit, Department of Biomedical Sciences, Neuroscience and Sensory Organs, University of Bari "Aldo Moro", Italy
E-mail: giadacavallaro@live.it

Funding
The authors received the "Research Projects of National Relevance 2017 n. 2017JNKCYZ" funding for this work.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Cavallaro G, Di Nicola V, Quaranta N, et al. Acoustic voice analysis in the COVID-19 era. Acta Otorhinolaryngol Ital 2021;41:1-5. https://doi.org/10.14639/0392-100X-N1002

cations have evolved from prevention of patient infection to prevention of employee exposure. However, there is ongoing debate about the use of surgical masks as respiratory protection devices [4]. For ENT specialists, dysphonia examination by laryngoscopy requires unavoidable contact with the upper airway, and any reflex coughing or sneezing during procedures will cause direct contamination to medical staffs and office workers [5,6]. Among the different procedures used by the ENT, acoustic analysis of voice has become widely used for correct diagnosis of dysphonia, but the instrumental measurements of acoustic perturbation was limited during the COVID-19 pandemic by the common belief that a face mask affects the results of the analysis. The purpose of our study was to investigate the impact of surgical mask on F0, jitter, shimmer and harmonics-to-noise ratio (HNR) in adults.

Materials and methods

The study was carried out on a selected group of 50 healthy subjects (20 men and 30 women, mean age 47 years, range 26-69) recruited among hospital staff of the ENT Department of the Polyclinic Hospital in Bari (South Italy).
Participants were approached and informed about the study objectives and significance. All participants who agreed to participate in the study signed an informed consent form, previously approved by the local hospital Ethics Committee.
Inclusion criterion was ability to phonate and sustain a vowel for at least 10 seconds. The participants were excluded if they met any of the following criteria: reporting recent voice problems or a voice disorder history, a condition that might affect the normal voice function, any previous formal voice training or voice therapy, any laryngeal, mouth, or throat abnormality, or any respiratory infection for the last 2 weeks before recording. The subjects who met selection criteria were recruited. The participants were asked to stand in front of a microphone (Samson Meteor Mic - USB Studio Condenser Microphone) at a distance of 20 cm from the lips, in a quiet room (< 30 dB background noise). Voice samples were recorded directly in Praat. All subjects were trained to voice a vocal sample of a sustained /a/, at a conversational voice intensity, always within 55 dB and 65 dB, on average (not including recordings the average intensity of which was out of range), as constant as possible, with no intensity or frequency variation, for the Maximum Phonation Time (MPT), wearing a surgical mask and then without a surgical mask. The vocal parameters analysed with Praat were median pitch, mean pitch, minimum pitch, maximum pitch, number of pulses, number of periods, jitter (local), jitter (rap), jitter (ppq5), jitter (ddp), shimmer (local), shimmer (apq3), shimmer (apq5), shimmer (apq11), shimmer (dda) and mean harmonics-to-noise ratio (HNR).

Results

The results are recorded as average and standard deviation (SD). Results were then submitted to statistical analysis by comparing mean values of each parameter. All parameters were analysed in the same patients during phonation with surgical mask (SM) and without surgical mask (NSM). We used Student's test with $p = 0.05$ significance level after evaluating the t value in each parameter.
As illustrated in Table I, the acoustic analysis showed that there was not a significant difference (at the 0.05 level) in median pitch values (Mean SM = 187.36; SD SM = 52.36; Mean NSM = 189.38; SD NSM = 55.52; $p = 0.8523$) and in the mean pitch values (Mean SM = 183.52; SD SM = 51.13; Mean NSM = 185.52; SD NSM = 55.12; $p = 0.8513$) in the two different situations (wearing surgical mask – not wearing surgical mask) (Tab. I).
As can be seen in Table II, differences in HNR values were not significant (Mean SM = 20.91; SD SM = 3.44; Mean NSM = 20.92; SD NSM = 3.47; $p = 0.9885$). At the same time, significant differences were not noticed in jitter or shimmer values (jitter local Mean SM = 0.327; SD SM = 0.134; Mean NSM = 0.298; SD NSM = 0.124; $p = 0.2641$; shimmer local Mean SM = 3.34; SD SM = 1.420; Mean NSM = 3.165; SD NSM = 1.572; $p = 0.5605$) (Tabs. III, IV). In conclusion, none of the variations in acoustic voice analysis detected in the same patients with surgical mask and without surgical mask were statistically significant.

Discussion

Acoustic voice analysis is considered to be a very useful technique for detection of voice disorders that can be detected by analysing several acoustic parameters[7]. Subjective assessment methods, such as auditory perceptual analysis, largely depend on the experience of professionals, and may lead to different results. This requirement encourages the use of objective measurement of voice. Processing of a speech signal is used to yield a set of voice parameters. It allows detection of vocal fold pathologies, or other related pathologies, by comparing patients' data with that of other individuals having normal healthy voices [7]. Voice disorders require often voice therapy and other treatments that are based on an initial assessment to quantify deviation from normal measures and an ongoing evaluation to record the progress. Measuring treatment outcomes is the basic component of evidence-based practice. The objective

Table I. Acoustic analysis of median pitch, mean pitch, minimum pitch and maximum pitch values wearing surgical mask (SM) and not wearing surgical mask (NSM). With significance level at 0.05, values obtained by Student t test (calculated) in the same patients with surgical mask and without surgical mask are not statistically significant.

	Median pitch (Hz) SM	Median pitch (Hz) NSM	Mean pitch (Hz) SM	Mean pitch (Hz) NSM	Minimum pitch (Hz) SM	Minimum pitch (Hz) NSM	Maximum pitch (Hz) SM	Maximum pitch (Hz) NSM
Mean	187.36	189.38	183.52	185.52	173.37	181.87	194.52	195.94
Standard Deviation	52.36	55.52	51.13	55.12	54.15	59.05	54.63	56.47
T-test	p = 0.8523	p = 0.8513	p = 0.4549	p = 0.8986				

Table II. Acoustic analysis of the number of pulses, number of periods and of the HN (harmonics-to-noise ratio) values wearing surgical mask (SM) and not wearing surgical mask (NSM). With significance level at 0.05, values obtained by Student t test (calculated) in the same patients with surgical mask and without surgical mask are not statistically significant.

	Number of pulses SM	Number of pulses NSM	Numbers of periods SM	Numbers of periods NSM	Mean HNR (dB) SM	Mean HNR (dB) NSM
Mean	574.18	575.00	573.14	574.00	20.91	20.92
Standard Deviation	157.88	168.76	157.85	168.76	3.44	3.47
T-test	p = 0.9800		p = 0.9791		p = 0.9885	

Table III. Acoustic analysis of jitter values wearing surgical mask (SM) and not wearing surgical mask (NSM).With significance level at 0.05, values obtained by Student t test (calculated) in the same patients with surgical mask and without surgical mask are not statistically significant.

	Jitter local SM (%)	Jitter local NSM (%)	Jitter rap SM (%)	Jitter rap NSM (%)	Jitter ppq5 SM (%)	Jitter ppq5 NSM (%)	Jitter ddp SM (%)	Jitter ddp NSM (%)
Mean	0.327	0.298	0.184	0.159	0.182	0.165	0.535	0.533
Standard Deviation	0.134	0.124	0.084	0.068	0.071	0.062	0.240	0.411
T-test	p = 0.2641		p = 0.1051		p = 0.2052		p = 0.9764	

Table IV. Acoustic analysis of shimmer values wearing surgical mask (SM) and not wearing surgical mask (NSM).With significance level at 0.05, values obtained by Student t test (calculated) in the same patients with surgical mask and without surgical mask are not statistically significant.

	Shimmer local SM (%)	Shimmer local NSM (%)	Shimmer apq3 SM (%)	Shimmer apq3 NSM (%)	Shimmer apq5 SM (%)	Shimmer apq5 NSM (%)	Shimmer apq11 SM (%)	Shimmer apq11 NSM (%)	Shimmer dda SM (%)	Shimmer dda NSM (%)
Mean	3.34	3.165	1.726	1.589	2.008	1.836	2.705	2.689	5.070	4.766
Standard Deviation	1.420	1.572	0.840	0.974	1.061	0.897	1.087	1.194	2.531	2.922
T-test	p = 0.5605		p = 0.4531		p = 0.3835		p = 0.9443		p = 0.5794	

assessment of voice, especially acoustic analysis, has received our attention because of its comparatively low cost, ease of application and quantitative output. Previous studies [8,9] have found that fundamental frequency (F0) can be affected by different factors, i.e., age, vocal fold length and language or ethnological background. Until now, no study has investigated the effects of the use of a surgical mask on acoustic parameters. According to previous studies, one of the most investigated voice acoustic parameters has been voice perturbation [10,11]. Subsequently, we investigated parameters such as F0, jitter, shimmer and harmonics-to-noise ratio (HNR) during phonation wearing surgical mask

and then not wearing surgical mask. The fundamental frequency or mean pitch (F0) of a speech signal refers to the approximate frequency of the (quasi-)periodic structure of voiced speech signals. Jitter (%) is defined as cycle-to-cycle and short-term perturbation in the fundamental frequency of the voice. The shimmer (%) is a cycle-to- cycle, short-term perturbation in the amplitude of voice. Another acoustic parameter (HNR) is influenced by both the shimmer and jitter and referred to as the mean ratio of harmonics to non-harmonics [12].

In accordance with such a high risk of infection, only emergency consultations and procedures should be performed by ENT specialists during the COVID-19 pandemic in areas with confirmed SARS-CoV-2 cases [13]. In China, Cheng et al. noted that the rate of work-related SARS-CoV-2 infection was higher among ENT specialists that in other medical specialties [14]. During the lockdown of the population in Italy, ENT activities were reduced to emergency treatments and those that could not be deferred without constituting a real loss of chance for the patient's recovery or survival. ENT specialists are exposed to SARS-CoV-2 infection because of the necessity to examine the upper respiratory tract. At the same time, they perform procedures that generate aerosolised secretions and often bleeding [15]. In the study by Krajewska et al. [16] ENT units are important for preoperative testing for SARS-CoV-2: this should be performed in all individuals undergoing high-risk procedures. The authors also assert that chest CT should be performed in patients before ENT interventions, because it could be of great value in individuals with negative RT-PCR.

According to Tysome et al., high-risk procedures must be performed using enhanced personal protective equipment [17]. As highlighted by Lescanne et al. [18], during ENT examinations or procedures that not need exposure to projection/aerosolisation of organic material of human origin, the ENT medical team should wear clean outfits as well as single-use gloves in case of contact with a mucosa. If worn properly, a face mask is a disposable device that is used to help block large-particle droplets, sprays, splashes, or splatters that may contain viruses and bacteria. It is used to create a physical barrier between the potential contaminants in the immediate environment and the mouth and nose of the wearer and it is also useful to block saliva and respiratory secretions from the wearer to another [19]. In our study, the surgical masks used were three-ply. This three-ply material is made up of a melt-blown polymer, most commonly polypropylene, placed between non-woven fabric. For examinations and procedures with exposure to projection/aerosolisation of organic material of human origin, protection must be supplemented by wearing a surgical mask, protective goggles, a single-use plastic apron and single-use gloves. Insofar as an asymptomatic patient may be infectious, the same precautions must be employed whether the patient is ill with, suspected of having, or without any clinical evidence of COVID-19 infection [20]. After the examination, the professional must carefully disrobe in compliance with hygiene rules, with the immediate elimination of gloves, hair cap, mask and gown. The room where the examination is carried out must undergo air renewal as per legislation [20]. Most of these best practice recommendations are not based on scientific data established for the COVID-19 infection, but come from what is known about other viral respiratory infections.

For ENT specialists, voice acoustic analysis is a very valuable technique for voice disorders diagnosis and therapy monitoring [21]. Speech signal processing allows the extraction of a set of voice parameters that may be used to diagnose many pathologies of the vocal cords in individuals by comparison with healthy voice. The parameters obtained by the acoustic analysis have the advantage of describing the voice objectively rather than subjective perceptual analysis, and they represent a useful method to objectify the dysphonia, even in the pandemic period. The use of the surgical mask provides the patient and operator with the right protection necessary to perform this procedure, and at the same time it does not involve important alterations of the vocal parameters to be analysed. Several types of software have been developed for acoustic analysis, namely, Praat [22], LingWAVES [23], Multidimensional Voice Program [24] etc. The current study used Praat (version 6.1.16) for voice analyses, which is a computer software package for speech, phonetic and voice analysis. It was first designed in 1992 by Paul Boersma and David Weenick from the Institute of Phonetic Sciences, University of Amsterdam. Praat can be used on various operating systems and uses the finest algorithms including the most accurate algorithm of pitch analysis, articulatory synthesis and gradual learning algorithm for free variation. We used the inbuilt option of voice report in Praat pulses menu, which includes pitch and perturbation analyses. In particular, the voice samples collected for perturbation measures were analysed by selecting the middle 3 seconds from the sound wave. Each acoustic signal was perceptually examined for instability and visually displayed using Praat with an oscillogram and "Show intensity" and "Show pulses" settings. We acoustically analysed the voice samples recorded by each participant wearing and not wearing the surgical mask in order to find objective voice measurements including the F0, jitter, shimmer, and HNR. The statistical comparison carried out between the parameters extracted with and without surgical mask did not reveal any significant differences that would lead to an avoidance of the procedure for health safety reasons.

Conclusions

Excluding positive COVID-19 cases for which the use of more adequate protective devices is necessary, our study demonstrates that the acoustic voice analysis procedure can continue to be performed with the use of surgical mask for the patient during the COVID-19 pandemic.

References

1 https://www.who.int/news-room/q-a-detail/q-a-on-covid-19-and-masks

2 European Centre for Disease Prevention and Control. Using face masks in the community. Reducing COVID-19 transmission from potentially asymptomatic or pre-asymptomatic people through the use of face masks. Stockholm: ECDC; 8 April 2020.

3 Belkin NL. A century after their introduction, are surgical masks necessary? AORN J 1996;64:602-7. https://doi.org/10.1016/s0001-2092(06)63628-4

4 Long Y, Hu T, Liu L, et al. Effectiveness of N95 respirators versus surgical masks against influenza: a systematic review and meta-analysis. J Evid Based Med 2020;13:93-101. https://doi.org/10.1111/jebm.12381

5 van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020;382:1564-7. https://doi.org/10.1056/NEJMc2004973

6 Ong SWX, Tan YK, Chia PY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient JAMA 2020;323:1610-2. https://doi.org/10.1001/jama.2020.3227

7 Gorris C, Ricci Maccarini A, Vanoni F, et al. Acoustic analysis of normal voice patterns in italian adults by using Praat. J Voice 2019:S0892-1997(19)30034-7. https://doi.org/10.1016/j.jvoice.2019.04.016.

8 Braun A. Fundamental frequency - how speaker-specific it is? In: Braun A, Koster JP, editors. Studies in Forensic Phonetics: BEIPHOL 64. 1995. pp. 9-23.

9 Mennen I, Schaeffler F, Docherty G. Cross-language differences in fundamental frequency range: a comparison of English and German. J Acoust Soc Am 2012;131:2249-60. https://doi.org/10.1121/1.3681950

10 Petrović-Lazić M, Babac S, Vuković M, et al. Acoustic voice analysis of patients with vocal fold polyp. J Voice 2011;25:94-7. https://doi.org/10.1016/j.jvoice.2009.04.002

11 Godino-Llorente JI, Osma-Ruiz V, Sáenz-Lechón N, et al. The effectiveness of the glottal to noise excitation ratio for the screening of voice disorders. J Voice 2010;24:47-56. https://doi.org/10.1016/j.jvoice.2008.04.006

12 Di Nicola V, Fiorella ML, Spinelli DA, et al. Acoustic analysis of voice in patients treated by reconstructive subtotal laryngectomy. Evaluation and critical review. Acta Otorhinolaryngol Ital 2006;26:59-68.

13 Cui C, Yao Q, Zhang D, et al. Approaching otolaryngology patients during the COVID-19 pandemic. Otolaryngol Head Neck Surg 2020;163:121-31. https://doi.org/10.1177/0194599820926144.

14 Cheng X, Liu J, Li N, et al. Otolaryngology providers must be alert for patients with mild and asymptomatic COVID-19. Otolaryngol Head Neck Surg 2020;162:809-10. https://doi.org/10.1177/0194599820920649

15 Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177-9. https://doi.org/10.1056/NEJMc2001737

16 Krajewska J, Krajewski W, Zub K, et al. COVID-19 in otolaryngologist practice: a review of current knowledge. Version 2. Eur Arch Otorhinolaryngol 2020;277:1885-97. https://doi.org/10.1007/s00405-020-05968-y

17 Tysome JR, Bhutta MF. COVID-19: protecting our ENT Workforce. Clin Otolaryngol 2020;45:311-2. https://doi.org/10.1111/coa.13542

18 Lescanne E, van der Mee-Marquet N, Juvanon JM, et al. Best practice recommendations: ENT consultations during the COVID-19 pandemic. Eur Ann Otorhinolaryngol Head Neck Dis 2020;S1879-7296(20)30126-5. https://doi.org/10.1016/j.anorl.2020.05.007

19 Brewster DJ, Chrimes N, Do TB, et al. Consensus statement: safe airway society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group. Med J Aust 2020;212:472-81. https://doi.org/10.5694/mja2.50598

20 Liang T, Yu L. Handbook of COVID-19 prevention and treatment. Zhejiang: Zhejiang University School of Medicine; 2020.

21 Di Nicola V, Fiorella ML, Luperto P, et al. La valutazione obiettiva della disfonia. Possibilità e limiti [Objective evaluation of dysphonia. Possibilities and limitations]. Acta Otorhinolaryngol Ital 2001;21:10-21.

22 Boersma P, Weenink D. Praat: doing phonetics by computer [Computer program]. Version 6.0.37, 2018; http://www.praat.org/, accessed August 5, 2020

23 Caffier PP, Möller A, Forbes E, et al. The vocal extent measure: development of a novel parameter in voice diagnostics and initial clinical experience. Biomed Res Int 2018;2018:3836714. https://doi.org/10.1155/2018/3836714

24 Lovato A, De Colle W, Giacomelli L, et al. Multi-dimensional voice program (MDVP) vs Praat for assessing euphonic subjects: a preliminary study on the gender-discriminating power of acoustic analysis software. J Voice 2016;30:765.e1-765.e5. https://doi.org/10.1016/j.jvoice.2015.10.012

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:6-17; doi: 10.14639/0392-100X-N0879

Review

Clinical and histopathological risk factors for distant metastasis in head and neck cancer patients

Fattori di rischio clinici e istopatologici per metastasi a distanza in pazienti con carcinoma della testa e del collo

Carlos Miguel Chiesa-Estomba[1,2], Jerome R. Lechien[2,3], Tareck Ayad[2,4], Christian Calvo-Henriquez[2,5], José Ángel González-García[1], Jon Alexander Sistiaga-Suarez[1], Didier Dequanter[6], Nicolas Fakhry[2,7], Gebeyehu Melesse[8], Cesare Piazza[9]

[1] Department of Otorhinolaryngology - Head and Neck Surgery, Hospital Universitario Donostia, San Sebastian, Spain; [2] Head & Neck Study Group of Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS); [3] Department of Human Anatomy and Experimental Oncology, University of Mons, Mons, Belgium; [4] Division of Otolaryngology - Head and Neck Surgery, Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [5] Department of Otolaryngology, Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain; [6] Department of Otolaryngology - Head and Neck Surgery, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium; [7] Department of Otolaryngology - Head and Neck Surgery, Universitary Hospital of la Conception, Marseille, France; [8] Department of Otolaryngology - Head and Neck Surgery, Bahir Dar University, Tibebe Ghion Specialised Hospital, Bahir Dar, Ethiopia; [9] Department of Otorhinolaryngology, Maxillofacial and Thyroid Surgery, Fondazione IRCCS, National Cancer Institute of Milan, University of Milan, Milan, Italy

SUMMARY

The incidence of distant metastasis (DM) in head and neck squamous cell cancer (HNSCC) is relatively low. Multiple risk factors have been described for development of DM at baseline and after treatment. However, to date, there is no meta-analysis or systematic review investigating the relationships between clinical and histopathological factors and the appearance of DM in HNSCC patients. Among 1,272 eligible articles, 23 met inclusion criteria for qualitative analysis, and 6 for quantitative analysis. The meta-analysis on 5,353 patients showed that hypopharyngeal site, T3-T4 categories, extranodal extension, positive lymph node size > 6 cm, locoregional failure after previous treatment(s) and poor differentiation all significantly increase the risk of DM. According to our results, patients with the above-mentioned clinical and histopathological risk factors should be considered at high risk for DM and therefore submitted to strict pre-treatment assessment and undergo careful post-therapeutic follow-up.

KEY WORDS: distant metastasis, head and neck, cancer, risk factors

RIASSUNTO

L'incidenza di metastasi a distanza nel carcinoma squamocellulare della testa e del collo è relativamente bassa. Sono stati descritti molteplici fattori di rischio per lo sviluppo di metastasi sistemiche, sia al momento della diagnosi che dopo il trattamento. In ogni caso, ad oggi, non esiste una meta-analisi o una revisione sistematica che indaghi i rapporti tra fattori clinico-istopatologici e la comparsa di metastasi a distanza nei pazienti con carcinoma squamocellulare della testa e del collo. Tra i 1,272 articoli utili, 23 presentavano i criteri di inclusione per un'analisi qualitativa e 6 erano adatti ad un'analisi di tipo quantitativo. La meta-analisi, condotta su un totale di 5,353 pazienti, ha mostrato come la sede ipofaringea, le categorie T3-T4, l'estensione extra-nodale, linfonodi metastatici di diametro > 6 cm, il fallimento loco-regionale dopo pregressi trattamenti e la scarsa differenziazione aumentino tutti in modo significativo il rischio di metastasi a distanza. In base ai nostri risultati, quindi, i pazienti con i fattori di rischio clinici e istopatologici sopra citati dovrebbero essere considerati ad alta probabilità di sviluppare metastasi a distanza e, pertanto, sottoposti ad una rigorosa valutazione pre-trattamento, così come ad un attento follow-up.

PAROLE CHIAVE: *metastasi a distanza, testa e collo, cancro, fattori di rischio*

Received: May 23, 2020
Accepted: June 6, 2020

Correspondence
Carlos Miguel Chiesa-Estomba
Department of Otorhinolaryngology - Head and Neck Surgery, Hospital Universitario Donostia, Calle Doctor Begiristain #1. CP. 20014, San Sebastian - Donosti, Spain
Tel. +34 635 793 435
E-mail: chiesaestomba86@gmail.com

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Chiesa-Estomba CM, Lechien JR, Ayad T, et al. Clinical and histopathological risk factors for distant metastasis in head and neck cancer patients. Acta Otorhinolaryngol Ital 2021;41:6-17. https://doi.org/10.14639/0392-100X-N0879

Introduction

In head and neck squamous cell carcinoma (HNSCC), the main sites of distant metastases (DM) are the lung, bone and liver, accounting for approximately 70-85%, 15-39% and 10-30% of events, respectively [1]. The incidence of DM in HNSCC is, however, relatively low, with a reported prevalence of clinically identified distant localisations at diagnosis ranging from 3% to 50% [2-18].

HNSCC patients with DM are generally candidates for palliative treatment since no systemic therapy has curative potential in such a clinical scenario [18]. As a consequence, the reported median overall survival (OS) in the literature is around 10 months [19], and extensive locoregional treatments are universally believed to be futile for their modest (if any) improvement in OS.

Multiple studies have evaluated the main risk factors for development of DM at baseline and/or after treatment of HNSCC [14,17,21-24]. These generally include the presence of ≥ 3 neck lymph nodes metastases [7,25], radiological or histological extranodal extension (ENE) [22,25,27-29], low jugular positive lymph nodes [25,30], nodal metastases ≥ 6 cm in size [7,25,31], bilateral lymph nodes metastases [7,25], presence of a second primary HNSCC [5], regional recurrence [25], primary tumour of the pharynx [4,7,22,30,31] and advanced T categories [4,31].

Using the Surveillance, Epidemiology, and End Results (SEER) database, Kuperman et al. [11] conducted a cohort study on 27,877 patients aimed at identification of risk factors for DM at the time of HNSCC diagnosis. The authors identified hypopharyngeal cancer, N3 category and size of the primary tumour > 4 cm as the most important risk factors for DM. In the same way, Liu et al. [18] used the National Cancer Database (NCDB) data on 151,730 patients to identify patterns of DM in HNSCC at the time of diagnosis. In that study, the authors identified age at diagnosis, ethnicity, HPV status, tumour grade, T4 and N3 categories as the most predictive variables for DM. Interestingly, high-risk HPV status was associated with a lower proportion of DM [18]. The design in these two studies was population-based and the findings help in partially understanding the behaviour of DM in HNSCC. However, to date, no systematic review or meta-analysis has been carried out to investigate the relationships between clinical-histopathological risk factors and DM in HNSCC patients. The objective of this work is, therefore, to better understand the available evidence in the contemporary literature about the clinical and histopathological risk factors for DM in HNSCC patients after treatment with curative intention.

Materials and methods

This systematic review used Population Intervention Comparison and Outcome (PICO) modeling and followed the guidelines proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Population and inclusion/exclusion criteria

Inclusion criteria consisted of clinical series comprehensively reporting clinical (age, pharyngeal site, T and N categories, neck lymph nodes status, local and regional control or failure) and histopathological data (ENE, p16 status, lymph node size > 6 cm, and number of lymph nodes) of HNSCC patients without DM at presentation to evaluate the appearance of DM during follow-up after treatment. Studies that evaluated the association between relevant clinical or histological factors with the appearance of DM through univariate and multivariate analysis were considered. Case reports, case series and expert opinion papers were excluded, as well as articles focusing on non-HNSCC patients, with different or multiple histology, and absence of detailed clinical and/or histopathological information.

Intervention and comparison

Intervention and comparison groups were defined according to risk factors: T1-T2 *versus* T3-T4, tobacco use, p16 status, ENE, positive *versus* negative lymph nodes, N category, age < 60 *versus* > 60 years, lymph node size < 6 cm *versus* > 6 cm, presence of < 3 *versus* ≥ 3 positive lymph nodes, and locoregional control *versus* locoregional failure. The degrees of histological differentiation (well, moderate, and poor) were also compared.

Outcomes

The primary outcome evaluated in this study was risk of developing DM in HNSCC patients according to the abovementioned clinical and histopathological factors.

Search strategy

A systematic search of electronic databases was conducted on MEDLINE/PUBMED, Google Scholar, Ovid Medline, Embase, Scopus, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effects. Papers in English language from January 1960 to July 2019 were included. The following keywords were used: (["distant metastasis" OR "head and neck cancer" OR "distant metastasis workup" OR "follow-up"]). Titles and abstracts were screened by two investigators (CMCE and JASS) to discard irrelevant publications. For each study, the following information were extracted: author, year of publication, number of patients evaluated, and clinical and histopathological characteristics.

Assessment of quality

Methodological quality of identified studies was appraised using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence. According to this, prospective or retrospective studies (Grading A-B) were included. Concerning assessment of risk of bias in individual cohort studies, the risk of bias in non-randomised studies of interventions tool (ROBIN-I) was used.

Statistical analysis

An inverse variance meta-analysis of selected studies with an odds ratio (OR) comparing information about tumour location, T and N categories, number of positive lymph nodes, age, histological differentiation, site of DM, ENE, locoregional control and recurrence rate was performed. The comparison was made using Cochrane Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). Heterogeneity was checked using the Q-test and I2 test. The I2 value was > 50%, and the random-effects model was more appropriate, in which both random variation within studies and variations among the different studies were incorporated.

Cochrane Review Manager uses the Mantel-Haenszel method for calculating the heterogeneity and statistic is incorporated to calculate the summary of adjusted OR under the random-effects model. The pooled OR with 95% confidence interval ($CI_{95\%}$) is given for the random-effects model.

In addition, a chi-square test with Yates correction for continuity was applied with a 2-tailed p value for comparison of proportions according to gender and histological differentiation from independent samples. A $p < 0.05$ was considered statistically significant.

Overview of clinical and epidemiological characteristics

In addition to the meta-analysis, we extended our research to all trials carried out during the past six decades with the aim to assess the clinical significance of HPV, impact of radiological development and type of organs affected by DM in HNSCC patients. Thus, in a second step, the two main investigators (CMCE and JASS) performed the same extraction and analysis of data for all controlled or uncontrolled, prospective, or retrospective studies conducted. The intent of this analysis was to allow robust overview of the characteristics of DM in HNSCC patients, which may allow elaboration of recommendations and perspectives.

Results

The literature search retrieved a total of 1,272 manuscripts, 72 of which met eligibility for full text review. Only 23 papers were included in the systematic review and commented in the Discussion section, while 6 (accounting for 5,353 patients) were included in the meta-analysis (Fig. 1). According to the OCEBM grading system, all the studies were rated as Level B (2c) and the overall bias according to ROBIN-I was considered to be at low to moderate risk in all studies. Demographic data of the studies included are summarised in Table I. A total of 4,814 (89.9%) patients were males and 535 (10.1%) females. DM were present in 516 (9.6%) patients and were more common in men (Tab. I). Variables between each group were only partially comparable, which made challenging every comparison between cohorts due to the heterogeneity of data reported in each study (Tab. II). Concerning the primary site, the hypopharynx was related to a higher risk of DM development (18.7%) (Tab. II). DM were more common in T4 tumors (17.1%), N3 category (17.1%), and in tumours with poorly differentiated histology (29.3%). The lung was the most commonly affected organ (61.8%). Additional data on T and N categories, histological differentiation and the organs affected by DM are reported in Tables III-V. Forest plots related to T and N categories, age, ENE, size and number of positive lymph node(s) and locoregional control (LRC) *versus* recurrence or treatment failure (R-F) are reported in Figures 2 and 3.

Subgroups analysis

a) *T category*

When stratifying patients according to T category (T1-T2 *versus* T3-T4), the incidence of DM was 4.85% ($CI_{95\%}$ 4.05-5.65%) *versus* 14% ($CI_{95\%}$ 12.6-15.3%) ($p = 0.0001$). These differences were significantly in favour of T3-T4 categories as a risk factor for DM (OR 0.39; $CI_{95\%}$ 0.32-0.47; $p = 0.001$) (Tab. III and Fig. 2A).

b) *Age*

When stratifying patients according to age (< 60 *versus* > 60-year-old), the incidence of DM was 9.4% ($CI_{95\%}$ 8.06-10.7%) *versus* 8.2% ($CI_{95\%}$ 7.05-9.35%) ($p = 0.173$). These differences were not significant (OR 1.14; $CI_{95\%}$ 0.92-1.43%; $p = 0.213$) (Tab. I and Fig. 2B).

c) *Locoregional control*

When stratifying patients according to LRC *versus* R-F, the incidence of DM was 5.9% ($CI_{95\%}$ 4.7%-7.07%) in patients with favorable disease control *versus* 16.5% ($CI_{95\%}$ 13.9%-19.07%) in those with recurrence or treatment failure ($p = 0.0001$). These differences were significant with the absence of locoregional control as a risk factor for DM (OR 0.35; $CI_{95\%}$ 0.26-0.47; $p = 0.0001$) (Fig. 2C).

d) *N category*

When stratifying patients according to N category (N0 *versus* N+), the incidence of DM was 3.27% ($CI_{95\%}$ 2.62-3.92%) *versus* 19.4% ($CI_{95\%}$ 17.7-21.05%) ($p = 0.0001$).

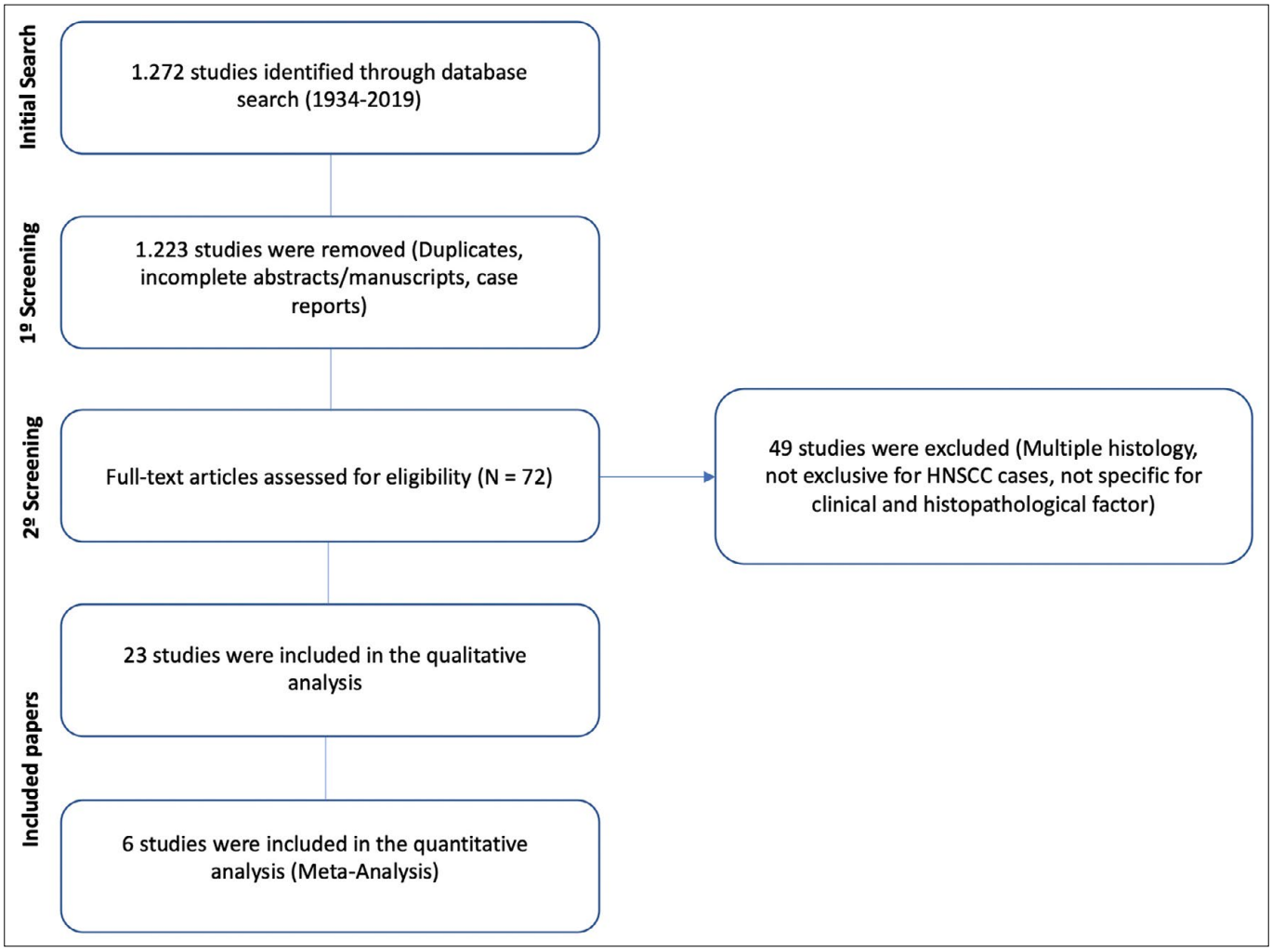


Figure 1. Algorithm for selection of studies.

Table I. Demographics, overall, and gender-related distant metastasis rates in the 6 studies included in the meta-analysis.

Authors	Type of study	Period	Mean age	Patients included	Male	Females	Overall DM rate	DM rate in men	DM rate in women
Leemans (1993) [28]	R	1973-1986	62	281	77.5%	22.5%	9.2%	NA	NA
León (2000) [4]	R	1984-1996	NA	1244	88.1%	11.9%	5.1%	5.5%	3.5%
Garavello (2006) [5]	R	1981-1998	62	1972	94%	6%	9.1%	9.1%	10.2%
Li (2009) [6]	R	1990-2000	NA	391	80%	20%	11.2%	12.4%	7.6%
Coca-Pelaz (2011) [7]	R	1999-2006	60.2	443	97.2%	2.8%	13.9%	13.2%	25%
Duprez (2017) [22]	R	1996-2015	61	1022	89.9%	10.1%	13.7%	NA	NA
Total			62	5353	89.9%	10.1%	9.6%	8.8%	8.2%

R: retrospective; NA: not available; DM: distant metastasis.

These differences were significantly in favour of a N+ neck as a risk factor for DM (OR 0.16; $CI_{95\%}$ 0.13-0.21; p = 0.0001) (Tab. III and Fig. 3A).

e) *Extranodal extension*

When stratifying N+ patients according to ENE (negative *versus* positive), the incidence of DM was 13.6% ($CI_{95\%}$ 11.2%-15.9%) *versus* 26% ($CI_{95\%}$ 22.9%-29.06%) (p = 0.0001). These differences were significantly in favour of the presence of ENE as a risk factor for DM (OR 0.52; $CI_{95\%}$ 0.40-0.67; p = 0.0001) (Fig. 3B).

Table II. Distant metastasis rates according to primary sites.

Authors	Oral cavity	Oropharynyx	Hypopharynx	Larynx	Glottis	Supraglottis	Oropharynx HPV-positive	CUP	Nasopharynx
León (2000) [4]	0.8%	7.3%	18.7%	4%	1.2%	8.4%	-	-	11.9%
Garavello (2006) [5]	2.9%	10.4%	16.7%	9.2%	8.7%	10.1%	-	-	-
Coca-Pelaz (2011) [7]	14.7%	16.6%	20.4%	7.6%	NA	NA	-	-	-
Duprez (2017) [22]	15.3%	12.6%[a]	20.5%	9%	NA	NA	22.2%[b]	19.6%	-
Total	6.3%	11.1%	18.7%	7.2%	NA	NA	-	-	-

CUP: carcinoma of unknow primary; NA, not available; [a] These patients correspond to those without HPV testing; [b] These patients correspond to those with known HPV-positive status.

Table III. Relationship between T, N categories and degree of histological differentiation with the rate of distant metastasis.

Authors	T0	T1	T2	T3	T4
León (2000) [4]	0	0.2%	4.9%	7.8%	13.7%
Garavello (2006) [5]	0	0.3%	7.8%	12.6%	20.9%
LI (2009) [6]	0	6%	8%	11.7%	14.9%
Coca-Pelaz (2011) [7]	0	5.7%	11.6%	14%	17.6%
Duprez (2017) [22]	15.8%	8%	12.9%	15.9%	15.2%
Total	15.8%	1.7%	8.5%	12%	17.1%
Authors	**N0**	**N1**	**N2**	**N3**	
León (2000) [4]	1.7%	1.5%	16.4%	24.1%	
Garavello (2006) [5]	2.5%	21.9%	23.7%	29.4%	
Coca-Pelaz (2011) [7]	4.7%	9%	23%	33%	
Duprez (2017) [22]	5%	11.2%	8.5%	28.8%	
Total	2.7%	16.6%	20.6%	29.3%	
Authors	**Well (G1)**	**Moderately (G2)**	**Poorly (G3)**		
León (2000) [4]	2.5%	4.7%	13.1%		
Garavello (2006) [5]	1%	8.4%	17.7%		
LI (2009) [6]	7.6%	13.6%	13.6%		
Coca-Pelaz (2011) [7]	5%	17%	25%		
Duprez (2017) [22]	9%	14%	15.6%		
Total	4.2%	9.2%	16.9%		

Table IV. Organs affected by HNSCC distant metastases.

Authors	Lung	Liver	Bone	Skin	Multiple DM	Parotid	External auditory canal	Soft tissues	Brain	Pleura	LN outside neck	LN mediastinum	LN axilla	Omentum	Spleen	Adrenal gland
Leemans (1993) [28]	44.9%	4%	16%	4%	22%	0	0	0	4%	0	0	4%	0	0	0	0
León (2000) [4]	51%	4.6%	12.5%	0	31.2%	0	0	0	0	0	0	0	0	0	0	0
Garavello (2006) [5]	55.8%	3.8%	9.9%	0	30.3%	0	0	0	0	0	0	0	0	0	0	0
Li (2009) [6]	48.7%	7.3%	2.4%	2.4%	26.8%	2.4%	2.4%	2.4%	0	2.4%	2.4%	0	0	0	0	0
Coca-Pelaz (2011) [7]	52.3%	1.6%	3.1%	1.6%	38%	0	0	1.6%	1.6%	0	0	0	0	0	0	0
Duprez (2017) [22]	40%	8.9%	15.6%	12.2%	0	0	0	0.7%	0.3%	4.8%	10.4%	4%	0.7%	0.3%	0.3%	0.7%
Total	61.8%	7.7%	15.3%	7.1%	23.4%	0.2%	0.2%	0.8%	1.1%	2.7%	5.6%	2.5%	0.4%	0.2%	0.2%	0.4%

Table V. Risk of bias in individual cohort studies ((ROBIN-I).

Author	Bias due to confunding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results
Coca-Pelaz (2011) [7]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk
Duprez (2017) [22]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk
León (2000) [4]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk
Garavello (2006) [5]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk
Li (2009) [6]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk
Leemans (1993) [28]	No information	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk

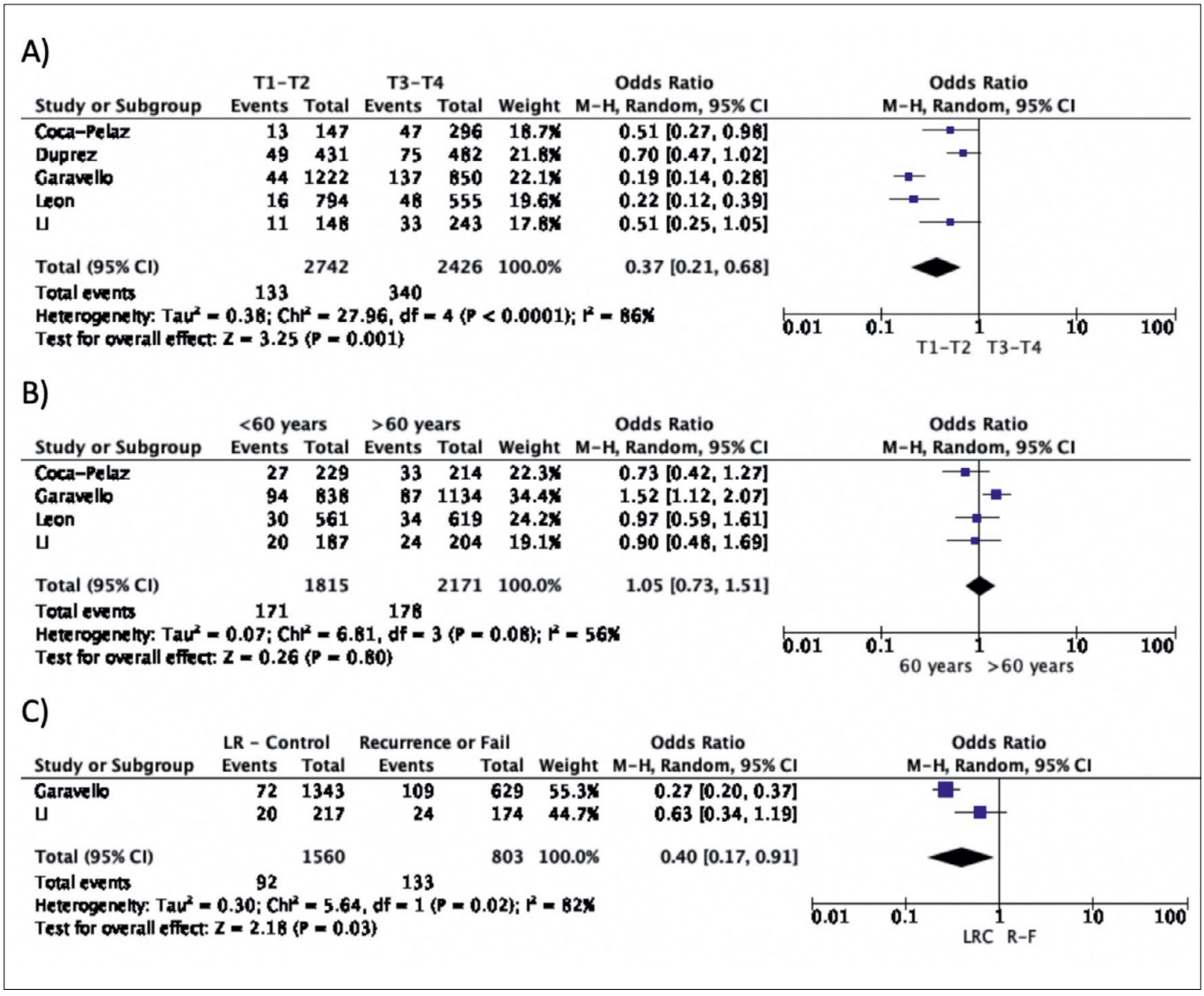


Figure 2. Forest plots showing the relationships between: (**A**) T-category; (**B**) Age; (**C**) Locoregional control and the appearance of DM. The experimental cohort was represented by patients with T1-T2 tumours and locoregional control, aiming to demonstrate the protective effect of these factors against the appearance of DM.

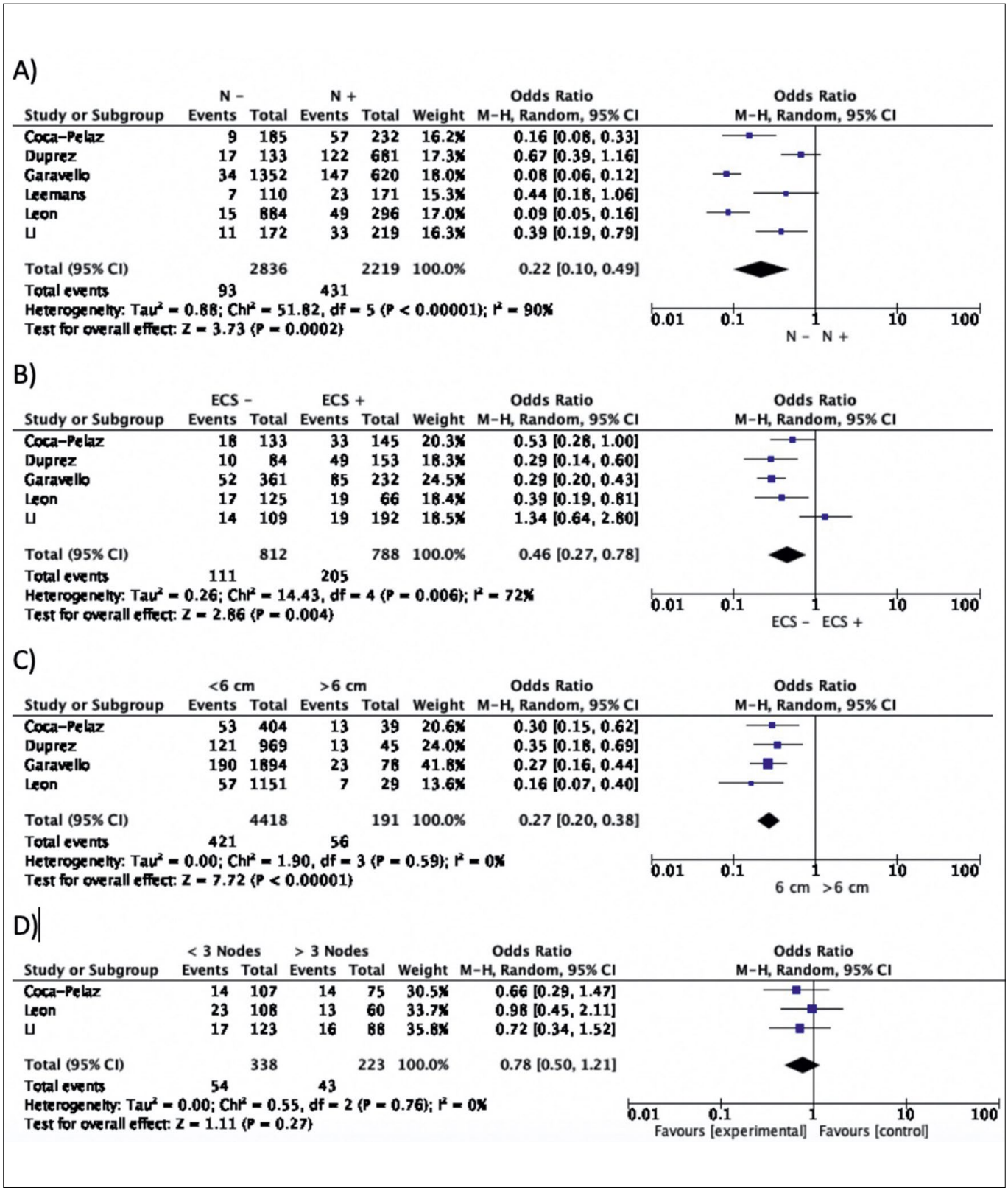


Figure 3. Forest plots showing the relationships between: (**A**) N-category; (**B**) Extranodal extension; (**C**) Lymph node size; (**D**) Number of lymph nodes and appearance of DM. The experimental cohort was represented by patients with negative lymph nodes, absence of ENE, lymph node < 6 cm in size, and less than 3 positive lymph nodes, aiming to demonstrate the protective effect of these factors on the development of DM.

f) *Lymph node size*
After stratifying N0 and N+ patients, comparing DM appearance according to lymph node size (N0 or N+ < 6cm *versus* > 6 cm), the incidence of DM was 9.5% ($CI_{95\%}$ 8.6%-10.3%) *versus* 29.3% ($CI_{95\%}$ 22.85%-35.7%) (p = 0.0001). These differences were significant with lymph node size > 6 cm as a risk factor for DM (OR 0.32; $CI_{95\%}$ 0.23-0.44; p = 0.00001) (Fig. 3C).

g) *Number of lymph nodes*
When stratifying N+ patients according to the number of lymph nodes (< 3 or ≥ 3), the incidence of DM was 15.9% ($CI_{95\%}$ 12%-19.8%) *versus* 19.3% ($CI_{95\%}$ 14.1%-24.4%) (p = 0.361). These differences were not significant (OR 0.82; $CI_{95\%}$ 0.53-1.27; p = 0.39) (Fig. 3D).

h) *Histological differentiation*
When stratifying patients according to histological differentiation (well *versus* moderate *versus* poorly differentiated), the incidence of DM was 4.2% ($CI_{95\%}$ 2.9%-5.5%) *versus* 9.2% ($CI_{95\%}$ 8.1%-10.2%) *versus* 16.9% ($CI_{95\%}$ 14.4%-19.4%) (p = 0.0001). These differences were significant, with DM being more common in patients with poorly differentiated tumours (Tab. IV).

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis to investigate the clinical and histopathological factors related to the appearance of DM in HNSCC patients. In the diagnostic workup of primary HNSCC, DM screening may have two main but distinct objectives: detection of occult DM in patients without curative options, and counseling on prognosis and how to optimise quality of life in patients who are already symptomatic. Moreover, the presence of DM at baseline evaluation influences survival, treatment selection and management of locoregionally recurrent disease. However, it is important to understand that, in selected cases, depending on histology and natural history of the disease, appropriate treatment schedules for palliative (when not potentially curative) trials may be available.

Studies which fulfilled criteria to be included in our meta-analysis are in line with the comprehensive results of our study. In particular, Leemans et al. [28] reported on the development of DM in 281 patients who underwent neck dissection and had locoregional control during follow up. Factors such as histologically proven lymph node metastasis, more than 3 positive lymph nodes, and the presence of ENE were associated with the highest risk for DM. Coca-Pelaz et al. [7] analysed risk factors for development of DM in 443 patients with surgically treated primary HNSCC. Patients with poorly differentiated tumours, 3 or more positive lymph nodes and bilateral nodal metastases were associated with the highest risk for development of DM. Duprez et al. [22] reported that advanced N category, advanced stages, presence of ENE, tumour location in the hypopharynx and oropharynx with HPV-negative status, and locoregional persistent/recurrent disease were risk factors for DM. León et al. [4] analysed the development of DM in 1,244 patients with oral cavity, pharyngeal and laryngeal SCC with apparently complete locoregional control, and found that 86% of DM appeared within the first 2 years after diagnosis of the primary tumour, and tumour location in the hypopharynx and supraglottis were independently associated with increased risk of DM. Li et al. [6] in a study including 391 patients reported that the number of neck levels involved, level of tumour invasion and site of primary tumour were decisive risk factors in determining the development of DM. Finally, Garavello et al. [5] in a study on 1,972 patients reported that the risk of DM was influenced by age, site of primary tumour, local and/or regional extension, grading and achievement of locoregional control.

Rate of DM in HNSCC patients

The rate of DM varies substantially in the literature depending on the type of study. As mentioned above, in population-based studies, Kuperman et al. [11] and Liu et al. [18] reported that the rates of DM in patients with HNSCC were 2.8% and 3.1%, respectively. On the other hand, in clinical studies, DM rates vary from 4.2 to 23.8% [4,12-14,21,32-38], while in autopsy studies the frequency is usually higher, ranging between 37%[7] and 57% [15-17,39-50]. Such figures might be also influenced by the site of tumours considered: in fact, DM are significantly higher in patients affected by nasopharyngeal carcinomas, with incidences varying from 36% to 51% in autopsy studies [51]. These higher rates have been also clinically confirmed in two studies published by Palazzi et al. analysing the outcomes of patients with regionally and non-regionally advanced nasopharyngeal carcinomas, where the authors reported DM in 21% and 18% of patients, respectively [52,53].

As previously highlighted by León et al. [4], a higher frequency of DM in autopsies could be explained by the greater sensitivity in finding DM in this type of study. Risk of bias from autopsy data is mainly related to the fact that most patients with unfavourable oncologic evolution die in hospitals, and these patients have a greater tendency of harbouring DM. Moreover, autopsy studies are more prone to detect small and incidental DM whose real occurrence can be higher than that reported in clinical and population-based studies. However, the DM rate found in our meta-analysis (9.6%) is similar to what has been reported in previous clinical papers, and higher than those in population-based studies.

Clinical and histopathological factors related to DM

According to our results and the previous studies mentioned above, poorly differentiated tumours, hypopharyngeal location, T3-T4 categories, presence of metastatic lymph nodes larger than 6 cm or with evidence of ENE and locoregional persistence or failure after treatment significantly increase the risk of developing DM. However, we were not able to find a significant impact of the presence of more than 3 positive lymph nodes and age on the risk of DM. Finally, we judged the overall quality of the evidence to be moderate, since the OCEBM graded all studies as Level B (2c) and the ensuing findings related to some factors remain uncertain, which should be addressed more carefully in future research.

Radiological implications in HNSCC and DM

Histopathological risk factors were based on postoperative specimen examination and were thus not available for pretreatment decision making. This can be a drawback in selection of patients for DM pretreatment screening, in which clinical risk factors would be much more valuable. However, modern radiological advances allow even more detailed investigation during preoperative diagnostic workup. In fact, as recently highlighted by de Bree et al. [2], some validated clinical-radiological high-risk factors are bilateral as well as more than 3 lymph node metastases, lymph node metastases of 6 cm or larger, low jugular lymph node metastases, regional recurrence and second primary tumours [25]. Other reported factors of increased risk for DM development like T4 category and/or N2-N3 status, oropharyngeal, hypopharyngeal, and supraglottic sites, levels IV and VB lymph nodes involvement and radiologic signs suspicious for ENE are all within the detection capability of modern imaging [29-31].

Organs affected by DM

The results from our meta-analysis are consistent with those described in the literature, being the lung, bone, liver and skin (61.8%, 15.3%, 7.7%, and 7.1%, respectively) the most common sites for DM in our study population. This represents the rationale for routine PET/CT or neck and chest CT in HNSCC patients with the abovementioned risk factors. The main argument in favour of chest CT instead of PET/CT, apart from a more favourable cost-effectiveness ratio and widespread geographic availability, is that the former would likely capture DM in the chest, cervical or thoracic spine, and in part of the liver. Combining these advantages, it is probable that chest CT should be viewed in terms of its overall superiority over PET/CT for detection of DM in the HNSCC population [18].

In a study by Jäckel et al. [13] on 1,087 patients with newly diagnosed SCC of the upper aerodigestive tract, the lung (68.5%), liver (23.8%) and bones (20%) were the most common sites of DM. Concerning the incidence of intracranial metastases, the rates reported are around 0.4%. Moreover, brain metastases are detected much more frequently (2-8% of patients) if another DM is already present [54].

The incidence of skin metastasis in HNSCC is reported to be between 1% and 2% and accounts for 10-15% of the overall DM burden. Pitman and Johnson [55] reported that rate of skin DM was 0.76%, an incidence consistent with the results of other studies [14], accounting for 10% of the DM load. It could be argued that regional skin metastases are, in fact, caused by changed lymphatic drainage patterns following locoregional treatment. However, skin of the head, neck, and chest are also common locations for metastasis from primary tumours arising outside the head and neck [56]. Finally, there is some debate about DM in the mediastinum, because these could also be lower extensions of regional metastases, as in the case of hypopharyngeal cancer, since the boundaries between VI and VII levels are notoriously ill-defined and wandering. In addition, occult second primary lung cancers may be responsible for this, especially if suboptimal diagnostic workup is performed.

Regarding DM treatment, the evidence for metastasectomy in HNSCC is still controversial, and large prospective studies are needed. A systematic review reported Level 2a evidence of the effectiveness of pulmonary metastasectomy for metachronous DM in HNSCC [57]. However, evidence for liver metastasectomy in HNSCC is scarce [58]. In a retrospective analysis recently published by Schultz et al. [59], the authors demonstrated a significant survival benefit for HNSCC patients who received specific treatments (surgery or RT) for DM regardless of their origin. They also described significantly worse outcomes in patients with metastases to multiple organs, underlying the importance of treating mainly oligometastatic and/or single metastatic clinical scenarios. Other approaches to disease eradication, such as stereotactic body RT, have also been used to treat one or a limited number of pulmonary metastases [60]. However, long-term follow-up data are even more limited than that available for surgical resection.

Oropharyngeal HPV-related carcinoma

Among the studies included in this meta-analysis, only Duprez et al.[22] reported the incidence of HPV in HNSCC. Therefore, at the moment, we were not able to extract any new conclusions about the relationships between HPV status and the risk of DM. From our systematic review, the evidence from the current literature is too heterogeneous to draw any meaningful assumptions about this aspect.

Regarding the identification of risk factors associated with a higher incidence of DM in HPV-positive oropharyngeal

SCC, Weller et al.[61] found that, among these patients, those with T4 tumours and/or active smokers had substantial rates of DM. They further reported an increased rate of DM in patients treated with cetuximab compared with those managed by cisplatin.
More recently, in a systematic review and meta-analysis by Tiedemann et al. [62], time to DM following primary treatment of patients with HPV-positive SCC appeared to be longer, with metastases more likely to disseminate to more than two organs compared to patients with HPV-negative oropharyngeal tumours.

Perspectives
One of the most intriguing issue related to the DM topic in HNSCC comes from the question of a real need for routine screening of asymptomatic patients during follow-up. The evidence to date has a limited clinical value since DM from HNSCC usually cannot be treated with curative intent, and asymptomatic DM may not require immediate palliative treatment [4,9,34,35,63]. Importantly, DM usually appear shortly after treatment, with typical curves during follow-up showing a rapid increase between months 0 and 8 after treatment, with a subsequent slow increase between months 8 and 24, and a substantial plateau between months 24 and 84, indicating the absence of late metastasis [64,65]. This is in contrast with other types of tumours in the head and neck area such as, for example, adenoid cystic carcinoma, which frequently metastasises late in the clinical history of patients [22].

Limitations
Due to its overall design, this meta-analysis presents an absence of uniformity and high heterogeneity across studies due to the retrospective nature and lack of randomization in the papers included. From this drawback derives also a low level of evidence extracted from them. Attempts were made to reduce bias and increase the study's validity by using the OCEBM grading system and including only studies with Level B (2c) evidence. According to the ROBIN-I, overall bias evaluation was considered to be at low to moderate risk in most studies, where the main reason for lowering the quality was the risk of bias due to missing data (differential loss to follow up affected by prognostic factors), measurement of outcomes (differential or non-differential errors in measurement of outcome data) and selection of the results depending on findings (Tab. V). Although this significantly minimised the potential for bias, it cannot be excluded.
Another limitation comes from the estimation of the real number of DM. All studies without autopsy confirmation probably underestimated the actual rate of DM, especially if they date before the radiology expansion era of the last three decades. Moreover, as different authors have hypothesised [22], in previous times a less aggressive locoregional treatment might have been used for patients who were more likely to die from locoregional recurrence before DM could even become clinically apparent. Finally, we need to highlight as another potential study limitation, the lack of adequate information about nasopharyngeal cancer in almost all the studies included.

Conclusions

According to the results of the present meta-analysis, hypopharyngeal site, advanced T and N categories, ENE, lymph node size > 6 cm, locoregional failure and poorly differentiated histology significantly increase the risk of developing DM in patients with HNSCC. Imaging can play a relevant role in the diagnostic work-up of these patients as it evaluates clinical and radiological factors related to DM and, possibly, can help modulate palliative/curative management. Larger studies comparing the risk of DM in HPV-positive and negative oropharyngeal SCC are needed.

References

1 Takes RP, Rinaldo A, Silver CE, et al. Distant metastases from head and neck squamous cell carcinoma. Part I. Basic aspects. Oral Oncol 2012;48:775-9. https://doi.org/10.1016/j.oraloncology.2012.03.013

2 de Bree R, Senft A, Coca-Pelaz A, et al. Detection of distant metastases in head and neck cancer: Changing landscape. Adv Ther 2018;35:161-172. https://doi.org/10.1007/s12325-018-0662-8

3 Ferlito A, Shaha AR, Silver CE, et al. Incidence and sites of distant metastases from head and neck cancer. ORL J Otorhinolaryngol Relat Spec 2001;63:202-7. https://doi.org/10.1159/000055740

4 León X, Quer M, Orús C, et al. Distant metastases in head and neck cancer patients who achieved loco-regional control. Head Neck 2000;22:680-6. https://doi.org/10.1002/1097-0347

5 Garavello W, Ciardo A, Spreafico R, et al. Risk factors for distant metastases in head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2006;132:762-6. https://doi.org/10.1001/archotol.132.7.762

6 Li X, Di B, Shang Y, et al. Clinicopathologic risk factors for distant metastases from head and neck squamous cell carcinomas. Eur J Surg Oncol 2009;35:1348-53. https://doi.org/10.1016/j.ejso.2009.06.010

7 Coca-Pelaz A, Rodrigo JP, Suárez C. Clinicopathologic analysis and predictive factors for distant metastases in patients with head and neck squamous cell carcinomas. Head Neck 2012;34:771-5. https://doi.org/10.1002/hed.21804

8 Lim JY, Lim YC, Kim SH, et al. Predictive factors of isolated distant metastasis after primary definitive surgery without systemic treatment for head and neck squamous cell carcinoma. Oral Oncol 2010;46:504-8. https://doi.org/10.1016/j.oraloncology.2010.02.005

9 Leibel SA, Scott CB, Mohiuddin M, et al. The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: results of an analysis from the RTOG head and neck database. Int J Radiat Oncol Biol Phys 1991;21:549-56. https://doi.org/10.1016/0360-3016(91)90669-u

10 Kowalski LP, Carvalho AL, Martins Priante AV, et al. Predictive fac-

tors for distant metastasis from oral and oropharyngeal squamous cell carcinoma. Oral Oncol 2005;41:534-41. https://doi.org/10.1016/j.oraloncology.2005.01.012

[11] Kuperman DI, Auethavekiat V, Adkins DR, et al. Squamous cell cancer of the head and neck with distant metastasis at presentation. Head Neck 2011;33:714-8. https://doi.org/10.1002/hed.21529

[12] de Bree R, Deurloo EE, Snow GB, et al. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 2000;110:397-401. https://doi.org/10.1097/00005537-200003000-00012

[13] Jäckel MC, Rausch H. Distant metastasis of squamous epithelial carcinomas of the upper aerodigestive tract. The effect of clinical tumor parameters and course of illness. HNO 1999;47:3844. https://doi.org/10.1007/s001060050356

[14] Alvi A, Johnson JT. Development of distant metastasis after treatment of advanced-stage head and neck cancer. Head Neck 1997;19:500-5. https://doi.org/10.1002/(sici)1097-0347(199709)19:6<500::aid-hed7>3.0.co;2-2

[15] Nishijima W, Takooda S, Tokita N, et al. Analyses of distant metastases in squamous cell carcinoma of the head and neck and lesions above the clavicle at autopsy. Arch Otolaryngol Head Neck Surg 1993;119:65-8. https://doi.org/10.1001/archotol.1993.01880130067009

[16] Zbären P, Lehmann W. Frequency and sites of distant metastases in head and neck squamous cell carcinoma. An analysis of 101 cases at autopsy. Arch Otolaryngol Head Neck Surg 1987;113:762-4. https://doi.org/10.1001/archotol.1987.01860070076020

[17] Kotwall C, Sako K, Razack MS, et al. Metastatic patterns in squamous cell cancer of the head and neck. Am J Surg 1987;154:439-42. https://doi.org/10.1016/0002-9610(89)90020-2

[18] Liu JC, Bhayani M, Kuchta K, et al. Patterns of distant metastasis in head and neck cancer at presentation: implications for initial evaluation. Oral Oncol 2019;88:131-6. https://doi.org/10.1016/j.oraloncology.2018.11.023

[19] Haigentz M Jr, Hartl DM, Silver CE, et al. Distant metastases from head and neck squamous cell carcinoma. Part III. Treatment. Oral Oncol 2012;48:787-93. https://doi.org/10.1016/j.oraloncology.2012.03.019

[20] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27. https://doi.org/10.1056/NEJMoa0802656

[21] Calhoun KH, Fulmer P, Weiss R, et al. Distant metastases from head and neck squamous cell carcinomas. Laryngoscope 1994;104:1199-205. https://doi.org/10.1288/00005537-199410000-00003

[22] Duprez F, Berwouts D, De Neve W, et al. Distant metastases in head and neck cancer. Head Neck 2017;39:1733-43. https://doi.org/10.1002/hed.24687

[23] Peters TT, Senft A, Hoekstra OS, et al. Pretreatment screening on distant metastases and head and neck cancer patients: validation of risk factors and influence on survival. Oral Oncol 2015;51:267-71. https://doi.org/10.1016/j.oraloncology.2014.12.006

[24] Spector ME, Chinn SB, Rosko AJ, et al. Diagnostic modalities for distant metastasis in head and neck squamous cell carcinoma: are we changing life expectancy? Laryngoscope 2012;122:1507-11. https://doi.org/10.1002/lary.23264

[25] Uyl-de Groot CA, Senft A, de Bree R, et al. Chest CT and whole-body 18F-FDG PET are cost-effective in screening for distant metastases in head and neck cancer patients. J Nucl Med 2010;51:176-82. https://doi.org/10.2967/jnumed.109.067371

[26] Huang B, Law MW, Khong PL. Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. Radiology 2009;251:166-74. https://doi.org/10.1148/radiol.2511081300.

[27] de Bree R, Ljumanovic R, Hazewinkel MJ, et al. Radiologic extranodal spread and matted nodes: important predictive factors for development of distant metastases in patients with high-risk head and neck cancer. Head Neck 2016;38(Suppl 1):E1452-8. https://doi.org/10.1002/hed.24257

[28] Leemans CR, Tiwari R, Nauta JJ, et al. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993;71:452-6. https://doi.org/10.1002/1097-0142(19930115)71:2<452::aid-cncr2820710228>3.0.co;2-b

[29] Ljumanovic R, Langendijk JA, Hoekstra OS, et al. Distant metastases in head and neck carcinoma: identification of prognostic groups with MR imaging. Eur J Radiol 2006;60:58-66. https://doi.org/10.1016/j.ejrad.2006.05.019

[30] Haerle SK, Schmid DT, Ahmad N, et al. The value of (18)F-FDG PET/CT for the detection of distant metastases in high-risk patients with head and neck squamous cell carcinoma. Oral Oncol 2011;47:653-9. https://doi.org/10.1016/j.oraloncology.2011.05.011

[31] Loh KS, Brown DH, Baker JT, et al. A rational approach to pulmonary screening in newly diagnosed head and neck cancer. Head Neck 2005;27:990-4. https://doi.org/10.1002/hed.20261

[32] Rubenfeld S, Kaplan G, Holder AA. Distant metastases from head and neck cancer. Am J Roentgenol Radium Ther Nucl Med 1962;87:441-8.

[33] Berger DS, Fletcher GH. Distant metastases following local control of squamous cell carcinoma of the nasopharynx, tonsillar fossa, and base of the tongue. Radiology 1971;100:141-3. https://doi.org/10.1148/100.1.141

[34] Probert JC, Thompson RW, Bagshaw MA. Patterns of spread of distant metastases in head and neck cancer. Cancer 1974;33:127-33. https://doi.org/10.1002/1097-0142(197401)33:1<127::AID-CNCR2820330119>3.0.CO;2-L

[35] Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977;40:145-51. https://doi.org/10.1002/1097-0142(197707)40:1<145::aid-cncr2820400124>3.0.co;2-9

[36] Black RJ, Gluckman JL, Shumrick DA. Screening for distant metastases in head and neck cancer patients. Aust NZ J Surg 1984;54:527-30. https://doi.org/10.1111/j.1445-2197.1984.tb05440.x

[37] Vikram B, Strong EW, Shah JP, et al. Failure at distant sites following multimodality treatment for advanced head and neck cancer. Head Neck Surg 1984;6:730-3. https://doi.org/10.1002/hed.2890060305

[38] Bhatia R, Bahadur S. Distant metastasis in malignancies of the head and neck. J Laryngol Otol 1987;101:925-8. https://doi.org/10.1017/s0022215100102993

[39] Troell RJ, Terris DJ. Detection of metastases from head and neck cancers. Laryngoscope 1995;105:247-50. https://doi.org/10.1288/00005537-199503000-00005

[40] Crile GW. Carcinoma of the jaw, tongue, cheek, and lips. Surg Gynecol Obstet 1923;36:159-84.

[41] Price LW. Metastasis in squamous carcinoma. Am J Cancer 1934;22:1-6.

[42] Burke EM. Metastases in squamous cell carcinoma. Am J Cancer 1937;30:493-503.

[43] Braund RR, Martin HE. Distant metastases in cancer of the upper respiratory and alimentary tracts. Surg Gynecol Obstet 1941;73:63-71.

[44] Peltier LF, Thomas LB, Crawford TH, et al. The incidence of distant metastasis among patients dying with head and neck cancers. Surgery 1951;30:827-33.

[45] Gowen GF, Desuto-Nagy G. The incidence of sites of distant metastases in head and neck carcinoma. Surg Gynecol Obstet 1963;116:603-7. https://doi.org/10.1097/00006534-196310000-00028

[46] Abramson AL, Parisier SC, Zamansky MJ, et al. Distant metastases

from carcinoma of the larynx. Laryngoscope 1971;81:1503-11. https://doi.org/10.1288/00005537-197109000-00015

47 O'Brien PH, Carlson R, Steubner EA Jr, et al. Distant metastases in epidermoid cell carcinoma of the head and neck. Cancer 1971;27:304-7. https://doi.org/10.1002/1097-0142(197102)27:2<304::aid-cncr2820270209>3.0.co;2-1

48 Bruger J, Blache R, Cachin Y. Extension métastatique des épithéliomas épidermoides des voies aéro-digestives supérieures: Bilan de l'autopsie de 220 malades. Bull Cancer 1972;59:435-48.

49 Dennington ML, Carter DR, Meyers AD. Distant metastases in head and neck epidermoid carcinoma. Laryngoscope 1980;90:196-201. https://doi.org/10.1288/00005537-198002000-00002

50 Ahmad A, Stefani S. Distant metastases of nasopharyngeal carcinoma: a study of 256 male patients. J Surg Oncol 1986;33:194-7. https://doi.org/10.1002/jso.2930330310

51 Palazzi M, Guzzo M, Bossi P, et al. Regionally advanced nasopharyngeal carcinoma: long-term outcome after sequential chemotherapy and radiotherapy. Tumori 2004;9:60-5.

52 Palazzi M, Guzzo M, Tomatis S, et al. Improved outcome of nasopharyngeal carcinoma treated with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:1451-58. https://doi.org/10.1016/j.ijrobp.2004.05.059

53 Langley RR, Fidler IJ. The seed and soil hypothesis revisited – the role of tumor-stroma interactions in metastasis to different organs. Int J Cancer 2011;128:2527-35. https://doi.org/10.1002/ijc.26031

54 de Bree R, Mehta DM, Snow GB, et al. Intracranial metastases in patients with squamous cell carcinoma of the head and neck. Otolaryngol Head Neck Surg 2001;124:217-21. https://doi.org/10.1067/mhn.2001.112478

55 Pitman KT, Johnson JT. Skin metastases from head and neck squamous cell carcinoma: incidence and impact. Head Neck 1999;21:560-5. https://doi.org/10.1002/(sici)1097-0347(199909)21:6<560::aid-hed10>3.0.co;2-q

56 Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995;33:161-82. https://doi.org/10.1016/0190-9622(95)90231-7

57 Young ER, Diakos E, Khalid-Raja M, et al. Resection of subsequent pulmonary metastases from treated head and neck squamous cell carcinoma: systematic review and meta-analysis. Clin Otolaryngol 2015;40:208-18. https://doi.org/10.1111/coa.12348

58 Florescu C, Thariat J. Local ablative treatments of oligometastases from head and neck carcinomas. Crit Rev Oncol Hematol 2014;91:47-63. https://doi.org/10.1016/j.critrevonc.2014.01.004

59 Schulz D, Wirth M, Piontek G, et al. Improved overall survival in head and neck cancer patients after specific therapy of distant metastases. Eur Arch Otorhinolaryngol 2018;275:1239-47. https://doi.org/10.1007/s00405-018-4920-9

60 Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. Int J Radiat Oncol Biol Phys 2008;72:398-403. https://doi.org/10.1016/j.ijrobp.2008.01.002

61 Weller MA, Ward MC, Berriochoa C, et al. Predictors of distant metastasis in human papillomavirus – associated oropharyngeal cancer. Head Neck 2017;39:940-6. https://doi.org/10.1002/hed.24711

62 Tiedemann D, Jakobsen KK, von Buchwald C, et al. Systematic review on location and timing of distant progression in human papillomavirus-positive and human papillomavirus-negative oropharyngeal squamous cell carcinomas. Head Neck 2019;41:793-8. https://doi.org/10.1002/hed.25458

63 Arons MS, Smith RR. Distant metastases and local recurrence in head and neck cancer. Ann Surg 1961;154:235-40. https://doi.org/10.1097/00000658-196108000-00007

64 Dietl B, Marienhagen J, Schaefer C, et al. Frequency and distribution pattern of distant metastases in patients with ENT tumors and their consequences for pretherapeutic staging. Strahlenther Onkol 2007;183:138-43. https://doi.org/10.1007/s00066-007-1611-7

65 Calvin DP, Hammond ME, Pajak TF, et al. Microvessel density > or = 60 does not predict for outcome after radiation treatment for locally advanced head and neck squamous cell carcinoma: Results of a correlative study from the Radiation Therapy Oncology Group (RTOG) 90-03 Trial. Am J Clin Oncol 2007;30:406-19. https://doi.org/10.1097/COC.0b013e3180342fd4

Head and neck

Head and neck cancer patients declining curative treatment: a case series and literature review

Rifiuto di trattamenti curativi nel distretto testa-collo: case series e review della letteratura

Axel Sahovaler[1,2], Tommaso Gualtieri[2,3], David Palma[4], Kevin Fung[1], S. Danielle MacNeil[1], John Yoo[1], Anthony Nichols[1]

[1] Otolaryngology-Head and Neck Surgery Department, Western University, London Ontario, Canada; [2] Guided Therapeutics (GTx) Program, Techna Institute, University Health Network, Toronto, Ontario, Canada; [3] Unit of Otorhinolaryngology - Head and Neck Surgery, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [4] Radiation Oncology Department, Western University, London Ontario, Canada

SUMMARY

There is a scarcity of data assessing outcomes of head and neck cancer patients who refuse treatment for potentially curable disease. We report the data of patients who refused curative treatment at a tertiary referral centre and perform a review of the literature. Patients with a potentially curable mucosal head and neck cancers that were discussed at the multidisciplinary tumour board of a referral centre in a two-year period were included. Two cohorts were obtained: patients who accepted the proposed treatment and those who declined it. Statistical analysis was performed using a univariate analysis with parametric and non-parametric tests. Of a total of 803 patients, 14 (1.74%) refused treatment despite being potentially curable. Their median survival was 6.92 months (range 3-12). Patients who refused treatment were older (73.07 years [95% CI, 66.86-79.28] *vs* 65.56 years [95% CI, 64.70-66.43], p = 0.030) and more likely to have T4 disease (50% *vs* 26.04%, p = 0.044). Most patients with curable disease accept conventional treatment and those who refuse it experience dismal outcomes. This report provides objective evidence and can be employed to better counsel patients who refuse curative treatment.

KEY WORDS: head and neck cancer, declining treatment, literature review

RIASSUNTO

Obiettivo. *I trattamenti per la patologia oncologica del distretto testa-collo possono causare disfunzioni di parola, di alimentazione e alterazione della percezione, esitando spesso in stati ansioso-depressivi che impattano sulla qualità di vita dei pazienti. Talvolta, questi pazienti chiedono che cosa succederebbe nel caso in cui scegliessero di non sottoporsi ad alcun trattamento. Ad oggi c'è una carenza di dati sull'outcome dei pazienti che rifiutano trattamenti per malattie potenzialmente curabili.*

Metodi. *Sono stati inclusi pazienti candidabili a trattamenti curativi con cancro delle vie aereo-digestive superiori discussi nel periodo 2014-2016 presso un centro di terzo livello, e suddivisi in due gruppi: 1) pazienti che hanno accettato il trattamento e 2) pazienti che lo hanno rifiutato.*

Risultati. *Su un totale di 803 pazienti, 14 (1,74%) hanno rifiutato il trattamento. I pazienti del gruppo 2 erano più anziani (73,07 anni vs 65,56 anni, p = 0,030), più spesso presentavano una malattia locale T4 (50% vs 26.04%, p = 0,044), e la loro mediana di sopravvivenza è risultata essere 6,92 mesi (range 3-12).*

Conclusioni. *Questo studio porta alla luce evidenze oggettive sui pazienti che rifiutano il trattamento per malattie potenzialmente curabili del distretto testa-collo e fornisce elementi utili per dare loro un aiuto efficace ed esaustivo.*

PAROLE CHIAVE: *neoplasie della testa e del collo, rifiuto del trattamento, review della letteratura*

Received: September 1, 2020
Accepted: September 28, 2020

Correspondence
Anthony C. Nichols
Otolaryngology-Head and Neck Surgery Department, Western University, Victoria Hospital, London Health Science Centre, Department of Otolaryngology - Head and Neck Surgery, Room B3-431A, 800 Commissioners Road East
London, ON, Canada N6A 5W9
Tel. 519-685-8804. Fax 519-685-8567
E-mail: anthony.nichols@lhsc.on.ca

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Sahovaler A, Gualtieri T, Palma D, et al. Head and neck cancer patients declining curative treatment: a case series and literature review. Acta Otorhinolaryngol Ital 2021;41:18-23. https://doi.org/10.14639/0392-100X-N1099

Introduction

The morbidity of head and neck cancer treatment can profoundly affect patients and their families. Patients can experience lifelong adverse effects including facial disfigurement and impairment of speech, swallowing, and breathing. These treatment-related sequelae often result in major psychosocial stress leading to high rates of anxiety and depression [1,2]. As a result, it is common that patients hesitate and even initially refuse receiving the proposed therapy after the treatment and its side effects are explained to them. Patients tend to ask about the outcomes of not treating the disease, and what to expect if their cancer remains untreated. There is a scarcity of data assessing outcomes of head and neck cancer patients who refuse treatment for potentially curable disease.

The purpose of this study was to assess the outcomes of head and neck cancer patients who declined conventional curative treatment, to compare their clinical features with patients who accepted the proposed curative-intent therapy and to review the literature on this topic. This information may help both patients and clinicians in decision making by providing information about the expected outcomes of not pursuing standard therapy for head and neck cancer.

Materials and methods

The London Regional Cancer Program (LRCP) reviews all patients who are diagnosed with head and neck cancers in Southwestern Ontario, encompassing a catchment area of 2 million people. All patients with a suspicion or confirmation of a head and neck cancer are referred to the LRCP and evaluated by a head and neck surgeon and a radiation oncologist in a combined clinic. After the consult, the proposed treatment is communicated to the patient with a detailed explanation of the advantages and side effects of the treatment.

We retrospectively analysed all patients with upper aerodigestive tract malignancies who were referred to LRCP multidisciplinary tumour board from January 2014 till December 2016. Two cohorts were obtained: patients who accepted the proposed treatment and those who declined it. Exclusion criteria included locally advanced unresectable tumours, patients who had metastatic disease and patients harbouring comorbidities that precluded any type of curative-intent treatment (surgical or non-surgical).

The variables analysed included age, gender, marital status, presence of psychiatric illnesses, site, tumour and lymph node staging (according to the American Joint Committee on Cancer [AJCC] 7th edition clinical staging criteria), p16 status and overall survival. Comorbidity was measured by the Charlson/Deyo score only in patients who declined therapy to corroborate that they were amenable to receive treatment. A value of 0 corresponds to no comorbidity; 1 to cardiovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, or diabetes; and 2 or greater corresponding to diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, or AIDS. Causes of death and management of patients who rejected treatment were accounted for.

A T-test was employed for continuous data and chi-squared test for categorical data. Wilcoxon rank sum test was used in cases of non-parametric distribution. Statistical significance was determined at the $P < 0.05$ level. Data analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). Institutional research ethics board approval was obtained for this study (REB# 19-5099.3).

Results

Clinical features of patients declining treatment

A total of 803 patients were available for analysis. Of these, 14 (1.74%) refused treatment despite being potentially curable. Table I depicts the characteristics of this subgroup. Average age at diagnosis was 73 years (range 55 to 88 years). Nine patients were male. Six (43%) patients were married and two (14%) lived with another family member, whereas the six (43%) remaining patients lived alone with no family support. None had a history of mental illness. The oral cavity was the most common cancer site with 7 (50%) cases, followed by the oropharynx 4 (28.5%), larynx 2 (14.2%) and hypopharynx 1 (7.1%). Most had locally-advanced T-classification, with 7 (50%) T4 cancers. Nearly all [13 (92.8%)] had positive cervical nodes. p16 status was assessed only for oropharyngeal primaries, and three of the four patients were p16 positive. Eleven patients had a Charlson/Deyo score of 1 (five were diabetic and six had cardiovascular disease). The remaining had a score of 0.

Survival outcomes

The median survival for untreated patients was 6.92 months (range 3-12). Comparing cohorts, patients who refused treatment were older (73.07 years [95% CI, 66.86-79.28] versus 65.56 years [95% CI, 64.70-66.43], $p = 0.03$) and more likely to have T4 disease (50% *vs* 26.04%, $p = 0.044$). There were no significant differences in gender, tumour site, or nodal staging. Table II shows the characteristics of both cohorts. Among the untreated cohort, outcomes for the p16-positive oropharyngeal cancer patients were comparable to p16-negative disease in all sites (7.7 *vs* 6.7 months, respectively, $p = 0.4$).

Table I. Characteristics of patients declining curative treatment.

Age	Gender	Site	T	N	P16	OS	Suggested treatment	Cause of death	Management
77	F	Larynx	4	2a		7	Surgery	Distant metastasis	-
71	M	Oral cavity	4	0		5	Surgery	Distant metastasis	Palliative chemotherapy
88	M	Oral cavity	3	2c		5	Surgery	Local progression	Tracheostomy
88	F	Oral cavity	2	1		4	Surgery	Distant metastasis	-
67	M	Oropharynx	4	0	+	5	ChemoRT	Local progression	Tracheostomy/ G tube
64	M	Oral cavity	4	2c		5	Surgery	Local progression/ distant metastasis	Palliative chemoRT
59	M	Oral Cavity	4	0		12	Surgery	Distant metastasis	Palliative chemotherapy
82	F	Larynx	1	1		12	RT	Pneumonia	-
80	M	Hypopharynx	2	1		6	RT	Local progression	Tracheostomy/ G tube
59	F	Oral cavity	4	2c		3	Surgery	Local progression	Palliative RT
79	M	Oral cavity	4	2b		6	Surgery	Local progression	Palliative RT
55	F	Oropharynx	2	2b	+	8	ChemoRT	Distant metastasis	Palliative chemotherapy
76	M	Oropharynx	3	2c	+	7	ChemoRT	Local progression	-
78	M	Oropharynx	2	2b	-	8	ChemoRT	Distant metastasis	-

Table II. Comparison of patients who accepted and patients who declined treatment.

	Accepted	Declined	p value
Age (average)	66.56	73	0.03
Gender (M/F	589/190	9/5	NS
Site			NS
Oral cavity	267	7	
Oropharynx	203	4	
Larynx	163	2	
Hypopharynx	30	1	
Nasopharynx	23	-	
Other	103	-	
T stage			(T4 vs T3-1) 0.044
T1	216	-	
T2	239	4	
T3	136	3	
T4	198	7	
N stage			NS
N0	354	1	
N1	69	4	
N2a	75	3	
N2b	137	2	
N2c	101	4	
N3	53	-	

Causes of death of patients who declined treatment were distant metastasis in seven cases, local progression in six patients and one case of aspiration pneumonia. Management of this cohort included palliative treatment for local symptoms and systemic therapy, all in the context of very advanced diseases after initial treatment refusals. Supportive and comfort measures such as palliative care, tracheostomy and G-tube placement were also implemented (Tab. I). Fifty percent of the patients were managed at the hospital or hospice and the remaining were managed at home by palliative care services.

Discussion

A unique feature of head and neck malignancies is that both the disease and treatment carry frequent acute and late toxicities that can have profound effects on patients' quality of life. Facial disfigurement, impaired oral intake and speech alterations predisposes patients to social isolation and depression [1]. Therefore, after a diagnosis is made and the treatment and its side effects are presented to the patients and their families, they face the difficult decision of undergoing curative therapy with the possibility of high morbidity, accepting palliative treatment, or declining treatment altogether in hopes of maintaining quality of

life [3]. In the internet era, patients have access to a myriad of information including the promises offered by alternative treatments from unreliable sources.

Our data has shown that 1.7% of patients presenting to our multi-disciplinary clinic elected to decline any conventional treatment, including three patients with highly curable HPV-positive disease. We found that these patients tended to be older and more likely to have T4 disease than patients who accepted the recommended therapy. The use of alternative medicine treatment was not well documented in the clinical notes; however, the senior investigators note that interest in pursuing alternative medicine was a frequently cited reason for treatment refusal. This paper serves to provide objective evidence for future patients that while conventional treatment has significant toxicity, refusal almost uniformly leads to a rapid demise.

There have been few attempts to analyse the subset of patients who refuse treatment. Kowalski et al. [4] published an experience of 797 patients with a wide range of tumour staging including unresectable and metastatic tumours, who refused any sort of treatment in a tertiary referral centre in Brazil. With a median overall survival of 3.82 months (range 1 day to 4 years), they found that the only predictor for increased overall survival was higher performance status. In their cohort, 19% of patients refused treatment based on their personal choice, whereas the remaining had advanced untreatable tumours or poor health status that precluded treatment. Another single institution experience from Great Britain [5] included 44 patients who received no form of treatment. In that study, median survival was 2.8 months (no range was provided) and they found no significant differences between overall survival and patient demographics, AJCC staging, or interventions such as tracheostomy or gastrostomy tube. In their series, only four (9%) patients were amenable to be cured (one of them being 92 years old) but refused treatment. The remaining patients harboured metastases or comorbidities that made them unsuitable for treatment. There were no "control groups" (comparison with patients who accepted the proposed treatment) in these reports.

More recent studies employing large databases have been published. A multi-institutional analysis by Choi et al. [6] using the Korean Health Insurance Review and Assessment Service, identified 605 head and neck cancer patients between 2003 and 2013. Surprisingly, 32.2% were left untreated. The median overall survival was 9 months, with advanced age at diagnosis the only significant risk factor for decreased overall survival in a multivariate analysis. Comparing patients who refused with those who accepted treatment, they found that advanced age at diagnosis, lower socioeconomic status, and lip and oral cavity locations were risk factors associated with patient refusal. Stage, comorbidities and tumour histology were not analysed. Hughley et al. [3] employed the Surveillance, Epidemiology, and End Results (SEER) cancer registry program between 1983 and 2011 and identified patients diagnosed with upper aero-digestive tract cancers, including only patients aged 70 and older at the time of diagnosis. A total of 35,834 patients was obtained with 3589 (10%) being untreated patients. The median overall survival was 4 months for the untreated cohort, but risk factors for overall survival were not analysed. Higher stage, primary pharyngeal site and black race were all significant predictors of untreated status. Finally, Cheraghlou et al. [7] included only patients with resectable oral cavity malignancies using the National Cancer Database (NCBD) from 2004 till 2012. Their total cohort was constituted by 36,261 patients, in which 356 (1%) were untreated. The median overall survival in this case was 13.7 months, with advanced age, higher T and N stages, comorbidities, and government insurance being significant risk factors for decreased survival of patients declining treatment in a multivariate analysis. Factors associated with treatment refusal in their final model were: higher T and N stages, age > 75 years, treatment at low/intermediate volume facilities and those with no insurance or government insurance. All patients had resectable tumours, but they did not consider comorbidities which might have precluded treatment. Table III summarises the findings of these studies.

Our study represents, to our knowledge, the first report to include both resectable and operable patients only, all of whom refused treatment despite being potentially curable. Our overall survival was within the range of prior studies (2.8 [5]-13.7 [7]). Patients declining treatment tended to have more advanced local disease [6,7] (present study), which is understandable as the curative treatment implies more extensive procedures with higher morbidity and disfigurement and may have led to treatment refusal. On the other hand, treatment refusal with higher stages can be related more with the fact that patients already have a negligent and denial component that results in choosing to not receive treatment. Advanced age at diagnosis was also frequently reported as a significant factor [6,7] (present study). We had two 88-year-old patients, which were deemed treatable and curable based on their low comorbidity scores and after being assessed by the multidisciplinary tumour board. At our centre, age per se does not represent an absolute limitation for offering curative treatment, and decisions are made based on patient health status, desires and treatment morbidity. The relation between advanced age and not receiving treatment has to be carefully interpreted as advanced age may be confounded by comorbid conditions that impede treatment.

Table III. Review of the literature of previous reports.

Source/Study years	Location	Pt N (% from the total cohort)	Inclusion criteria	Reasons for no treatment	Overall survival (months)	Significant factors for overall survival (in untreated patients)	Risk factors for not receiving treatment
Kowalski et al./1953-1990	Brazil Tertiary Referral Centre	797 (100%)	UADT SCC, no oncologic treatment	Unresectable tumours (603/74.6%) Clinical status (52/6.4%) Patient refusal (153/19%)	3.82 (1d-54)	Performance status	No control group
Jeannon et al./2006-2007	Great Britain Tertiary Referral Centre	44 (9%)	UADT SCC, no oncologic treatment	Unresectable tumours (16/36%) Clinical status (24/54%) Patient refusal (4/9%)	2.8	None	No control group
Choi et al./2002-2013	Korea National Database	195 (32%)	UADT, no oncologic treatment	Not provided	9	Advanced age	Advanced age Lower SE status Oral cavity locations
Hughley et al./1983-2011	United States National Database	3589 (9.7%)	UADT, >70 y.o., no oncologic treatment	Not provided	4	Not analysed	Higher stages Lower SE status Black race Pharyngeal site
Cheraghlou et al./2004-2012	United States National Database	356 (1%)	Oral Cavity SCC, no oncologic treatment, resectable tumours	Patient refusal (356/100%)	13.7	Advanced age Higher stages Increased comorbidities Government insurance	Higher stages Age > 75 Low or intermediate volume facilities No insurance or government insurance
Sahovaler et al./2014-2016	Canadian Tertiary Referral Centre	14 (1.7%)	UADT, no oncologic treatment, resectable tumours	Patient refusal (14/100%)	6.9 (3-12)	Not analysed	Advanced age Higher T stages

UADT: upper aerodigestive tract.

Although we were unable to do a pair-matched analysis to compare our cohorts, ours was the only study that included only potentially curable and fit patients, and this allowed us to compare the dismal median overall survival of our series (6.92 months; range 3-12) with the outcomes reported in the literature in similar populations who underwent a curative treatment. In a recent series of 244 patients affected by oral cavity carcinoma (stage I-IV, mean age 63.8 years), 5-year OS was 60.5% [8], whereas none of our patients survived more than a year. An experience from our centre showed that even in patients with recurrent oral cavity cancer treated with salvage surgery, 5-year OS was 43% [9], and even higher than in our cohort. Differences with OS of oropharyngeal malignancies are even more notorious, with a reported 3-year OS between 87%-82% in HPV+ and 57.1%-41% in HPV- patients [10,11]. Even in recurrent cases, 5-year OS was higher than 50% in a recently published meta-analysis [12]. Patients harbouring laryngeal cancer recurrences treated with salvage laryngectomies have a 2 year OS of 71% after organ preservation therapies have failed. All this surmises that the option of not receiving evidence-based curative treatment carries a much worse prognosis, even in the recurrent setting.

In some jurisdictions, socioeconomic status and its derivatives (e.g. type of insurance) may play an important role in not treating patients [3,6,7]. This is intimately related with advanced stages at diagnosis, and even in countries with universal access to healthcare system [13], individuals with lower socioeconomic status have more limited access to primary care and periodic health examinations. Oral cavity [6] and pharyngeal [3] locations were treated in smaller proportions in two studies. A potential explanation with the oral cavity location is that treatment gener-

ally include extensive surgical approaches, which result discouraging to patients, even though advanced presentations already cause a certain degree of disfigurement. We cannot justify the pharyngeal location as they are initially treated non-surgically, which can be perceived less morbid for the general population. In previous studies, p16 status of patients was not commented on. In our cohort, there were three patients with HPV related oropharyngeal carcinomas, and surprisingly their overall survival was similar to the rest of the cohort, given that they tend to progress more indolently.

Limitations of this study are represented by the small sample size, retrospective nature of the study and the fact that some patients who refuse any sort of treatment before being referred to the LRCP multidisciplinary tumour board would not been captured in the study. Moreover, we were not able to account for other variables which might have impacted on patients' decision such as financial status and the exact reason for treatment refusal was not specified in patients' charts.

Conclusions

The vast majority of patients with curable head and neck cancers accept conventional treatment. However, a small minority refuse therapy and experience dismal survival outcomes. These patients are more likely to be older with advanced T stage disease. P16 + patients did as poorly as P16 negative head and neck cancer patients. This study provides objective evidence of the risks of refusing conventional therapy and can be used to counsel future patients who are considering declining treatment.

Acknowledgements

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. This manuscript was presented in the 6th World Congress of the International Federation of Head and Neck Oncologic Societies (IFHNOS) in Buenos Aires, Argentina.

References

1 Fan CY, Chao HL, Lin CS, et al. Risk of depressive disorder among patients with head and neck cancer: a nationwide population-based study. Head Neck 2018;40:312-23. https://doi.org/10.1002/hed.24961

2 Zimmaro LA, Sephton SE, Siwik CJ, et al. Depressive symptoms predict head and neck cancer survival: examining plausible behavioral and biological pathways. Cancer 2018;124:1053-60. https://doi.org/10.1002/cncr.31109

3 Hughley BB, Sperry SM, Thomsen TA, et al. Survival outcomes in elderly patients with untreated upper aerodigestive tract cancer. Head Neck 2017;39:215-8. https://doi.org/10.1002/hed.24565

4 Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000;36:1032-7. https://doi.org/10.1016/s0959-8049(00)00054-x

5 Jeannon JP, Ofu E, Balfour A, et al. The natural history of untreated squamous cell carcinoma of the head and neck: how we do it. Clin Otolaryngol 2011;36:384-8. https://doi.org/10.1111/j.1749-4486.2011.02325.x

6 Choi HG, Park B, Ahn SH. Untreated head and neck cancer in Korea: a national cohort study. Eur Arch Otorhinolaryngol 2017;274:1643-50. https://doi.org/10.1007/s00405-016-4392-8

7 Cheraghlou S, Kuo P, Mehra S, et al. Untreated oral cavity cancer: long-term survival and factors associated with treatment refusal. Laryngoscope 2018;128:664-9. https://doi.org/10.1002/lary.26809

8 Mattavelli D, Ferrari M, Taboni S, et al. The 8th TNM classification for oral squamous cell carcinoma: what is gained, what is lost, and what is missing. Oral Oncology 2020;111:104937. https://doi.org/10.1016/j.oraloncology.2020.104937

9 Tam S, Araslanova R, Low T-H, et al. Estimating survival after salvage surgery for recurrent oral cavity cancer. JAMA Otolaryngol Head Neck Surg 2017;143:685-90. https://doi.org/10.1001/jamaoto.2017.0001

10 Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Ann Oncol 2011;22:1071-7. https://doi.org/10.1093/annonc/mdr006

11 Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35. https://doi.org/10.1056/NEJMoa0912217

12 Jayaram SC, Muzaffar SJ, Ahmed I, et al. Efficacy, outcomes, and complication rates of different surgical and nonsurgical treatment modalities for recurrent/residual oropharyngeal carcinoma: a systematic review and meta-analysis. Head Neck 2016;38:1855-61. https://doi.org/10.1002/hed.24531

13 Siu S, McDonald JT, Rajaraman M, et al. Is lower socioeconomic status associated with more advanced thyroid cancer stage at presentation? A study in two Canadian centers. Thyroid 2014;24:545-51. https://doi.org/10.1089/thy.2013.0090

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:24-30; doi: 10.14639/0392-100X-N0688

Head and neck

Flexible transoral robotic surgery: the Italian experience

Chirurgia robotica transorale flessibile: l'esperienza italiana

Francesco Barbara, Francesco Cariti, Valentina De Robertis, Michele Barbara
Otolaryngology and Head and Neck Unit, Ospedale "Mons. Dimiccoli", Barletta (BAT), Italy

SUMMARY
Objective. This prospective, non-randomised study documents our initial experience using the Flex® Surgical System for transoral surgery in Italy.
Methods. All patients who underwent transoral robotic surgery using the Medrobotics® Flex® Robotic System (Raynham, MA, USA) between March 2018 and April 2019 were reviewed. Rates of successful surgery, surgical time and complications were evaluated. 43 surgical procedures were performed in the study. The average age was 62.56 years (range 36-90 years). The Flex® system was used successfully in surgery of the base of the tongue, palatine tonsils, supraglottis, hypopharynx and glottis, which was the most frequent target.
Results. All procedures were successfully completed. There were no intraoperative or serious postoperative complications, with no cases of intraoperative haemorrhage.
Conclusions. This is the first study in Italy evaluating the use of the Flex® system to safely resect lesions in the oral cavity, larynx and pharynx.

KEY WORDS: larynx, pharynx, transoral surgery, flexible endoscope

RIASSUNTO
Obiettivo. *Questo studio prospettico, non randomizzato, documenta l'esperienza iniziale con il sistema chirurgico Flex® nella chirurgia transorale in Italia tra Marzo 2018 ed Aprile 2019.*
Metodi. *Sono state eseguite 43 procedure chirurgiche su 41 pazienti con età media di 62,56 anni (intervallo 36-90 anni). Sono stati valutati i tassi di successo dell'intervento chirurgico, il tempo chirurgico e le complicanze. Il sistema Flex® è stato utilizzato nella chirurgia della base della lingua, delle tonsille palatine, della regione sovraglottica, dell'ipofaringe e della glottide: quest'ultimo è stato il target chirurgico più frequente.*
Risultati. *Tutte le procedure sono state completate con successo. Non ci sono state complicanze intraoperatorie e postoperatorie gravi, nè casi di emorragia.*
Conclusioni. *Questo è il primo studio in Italia in cui viene utilizzato il sistema Flex® per la resezione di lesioni faringee e laringee e ne documenta l'affidabilità e la sicurezza.*

PAROLE CHIAVE: *laringe, faringe, chirurgia transorale, endoscopio flessibile*

Introduction

In recent decades, transoral surgery for tumours of the upper aerodigestive tract has become a standard procedure for treating different pathologies in this region at the early and/or intermediate stages, although sometimes there may be procedural difficulties depending on anatomical variations of the patient [1]. Over the years, transoral laser microsurgery (TLM) has been proven to be effective in treating neoplasms of the upper aerodigestive tract, especially of the larynx, while achieving satisfactory oncological results and with better functionality compared to open reconstructive approaches. However, some hypopharyngeal and laryngeal lesions remain difficult to visualise and treat through a transoral, surgical approach [2,3].

Received: April 28, 2020
Accepted: October 8, 2020

Correspondence
Francesco Barbara
Otolaryngology and Head and Neck Unit, Ospedale "Mons. Dimiccoli", Barletta (BAT), Italy
E-mail: francescobarbara89@gmail.com

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Barbara F, Cariti F, De Robertis V, et al. Flexible transoral robotic surgery: the Italian experience. Acta Otorhinolaryngol Ital 2021;41:24-30. https://doi.org/10.14639/0392-100X-N0688

Transoral robotic surgery (TORS) is a recent approach in managing pharyngeal and supraglottic neoplasms. The use of 3D HD angled endoscopes combined with robotic arms allows better exposure, visualisation and evaluation of anatomical regions that are otherwise difficult to manage with TLM [4]. The most commonly used robotic system in head and neck surgery is the da Vinci Si® HD (Intuitive Surgical®, Sunnyvale, CA, USA), through which surgeons are able to perform procedures in the pharyngeal region [5], at the base of the tongue and in some laryngeal sites, mainly in the supraglottic region [6]. However, there are some limitations which are mainly caused by the conflict between rigid robotic arms that may result in obstruction at the surgical site and limitation of movement. Unlike this well-known system, which was originally designed for surgery within larger cavities (such as abdominal and pelvic surgery), a new flexible robotic system – the Flex® Robotic System (Medrobotics®, Raynham, MA, USA) – has been developed to expand the field of TORS by responding specifically to the unmet needs of minimally invasive surgery of the upper aerodigestive tract [7]. This is a hybrid technology, combining the flexibility of an endoscope to gain access to the surgical site and capable of becoming rigid to perform the procedure. This technology is described as a hybrid because, on one hand, it uses the characteristics of flexible endoscopy, offering 102° of freedom in angular motion, and, on the other, is capable of navigating in non-linear spaces and becoming rigid near the surgical site [8,9]. After demonstrating feasibility and safety with successful cadaver dissections, the system obtained the CE Mark in March 2014 and the first patients were treated clinically in Europe beginning in July 2014 [10,11]. The surgical site is visualised using a 3D video camera incorporated into the distal end of the flexible endoscopic arm. The robotic arm has two accessory instrument channels for the delivery of 3.5-mm flexible instruments and, recently, 2-mm flexible instruments for laryngeal microsurgery. These instruments provide haptic feedback and allow the surgeon to have full control of the tip of the instrument. The system consists of two components: the 1) Flex® Cart, which carries the Flex® base, the Flex® Scope, and 2) the Flex® Console which has a 2D touchscreen and physician controller. The flexible robotic arm is controlled by the physician controller and a 2D touchscreen monitor. A reusable 3DHD camera and light source consisting of four LED lights are mounted on the tip of the flexible robotic arm. Thanks to a 3D monitor and passive 3D glasses, all of the room is able to follow the surgical procedure in real time [12].

There are numerous studies in literature in which Flex technology has been applied in the pharyngeal and supraglottic regions [13-15]. However, clinical work on the glottic plane as the surgical target is limited [16]. The development of new, laryngeal robotic arm, flexible micro-instruments and curved laryngeal blades as a component of the Flex® Retractor System allows surgeons to easily reach the glottic plane with excellent exposure and to operate safely. The purpose of this study is to evaluate the flexible robotic system in laryngeal transoral robotic surgery of the head and neck. We demonstrate our experience with the Flex® Robotic System on the glottic region as this anatomy has not been the focus of previous clinical studies.

Materials and methods

From March 2018 to April 2019, a prospective, non-randomised study, approved by the local ethics committee, was carried out at our Department to assess the safety, efficacy and potential of the flexible robotic system in the treatment of laryngeal lesions. A total of 41 patients were enrolled and treated. The average patient age was 62.56 (range 36-90) and, of these, 28 patients were men and 13 patients were women.

A total of 43 surgical procedures were performed because in 2 cases two separate procedures were performed (in the first, two laryngeal neoformations and, in the second, a laryngeal neoformation and a pharyngeal neoformation) (Tab. I). Six procedures (13.95%) were performed for a pharyngeal lesion, and 37 (86.05%) for laryngeal lesions (Tab. II). All patients underwent a pre-operative visit and fibre-optic laryngoscopy with NBI. All patients spent one night in hospital. A new dedicated retractor was used in all procedures (Flex® Retractor System: Medrobotics). Positioning of the retractor was video-assisted using a GlideScope® Core (Verathon) portable video laryngoscope supplied by our anaesthetists. Nasotracheal intubation was chosen in all procedures; in our opinion, this allows better exposure and less obstruction of the surgical field using a 5-mm armored endotracheal tube. All procedures were performed by the same surgeon and nursing team. Each procedure required the use of two Flex® Instruments. Either a Flex® Monopolar Maryland Dissector, a Flex® Fenestrated Grasper or a Micro Flex® Triangle Grasper were selected as a grasping and retraction instrument. A Flex® Monopolar Needle Knife or a Flex® Monopolar Spatula was used as a cutting tool in 40 procedures (93%). In 3 of the laryngeal procedures (7%), however, a Micro Flex® Sickle Knife, a cold cutting instrument, was preferred. In all operations, a suction tube for smoke evacuation was connected to the Flex® Retractor and a second operator helped the surgeon with the suction and traction of tissues using an external rigid double-edged curved laryngeal suction unit.

Table I. In 41 patients, 43 surgical procedures were performed.

Patient no.	Sex	Age, Y	Malignant/benign (M/B)	Histology	Surgical procedure	Site	Subsite
1	M	64	B	Laryngocele	Resection	L	Vestibule
2	M	70	B	Dysplasia	Type II cordectomy	L	Vocal fold
3	M	63	B	Synechia	Resection	L	Vocal fold
4	M	64	B	Cyst	Resection	0	Tonsil
5	M	65	B	Dysplasia	Type III cordectomy	L	Vocal fold
6	M	58	B	Laryngocele	Resection	L	Vestibule
7	M	71	M	SCC pT1a	Type Va cordectomy	L	Vocal fold
8	M	72	M	SCC pT1a	Type III cordectomy	L	Vocal fold
9	M	57	B	Dysplasia	Type I cordectomy	L	Vocal fold
10	M	64	B	Synechia	Resection	L	Infraglottic cavity
11	F	68	M	SCC pT1a	Type III cordectomy	L	Vocal fold
12	F	56	B	Cyst	Resection	0	Base of tongue
13	F	60	B	Cyst	Resection	L	Epiglottis
14	F	62	B	Cyst	Resection	0	Base of tongue
15	F	45	B	Reinke oedema	Resection	L	Vocal fold
16	M	64	B	Mucosal flap	Resection	L	Vestibule
16 BIS	M	64	B	Sovraglottic obstruction	Epiglottectomy	L	Epiglottis
17	M	66	M	SCC pT1a	Type Va cordectomy	L	Vocal fold
18	M	70	B	Papilloma	Resection	L	Infraglottic cavity
19	M	71	M	SCC pT1b	Type VI cordectomy	L	Vocal fold
20	M	65	M	SCC pT1a	Type III cordectomy	L	Vocal fold
21	M	56	B	Cyst	Resection	L	Epiglottis
22	M	90	M	SCC pT1	Bot resection	0	Base of tongue
23	M	62	B	Taratoma	Tonsillectomy	0	Tonsil
24	F	67	B	Polyp	Resection	L	Vocal fold
25	M	70	M	SCC pT1a	Type IV cordectomy	L	Vocal fold
26	F	65	B	Cyst	Resection	L	Vocal fold
27	F	58	B	Cyst	Resection	L	Vestibule
28	M	66	B	Laryngocele	Resection	L	Vestibule
29	F	36	B	Cyst	Resection	L	Vocal fold
30	F	46	B	Cyst	Resection	L	Vocal fold
31	F	69	M	SCC pT1a	Type III cordectomy	L	Vocal fold
32	M	71	M	Mixed tumour T1	Epiglottectomy	L	Epiglottis
33	M	69	M	SCC pT1a	Type iii cordectomy	L	Vocal fold
34	F	58	B	Laryngocele	Resection	L	Vestibule
35	M	43	M	SCC pT1a N2	Epiglottectomy + snd	L	Epiglottis
36	M	41	M	SCC pT1	Epiglottectomy	L	Epiglottis
37	F	52	B	Cyst	Resection	L	Vocal fold
38	M	74	B	Cyst	Resection	0	Tonsil
38 BIS	M	74	B	Cyst	Resection	L	Vestibule
39	M	71	B	Dysplasia	Type III cordectomy	L	Vocal fold
40	M	70	B	Dysplasia	Type III cordectomy	L	Vocal fold
41	M	56	B	Reinke edema	Resection	L	Vocal fold

Table II. Surgical subsites.

Surgical subsite	N	Tot
Pharynx		6
Tonsil	3	
Base of tongue	3	
Larynx		37
Epiglottis	6	
Vestibule	7	
Vocal fold	22	
Infraglottic cavity	2	
	Tot	43

Setup time, retractor positioning time, surgical procedure time and resection time were calculated during surgery. Access to the surgical site and exposure were evaluated with a score from 1 to 5 (1 = impossible to expose, 5 = easy to expose). The score was given by the single operator.

The following aspects were investigated:

Postoperative pain at 24 h and 48 h was rated on a scale of 0 to 10 (0 = no pain, 10 = severe pain) and the presence of intraoperative complications, postoperative complications (0-7 days following surgery) and surgical outcomes (> 7 days) were also evaluated.

All patients underwent endoscopic examinations on the first, seventh and fourteenth day following surgery.

Patients who had malignant lesions (13; 30%) or dysplasia (5; 11.6%) followed the standard follow-up protocol as per institutional guidelines.

Results

The average setup time was 15.07 minutes (range 7-40), demonstrating a quick learning curve, as the first case setup time was 40 minutes and the most recent cases ranged between 7-15 minutes. The average retractor positioning time was 10.82 minutes (range 4-26). Exposure was possible in 100% of cases and the procedure was successfully completed in all patients without the need for conversion to another type of transoral surgery (TOLS: Trans Oral Laryngeal Surgery, TOUSS: Trans Oral UltraSonic Surgery). The mean time for the surgical procedure was 32.78 minutes (range 15-75). The mean resection time was 24.74 minutes (range 4-55). The mean exposure score was 3.42 (range 2-5). There were no cases where the exposure score was 1 or where a site could not be exposed.

There were 25 (58.14%) benign lesions, of which 5 (20%) were pharyngeal and 20 (80%) were laryngeal. The anatomical subsites of the two surgical targets and histologies are shown in Table III.

Table III. Benign lesions. Anatomical subsites and histologies.

Surgical subsite	N	Tot	Histology
Pharynx		5	
Tonsil	3		Cyst (2), Taratoma (1)
Base of tongue	2		Cyst (2)
Larynx		20	
Epiglottis	3		Cyst (2), Sovraglottic obstriction (1)
Vestibule	7		Laryngocele (4), Mucosal flap (1), Cyst (2)
Vocal fold	8		Synechia (1), Reinke edema (2), Polyp (1), Cyst (4),
Infraglottic cavity	2		Synechia(1), Papilloma(1)
	Tot	25	

There were 5 dysplastic lesions (11.6%), of which 3 were SIN I (60%), 1 was SIN II (20%) and 1 was SIN III (20%). The margins were negative in two cases. In one case, the deep margin was close and, after two months of follow-up and NBI examinations, due to the presence of pseudo-granulomatous tissue in the surgical site, we preferred to opt for TOLS revision surgery, with negative resection margins. (Tab. IV).

There were 13 malignant lesions (30%), of which 1 (7.7%) was pharyngeal and 12 (92.3%) were laryngeal. Specifically, the pharyngeal lesion involved the base of the tongue, while the laryngeal lesions were localised in 3 (25%) cases in the supraglottic region and in 9 (75%) cases in the glottic plane. In 12 cases, the histology was squamous cell carcinoma (92.3%); in a single case, the histological diagnosis was a mixed tumour (7.7%). Resection margins were negative in 11 (84.6%) cases. Margins were close in 2 cases (15.4%). In one case, the patient underwent TOLS revision surgery one month after the first operation due to persistence of pathology, although the margins were negative at the histological examination. In one case, a contralateral neck dissection to the lesion was carried out for N+ on one

Table IV. Dysplastic lesions.

Surgical subsite	N	Tot	Histology
Larynx		5	
Vocal fold	5		SIN I (3), SIN II (1), SIN III (1)
	Tot	5	

Table V. Malignant lesions. Staging, grading, location of lesions.

Surgical subsite	N	Tot	Histology
Pharynx		1	
Base of tongue	1		SCC pT1 G1 HPV-
Larynx		12	
Vocal fold	9		SCC pT1a G1 (8), SCC pT1b G1 (1)
Epiglottis	3		SCC pT1 G1 (1), SCC pT1 G2 (1), Mixed tumour pT1 G2 (1)
	Tot	13	

patient that had already been treated with neck dissection at another centre. No patients underwent postoperative adjuvant therapy. All patients (100%) are currently free of disease. The duration of follow-up ranges from 1 month to 11 months. Staging, grading, location of lesions and type of transoral surgery are shown in Table V.

All procedures were successfully completed. There were no intraoperative complications. In one case, postoperative arytenoid oedema appeared (one day following the surgery), which was resolved after 12 hours of corticosteroid therapy.

At one-month follow-up, we found a granuloma in two patients: in the 1st case the granuloma appeared in the paracommissural area and in the 2nd case in the posterior area; both were treated with medical therapy. In one case, we found the appearance of para-commissural leukoplakia near the resection margin, NBI negative, and not in progression. The postoperative pain score at 24 h and 48 h was 2.88 and 0.77 of 10, respectively. All patients who underwent transoral surgery only were discharged on the first day following the surgery with an indication for complete vocal rest and hyaluronic acid therapy. No patients were prescribed antibiotic or anti-inflammatory treatment.

Discussion

The most commonly used system for TORS in the United States today is the da Vinci Si® HD (Intuitive Surgical®, Sunnyvale, CA, USA), which has been used since 2005 and was approved by the Food and Drug Administration (FDA) in 2009 [17]. Over the years, this system has allowed progress in transoral and conservative surgery of the aerodigestive tract; however, multiple rigid arms limit access to some hypopharyngeal-laryngeal regions that cannot be exposed through line of sight [18].

The Flex® Robotic System (Medrobotics, Raynham, MA, USA) is a hybrid approach specifically designed for head and neck surgery. Animal and cadaveric studies have validated the feasibility of using the Flex Robotic System in various head and neck procedures [8,9]. Lerner et al. [19] demonstrated the possibility of transoral surgical access to the oropharynx and hypopharynx without risks or complications. Additionally, others have demonstrated the feasibility of performing supraglottic laryngectomy, total laryngectomy, removal of a Zenker's diverticulum, thyroid lobectomy, dissection of the neck, removal of the submandibular gland, cranial base surgery and nasopharyngeal surgery [20,21].

In the literature, there are fewer publications on the Flex® Robotic System compared to the da Vinci® system. This is due to the recent introduction of the Flex® Robotic system in transoral surgery.

The Flex® Robotic System obtained the European CE Mark (Conformité Européenne) in March 2014 and FDA clearance in July 2015 to allow the use in the oropharynx, hypopharynx and larynx in adults (aged ≥ 22 years). More recently, the CE Mark approval (2016) and FDA clearance (2017) also provides for transanal surgical procedures in the anus, rectum and distal colon.

The most significant experience in Europe is that of the University of Essen. In a prospective study (N = 40), Mattheis et al. demonstrated important surgical results using the Flex system. They showed that 95% of T1 and T2 carcinomas of the oropharynx, hypopharynx and supraglottis in their cohort were accessible, allowing for an oncologically correct resection with no major complications [15]. Lang et al. also demonstrated excellent exposure of the oropharynx and the supraglottic larynx, noting that in 75 of 80 patients with lesions in these locations, exposure and resection was possible. Additionally, they showed that there is a reasonable setup time between 9 and 12.4 minutes, demonstrating a shorter setup time with the Flex® Robotic system than that of the da Vinci system [12]. These studies have demonstrated the feasibility of using this technology in TORS; however, further studies are needed to support these results in the long term.

The American experience has also shown similar and comparable results. In a multicentre study, Persky et al. successfully used the Flex® system in 66 of 70 cases, demonstrating that it can be used to perform complex pharyngeal and laryngeal surgical procedures. In this study, the Flex® Robotic System was used both for transoral surgical procedures (tonsils) and for procedures with indications similar to those of TOLS surgery. It was concluded that flexible robotic surgery provides better visualisation of the surgical site and greater precision than classic transoral surgery and allows, with respect to TOLS, three-handed surgery (second operator) and the ability to modify both the visual and the cutting angle with a simple wrist movement. In this study, however, the failures on the glottic plane are

highlighted: 2 of 4 procedures were not completed (50%). Although the number of patients that underwent surgery in these centres on this subsite is too low, the Authors conclude that anatomical variants (such as macroglossia or laryngeal anteriorisation), trismus and radiations could make exposure a challenge [14].

Therefore, in the literature, the surgical targets where this surgery was evaluated were the pharynx and the supraglottic region. There are few experiences on the glottic region.

For around 6 months, our multi-specialty department has had the new hyper curved blades that allow excellent exposure of the glottis using the Flex® Retractor System. Most of the interventions we carried out were due to vocal cord lesions. We did not find any complications for either benign lesions or malignant lesions, and functional and oncological outcomes were good. In fact, only one patient needed revision surgery for recurrence. Although follow-up is less than one year, all patients are currently free of disease. We think that, while the superiority of robotic surgery vs. TOLS regarding the supraglottic region is now a fact, in terms of handling, exposure, visualisation and surgical duration in the glottic region, TOLS has been the standard in terms of surgical precision. The Flex® technology is constantly evolving, and dedicated engineers bring monthly innovations to our attention. We believe that within a few years the Flex® system will achieve the same performance as TOLS on the glottic plane. We will add a fact to this consideration: in our experience, more than 90% of patients were treated with a monopolar cutting instrument. On the first day following surgery, fibrin at the surgical site was almost nonexistent. This meant no endoscopic medications were required, even when surgery was performed on anterior commissural neoformations. CO2 laser cutting tools are also compatible with the Flex® system, but we have no experience with these.

Nasotracheal intubation is very useful because it leaves the oral cavity free and the tube runs down against the rear wall of the pharynx; accordingly, it is less of an obstruction to movement of the flexible arm.

The 3D view is good, although the monitor needs to be in the same line of sight as that of the operator. In our opinion, the da Vinci® system has a good 3D camera that allows better view of anatomical structures. It is questionable whether this type of magnification is indispensable for this surgery.

Surgery is a single-operator procedure; a second operator sits beside the surgeon and uses a dedicated suction device that allows the suction of secretions and smoke and helps surgical micro-instruments with tissue traction.

Setup times are very fast and in line with other international experiences. The choice of the retractor blade is fundamental; this is guided by the shape of the patient's neck and aerodigestive tract, the surgical site and the experience of the operator. It would be useful if the different centres that use this technology will follow a standardised algorithm in the future.

It would also be interesting to find relevant parameters and create a score to identify patients that are difficult to expose. In our experience, all the patients were exposed and patients with an exposure score of 2 would have been difficult to expose even with TOLS surgery.

The haptic feedback of the instruments is very accurate and it is possible to recognise the consistency and tension of different tissues.

In their work, Friedrich et al. [22] concluded that the flexible instruments of the Flex® Robotic System allow better haptic feedback than the da Vinci® system due to the direct transmission of the force of the Flex® Instruments compared to the electromechanical transformation of the da Vinci® system. In addition, flexible microinstruments have a moderate force and grip that allow space to be made between tissues to reach the surgical targets, inspect anatomical structures such as the pyriform sinuses and move the tracheal tube. The use and manageability of these instruments is very instinctive, and the learning curve to use them is quick.

Another advantage, in our opinion, is the rapid repositioning of the Flex® Scope and microsurgical instruments. In our experience, two patients were each treated for two different lesions at different anatomical sites. In both cases, it was not necessary to reposition the retractor and the transition from one site to the other was immediate, using the Flex® Physician Controller. In addition, the times to reverse (swap) the position of the microlaryngeal instruments are very fast.

Conclusions

The Flex® Robotic System is a safe instrument that consistently provides good surgical exposure to treat benign and malignant lesions of the upper aerodigestive tract. Further technological innovations will be needed for better surgical precision, especially in the field of phonosurgery, and to better treat more extensive lesions. Choosing the correct retractor blade for each individual patient remains fundamental to the outcome of the surgery. The increasing number of ORL centres that utilise the Flex® Robotic System will allow more experiences to be shared and will be useful for development purposes.

References

[1] Takes RP, Strojan P, Silver CE, et al. Current trends in initial management of hypopharyngeal cancer: the declining use of open surgery. Head Neck 2012;34:270-81. https://doi.org/10.1002/hed.21613

[2] Weiss BG, Ihler F, Anczykowski MZ, et al. Transoral laser microsurgery for treatment of oropharyngeal cancer in 368 patients. Head Neck 2019;41:3144-58. https//doi.org/10.1002/hed.25806

[3] Djukic V, Milovanović J, Jotić AD, et al. Laser transoral microsurgery in treatment of early laryngeal carcinoma. Eur Arch Otorhinolaryngol 2019;276:1747-55. https//doi.org/10.1007/s00405-019-05453-1

[4] Vicini C, Leone CA, Montevecchi F, et al. Successful application of transoral robotic surgery in failures of traditional transoral laser microsurgery: critical considerations. ORL J Otorhinolaryngol Relat Spec 2014;76:98-104. https//doi.org/10.1159/000359953

[5] Meccariello G, Montevecchi F, D'Agostino G, et al. Trans-oral robotic surgery for the management of oropharyngeal carcinomas: a 9-year institutional experience. Acta Otorhinolaryngol Ital 2019;39:75-83. https://doi.org/10.14639/0392-100X-2199

[6] Weinstein GS, O'Malley BW Jr, Snyder W, et al. Transoral robotic surgery: supraglottic partial laryngectomy. Ann Otol Rhinol Laryngol 2007;116:19-23. https//doi.org/10.1177/000348940711600104

[7] Peters BS, Armijo PR, Krause C, et al. Review of emerging surgical robotic technology. Surg Endosc 2018;32:1636-55. https//doi.org/10.1007/s00464-018-6079-2

[8] Richmon JD. Transoral palate-sparing nasopharyngectomy with the Flex® System: preclinical study. Laryngoscope 2015;125:318-22. https//doi.org/10.1002/lary.24918

[9] Johnson PJ, Rivera Serrano CM, Castro M, et al. Demonstration of transoral surgery in cadaveric specimens with the medrobotics flex system. Laryngoscope 2013;123:1168-72. https//doi.org/10.1002/lary.23512

[10] Mandapathil M, Greene B, Wilhelm T. Transoral surgery using a novel single-port flexible endoscope system. Eur Arch Otorhinolaryngol 2015;272:2451-6. https//doi.org/10.1007/s00405-014-3177-1

[11] Remacle M, Prasad VMN, Lawson G, et al. Transoral robotic surgery (TORS) with the Medrobotics Flex™ System: first surgical application on humans. Eur Arch Otorhinolaryngol 2015;272:1451-5. https//doi.org/10.1007/s00405-015-3532-x

[12] Lang S, Mattheis S, Hasskamp P, et al. A European multicenter study evaluating the flex robotic system in transoral robotic surgery. Laryngoscope 2017;127:391-5. https//doi.org/10.1002/lary.26358

[13] Sethi N, Gouzos M, Padhye V, et al. Transoral robotic surgery using the Medrobotic Flex® system: the Adelaide experience. J Robot Surg 2020;14:109-13. https//doi.org/10.1007/s11701-019-00941-2

[14] Persky MJ, Issa M, Bonfili JR, et al. Transoral surgery using the Flex Robotic System: initial experience in the United States. Head Neck 2018;40:2482-6. https//doi.org/10.1002/hed.25375

[15] Mattheis S, Hasskamp P, Holtmann L, et al. Flex Robotic System in transoral robotic surgery: the first 40 patients. Head Neck 2017;39:471-5. https//doi.org/10.1002/hed.24611

[16] Remacle M, Prasad VMN. Preliminary experience in transoral laryngeal surgery with a flexible robotic system for benign lesions of the vocal folds. Eur Arch Otorhinolaryngol 2018;275:761-5. https//doi.org/10.1007/s00405-018-4900-0

[17] Liederbach E, Lewis CM, Yao K, et al. A contemporary analysis of surgical trends in the treatment of squamous cell carcinoma of the oropharynx from 1998 to 2012: a report from the National Cancer Database. Ann Surg Oncol 2015;22:4422-31. https//doi.org/10.1245/s10434-015-4560-x

[18] Weinstein GS, O'Malley BW Jr, Rinaldo A, et al. Understanding contraindications for transoral robotic surgery (TORS) for oropharyngeal cancer. Eur Arch Otorhinolaryngol 2015;272:1551-2. https//doi.org10.1007/s00405-014-3331-9

[19] Lerner MZ, Tricoli M, Strome M. Abrasion and blunt tissue trauma study of a novel flexible robotic system in the porcine model. Am J Otolaryngol 2017;38:447-51. https//doi.org/10.1016/j.amjoto.2017.04.002

[20] Friedrich DT, Scheithauer MO, Greve J, et al. Application of a computer-assisted flexible endoscope system for transoral surgery of the hypopharynx and upper esophagus. Eur Arch Otorhinolaryngol 2017;274:2287-93.https//doi.org/10.1007/s00405-017-4498-7

[21] Schuler PJ, Scheithauer M, Rotter N, et al. A single-port operator-controlled flexible endoscope system for endoscopic skull base surgery. HNO 2015;63:189-94. https//doi.org/10.1007/s00106-014-2950-1

[22] Friedrich DT, Dürselen L, Mayer B, et al. Features of haptic and tactile feedback in TORS-a comparison of available surgical systems. J Robot Surg 2018;12:103-8. https//doi.org/10.1007/s11701-017-0702-4

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:31-38; doi: 10.14639/0392-100X-N1089

Thyroid

Clinical significance of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio and prognostic nutritional index in low-risk differentiated thyroid carcinoma

Significato clinico del rapporto neutrofili/linfociti, rapporto linfociti/monociti, rapporto piastrine/linfociti e indice prognostico nutrizionale nei carcinomi differenziati della tiroide a basso rischio

Chiara Offi, Roberto Maria Romano, Angelo Cangiano, Giancarlo Candela, Giovanni Docimo

Division of Thyroid Surgery, Department of Medical and Advanced Surgical Sciences, University of Campania "Luigi Vanvitelli", School of Medicine, Naples, Italy

SUMMARY

Objective. Inflammation and nutritional status play an important role in the prognosis of cancer. Lymphocyte-to monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutritional index (PNI) are independent prognostic scores in numerous cancers. However, any study showed their prognostic role in low-risk differentiated thyroid carcinoma (DTC). We aimed to clarify and identify the prognostic value of inflammation indices in low-risk DTC patients.

Methods. We analysed data from 116 patients, dividing the population into two groups, according to AJCC staging system (8th edition). The LMR, NLR, PLR and PNI cut-off value were determined using receiver operating characteristic (ROC) curve. Disease-free survival (DFS) was calculated with Kaplan-Meyer and Log-Rank tests and the risk of recurrence was calculated with univariate and multivariate Cox regression. Statistical significance was $p < 0.05$.

Results. We found a baseline NLR value ≥ 1.750 (75% sensitivity, 40.2% specificity) and a baseline LMR value of 3.83 (66.7% sensitivity, 48.9% specificity). Overall DFS was 74.995 ± 3.236 with a p value of 0.678. NLR showed a hazard ratio for recurrence with almost twice the risk of recurrence (Adjusted Hazard Ratio /HR[A]): 1.828, p-value = 0.019).

Conclusions. NLR can be considered a prognostic score with twice the risk of recurrence in low-risk DTC patients with NLR < 1.750.

KEY WORDS: thyroid carcinoma, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphoctye ratio, prognostic nutritional index

RIASSUNTO

Oggetto. *L'infiammazione e lo stato nutrizionale giocano un ruolo fondamentale nella prognosi del cancro. LMR, NLR, PLR, e PNI sono considerati fattori prognostici indipendenti in numerosi carcinomi. Tuttavia, nessuno studio ha dimostrato il loro ruolo nella prognosi dei DTC-basso rischio. L'obiettivo del nostro studio è chiarire e indentificare il valore prognostico di tali valori nei pazienti con DTC-basso rischio.*

Metodi. *Abbiamo analizzato 116 pazienti, dividendo la popolazione in due gruppi secondo la stadiazione AJCC. Il valore di LMR, NLR, PLR e di PNI è stato determinato con la curva ROC. La DFS è stata calcolata con il test di Kaplan-Meyer e con il test Log-Rank, mentre il rischio di recidiva è stato calcolato con la regressione univariata e multivariata di Cox. La significatività statistica è stata considerata con valori di p-value < 0,05.*

Risultati. *Abbiamo trovato un valore di NLR ≥ 1,750 (75% sensibilità, 40,2% specificità)*

Received: August 29, 2020
Accepted: October 26, 2020

Correspondence
Chiara Offi
Department of Medical and Advanced Surgical Sciences, University of Campania "Luigi Vanvitelli", School of Medicine, piazza Miraglia 2, 80138 Naples, Italy
Tel. +39 081 5665275. Fax +39 081 5665257
E-mail: chiara.o@live.com

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Offi C, Romano RM, Cangiano A, et al. Clinical significance of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio and prognostic nutritional index in low-risk differentiated thyroid carcinoma. Acta Otorhinolaryngol Ital 2021;41:31-38. https://doi.org/10.14639/0392-100X-N1089

e di LMR di 3,83 (66,7% sensibilità, 48,9% specificità). La DFS è di 74,995 ± 3,236 con p-value di 0,678. NLR ha mostrato un Hazard Ratio con un rischio di recidiva doppio (HR^A 1,828, p-value = 0,019).
Conclusioni. *NLR può essere considerato un fattore prognostico con un rischio di recidiva duplicato nei pazienti con DTC-basso rischio con valori di NLR < 1,750.*

PAROLE CHIAVE: *carcinoma tiroideo, rapporto neutrofili/linfociti, rapporto linfociti/monociti, rapporto piastrine/linfociti, indice prognostico nutrizionale*

Introduction

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) account for 85% and 12%, respectively, of all thyroid cancers and are defined as differentiated thyroid carcinomas (DTC) [1]. The incidence of DTC has doubled (28.2/100,000 new cases per year in women and 10.1/100,000 new cases in men) in the past decade and the increase is more marked than any other cancer [2]. DTC is more frequent in women, but the mortality is similar between genders (1 death per year per 100,000 people) [3]. The clinical presentation of DTC varies from an indolent tumour with very low mortality to a very aggressive malignancy [3]. PTC has a predominantly lymphatic spread, while FTC shows haematic spreading [2]. Diagnostic suspicion is confirmed with ultrasonography imaging and echo-guided fine needle cytology (FNC) [3]. According to the American Thyroid Association (ATA), the recurrence rate in low-risk DTC is less 1-2% [3]. The treatment of choice in DTCs is surgery followed or not by radioactive iodine (RAI) therapy [3]. Pathological tumour-node-metastases (TNM) stage is the major prognostic factor in DTC [3]. The lymph node recurrence rate is variable in low-risk DTC changes according to histotype of the neoplasm and response to surgical treatment and RAI therapy [1]. Therefore, finding indices that can predict the presence of lymph node metastases at diagnosis or the rate of lymph node recurrence in low-risk DTCs can be a valid help in planning tailored treatment (thyroidectomy versus hemithyroidectomy and postoperative RAI therapy).

The immune system is potentially able to eradicate tumours; the inflammatory response is associated with initiation, progression, metastasis and prognosis [4]. Neutrophils, lymphocytes, monocytes and platelets are inflammatory mediators. Neutrophils and platelets product pro-inflammatory cytokines such as endothelial growth factor (VEGF), tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2), interleukin-6 (IL-6) and interleukin-10 (IL-10), which contribute to tumourigenesis. Monocytes and lymphocytes, on the other hand, have anti-tumoural effects [4]. The literature confirms that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are independent prognostic factors in many solid cancers, including colorectal cancer, lung cancer, oesophagus cancer and laryngeal squamous cell carcinoma [5-7]. Prognostic nutritional index (PNI) is a new prognostic score that reflects inflammatory and nutritional status of patient [8]. The recent literature shows that PNI is a predictive and prognostic index in many solid tumours, such as colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, pancreatic cancer and breast cancer [9-11]. All these indices can be calculated on routine preoperative blood samples and biochemical tests, with no additional costs.

NLR, LMR, PLR and PNI, to our knowledge, have never been investigated in patients with low-risk DTC. Therefore, the routine use of these inflammatory prognostic indices might add prognostic stratification in low-risk DTC patients.

According to the 2015 ATA guidelines, low-risk DTC is defined as: PTC without local or distant metastases; PTC with R0 after surgery; PTC without invasion of locoregional tissues; PTC without an aggressive histology; PTC without metastatic foci outside thyroid bed after RAI therapy; PTC without vascular invasion; PTC with clinical N0 or with ≤ 5 pathological micrometastases (N1c); intrathyroidal follicular variant of PTC; intrathyroidal FTC with capsular invasion and no or < 4 foci of vascular invasion and intrathyroidal papillary unifocal or multifocal microcarcinoma with or without $BRAF^{V600E}$ mutations [1]. We have investigated the association between preoperative NLR, PLR, LMR, PNI and the presence of lymph node metastasis and overall survival (OS) and disease-free survival (DFS) in patients with low-risk DTC undergoing or not RAI therapy. Therefore, the aim of this study was to understand the prognostic value of inflammation indices in low-risk DTC patients.

Materials and methods

We have retrospectively collected data on 208 patients who underwent thyroidectomy or hemithyroidectomy at the Department of Thyroid Surgery at the University of Campania "Luigi Vanvitelli". All patients had an anatomopathological diagnosis of DTC and underwent surgery between March 2012 and December 2019. Clinical and pathological TNM staging was performed according to the American Joint Committee on Cancer (AJCC) staging system (8^{th} edition) [12]. We enrolled 116 patients.

We included patients aged over 18 years and not pregnant with: single or multiple thyroid nodule with cytological diagnosis of TIR1c, TIR3a, TIR3b, TIR4 and TIR5 to FNC; characteristic of low-risk DTC, according to 2015 ATA guidelines; complete medical history and complete preoperative blood tests. We excluded patients with: presence of single or multiple thyroid nodule with cytological diagnosis of TIR1 or TIR2; other histopathological thyroid cancer as medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC); autoimmune thyroid disease (Hashimoto's thyroiditis or Basedow's disease); neck surgery within 5 years; neck radiation therapy; previous thyroid tumour; previous tumour of the head-neck district; chronic inflammation due to HBV, HCV, chronic gastritis, nephritis or gout; immune or haematological disease; history of chronic anticoagulant drugs use and proliferative haemopoietic disorders. The flow chart (Fig. 1) shows the patients enrolled according to the inclusion and exclusion criteria.

We divided the population into two groups based on age: ≤ 55 years and > 55 years, according to the AJCC thyroid staging system (8th edition). All patients underwent blood and biochemical analyses, FNC, thyroid and laterocervical lymph node ultrasound and fibreoptic-laryngoscopy in the 30 days prior to surgery. Clinical and demographic data as age and sex were obtained from the archive files. Anatomopathological findings suchas histopathological type, dimension, capsular invasion, vascular invasion, laterality, unifocality, multifocality and stage were obtained from archive files. Laboratory data on white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets were obtained from archive data. NLR, LMR and PLR were obtained from the simple relationship between the two values; PNI was obtained using the following formula: [10 x albumin (g/dL) + (0.005 x total lymphocytes count (10^3/μL)]. All surgical procedures were performed by two surgeons. The surgical treatments performed were total thyroidectomy (TT), near total thyroidectomy (NTT) or hemithyroidectomy (HT). TT is the surgical treatment of choice in the treatment of thyroid diseases that requires extracapsular removal of the gland in its entirety. NTT involves the extracapsular removal of the gland leaving a small thyroid residue at the level of the recurrent laryngeal nerve or at the level of the nerve entrance at the laryngeal level where total removal is associated with a sacrifice of the nerve itself. HT involves the removal of the thyroid lobe associated with the removal of the isthmus. These surgical treatments are foreseen in the treatment of DTC by the ATA guidelines [1].

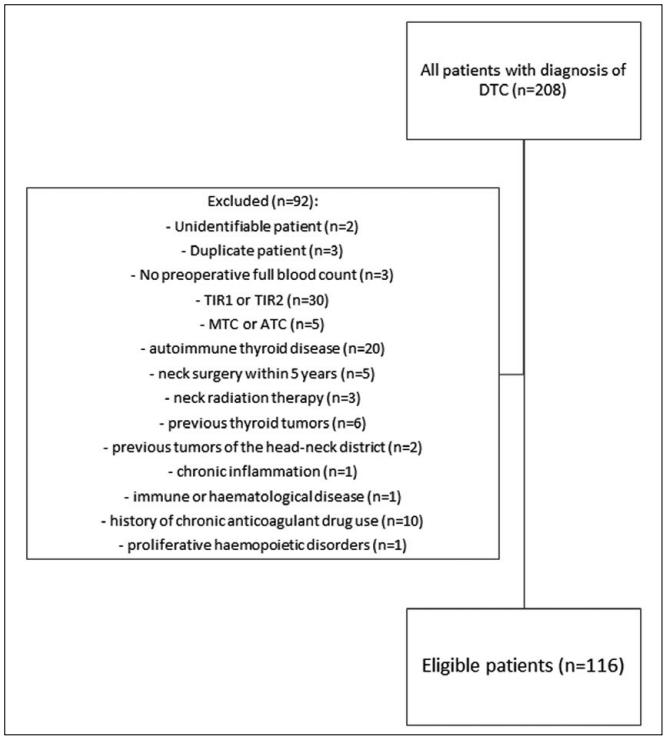


Figure 1. Flow chart of eligible patients.

During follow-up we assessed postoperative RAI therapy I^{131}, the rate of lymph node recurrence and DFS. After primary surgery, a follow-up programme was carried out for all patients. During the first years, physical examination, serum thyroglobulin (Tg) and neck ultrasound were performed every 3 months and every 6 months from the second year. In our population we had a follow-up ranging from 3 to 93 months. Recurrence was defined by increased serum Tg (≥ 20 μg/L) and the appearance of suspicious lymph node metastases on neck ultrasound, and then confirmed with FNC and Tg measurement in FNC eluates. DFS was defined as the interval between primary surgery and lymph node recurrence.

This study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (AOU4588/2020). Written informed consent was obtained from all participants. All procedures performed were in according to Helsinki Declaration.

Statistical analysis

Continuous variables were described as mean and standard deviation (SD), while categorical variables were described as number of cases and percentage. Independent t-tests were performed to compare continuous variables (month of recurrences, maximum diameter of neoplasm and all haematological values with their relatives score), and a test of proportions was applied to categorical variables (number of patients, FNC, RAI, lymph node recurrences and microcarcinoma). The LMR, NLR, PLR and PNI cut-off values

were determined using a receiver operating characteristic (ROC) curve. Moreover, Fisher's exact test was used to analyse gender, surgical treatment, laterality of neoplasm and histopathological reports. DFS was calculated with the Kaplan-Meyer method and Log-Rank test was used to compare recurrences. The risk of recurrence (Hazard Ratio, HR) was calculated using univariate and multivariate Cox's regression. Statistical significance was considered in case of p value < 0.05. Statistical analysis was performed with SPSS version 23 (SPSS©, Chicago, IL, USA).

Results

We retrospectively enrolled 116 consecutive patients who underwent surgery for a low-risk DTC in our department from March 2012 and December 2019. According to AJCC stage, patients were divided in two groups: low-risk DTC ≤ 55 years and low-risk DTC ≤ 55 years. Baseline demographic characteristics, cytology details, surgical treatment and anatomopathological report are shown in Table I. The study cohort included 80 (68.9%) patients ≤ 55 years and 36 (31.1%) patients > 55 years; the mean age was 43.1 years in the group ≤ 55 years and 63.8 years in the group > 55 years. Female patients were 85.3% without no significant difference (p-value 0.26) between groups. There was no TIR1c in our population. TIR3a, TIR3b, TIR4 and TIR5 in the ≤ 55 year group were 3.75%, 40%, 18.75% and 37.5%, respectively, and 8.34%, 25%, 30.55% and 36.11%, respectively, in the > 55 year group with no significant difference. The principal surgical procedures applied were TT/NTT, and HT was performed in only 5.2% of the cohort (p = 0.08). Tumours were present in 41.4% in the right lobe and in 58.6% in the left lobe (p = 0.06). We analysed only low-risk DTC and recorded 106 cases (91.4%) of PTC and 10 cases (8.6%) of FTC (p = 0.49). We found a microcarcinoma in 50% of the cohort (p = 0.99). In the entire population, we recorded a maximum diameter of neoplasia of 1.37 cm (p = 0.403). In the ≤ 55 year group, 100% of

Table I. Baseline characteristics of patients.

Characteristic	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
Patients (%)	116	80 (68.9)	36 (31.1)	< 0.001
Mean age in years (SD)	49.2 (± 12.45)	43.1 (± 8.45)	63.8 (± 8.58)	< 0.001
Sex (%)				
Male	17 (14.7)	14 (17.5)	3 (8.4)	0.26
Female	99 (85.3)	66 (82.5)	33 (91.6)	
FNC (%)				
TIR1c	0 (0)	0 (0)	0 (0)	0.99
TIR3a	6 (5.2)	3 (3.75)	3 (8.34)	0.56
TIR3b	41 (35.3)	32 (40)	9 (25)	0.17
TIR4	26 (22.4)	15 (18.75)	11 (30.55)	0.24
TIR5	43 (37.1)	30 (37.5)	13 (36.11)	0.72
Surgery (%)				
TT/NTT	110 (94.8)	78 (97.5)	32 (88.9)	0.08
HT	6 (5.2)	2 (2.5)	4 (11.1)	
Laterality of tumour (%)				
Right	48 (41.4)	29 (35)	19 (52.8)	0.06
Left	68 (58.6)	53 (65)	15 (47.2)	
Anatomopathological reports (%)				
PTC	106 (91.4)	74 (92.5)	32 (88.9)	0.49
FTC	10 (8.6)	6 (7.5)	4 (11.1)	
Mean maximum diameter in cm (SD)	1.37 (± 1.89)	1.47 (± 2.2)	1.15 (± 0.8)	0.403
Stage (%)				
I	111 (95.7)	80 (100)	31 (86.1)	0.002
II	5 (4.3)	0 (0)	5 (13.9)	
Microcarcinoma (%)	58 (50)	40 (50)	18 (50)	0.99

SD: standard deviation; PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; TT: total thyroidectomy; NTT: near total thyroidectomy; HT: hemithyroidectomy.

Table II. Baseline haematological values.

Blood values	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
Mean albumin (SD)	4.49 (± 0.31)	4.51 (± 0.26)	4.45 (± 0.40)	0.356
Mean white blood cells (SD)	6.82 (± 2.17)	7.03 (± 2.18)	6.53 (± 2.09)	0.116
Mean neutrophils (SD)	4.37 (± 1.67)	4.61 (± 1.74)	3.84 (± 1.38)	0.21
Mean lymphocytes (SD)	2.45 (± 4.29)	2.65 (± 5.15)	2.02 (± 0.73)	0.467
Mean monocytes (SD)	0.42 (± 0.14)	0.43 (± 0.14)	0.39 (± 0.13)	0.157
Mean eosinophils (SD)	0.16 (± 0.10)	0.16 (± 0.10)	0.17 (± 0.09)	0.549
Mean basophils (SD)	0.04 (± 0.03)	0.04 (± 0.03)	0.03 (± 0.01)	0.06
Mean platelets (SD)	259.8 (± 52.05)	266.08 (± 51.10)	245.69 (± 52.09)	0.051
Mean LMR (SD)	6.20 (± 8.29)	6.37 (± 9.61)	5.48 (± 4.12)	0.751
Mean NLR (SD)	2.41 (± 1.09)	2.59 (± 1.20)	2.01 (± 0.66)	0.001
Mean PLR (SD)	145.05 (± 48.8)	151.14 (± 51.8)	131.5 (± 38.8)	0.045
Median PNI (SD)	44.94 (± 3.17)	45.13 (± 2.69)	44.53 (± 4.06)	0.354

SD: standard deviation; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

Table III. RAI, recurrences and lymph nodes recurrence frequency.

	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
RAI therapy (%)	59 (50.86)	47 (58.8)	12 (33.3)	0.01
Lymph node recurrences (%)	24 (20.68)	18 (22.5)	6 (16.7)	0.63
Mean months of recurrence (SD)	22.45 (± 21.71)	26.44 (± 23.81)	10.50 (± 3.50)	0.13

SD: standard deviation; RAI: radioactive iodine.

patients were in TNM stage I, while in the > 55 year group 13.9% of patients were in TMN stage II, with a significant difference between groups (p = 0.002). This difference is due to staging of the malignancy. The patients in stage II had a T3a, and therefore neoplasm size and age determinate the stage [15].

Table II shows baseline haematological values. Only two values, mean NLR and mean PLR, showed a significant difference between groups. Mean NLR was 2.41 (SD ± 1.09) in entire population, 2.59 (SD ± 1.20) in the ≤ 55 year group and 2.01 (SD ± 0.66) in the > 55 year group (p = 0.001). Mean PLR was 145.05 (SD ± 48.8) in the entire population, 151.14 (SD ± 51.8) in the ≤ 55 year group and 131.5 (SD ± 38.8) in the > 55 year group (p = 0.045).

Table III shows data from patients who underwent RAI therapy, lymph node recurrence and DFS in months. The percentage of lymph node recurrence and DFS in months showed no significant differences between groups. In all, 47 patients underwent RAI therapy (58.8%) in the ≤ 55 year group and 12 patients (33.3%) in the > 55 year group with a significant difference between groups (p = 0.01). Our data showed that the indication to RAI was common in young patients.

Table IV shows prognostic scores to evaluate recurrence risk factors; in particular, adjusted NLR showed a HR of 1.828 (p = 0.019). Other haematological values showed no significant differences in the HR.

We calculated the receiver operating characteristic

Table IV. Univariate and multivariate analysis evaluating risk factors affecting recurrences.

	Unadjusted HR (95% CI)	p-value	Adjusted HR[a] (95% CI)	p-value
PNI	1.110 (0.985-1.252)	0.088	1.088 (0.966-1.225)	0.162
NLR	1.240 (0.873-1.760)	0.229	1.828 (1.103-3.029)	0.019
LMR	1.008 (0.961-1.057)	0.739	1.011 (0.958-1.066)	0.696
PLR	0.997 (0.998-1.005)	0.47	0.988 (0.975-1.001)	0.079

[a]Adjusted for age, full blood count values, procedure and dimension of lesion. HR: hazard ratio; CI: confidential interval; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.

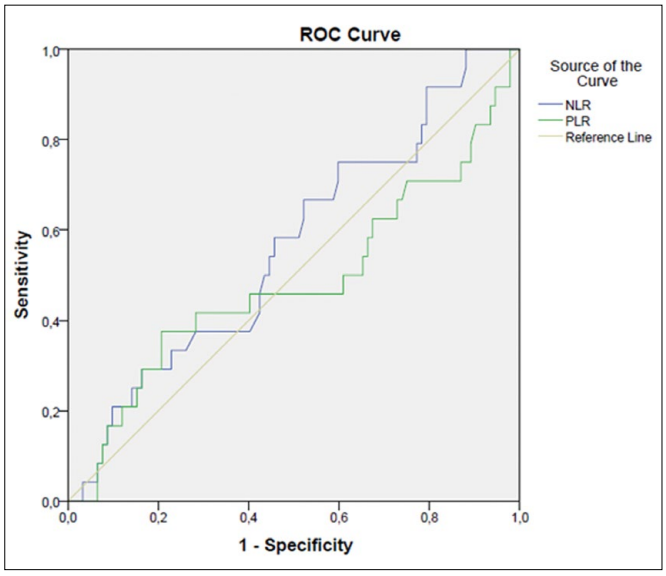


Figure 2. ROC curve of LMR with a cut-off value of 4.635 (AUC 0.540 ± 0.066, 66.7% sensitivity, 48.9% specificity) and PNI (AUC 0.417 ± 0.079). (LMR: lymphocyte-to-monocyte ratio; PNI: prognostic nutritional index; AUC: area under curve).

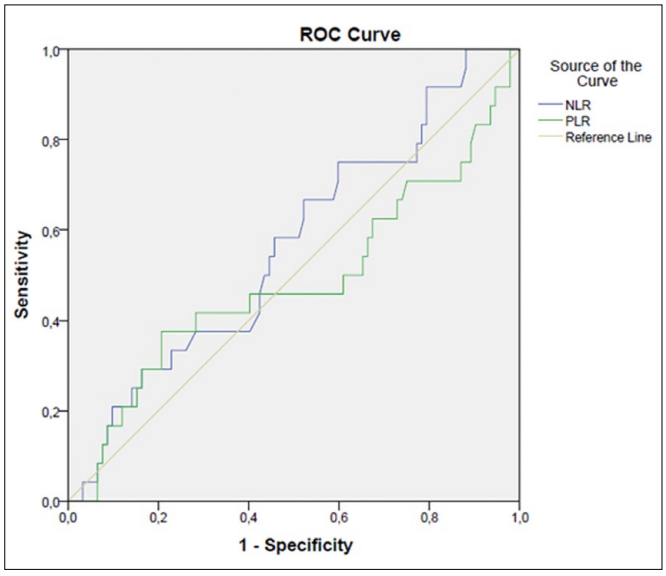


Figure 3. ROC curve of NLR with a cut-off value of 1.750 (AUC 0.564 ± 0.065, 75% sensitivity, 40.2% specificity) and PLR and (AUC 0.484 ± 0.075). (NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; AUC: area under curve).

(ROC) curves for LMR and PNI values (Fig. 2). We found 4.635 as best cut-off value for LMR with 66.7% sensitivity, 48.9% specificity and an area under the curve (AUC) of 0.540 ± 0.066. We did not find a cut-off value for PNI. All PNI values entered in the ROC curve were below the reference line with an area under the curve of 0.417 ± 0.079.

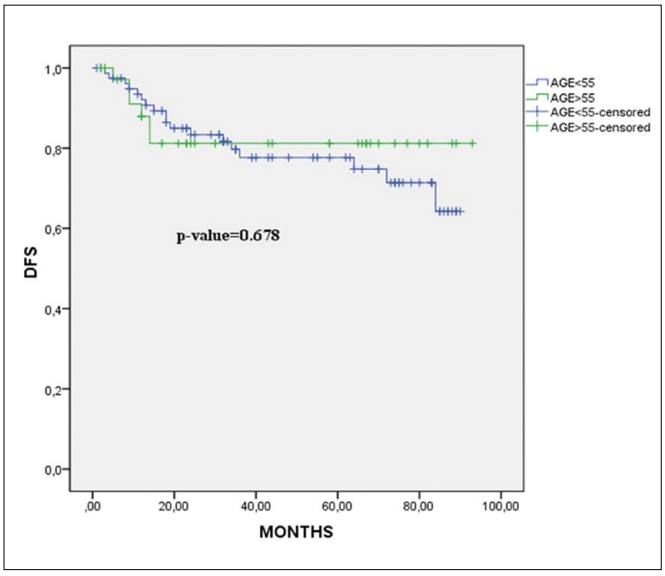


Figure 4. DFS functions distinguished between patients ≤ 55 years and > 55 years. DFS was 74.995 ± 3.236; DFS was 72.249 ± 3.689 in patients ≤ 55 and DFS was 77.514 ± 5.717 in patients >55 years. Log-rank test was used to compare recurrences (p = 0.678). (DFS: disease-free survival).

We also calculated a ROC Curve for NLR and PLR (Fig. 3). NLR cut-off values was 1.750 with 75% sensitivity, 40.2% specificity and an AUC of 0.564 ± 0.065. As for the PNI cut-off value, we found no cut-off value for PLR. All PLR values were below the ROC curve reference line with an AUC of 0.484 ± 0.075.

Figure 4 shows DFS curves in the two groups. Overall DFS was 74.995 ± 3.236; DFS in the ≤ 55 year group was 72.249 ± 3.689 and in the > 55 year group was 77.514 ± 5.717 (p = 0.678). There was no significant difference between recurrences based on age, as shown above.

Discussion

Herein, we tried to find a correlation between haematological inflammation indexes and prognosis and risk of recurrence. This is the first study that has examined correlations between LMR, NLR, PLR, PNI and the risk of recurrence in patients with low-risk DTC. The 2015 ATA guidelines suggest undergoing HT in low-risk DTC patients and to undergo NTT/TT in case of expected postoperative RAI therapy, follow-up based on increased serum Tg and patient preference [1]. Various studies have documented a recurrence rate of 1-2% in patients who underwent thyroid surgery without postoperative RAI therapy over a follow-up of 5-10 years [13,14]. Indeed, with a low risk of recurrence, the risk stratification changes during follow-up [1]. The aim of our study was to find an instrument that can identify, at

the time of diagnosis, patients at higher risk of recurrence which would allow improving the follow-up protocols and plan tailored treatment.

Blood inflammatory cells play an important role in initiation, progression, metastasis and prognosis in oncological patients. Inflammatory blood mediators include neutrophils, lymphocytes, monocytes and platelets. Monocytes and lymphocytes play an important role as anti-tumoural mediators. Low levels of lymphocytes and monocytes has been observed in advanced stage neoplasms and are associated with a poor prognosis [15]. Monocytes penetrate the tumour mass, reduce angiogenesis and induce apoptosis of cancerous cells, thus reducing cancer invasion and progression [15,16]. In the literature, low LMR has been associated with poor prognosis in numerous solid cancers and is an independent prognostic factor. This alteration of the immune system promotes angiogenesis, progression and tumour invasion [17,18]. In thyroid carcinoma the low LMR value is associated with worse prognosis, a high risk of recurrence of ATC and high-risk DTC [19,20]. At the moment no study has examined whether a low LMR value in low-risk DTCs can be an indicator of worse prognosis and increased risk of lymph node recurrence. In our study, the LMR cut-off value was 4.635 with 66.7% sensitivity and 48.9% specificity.

In the literature, various studies have reported that NLR is an independent prognostic factor in numerous solid tumours [5,21]. However, there are few in DTC. A high ratio is due to an increased neutrophil count compared to lymphocyte count. As mentioned above, neutrophils produce VEGF and inhibit TNF-α, facilitating tumour progression and invasion, and a decreased lymphocyte and monocyte count is associated with reduction in antineoplastic activity [4,15,16]. Moreover, neutrophils promote the secretion of IL-2, IL-6 and IL-8, contributing to tumourigenesis [4]. Despite this, the exact correlation between NLR and cancer prognosis still is not entirely clear. Chen et al. suggested that a low NLR (≤ 1.6) is associated with a high risk of PTC recurrence, but with a follow-up of 12.2 ± 3.8 months it is not possible to have an estimate of DFS and OS at 5 or 10 years [22]. Ceylan et al. suggested an NLR cut-off value of 1.92 and a correlation between a high NLR, large tumour size and positivity of extra-thyroidal spread [23]. Seretis et al. reported that an elevated preoperative mean NLR is present in patients with microcarcinoma and in DTC, and found that elevated mean NLR does not show any significant difference between patients with multifocal or unifocal microcarcinoma. They did not evaluate an NLR cut-off, but only the NLR preoperative mean [24]. In the literature there are no univocal and concordant data, and thus further studies are needed to find possible correlations between inflammatory indexes and risk of DTC lymph node recurrence to validate them as independent risk factors. In our population, we found an NLR cut-off value of 1.750 with 75% sensitivity and 40.2% specificity. This suggests that we have a good chance of finding unwell patients with NLR values ≥ 1.750, but a poor chance of finding healthy patients. Therefore, only NLR showed a valid HR for recurrence, and indeed it is associated with almost twice the risk of recurrence (Adjusted HR 1.828, p = 0.019), while patient age showed no significant difference in terms of risk of recurrence. Even if patients with > 55 years had higher DFS, there was no significant difference between groups (p = 0.678). This can be explained by the fact that in our cohort there were more patients ≥ 55 years undergoing RAI therapy.

According to the most recent studies, there are few correlations between PLR and prognosis of patients with DTC. Ceylan et al. found no correlation between clinicopathologic features of PTC and PLR [23]. Ozmen et al. reported that PLR and NLR are more successful indexes for diagnosis and recurrence of DTC than C-reactive protein (they included FTC, PTC and microcarcinoma). They found that high NLR and PLR are associated with high levels of thyroglobulin and worse prognosis, but their study did not evaluate cut-off values of these indexes [25]. In our study, we did not find a cut-off value for PLR because the PLR AUC was 0.484 ± 0.075 and all values were under reference line. Therefore, further studies are necessary to correlate PLR with multiple variables.

PNI is a score that assesses the patient's nutritional status and immune status based on evaluation of lymphocyte counts and albumin. PNI is a prognostic independent score in most solid cancers, including colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, pancreatic cancer and breast cancer. Studies show that a low PNI value is associated with worse prognosis due to the deficiency in the nutritional state and deficits of the immune system [9-11]. In our study, we did not found a cut-off value for PNI. Our hypothesis was that we selected a population without concomitant pathologies and with low-risk DTC, a type of indolent tumour with good prognosis.

This study showed that only NLR was a prognostic score, but further studies are necessary to clarify and validate its specific role.

Conclusions

The correlation between inflammatory indexes and OS and DFS has been established in numerous solid tumours. In our study, NLR emerged as a prognostic factor. Obviously, additional studies are needed to demonstrate this correlation and cannot yet be used to stage and stratify patients

with low-risk DTC. The limitation of our study is its retrospective nature. Follow-up should be extended to 10 years to better assess the risk of long-term recurrence and a larger population should be examined. Our hope is that in the future these scores can be used to predict the risk of recurrence and to identify patients with low-risk DTC to be submitted to RAI therapy to avoid delays in treatment and to avoid overtreatment by implementing tailored therapy.

Acknowledgements

The ethical committee of University of Campania "Luigi Vanvitelli" approved the study protocol: AOU4588/2020. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1 Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1-133. https://doi.org/10.1089/thy.2015.0020

2 Gambardella C, Patrone R, Di Capua F, et al. The role of prophylactic central compartment lymph node dissection in elderly patients with differentiated thyroid cancer: a multicentric study. BMC Surg 2018;18(Suppl 1):110. https://doi.org/10.1186/s12893-018-0433-0

3 Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet 2016;388:2783-95. https://doi.org/10.1016/S0140-6736(16)30172-6

4 Dupré A, Malik HZ. Inflammation and cancer: what a surgical oncologist should know. Eur J Surg Oncol 2918;44:566-70. https://doi.org/10.1016/j.ejso.2018.02.209

5 Mercier J, Voutsadakis IA. Comparison of hematologic and other prognostic markers in metastatic colorectal cancer. J Gastrointest Cancer 2019;50:493-506. https://doi.org/10.1007/s12029-018-0108-1

6 Liu D, Jin J, Zhang L, et al. The neutrophil to lymphocyte ratio may predict benefit from chemotherapy in lung cancer. Cell Physiol Biochem 2018;46:1595-605. https://doi.org/10.1159/000489207

7 Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World J Surg Oncol 2014;12:58. https://doi.org/10.1186/1477-7819-12-58

8 Sun G, Li Y, Peng Y, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. Int J Colorectal Dis 2019;34:681-9. https://doi.org/10.1007/s00384-019-03241-1

9 Migita K, Takayama T, Saeki K, et al. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol 2013;20:2647-54. https://doi.org/10.1245/s10434-013-2926-5

10 Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer 2012;106:1439-45. https://doi.org/10.1038/bjc.2012.92

11 Wang Y, Battseren B, Yin W, et al. Predictive and prognostic value of prognostic nutritional index for locally advanced breast cancer. Gland Surg 2019;8:618-26. https://doi.org/10.21037/gs.2019.10.08

12 Zanoni DK, Patel SG, Shah JP. Changes in the 8th edition of the American Joint Committee on Cancer (AJCC) staging of head and neck cancer: rationale and implications. Curr Oncol Rep 2019;21:52. https://doi.org/10.1007/s11912-019-0799-x

13 Vaisman F, Shaha A, Fish S, et al. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. Clin Endocrinol (Oxf) 2011;75:112-9. https://doi.org/10.1111/j.1365-2265.2011.04002.x

14 Durante C, Montesano T, Attard M, et al. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab 2012;97:2748-53. https://doi.org/ 10.1210/jc.2012-1123

15 Chanmee T, Ontong P, Konno K, et al. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 2014;6:1670-90. https://doi.org/10.3390/cancers6031670

16 Goswami KK, Ghosh T, Ghosh S, et al. Tumor promoting role of anti-tumor macrophages in tumor microenvironment. Cell Immunol 2017;316:1-10. https://doi.org/10.1016/j.cellimm.2017.04.005

17 Pan YC, Jia ZF, Cao DH, et al. Preoperative lymphocyte-to-monocyte ratio (LMR) could independently predict overall survival of resectable gastric cancer patients. Medicine (Baltimore) 2018;97:13896. https://doi.org/10.1097/MD.0000000000013896

18 Sun Y, Zhang L. The clinical use of pretreatment NLR, PLR, and LMR in patients with esophageal squamous cell carcinoma: evidence from a meta-analysis. Cancer Manag Res 2018;10:6167-79. https://doi.org/10.2147/CMAR.S171035

19 Yokota M, Katoh H, Nishimiya H, et al. Lymphocyte-monocyte ratio significantly predicts recurrence in papillary thyroid cancer. J Surg Res 2020;246:535-43. https://doi.org/10.1016/j.jss.2019.09.034

20 Ahn J, Song E, Oh HS et al. Low lymphocyte-to-monocyte ratios are associated with poor overall survival in anaplastic thyroid carcinoma patients. Thyroid 2019;29:824-9. https://doi.org/10.1089/thy.2018.0684

21 Szkandera J, Gerger A, Liegl-Atzwanger B, et al. The derived neutrophil/lymphocyte ratio predicts poor clinical outcome in soft tissue sarcoma patients. Am J Surg 2014;210:111-6. https://doi.org/10.1016/j.amjsurg.2014.10.021

22 Chen W, Wei T, Li Z, et al. Association of the preoperative inflammation-based scores with TNM stage and recurrence in patients with papillary thyroid carcinoma: a retrospective, multicenter analysis. Cancer Manag Res 2020;12:1809-18. https://doi.org/10.2147/CMAR.S239296

23 Ceylan Y, Kumanlıoğlu K, Oral A, et al. The correlation of clinicopathological findings and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in papillary thyroid carcinoma. Mol Imaging Radionucl Ther 2019;28:15-20. https://doi.org/10.4274/mirt.galenos.2018.60490

24 Seretis C, Gourgiotis S, Gemenetzis G, et al. The significance of neutrophil/lymphocyte ratio as a possible marker of underlying papillary microcarcinomas in thyroidal goiters: a pilot study. Am J Surg 2013;205:691-6. https://doi.org/10.1016/j.amjsurg.2012.08.006

25 Ozmen S, Timur O, Calik I, et al. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) may be superior to C-reactive protein (CRP) for predicting the occurrence of differentiated thyroid cancer. Endocr Regul 2017;51:131-6. https://doi.org/10.1515/enr-2017-0013

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:39-42; doi: 10.14639/0392-100X-N1141

Thyroid

Scar satisfaction assessment after conventional thyroidectomy: follow-up results

Il livello di soddisfazione riguardante la cicatrice dopo intervento di tiroidectomia: risultati a distanza

Puthen Veetil Pradeep

Department of Endocrine Surgery, Baby Memorial Hospital, Kozhikode, Kerala, India 673004

SUMMARY

Objective. With the introduction of remote access thyroidectomy questions regarding patient satisfaction after trans-cervical thyroidectomy has been raised in several publications. As far as neck scars are concerned, patient satisfaction in the early post-operative period and long term are different. This study assessed patient satisfaction regarding their neck scar in the early post-operative period and at long term follow-up.

Methods. Retrospective study. Patients underwent total thyroidectomy by single surgeon. Scar satisfaction scores assessed at different time intervals (< 6 weeks, 6 months, 2 years and 5 years after procedure). Scores of patients aged < 35 years and > 35 years were compared. Patient and observer scar assessment scales (PSAS, OSAS) and patient satisfaction score (PSS) were used.

Results. 595 patients were included (443 females and 152 males, age 19-77 years). Improvement was observed in the PSAS (13.5 ± 2.3 at 6 weeks; to 4.32 ± 1.37 at 5 years; $p < 0.05$) and OSAS (7.32 ± 1.35 to 4.18 ± 1.51; $p < 0.05$). PSS improved over time from 1.8 ± 0.8 to 0.92 ± 0.66 ($p < 0.05$). The satisfaction scores were higher in patients < 35 years ($p = 0.003$). The scores indicated excellent patient satisfaction and are similar to those published in the literature regarding minimally invasive surgery (MIS).

Conclusions. Proper incision placement and suturing resulted in excellent patient satisfaction regarding scars after conventional thyroidectomy.

KEY WORDS: thyroidectomy scar, patient satisfaction, scar assessment scale

RIASSUNTO

Obiettivo. *Con l'introduzione delle interviste telematiche da accesso remoto, sono emerse diverse perplessità circa il grado di soddisfazione dei pazienti sottoposti a tiroidectomia. Per quanto riguarda le cicatrici sul collo, vi sono diversi livelli di soddisfazione del paziente nel primo periodo post operatorio rispetto al lungo periodo. Questo studio si propone di valutare la soddisfazione del paziente in relazione alla cicatrice sul collo nel primo periodo post-operatorio e nel follow-up a lungo termine.*

Metodi. *Studio retrospettivo. 595 pazienti sono stati sottoposti a tiroidectomia totale da parte dello stesso chirurgo. Sono stati assegnati diversi punteggi di soddisfazione della cicatrice, valutati a diversi intervalli di tempo (< 6 settimane, a 6 mesi, 2 anni e 5 anni dopo la procedura). Sono stati confrontati i punteggi dei pazienti di età < 35 anni e > 35 anni. Sono state utilizzate le scale di valutazione della cicatrice del paziente e dell'osservatore (PSAS, OSAS) e il punteggio di soddisfazione del paziente (PSS).*

Risultati. *595 pazienti sono stati inclusi nel presente studio (443 femmine e 152 maschi, età 19-77 anni). Il miglioramento è stato osservato nel PSAS (13,5 ± 2,3 a 6 settimane; a 4,32 ± 1,37 a 5 anni; $p < 0,05$) e OSAS (7,32 ± 1,35 a 4,18 ± 1,51; $p < 0,05$). La PSS è migliorata nel tempo da 1,8 ± 0,8 a 0,92 ± 0,66 ($p < 0,05$). I punteggi di soddisfazione erano più alti nei pazienti con età inferiore ai 35 anni ($p = 0,003$). I punteggi hanno indicato un'eccellente grado di soddisfazione del campione esaminato, i punteggi sono simili a quelli pubblicati in letteratura per quanto riguarda la chirurgia mininvasiva (MIS).*

Conclusioni. *L'adeguata pianificazione dell'incisione e adeguata sutura chirurgica produce un'eccellente grado di soddisfazione del paziente riguardo alle cicatrici dopo la tiroidectomia convenzionale.*

PAROLE CHIAVE: *cicatrice tiroidectomia, soddisfazione del paziente, scala di valutazione della cicatrice*

Received: September 27, 2020
Accepted: November 17, 2020

Correspondence
Puthen Veetil Pradeep
Department of Endocrine Surgery, Baby Memorial Hospital, Kozhikode, Kerala, India 673004
Tel. +91 8281021234, +91 495 2988234
E-mail: pradeepputhenveetil@yahoo.co.in

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Pradeep PV. Scar satisfaction assessment after conventional thyroidectomy: follow-up results. Acta Otorhinolaryngol Ital 2021;41:39-42. https://doi.org/10.14639/0392-100X-N1141

Introduction

Thyroid diseases are very common in India. Apart from hypothyroidism and hyperthyroidism, patients also present with goiters that can be benign or malignant. Malignant goiters and a significant proportion of benign goiters need thyroidectomy. Conventional neck surgery has stood the test of time and all surgeons are trained in this technique, even though outcomes differ based on individual experience [1]. One of the concerns raised with conventional thyroidectomy is related to the neck scar, especially after the alternative procedures like remote access and minimally invasive thyroidectomy (MIS) were introduced. As far as neck scars are concerned, patient satisfaction in the early post-operative period and long term are different. In this paper, the patient satisfaction regarding their scar in the neck in the early/late post-operative periods and at long term follow-up were assessed in Indian subjects.

Methods

We conducted a retrospective study in patients who underwent thyroid surgery at two tertiary care centres in South India. A total of 2594 patients underwent thyroidectomy during the period from 2008 to 2019. Patients who underwent neck dissection, central compartment dissection, hemi-thyroidectomy and foreign nationals were excluded. Patients who did not consent and those who did not present for follow-up were excluded. Patients with diabetes mellitus, obesity, smokers and those with keloid tendency (n = 9) were excluded. Cases of total thyroidectomy performed for benign or malignant goiters were included (Tab. I).

Patients were divided into groups based on duration of follow-up (< 6 weeks, 6 weeks to 6 months, 6 months to 2 years, 2 to 5 years and more than 5 years). It is well known that healing and scarring is different in younger and older individuals, especially in the long term. Hence, scoring was also assessed in patients who were < 35 years and > 35 years where the follow-up was > 1 year. In these subgroups, the age and sex distribution did not show any significant differences.

The standard patient and observer scar assessment scale was used in this study (POSAS) [2]. This scale is shown in Table II. Observer scar assessment scale has five items and is scored 1-10, where a value of 1 indicates normal skin and 10 the worst scar. The patient scar assessment scale considers six items with scores from 1 to 10, with a score of 6 indicating normal skin and 60 the worst scar. Overall satisfaction was assessed with the patient satisfaction score (PSS). Very satisfied (1), satisfied (2), unsatisfied (3) and very unsatisfied (4) was the scoring system used for PSS. There are many different scar scales for assessing scar satisfaction, but the POSAS scale was used in this study [3].

All surgeries were performed by a single endocrine surgeon.

Table I. Number of patients with duration of follow up.

Follow-up duration	N = 595	Mean age (years)
< 6 weeks	16	43 ± 11.2
6 weeks to 6 months	101	52 ± 9.8
6 months-1 year	93	51 ± 12.3
1-2 years	105	49 ± 11.6
2- 5 years	132	54 ± 13.6
> 5 years	148	56 ± 14.8

The incision site is marked in one of the neck creases with the patient in the sitting position prior to the anaesthesia. Sub-platysmal flaps are raised. Straps are either cut/ divided depending on the size/difficulty in surgery. The rest of the procedure is as in standard thyroid surgery, preserving the recurrent and external laryngeal nerves and the parathyroids. Since the operating team of assistants and nurses were the same, the traction on the skin edges was kept to the minimum. Closures of the wound in all cases included subcutaneous absorbable vicryl (3,'O') followed by sub-cuticular suturing with 4 'O' vicryl. A drain was kept in place on a case to case basis.

Statistical analysis was performed using the SPSS (version 16.0, SPSS, Inc., Chicago, IL). Continuous values were reported as mean ± standard deviation (SD). Differences in continuous variables were assessed by the student t-test. A p value of < 0.05 was considered statistically significant. Repeated measures ANOVA was applied to compare scar satisfaction scores during follow-up.

Results

The number of patients available for follow-up after applying the exclusion/inclusion criteria is shown in Table I (n = 595). These were further divided into subgroups depending on the duration of follow-up as shown in Table I. Table I also shows the age distribution. The age and sex distribution did not show any significant differences. There were 443 females and 152 males. All patients were between 19 years to 77 years. Patients who had more than 1 year follow-up were further subgrouped by age less than 35 years and more than 35 years. Among patients who had follow up of > 1 year, 210 were less than 35 years and 175 were more than 35 years. The mean length of the neck incision was 5.1 ± 1.8cm. Tables III and IV show the results of the scores in the various groups. Table III shows that the patient (PSAS) and observer (OSAS) scar assessment scale scores improved as the duration of follow-up increased. Among patients with one year of follow-up the PSAS and OSAS scores were comparable to the scores seen in the study by Ma et al. on minimally-invasive thyroidectomy patients (PSAS: 13.27 ± 4.56 and OSAS 11.48 ± 3.6) [4]. Table IV shows that the PSAS showed better scores in patients who are more than 35 years old irrespective of the duration

Table II. The patient and observer scar assessment scales.

Observer component	Normal skin							Worst scar imaginable		
	1	2	3	4	5	6	7	8	9	10
Vascularity										
Pigmentation										
Thickness										
Relief										
Pliability										
Patient component	**No**							**Yes**		
	1	2	3	4	5	6	7	8	9	10
Is the scar painful?										
Is the scar itching?										
Is the colour of the scar different?										
Is the scar more stiff?										
Is the thickness of the scar different?										
Is the scar irregular?										

Table III. Scar satisfaction scores with duration of follow up.

Follow-up duration	N = 595	PSAS	P	OSAS	P	PSS	P
< 6weeks	16	13.5 ± 2.3	< 0.05	7.32 ± 1.35	< 0.05	1.8 ± 0.8	< 0.05
6 weeks to 6 months	101	15.7 ± 2.1		7.72 ± 2.24		2.2 ± 1.1	
6 months -1 year	93	11.36 ± 1.96		10.12 ± 2.32		2.1 ± 0.94	
1-2 years	105	10.62 ± 2.37		8.12 ± 1.76		1.3 ± 0.52	
2-5 years	132	6.32 ± 1.97		6.1 ± 1.86		1.2 ± 0.36	
> 5 years	148	4.32 ± 1.37		4.18 ± 1.51		0.92 ± 0.66	

Table IV. Scores in patients aged < 35 years and > 35 years.

Follow-up duration		PSAS	P	OSAS		PSS	P
1-2 years	< 35 yr (n = 56)	11.13 ± 2.11	0.003	8.88 ± 1.96	0.01	1.6 ± 0.52	0.0001
N = 105	> 35 yr (n = 49)	10.11 ± 1.21		7.91 ± 1.82		1.1 ± 0.62	
2-5 years	< 35 yr (n = 79)	6.88 ± 1.32	0.003	6.46 ± 1.88	0.09	1.4 ± 0.45	0.0001
N = 132	> 35 yr (n = 53)	6.11 ± 1.62		5.95 ± 1.45		1.01 ± 0.25	
> 5 years	< 35 yr (n = 75)	4.66 ± 1.42	0.003	4.46 ± 1.49	0.05	0.98 ± 0.56	0.28
N =148	> 35 yr (n = 73)	4.02 ± 1.14		4.03 ± 1.21		0.87 ± 0.68	

of follow-up. The OSAS also showed better satisfaction in patients > 35 years during long term follow-up. The digital images of scars shown in Figure 1 along with duration of follow-up.

Discussion

On tracing the history of thyroid surgery in our department, the initial years showed high morbidity and even mortality [1]. With progress in anaesthesiology, the mortality became nil. However, the morbidity of hypocalcaemia and voice change persisted [1]. As surgical techniques were refined and the experience of surgeons increased, this was reduced to less than 1%. The closure of a neck incision was given least importance and resulted in unsightly scars in the neck due to poor placement of incisions and poor suturing techniques (e.g. use of interrupted skin sutures). At this point in time, two developments took place: a group of surgeons adopted an aesthetic way of skin closure which included proper placement of incision in neck creases, and applying minimum traction on skin edges and closure using sub-cuticular absorbable sutures as do plastic surgeons. Another group introduced the evolving endoscopic surgery into the thyroid area thereby taking the incision in the neck to the axilla. Both these methods gave relief to patients who were disturbed due to the scar in their neck.

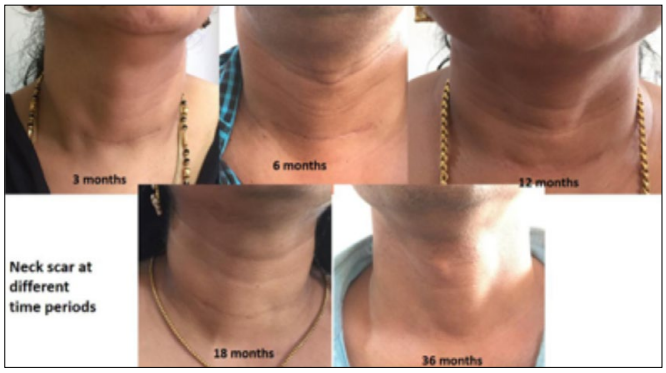


Figure 1. Neck scars at different times during follow-up.

Almost all Indian patients have creases in their neck, unlike the patients from Korea, Japan and Thailand. We have used these skin creases in our patient population who undergo thyroid surgery to mask the neck incision and resultant scar. However, whether this increases the patient satisfaction with their neck scars has not been addressed extensively in various ethnic populations. In this study, we investigated the patient's assessment of their scars and satisfaction using the POSAS and OSAS scale [2]. A number of scales are available for the assessment of scars [3]. POSAS focuses on scar severity from the clinician's and patient's point of view, although items represented in this scale may not adequately express the patient's perceptions and concerns [3]. Scales like the Vancouver scar scale, visual analogue scale and Stony Brook scar evaluation scales lack patient perception, while the latter two are photo-based without patient assessment of the scar [3]. Studies have shown that the POSAS is a reliable and complete scar evaluation tool [2]. With the POSAS, the consistency (internal) of the patient and observer scales appeared to be most acceptable (Cronbach's alpha 0.76 and 0.69 respectively) [2]. It is well known that as time passes scars reduce in thickness and become cosmetically more acceptable. Hence, in our study we applied this scoring system to patients who had conventional neck surgery for thyroid after separating them into subgroups based on duration of follow-up. The scoring was separately applied to the different groups based on duration of follow-up (within 6 weeks, 6 weeks to 6 months and 6 months to 1 year). The scoring was also applied to patients who had long-term follow-up of > 1 year. Since it has also seen that scar healing is better in older subjects, we examined long-term outcomes in patients less than 35 years and more than 35 years of age. A study by Ma et al. [4], looked at scar scores in patients undergoing different types of surgery on the neck. They had excellent outcomes in patients undergoing aesthetic principles access thyroidectomy through the neck. Similarly, the study done by Lang et al. [5] investigated scar outcomes in patients undergoing endoscopic surgeries through the axilla for the thyroid.

Studies have shown that scar maturation takes 6-18 months. Hence, the observation time is critical to judge outcomes of a surgical scar. Many factors influence patient satisfaction regarding their surgical scars. This includes the length, degree of hypertrophy, keloid formation, pigmentation and discomfort [6]. It has been shown that skin and soft tissue damage are produced by high retractor pressure and hence cosmesis is poor [7]. Thus, a small incision may not result is a good cosmetic result. Also, approaching a thyroidectomy through a small incision in the neck leads to a poor surgical field and increased risk of damage to structures like laryngeal nerves and parathyroid, apart from poor cosmesis due to excessive traction [4]. Our study has a large number of patients and we have used a validated scoring system to assess patient satisfaction regarding neck scars. All publications on endoscopic thyroidectomy highlight that a unsightly scar in the neck and patient dissatisfaction as reasons to adopt endoscopic remote access thyroidectomy. In this paper, we share our extensive experience in scar-related satisfaction (which is quite high) and also report that satisfaction improves as over long-term follow-up. Scar satisfaction improvement over longer periods of time has not been published to date.

Conclusions

Conventional thyroidectomy has stood the test of time in terms of safety and adoption of the technique. Scar satisfaction scores are excellent given the fact that the scar is in the anterior visible part of the neck. Scar satisfaction improves further with the longer duration of follow-up.

References

1 Dorairajan N, Pradeep PV. Vignette thyroid surgery: a glimpse into its history. Int Surg 2013;98:70-5. https://doi.org/ 10.9738/CC185.1

2 Draaijers LJ, Tempelman FRH, Yvonne A, et al. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. Plast Reconstr Surg 2004;113:1960-5. https://doi.org/ 10.1097/01.prs.0000122207.28773.5

3 Fearmonti R, Bond J, Erdmann D, et al. A review of scar scales and scar measuring devices. Eplasty 2010;10:354-63.

4 Xiao Ma, Qi-jun Xia, Guojun Li, et al. Aesthetic principles access thyroidectomy produces the best cosmetic outcomes as accessed using the patient and observer scar assessment scale. BMC Cancer 2017;17:654-62. https://doi.org/10.1186/s12885-017-3645-2

5 Lang BH, Wong KP. A comparison of surgical morbidity and scar appearance between Gasless, transaxillary endoscopic thyroidectomy and minimally invasive video assisted thyroidectomy. Ann Surg Oncol 2013;20:646-52. https://doi.org/10.1245/s10434-012-2613-y

6 Toll EC, Loizou P, Davis CR, et al. Scars and satisfaction: do smaller scars improve patient reported outcome? Eur Arch Otorhinolaryngol 2012;269:309-13. https://doi.org/10.1007/s00405-011-1613-z

7 Mow CS, Woolson ST, Ngarmukos SG, et al. .Comparison of scars from total hip replacements done in standard or a mini incision. Clin Orthop Relat Res 2005;441:80-5. https://doi.org/10.1097/01.blo.0000191317.85422.c3

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:43-50; doi: 10.14639/0392-100X-N0848

Rhinology

Definition and management of invasive fungal rhinosinusitis: a single-centre retrospective study

Definizione e gestione della rinosinusite fungina invasiva: uno studio retrospettivo monocentrico

Gian Luca Fadda[1], Federica Martino[1,2], Giacomo Andreani[3], Giovanni Succo[4,5], Maurizio Catalani[6], Stefano Di Girolamo[2], Giovanni Cavallo[1]

[1] Department of Otolaryngology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy; [2] Otorhinolaryngology Unit, Department of Clinical Sciences and Translational Medicine, Tor Vergata University, Rome, Italy; [3] Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy; [4] FPO IRCCS, Head & Neck Oncology Unit, Candiolo Cancer Institute, Turin, Italy; [5] Oncology Dept. University of Turin, Italy; [6] Department of Otolaryngology, Humanitas Cellini, Turin, Italy

SUMMARY

Objectives. The purpose of this study was to correlate acute invasive fungal rhinosinusitis (AIFRS) and chronic invasive fungal rhinosinusitis with underlying diseases, aetiological microorganisms, clinical symptoms, radiological findings, and surgical and medical treatment to determine the subset of patients who require more accurate diagnostic investigation and to prevent irreversible complications.

Methods. This retrospective monocentric study included 17 patients who underwent endoscopic sinus surgery evaluated by paranasal computed tomography and magnetic resonance imaging. Age, sex and symptoms, and location of the invasive fungal infection and the causative fungus were analysed.

Results. In total, 4 patients were affected by the AIFRS form, and 13 by the chronic form. Diabetes mellitus was reported in 41.17% of cases, and haematological diseases in 23.52%. The maxillary sinuses were involved in 47.05% of cases and sphenoidal sinuses in 52.94%; Aspergillus fumigatus was the fungus in 76.47% of cases, and Zygomycetes in 23.53%.

Conclusions. An understanding of the different types of fungal sinusitis and knowledge of their features play a crucial role in reaching prompt diagnosis and initiation of appropriate therapy, which is essential to avoid a protracted or fatal outcome.

KEY WORDS: *Aspergillus, Mucormycosis*, invasive fungal rhinosinusitis, isavuconazole, liposomal amphotericin B

RIASSUNTO

Obiettivi. *Nonostante i progressi in termini di trattamento, la mortalità nei casi di rinosinusite fungina invasiva rimane elevata, pertanto, scopo dello studio è stato correlare le forme acute invasive e quelle croniche con patologie concomitanti, agenti eziologici, i sintomi clinici, radiologia e trattamento, al fine di identificare e trattare i pazienti con prognosi peggiore.*

Metodi. *Il seguente studio retrospettivo monocentrico ha incluso 17 pazienti sottoposti a chirurgia endoscopica sinusale, valutati mediante TC e RM e analizzati per età, sesso, sintomi, sede dell'infezione fungina invasiva e microrganismi eziologici.*

Risultati. *4 pazienti sono risultati affetti dalla forma invasiva acuta,13 pazienti dalla forma cronica. Il diabete mellito è stato riscontrato nel 41,17% dei casi, malattie ematologiche nel 23,52%. I seni mascellari sono risultati coinvolti nel 47,05% dei pazienti e seni sfenoidali nel 52,94%; Aspergillus ha provocato il 76,47% dei casi, Zigomiceti il 23,53%.*

Conclusioni. *Un'adeguata comprensione dei diversi tipi di sinusite fungina e la conoscenza delle loro caratteristiche svolgono un ruolo cruciale ai fini di una diagnosi precoce e l'avvio di una terapia appropriata con lo scopo di ridurne la mortalità.*

PAROLE CHIAVE: *Aspergillus, Mucormycosis, rinosinusite fungina invasiva, Isavuconazolo, amfotericina B liposomiale*

Received: May 12, 2020
Accepted: September 14, 2020

Correspondence
Gian Luca Fadda
Department of Otolaryngology, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Turin, Italy
Tel. +39 011 9026463
E-mail: dott.fadda@gmail.com

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Fadda GL, Martino F, Andreani G, et al. Definition and management of invasive fungal rhinosinusitis: a single-centre retrospective study. Acta Otorhinolaryngol Ital 2021;41:43-50. https://doi.org/10.14639/0392-100X-N0848

Introduction

The concept of invasiveness for a fungal infection refers to the potential for fungal hyphae to invade epithelial tissue with potential neural and vascular involvement [1,2]. We can categorise invasive fungal rhinosinusitis (IFRS) into three subgroups: acute invasive fungal rhinosinusitis (AIFRS), chronic invasive fungal rhinosinusitis and chronic granulomatous invasive fungal rhinosinusitis [3].

Invasive fungal rhinosinusitis (IFRS) generally occurs in immunocompromised patients, i.e. those with haematological malignancies or undergoing chemotherapy or allogeneic haematopoietic transplantation, patients with AIDS, and in poorly controlled diabetic patients undergoing immunosuppressive therapy [4].

Acute invasive fungal rhinosinusitis (AIFRS) is defined by a time course of less than 4 weeks' duration, with predominant vascular invasion. The infection results from rapid spread of fungi from the paranasal sinuses to the adjacent orbits and central nervous system with hyphal invasion of blood vessels, vasculitis with thrombosis, haemorrhage, tissue infarction and acute neutrophilic infiltrates with a necrotising pathological reaction [5].

Chronic IFRS is an indolent infection with a slow destructive process that most commonly affects the ethmoid and sphenoid sinuses, but may involve any paranasal sinus [6,7].

Despite improvements in both medical and surgical therapies, the mortality of patients with IFRS remains high (50-80%) mostly due to invasion of the orbit and intracranial cavity [8,9]; in fact, early and accurate diagnosis is essential because prognosis is often governed by the rapid initiation of antifungal therapy and/or surgical debridement [10].

Therefore, the purpose of this article was to correlate AIFRS and chronic indolent IFRS with underlying diseases, aetiological microorganisms, clinical symptoms, radiological findings, and surgical and medical treatment.

The study aimed to aid clinicians in the decision-making process by systematically assembling previously published evidence and new updates on medical treatment, and to consider the possibility of identifying a subset of patients who require more accurate diagnostic investigation to prevent irreversible complications.

Materials and methods

This single-centre retrospective study included 17 patients affected by IFRS who underwent endoscopic sinus surgery (ESS) at the ENT Department in San Luigi Gonzaga Hospital, Turin, Italy between January 2016 and January 2020. For inclusion, patients were required to have histopathologically confirmed IFRS, defined by the evidence of fungal hyphae in the mucosa of the affected sinus. Patients aged < 18 years, those who had previously received nasal surgery or who had been diagnosed with non-invasive fungal rhinosinusitis were excluded.

Patients' records were analysed retrospectively for presenting symptoms, underlying diseases, causative microorganisms, radiological findings, and medical and surgical treatment. All enrolled patients were evaluated preoperatively with paranasal computed tomography (CT) and magnetic resonance imaging (MRI). In addition, age, sex and symptoms as well as the location of the invasive fungal infection and the causative fungus were analysed for each patient.

Tissue samples were collected for both microbiological and histopathological examination to provide a definitive diagnosis. A mucosal biopsy sample was also collected from the sinus wall and evaluated histologically. A swab sample was taken from purulent sinus secretions and sent to the microbiology laboratory for bacterial culture under both aerobic and anaerobic conditions. When feasible, galactomannan and beta-D-glucan were tested in blood samples. Galactomannan (GM) is a molecule that is present in the cellular walls of *Aspergillus* species and can be secreted extracellularly. Several studies have shown that the determination of GM is beneficial for diagnosis and, together with 1,3-beta-D-glucan (BDG) antigens, can improve the sensitivity of invasive aspergillosis diagnosis [11].

All patients underwent debridement through endoscopic sinus surgery (ESS) under general anaesthesia as the first choice to remove the entire lesion in the sinus using rigid endoscopes (Karl Storz Endoskope, Germany) with a diameter of 4 mm and viewing angles of 0°, 45° and 70°. After surgery, specific medical antifungal treatment was initiated as prescribed by an infectious disease specialist, and in the case of positive cultures indicating bacterial coinfection, the type of antibiotic therapy was determined by antibiogram results. All patients were prospectively followed through endoscopic monitoring performed at intervals of 15, 30, 60, 90 days, 6 months and 1 year after surgery. Using a rigid endoscope, secretions and crusts were removed at the outpatient department and postoperative home treatment included nasal saline irrigation twice a day for at least 3 months. Therapeutic success was clinically and endoscopically defined as patients who were asymptomatic at 6 months after completing the antifungal therapy. Follow-up with MRI was only performed when recurrence was suspected. No patient was lost during the follow-up period. This study was in line with the guidelines of the Helsinki Declaration for ethical consideration. Accordingly, written informed consent was obtained from all patients. Categorical data are presented as frequencies.

Results

The study included 17 patients (8 women and 9 men) affected by IFRS, diagnosed between January 2016 and January 2020. Their median age was 57 years, range: 31-82 years, and the interquartile range (IQR) was 27 ± 14.77 years. In total, 4 patients were affected by the AIFRS form (Tab. I) and 13 patients had the chronic indolent form (Tab. II).

The most common underlying disease was diabetes mellitus reported in 7 cases (41.17%) followed by haematological diseases in 4 cases (23.52%): myelodysplastic syndrome (n = 1), non-Hodgkin lymphoma (n = 1) and acute myeloid leukaemia (n = 2). Furthermore, 5 patients (29.41%) had neutropenia. An autoimmune condition, rheumatoid arthritis, was recognised in 1 case. Another cause of immunodeficiency was steroid therapy, found in 1 patient. Alveolar rhabdomyosarcoma together with chemoradiotherapy and neutropenia were observed in 1 patient. As reported in Tables I and II, several patients showed different associations of these underlying diseases, with different symptoms occurring simultaneously in the same patient.

Facial pain and headache were the most commonly reported presenting signs and symptoms in 12 (70.58%) and 8 (47.05%) patients, respectively; 6 patients had ocular diseases (35.29%): diplopia was observed in 4 patients (23.52%), proptosis in 3 (17.64%) and bilateral amaurosis in 1 case (5.88%). Cranial nerve palsy (VI) was present in 2 patients (11.76%) and trigeminal neuralgia in 1 patient (5.88%). The average time between the onset of symptoms to presentation in the emergency room and the beginning of the diagnostic process was about 2 days for AIFRS and 10 days for the chronic indolent form. No patient had received medical treatment at other healthcare facilities.

CT and MRI were used preoperatively to determine the extent of fungal invasion: 14 (82.35%) patients had unilateral involvement of the paranasal sinuses and one of them (5.88%) also showed the simultaneous involvement of two different sinuses, the maxillary and sphenoid sinus (#4 Tab. II) on the right side. Three patients (17.64%) had bilateral fungal invasion.

Our data also showed involvement of the maxillary sinuses in 8 patients (47.05%) and of the sphenoid sinuses in 9 patients (52.94%); there was simultaneous involvement of both paranasal sinuses in 1 patient (5.88%). The principal radiologic findings with CT and MRI are summarised in Tables III and IV, respectively.

Five patients showed extra-sinus involvement of the fungal disease (29.41%): the cavernous sinus was the site of the most frequent dissemination being present in 5 patients (29.41%), followed by 2 cases (11.76%) with intracranial involvement and 2 cases (11.76%) with thrombosis of the internal carotid artery (ICA) (11.76%). Ocular manifestations were also detected: orbital and optic nerve involvement (n = 2, 11.76%) and VI cranial nerve palsy (n = 4, 23.52%).

All patients underwent endoscopic debridement with endoscopic sinus surgery (ESS) under general anaesthesia, with complete removal of all necrotic tissue. No other surgical procedures were performed. The time from the patient's arrival at the hospital to ESS varied from less than 1 day to 70 days (median: 35 days, IQR: 57.5 days): all AIFRS patients underwent emergency ESS immediately. In the group

Table I. Clinical and radiological features of the 4 patients with AIFRS.

ID sex, age	Underlying diseases	Presenting symptoms and signs	Sinuses involved	Extra sinonasal sites	Fungal species	Microbiologic	Antifungal therapy	F/U
1 M, 57	Acute myeloid leukaemia, Neutropenia	Diplopia cranial nerve palsy (VI), trigeminal neuralgia	SS (r)	Cavernous sinus thrombosis ICA, cerebral fungal infection	Zygo	*Rhizomucor*	L-AmB (74 d) ISC (12 m)	25 m
2 F, 56	Myelodysplastic syndrome Neutropenia	Facial pain proptosis	MS (r)	–	Asper	*Asp. fumigatus*	Vorico (12 m)	23 m
3 F, 53	Non-Hodgkin lymphoma Neutropenia	Diplopia, headache, proptosis, cranial nerve palsy (VI)	SS (r)	Cavernous sinus, VI cranial nerve, thrombosis ICA	Zygo	Neg.	L-AmB (15 d) ISC (9 m)	13 m
4 M, 76	Diabetes mellitus Debilitated	Headache amaurosis bilateral	SS (b)	Cavernous sinus, intracranial involvement, Optic nerve, Orbit	Zygo	*Asp. fumigatus*	L-AmB (3 d)	2 d/D

AIFRS: acute invasive fungal rhinosinusitis; CHT: chemotherapy; MS: maxillary sinus; SS: sphenoid sinus; b: bilateral; l: left; r: right; Asper: Aspergillus; Zygo: Zygomycetes; L-AmB: Liposomal-Amphotericin B; ICA: internal carotid artery; ISC: Isavuconazole; Vorico: Voriconazole; Posa: Posaconazole; m: months; d:days; F/U: follow-up; D: dead; d: day.

Table II. Clinical and radiological features of the 13 patients with chronic IFRS.

ID sex, age	Underlying diseases	Presenting symptoms and signs	Sinuses involved	Extra sinonasal sites	Fungal species	Microbiologic	Antifungal therapy	F/U
1 F, 52	Acute myeloid leukaemia Neutropenia	Facial pain	MS (b)	–	Zygo	Neg.	Vorico (1 m)	52 m
2 M, 65	Diabetes mellitus	Headache	SS (l)	–	Asper	*Penicillium*	Vorico (2 m)	49 m
3 F, 31	Alveolar rhabdomyosarcoma CHT+RT. N	Facial pain	MS (l)	–	Asper	Neg.	Vorico (2 m)	44 m
4 F, 43	Diabetes mellitus	Headache Facial pain	SS + MS (r)	–	Asper	*Asp. fumigatus*	Vorico (2 m)	40 m
5 M, 47	–	Facial pain	MS (r)	–	Asper	*Asp. fumigatus*	Vorico (1 m)	33 m
6 M, 47	Diabetes mellitus	Facial pain	MS (l)	–	Asper	*Asp. fumigatus*	Vorico (3 m)	29 m
7 M, 82	Steroid therapy	Headache, facial pain, diplopia	SS (r)	Cavernous sinus, intracranial involvement V3, Orbit	Asper	Neg.	Vorico (12 m)	16 m/D
8 M, 77	–	Facial pain	MS (l)	–	Asper	Neg.	Vorico (1 m)	14 m
9 F, 59	Diabetes mellitus	Facial pain	MS (l)	–	Asper	Neg.	Vorico (20 d)	14 m
10 F, 53	Rheumatoid arthritis	Headache facial pain	SS (b)	–	Asper	Neg.	Vorico (3 m)	13 m
11 M, 68	Diabetes mellitus	Facial pain	MS (r)	–	Asper	Neg.	Vorico (3 m)	12 m
12 F, 79	Diabetes mellitus	Headache Facial pain Proptosis, diplopia	SS (l)	Cavernous sinus	Asper	*Asp. fumigatus*	L-AmB (1 m), Posa (2 m)	8 m
13 M, 79	–	Headache	SS (l)	–	Asper	*Asp. fumigatus*	Vorico (3m)	4 m

CHT: chemotherapy; RT: radiotherapy; MS: maxillary sinus; SS: sphenoid sinus; b: bilateral; l: left; r: right; Asper: Aspergillus; Zygo: Zygomycetes; L-AmB: Liposomal-Amphotericin B; ISC: Isavuconazole; Vorico: Voriconazole; Posa: Posaconazole; m: months; d: days; F/U: follow-up; D: dead; d: day.

Table III. Radiologic characteristics of IFRS in non-contrast CT scan.

Sinus involved	Calcification	Bony sclerosis	Bone erosion
MS	10 (58.8)	3 (17.6)	3 (17.6)
SS	5 (29.4)	6 (35.3)	4 (23.5)
Total n (%)	15/17 (88.2%)	9/17 (52.9%)	7/17 (41.1%)

IFRS: invasive fungal rhinosinusitis; MS: maxillary sinus; SS: sphenoid sinus.

with the chronic indolent form, the delay to surgery in 1 patient (#13) was linked to the onset of concomitant diseases which required further investigations by other specialists and, consequently, postponed the anaesthesiologic eligibility for surgery.

Bilateral nasal packing was performed in each patient and was removed 48 hours after surgery. No intraoperative complications occurred (Figs. 1-3).

Histological examination confirmed the invasive fungal disease in all cases: *Aspergillus* was detected in 13 patients (76.47%) (1 patient in the AIFRS group and 12 patients in the group with the chronic form), and Zygomycetes was detected in 4 patients (23.52%): the intraoperative view showed typical friable cheesy-like yellow to brown material in sinus cavities, confirming the fungal aetiology of the disease already diagnosed macroscopically.

Table IV. Radiologic findings of IFRS in MRI.

	Signal intensity			Extra-sinonasal involvement				
Sinus involved	T1WI iso/ hypointense	T2 WI markedly hypointense	Peripheral enhancement	Cavernous sinus	Intracranial	Perineural spread	Orbital	Thrombosis ICA
MS	7 (41.1)	7 (41.1)	2 (11.7)	-	-	-	-	-
SS	9 (52.9)	9 (52.9)	3 (17.7)	5 (29.4)	2 (11.7)	4	2 (11.7)	2 (11.7)
Total n (%)	16/17 (94%)	16/17 (94%)	5/17 (29.4%)	5/17 (29.4%)	2/17 (11.7%)	4/17 (23.5%)	2/17 (11.7%)	2/17 (11.7%)

IFRS: invasive fungal rhinosinusitis; MS: maxillary sinus; SS: sphenoid sinus; ICA: internal carotid artery.

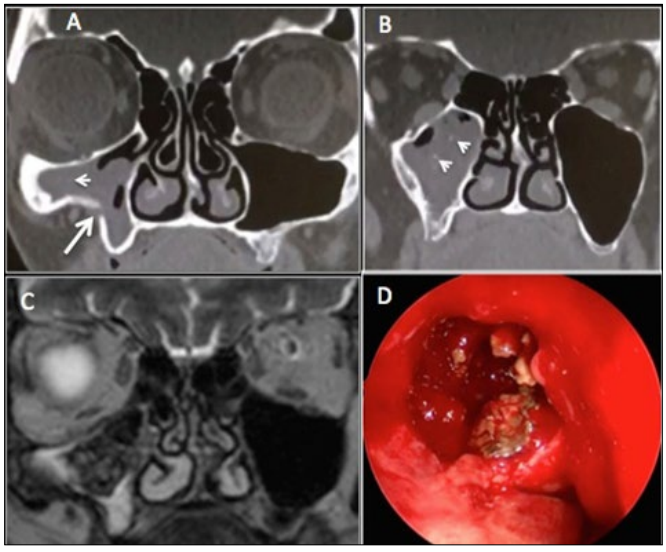


Figure 1. Patient #2 in the AIFRS group – (A, B) Coronal CT scan shows an opacity of the right maxillary sinus (MS) with associated multiple foci of microcalcifications (white arrowhead) and sclerosis of the MS walls by reactive osteitis. Focal interruption (white arrow) of the lateral wall is also present. (C) Coronal T2-MRI shows marked hypointense signal with areas of hyperintense signal in the lateral and inferior recess of the MS. (D) Intraoperative view showing typical friable cheesy-like yellow to brown material on the floor of the maxillary sinus.

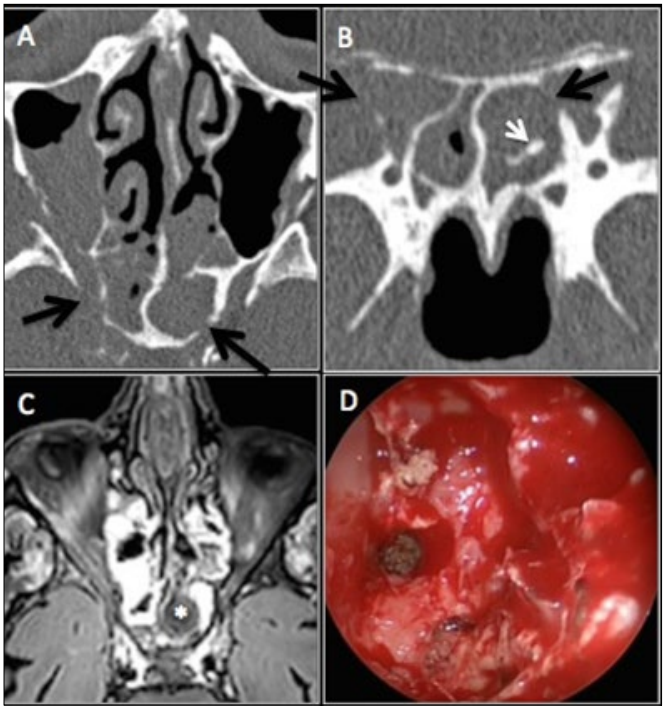


Figura 2. Patient #4 in the AIFRS group – Axial (A) and coronal (B) CT scans display heterogeneous opacity of the sphenoid sinuses (SS) with associated microcalcification (white arrowhead), thickening and sclerosis of the bone surrounding the SS, and multiple interruptions of its bony wall (black arrow). (C) Axial gadolinium-enhanced T1-weighted MRI demonstrates a marked hypointense signal (asterisk) in the left SS with inflamed mucosa at the periphery. (D) Endoscopic removal of fungal concretion after opening the anterior wall of the left SS.

Microbiological analysis was also performed: *Aspergillus fumigatus* was isolated in 7 patients (41.17%), *Rhizomucor* in 1 (5.88%), and *Penicillium* in 1 case (5.88%). The causative microorganism could not be determined in 8 patients (47.05%).

Bacterial co-infections occurred in 6 patients (35.29%) and were most frequently caused by *Staphylococcus* species and *Pseudomonas aeruginosa* (11.76%), followed by one case of *Streptococcus pyogenes* (5.88%), one case of *Actinomyces* (5.88%) and one of *Haemofilus influenzae* (5.88%).

All patients promptly started systemic antimycotic treatment. Voriconazole was administered to 13 patients (76.47%); the 200 mg bid intravenous formulation was preferred initially and was switched to an oral formulation when possible, on average after a period of 3.41 months (range = 20 days-12 months, median = 2 months, IQR = 2); 4 patients (23.52%) were treated with liposomal amphotericin B (L-AmB) (range = 3 days-12 months, median = 0.74 months, IQR = 1.88) with dosages from 3 to 10 mg/kg/day; in 3 selected cases, isavuconazole with a dosage of 200 mg/day in intravenous or oral formulation or posaconazole at 300 mg/day were also used in association. In total, 15 patients are still in follow-up with a mean

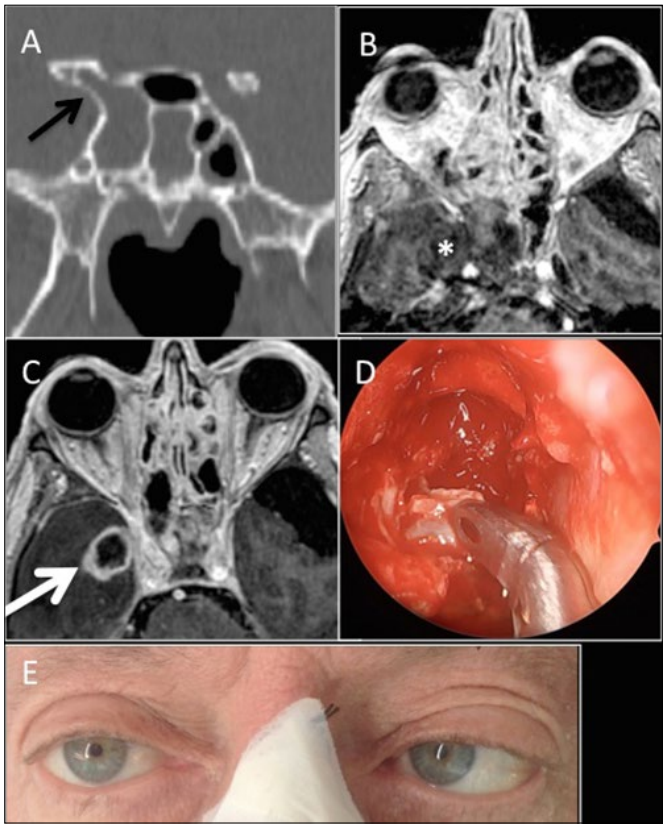


Figura 3. Patient #1 in the AIFRS group – (A) Coronal CT scan showing complete opacification of the right sphenoid sinus with optical right nerve canal wall erosion (black arrows). (B) Axial MRI with contrast shows a hypointense signal in a large space-occupying lesion in the right SS extending into the right cavernous sinus (asterisk). The cavernous carotid artery appears unobstructed. (C) Endocranial mycotic abscess (white arrow) with inflamed mucosa within Meckel's cave on the right at periphery at day 41. (D) Intraoperative view during endoscopic sinus surgery in the right SS. (E) Absence of motility of the right eye in lateral gaze related to the deficit of the right lateral rectus muscle for abducens nerve palsy.

duration of 20.12 months (range = 0.06-58 months; median = 16 months, IQR = 24), 2 patients died (11.76%), 1 patient from cerebral ischaemia and the other from uncontrolled rhinocerebral infection.

Only one relapse was observed with persistence of fungal pathology in the sphenoidal sinus, requiring revision surgery at 6 months and with a histological diagnosis of *Aspergillus*.

Discussion

A diagnosis of IFRS requires histopathologic evidence of fungi invading nasal tissue, characterised by a dense accumulation of hyphae, the occasional presence of vascular invasion and a diffuse inflammatory reaction [12].

Acute IFRS is characterised by a rapid evolution and is associated with a high mortality rate that can reach 100% in cases of intracranial mycotic dissemination: Zygomycetes (*Rhizopus*, *Mucor*, *Rhizomucor*) and species of *Aspergillus* are the most common aetiologic agents in the sinonasal cavity, with more frequent neurovascular and orbital invasion [13]. CT scans show homogeneous opacification of the sinus with calcification, adjacent bone erosion, dehiscence of the lateral sphenoid's recess with signs of remodeling in the wall of the sphenoid sinus, especially in immunocompromised patients [14]. Signal intensity was evaluated using MRI, and was grouped into three categories: slightly T1-weighted iso- or hypointense, markedly T2-weighted hypointense (near signal void), and peripheral enhancement of the surrounding mucosa. On MRI, orbital and intracranial involvement were present as suggested findings, together with perineural spread and expansion outside the confines of the sinonasal cavity with cavernous sinus involvement or thrombosis of the ICA, and have been reported previously [15].

Clinical suspicion of AIFRS should be raised in the immunocompromised patient presenting with new-onset, rapidly progressive sinusitis or facial discomfort [16].

In our experience, symptomatology in AIFRS patients was very evident when a sphenoidal localisation was present (proptosis, diplopia, cranial nerve palsy (VI), trigeminal neuralgia, or visual abnormalities) because of a connection between the sphenoidal sinus and anatomic structures such as the ICA, cavernous sinus, optic nerve, eyehole, or brain [17]. Therefore, thanks to the rapidity of onset, patients with AIFRS came immediately to our clinic, and we performed an emergency surgical intervention thereby preventing serious cerebral and ocular complications. On the other hand, patients with the chronic indolent form showed nonspecific and slowly progressive signs and symptoms that did not arouse suspicion in the patient, delaying access to the emergency room and consequently, to the diagnostic and therapeutic process.

As reported in a review of over 800 patients by Turner et al., *Aspergillus* spp. and *Mucor* spp. can both be found in neutropenic patients and in those with chronic systemic steroid treatment, whereas *Mucor* spp. has a propensity for diabetic and iron-overloaded patients [18].

Neutropenia plays a key role as a factor contributing to the development of infection in patients with haematological disease. In the present study, 29.41% of patients were affected by a severe neutropenic state, defined as a neutrophil count < 500/mmc [19], and 23.52% of patients had an underlying haematological disease, such as non-Hodgkin lymphoma, myelodysplastic syndrome or acute myeloid leukemia. Other underlying conditions included poorly controlled DM, immunosuppressive treatment and corticosteroid exposure [20].

Our data show a significant proportion of patients infected by *Aspergillus fumigatus* in the chronic indolent group (92.30%) and only one patient was affected (pt#1) by Zygomycetes (7.70%). Conversely, in AIFRS patients, Zygomycetes were the fungi mainly responsible for the infection and only in one patient (#2) was *Aspergillus fumigatus* isolated.

In line with the results obtained in our previous study [21], it is still unclear why the microbiological evidence for fungal disease was negative in 8 cases, although the radiologic and endoscopic intraoperative findings were strongly indicative of IFRS.

Treatment for both groups was based on a combination of antifungal therapy, reversal of immunocompromising factors, surgical debridement through ESS when possible and obtaining material for histopathological and cultural examinations [22].

Vaughan et al. analysed 37 mucormycosis cases and found no significant difference in survival between patients having surgery 1-30 days after diagnosis [23]. These data agree with our study, with an onset of treatment on average 32.41 days after diagnosis, highlighting why the start of treatment should be initiated as soon as IFRS is diagnosed.

For an early surgical approach, the correct medical therapy must be promptly selected based on the fungal pathogen affecting the patient: we can generalise that the current mainstay of therapy for IFRS is L-AmB (recommended dosage from 3 to 10 mg/kg per day) [24]. For invasive aspergillosis, treatment with voriconazole is recommended primarily for patients with cranial nerve involvement. Alternatively, isavuconazole, a second generation triazole, has been shown to be as effective as voriconazole and better tolerated. For mucormycosis IFRS treatment, L-AmB and posaconazole are the most recommended drugs, together with isavuconazole which can be administered in patients in whom amphotericin B cannot be administered because of intolerance or in the case of kidney disease. Combination therapy with two drugs has been reported. In the current study, 76.47% of our patients were treated with voriconazole, showing fewer systemic side effects than L-AmB, a favourable bone penetration and good tolerance as maintenance therapy.

Isavuconazole is an innovative and effective therapeutic option with a very high oral bioavailability (98%), a good profile of tolerability and efficacy and a low risk of interactions with other drugs [25]. However, further studies are needed to better integrate isavuconazole in the management of patients with IFRS, with the aim to define a clear correlation between plasma levels and efficacy end points and to identify the best therapeutic window in which to administer it.

Due to the relative rarity of AIFRS, our data was limited to acute and chronic indolent IFRS, and unfortunately did not include granulomatous forms, thus precluding larger cohort studies. The results are dependent on the quality of the limited data available, but are in line with the current literature. Moreover, our study focused on differentiating acute and chronic indolent forms, which was not always easy to recognise with certainty in previous studies, so as to guide the most appropriate diagnostic and therapeutic process.

Conclusions

Invasive fungal rhinosinusitis is a difficult infection to diagnose and treat. Early diagnosis is the key to managing IFRS successfully, and with a systematic approach, it is possible to improve survival, taking into account the context of the temporal course of the diagnostic work-up and treatment. The goal is diagnosis of the disease at an earlier stage while it is confined to the sinonasal cavities before mucosal dissemination. A multidisciplinary approach consisting of antifungal therapy, surgical debridement, and reversal of predisposing conditions is the best therapy to improve survival.

References

1. Ergun O, Tahir E, Kuscu CO, et al. Acute invasive fungal rhinosinusitis: Presentation of 19 cases, review of the literature and a new classification system. J Oral Maxillofac Surg 2016;75:767.e1-e9. https://doi.org/10.1016/j.joms.2016.11.004
2. Montone KT. Pathology of fungal rhinosinusitis: a review. Head Neck Pathol 2016;10:40-6. https://doi.org/10.1007/s12105-016-0690-0
3. Deutsch PG, Whittaker J, Prasad S. Invasive and non-invasive fungal rhinosinusitis – a review and update of the evidence. Medicina (Kaunas) 2019;55:319. https://doi.org/10.3390/medicina55070319
4. Trief D, Gray ST, Jakobie C, et al. Invasive fungal disease of the sinus and orbit: a comparison between mucormycosis and Aspergillus. J Ophthalmol 2016;100:184-8. https://doi.org/10.1136/bjophthalmol-2015-306945
5. Duggal P, Wise SK. Invasive fungal rhinosinusitis. Am J Rhinol Allergy 2013;27(Suppl 1):S28-30. https://doi.org/10.2500/ajra.2013.27.3892
6. Zuniga MG, Turner JK. Treatment outcomes in acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg 2014;22:242-8. https://doi.org/10.1097/MOO.0000000000000048
7. Shanbag R, Rajan NR, Kumar A. Acute invasive fungal rhinosinusitis: our 2-year experience and outcome analysis. Eur Arch Otorhinolaryngol 2019;276:1081-7. https://doi.org/10.1007/s00405-019-05288-w
8. Chang C, Gershwin ME, Thompson III GR. Fungal disease of the nose and sinuses: an updated overview. Curr Allergy Asthma Rep 2013;13:152-61. https://doi.org/10.1007/s11882-012-0320-1
9. Kovanda LL, Marty FM, Maertens J, et al. Impact of mucositis on absorption and systemic drug exposure of isavuconazole. Antimicrob Agents Chemother 2017;61:e00101-17. https://doi.org/10.1128/AAC.00101 17.2017
10. Thompson GR, Patterson TF. Fungal disease of the nose and paranasal sinuses. J Allergy Clin Immunol 2012;129:321-6. https://doi.org/10.1016/j.jaci.2011.11.039

[11] Bölük G, Kazak E, Özkalemkaş F, et al. Comparison of galactomannan, beta-D-glucan, and Aspergillus DNA in sera of high-risk adult patients with hematological malignancies for the diagnosis of invasive aspergillosis. Turk J Med Sci 2016;46:335-42.

[12] Pagella F, Matti E, De Bernardi F, et al. Paranasal sinus fungus ball: diagnosis and management. Mycoses 2007;50:451-6. https://doi.org/10.1111/j.1439-0507.2007.01416.x

[13] Craig JR. Updates in management of acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg 2019;27:29-36. https://doi.org/10.1097/MOO.0000000000000507

[14] Groppo ER, El-Sayed IH, Aiken AH, et al. Computed tomography and magnetic resonance imaging characteristics of acute invasive fungal sinusitis. Arch Otolaryngol Head Neck Surg 2011;137:1005-10. https://doi.org/10.1001/archoto.2011.170

[15] Mossa-Basha M, Ilica AT, Maluf F, et al. The many faces of fungal disease of the paranasal sinuses: CT and MRI findings. Diagn Interv Radiol 2013;19:195-200. https://doi.org/10.5152/dir.2012.003

[16] Silveira MLC, Anselmo-Lima WT, Faria FM, et al. Impact of early detection of acute invasive fungal rhinosinusitis in immunocompromised patients. BMC Infect Dis 2019;19:310. https://doi.org/10.1186/s12879-019-3938-y

[17] Fadda GL, D'Eramo A, Grosso A, et al. Isolated sphenoid sinus inflammatory disease – a report of 14 cases. Iran J Otorhinolaryngol 2020;32:101-7. https://doi.org/10.22038/ijorl.2019.39416.2304

[18] Turner JH, Soudry E, Nayak JV, et al. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence. Laryngoscope 2013;123:1112-8. https://doi.org/10.1002/lary.23912

[19] Zappasodi P, Rossi M, Castagnola C, et al. Resolution of invasive fungal sinusitis in immunocompromised patients: neutrophil count is crucial beside a combined medical and surgical approach. Ann Hematol 2010;89:737-9. https://doi.org/10.1007/s00277-009-0854-z

[20] Di Girolamo S, Mazzone S, Di Mauro R, et al. Surgical management of rhinosinusitis in onco-hematological patients. Clin Exp Otorhinolaryngol 2014;7:302-6. https://doi.org/10.3342/ceo.2014.7.4.302

[21] Fadda GL, Succo G, Moretto P, et al. Endoscopic endonasal surgery for sinus fungus balls: clinical, radiological, histopathological, and microbiological analysis of 40 cases and review of the literature. Iran J Otorhinolaryngol 2019;31:35-44.

[22] Fadda GL, D'Eramo A, Gned D, et al. An unusual case of complicated rhinosinusitis of the sphenoid sinus involving the cavernous sinus and skull base: endoscopic sinus surgery and medical therapy. SAGE Open Med Case Rep 2019 May 26;7:2050313X19852885. https://doi.org/10.1177/2050313X19852885

[23] Vaughan C, Bartolo A, Vallabh A, et al. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis – has anything changed in the past 20 years. Clin Otolaryngol 2018;43:1454-64. https://doi.org/10.1111/coa.13175

[24] Debbarma S, Gupta R, Patro SK, et al. Randomised comparison of safety profile and short-term response of itraconazole, voriconazole and amphotericin b in the management of chronic invasive fungal rhinosinusitis. Indian J Otolaryngol Head Neck Surg 2019;71(Suppl 3):2165-75. https://doi.org/10.1007/s12070-019-01602-4

[25] Andreani G, Fadda GL, Gned D, et al. Rhino-orbital-cerebral mucormycosis after allogeneic hematopoietic stem cell transplantation and isavuconazole therapeutic drug monitoring during intestinal graft versus host disease. Mediterr J Hematol Infect Dis 2019;11:e2019061. https://doi.org/10.4084/MJHID.2019.06

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:51-58; doi: 10.14639/0392-100X-N0920

Rhinology

A clinical and histopathological comparison of saline, adrenaline and 2-mercaptoethanesulfonate (MESNA) in mucoperichondrial elevation: which is superior?

Studio comparativo istopatologico e clinico nello scollamento mucopericondrale mediante infiltrazione di soluzione salina, mercaptoetanesuflonato (MESNA): quale tecnica è migliore?

Zehra Çınar[1], Özgür Yiğit[1], Fulya Savran Turanoğlu[1], Sevim Baykal Koca[2]

[1] *Department of Otorhinolaryngology-Head and Neck Surgery, Istanbul Training and Research Hospital, Istanbul, Turkey;*
[2] *Department of Pathology, Istanbul Training and Research Hospital, Istanbul, Turkey*

SUMMARY

Objective. To determine whether submucosal mesna (2-mercaptoethane sodium sulfonate) infiltration is superior to normal saline or adrenaline + lidocaine in mucoperichondrial hydrodissection.

Methods. Twenty-one rabbits were administered adrenaline + lidocaine, saline or mesna. Bilateral septal mucoperichondrial flap elevations were performed following submucosal infiltration. The intraoperative bleeding amount, operation time, accessibility of the surgical plane, field quality and degree of mucoperichondrial injury were recorded. The three groups were compared histopathologically.

Results. The amount of bleeding and duration of the operation were significantly higher and the accessibility of the surgical plane score was significantly lower in the saline group vs. the other groups ($p < 0.05$). The mucosal damage rate was significantly higher in the saline group compared with adrenaline + lidocaine ($p < 0.05$). The surgical field quality was significantly lower in the saline group compared with adrenaline + lidocaine ($p < 0.05$). The accessibility of the correct surgical plane score was significantly lower in the saline group compared with the adrenaline + lidocaine and mesna groups ($p < 0.05$). The amount of bleeding, duration of operation, surgical field quality and accessibility of the surgical plane did not differ significantly between the adrenaline + lidocaine and mesna groups ($p > 0.05$). The pericondrium thickness was significantly lower in the saline group than the other groups. Cartilage thickness was significantly higher in the saline group compared with the mesna group ($p > 0.05$).

Conclusion. Use of mesna instead of normal saline or adrenaline + lidocaine in septoplasty was not more advantageous in terms of intraoperative parameters. The adrenaline + lidocaine group was superior to normal saline for all intraoperative parameters. In conclusion, the use of adrenaline may be more advantageous in facilitating septal mucoperichondrium elevation due to its widespread use, low cost and superiority to physiological saline.

KEY WORDS: adrenaline, mesna, saline, septoplasty, mucoperichondrial flap elevation

RIASSUNTO

Obiettivo. *Determinare se l'infiltrazione sottomucosa di mesna (2-mercaptoetano sodico solfonato) è superiore nell'idrodissezione mucopericondriale.*

Metodi. *Ventuno conigli sono stati divisi in due gruppi a seconda del trattamento: adrenalina + lidocaina, soluzione salina e mesna. Sono stati eseguiti scollamenti mucopericondriali del setto per infiltrazione sottomucosa. Sono stati registrati la quantità di sanguinamento intraoperatorio, il tempo dell'intervento, l'accessibilità del piano chirurgico, la qualità del campo operatorio e il grado di lesione mucopericondriale. Questi tre gruppi sono stati confrontati istopatologicamente.*

Risultati. *La quantità di sanguinamento e la durata dell'operazione erano significativamente più alte, tuttavia l'accessibilità del piano chirurgico era significativamente inferiore*

Received: June 13, 2020
Accepted: October 1, 2020

Correspondence
Zehra Çınar
Istanbul Training and Research Hospital, Department of Otorhinolaryngology & Head and Neck Surgery, Kasap İlyas Mah., Org. Abdurrahman Nafiz Gürman Cd., 34098 Fatih/İstanbul, Turkey
Tel. +90 212 459 60 00. Fax +90 212 459 61 45
E-mail: drzehradonmez@hotmail.com

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Çınar Z, Yiğit O, Savran Turanoğlu F, et al. A clinical and histopathological comparison of saline, adrenaline and 2-mercaptoethanesulfonate (MESNA) in mucoperichondrial elevation: which ıs superior? Acta Otorhinolaryngol Ital 2021;41:51-58. https://doi.org/10.14639/0392-100X-N0920

nel gruppo trattato con soluzione salina rispetto agli altri gruppi (p < 0,05). Il tasso di lesione della mucosa era significativamente più alto nel gruppo trattato con soluzione salina rispetto al gruppo adrenalina + lidocaina (p < 0,05). La qualità del campo chirurgico era significativamente inferiore nel gruppo trattato con soluzione salina rispetto al gruppo adrenalina + lidocaina (p < 0,05). L'accessibilità del piano chirurgico era significativamente inferiore nel gruppo con soluzione salina rispetto ai gruppi adrenalina + lidocaina e mesna (p < 0,05). La quantità di sanguinamento, la durata dell'intervento, la qualità del campo chirurgico e l'accessibilità al piano chirurgico non differivano significativamente tra i gruppi adrenalina + lidocaina e mesna (p < 0,05). Lo spessore del pericondrio era significativamente inferiore nel gruppo salino rispetto agli altri gruppi. Lo spessore della cartilagine era significativamente più alto nel gruppo salina rispetto al gruppo mesna (p < 0,05).
Conclusione. *L'uso di mesna al posto della normale combinazione di soluzione fisiologica o lidocaina e adrenalina nella settoplastica non è risultato più vantaggioso in termini di parametri intraoperatori. Il gruppo trattato con lidocaina e adrenalina è risultato superiore rispetto al trattamento con soluzione salina normale in termini di tutti i parametri intraoperatori. In conclusione, l'uso dell'adrenalina può essere più vantaggioso nel facilitare l'elevazione del mucopericondrio settale a causa del suo uso diffuso, del basso costo e della superiorità alla soluzione salina fisiologica.*

PAROLE CHIAVE: *adrenalina, mesna, soluzione salina, settoplastica, elevazione del lembo mucopericondriale*

Introduction

Nasal airway obstruction is a common complaint in otorhinolaryngology and has been described as a source of significant patient discomfort and financial burden [1]. Diagnosis of nasal obstruction includes symptom assessment via the Nasal Obstruction Symptom Evaluation (NOSE) instrument and physical exam of the septum and the other nasal anatomical subunits [2]. Nasal obstruction is associated with anatomical as well as mucosal conditions. The most frequent anatomical cause is a deviated nasal septum, which can be accompanied by hypertrophy of the turbinate contralateral to the deviation [2,3]. Although the actual prevalence of nasal septal deviation is not known, one study reported a prevalence of 90% [4]. Septoplasty, i.e., surgical correction of the deviated nasal septum, is the most common ENT-operation in adults [5]. Indications for septoplasty are practice-based rather than evidence-based, and internationally accepted guidelines are lacking [6]. Septoplasty (with or without concurrent turbinate surgery) is performed to widen nasal passages and improve nasal airflow [7].

Mucoperichondrial flap elevation is the first step of septoplasty and is used to lessen the amount of bleeding, obtain better vision of the surgical area, shorten the operation time and minimise mucosal damage [8,9].

Prior to mucoperichondrial flap elevation, vasoconstrictor agents combined with local anaesthetics are frequently used to reduce bleeding and increase the surgical field of view in nasal surgeries. Using increasing pressure, this hydrodissection technique aims to dissect the perichondrium from the nasal septum [10,11]. There are also studies where only saline has been applied for hydrodissection [12]. In these studies, it was concluded that vasoconstrictor agents were not superior to saline in terms of intraoperative parameters.

Mesna, which is the sulphur salt of 2-mercaptoethanolsulphamic acid, received a patent for 'chemical assisted dissection' and enables de-adhesion between pathological and healthy tissues, thus facilitating healthy tissues in dissociating from the surrounding tissues. Therefore, numerous surgical branches, from otolaryngology to gynaecology and orthopaedics, use mesna for intraoperative chemical dissection [13,14].

The effectiveness of mesna in facilitating dissection of the cholesteatoma matrix from surrounding tissues has been demonstrated [15]. It has been reported that mesna facilitates elevation of the tympanic membrane in atelectatic ears and adhesive otitis media [16]. It is also known to be used in acoustic neuroma, glomus tumour, meningioma and all other skull base tumours because it facilitates finding the right surgical plan between solid tissue and tumour tissue [14].

In severe septum deviations, mucoperichondrium elevation cannot always be as successful as expected. This situation increases the possibility of complications, such as septal mucoperichondrial perforation and need for revision surgery. The earlier we perform the elevation of the mucoperichondrium, which is the first stage of septoplasty, the easier we can perform surgery in conditions where bleeding and mucoperichondrial perforation are minimal: the rate of complications decreases and surgical success increases. In patients with traumatic septal deviation in whom mucoperichondrium elevation is expected to be difficult, we theorised that mesna could facilitate mucoperichondrium elevation, which is the first step of septoplasty.

Because vasoconstrictor agents and saline do not provide satisfactory outcomes regarding intraoperative parameters, we hypothesised that mesna would be superior to adrenaline and saline regarding the facilitation of the septal mucoperichondrial flap elevation. For this purpose, submucosal mesna infiltration was compared with submucosal saline and adrenaline in terms of intraoperative parameters and histopathological findings.

Materials and methods

Study design

Twenty-one adult female albino New Zealand rabbits (3000-4500 g, mean 3500 g) were equally divided into

three groups as follows: adrenaline + lidocaine (Jetokain 2 ml, Adeka İlaç, Istanbul, Turkey), physiological saline and mesna (Uromitexan 400 mg, Eczacıbaşı, Baxter İlaç, Istanbul, Turkey).

The study was approved by the Local Animal Ethics Committee of the Bezmi Alem Foundation University (Animal Care and Use) (2016/291). All applicable international, national and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted. The protocol was blinded to the investigators performing the procedure. The same surgeon performed the operations, and each group underwent surgery on different days. For general anaesthesia, 40 mg/kg phenobarbital and 5 mg/kg xylazine were used. Afterwards, by using dental injectors and being assisted by the original 10th magnification of the dissection microscope (Imaging source, DFK 31AU03, Germany), adrenaline + lidocaine (total amount 0.5 ml; the dose of lidocaine and adrenaline that 20 mg/ml and 0.0125 mg/ml respectively), saline (total amount 0.5 ml) and mesna (total amount 0.5 ml), for the first, second and third group, respectively, were injected at multiple sides bilaterally through the anterior and posterior septal submucosal regions.

The open rhinoplasty technique was used to access the septum of rabbits (Fig. 1a). Microsurgical scissors were used to determine the caudal end of the nasal septum, which was accessed with a sharp dissection starting from the columellar region. Mucoperichondrial flap elevation was performed on both sides of the nasal septum using a blunt-tipped elevator. The surgical plane was advanced up to the nasal septal bone in the posterior region.

Maximum precautions were applied to prevent any possible trauma from affecting the septal cartilage. Following flap elevation, the flap was laid on the septal cartilage using the miniature Doyle splint (Fig. 1b). Doyle splints were placed bilaterally to reattach the mucoperichondrium onto the septal cartilage and were removed 48 hours later. The learning curve needed to be overcome. In each group, the operation duration was shortened after the first case.

The intraoperative evaluation criteria of this study were determined by refering to the study of Gungor V. et al. [11]. During the operation, five parameters were recorded in all three groups: intraoperative septal mucoperichondrial injury, amount of bleeding, operation duration, surgical site quality and accessibility to the correct surgical plane. Septal mucoperichondrial injuries were defined as simple or severe. Unilateral septal mucoperichondrial tear without any mucosal loss was accepted as simple damage. Unilateral damage revealing the cartilage because of loss of mucoperichondrium and bilateral mucoperichondrial damage were considered serious injuries. The same surgeon rated the surgical site quality and accessibility of the correct surgical plane from 1 to 5. Regarding the surgical site quality, 1 was considered very poor (not suitable for a comfortable operation) and 5 was considered excellent (suitable for a comfortable operation). A surgical site quality of 5 means that there is no mucoperichondrial damage and bilateral septal mucoperichondrial tunnels are opened without any difficulty. Technically, a much more comfortable surgery is performed. A surgical site quality of 1 means that there is difficulty in opening bilateral submucoperichondrial tunnels due to multiple or severe mucoperichondrial damage and perforation, and therefore may cause interruption of intervention to the septal cartilage safely. Regarding the accessibility of the correct surgical plane, 1 was considered to be very poor (very difficult to find a convenient surgical

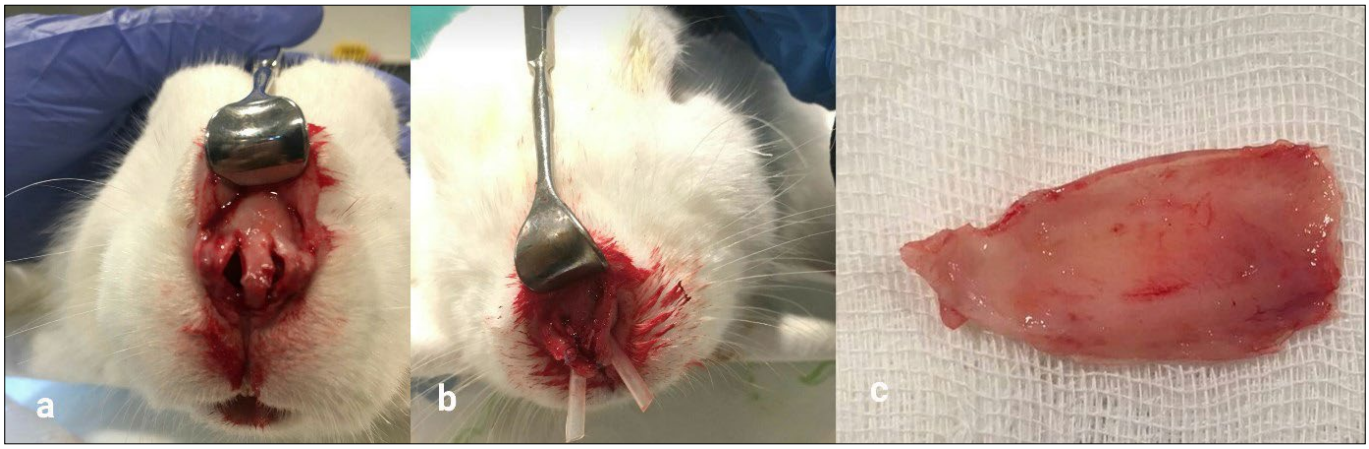


Figure 1. (**A, B**) An open septoplasty technique was used to reach the nasal septum in the rabbits. (**C**) Totally removed septal cartilage.

plane), and 5 was considered excellent (not hard to find a convenient surgical plane).
4.0 vicryl (Ethicon Inc., Somerville, NJ) was used to close the initial skin incision. Procaine penicillin (40,000 IU) was administered intramuscularly (IM) for 3 days for infection prophylaxis. Six weeks after the operation, the animals were sacrificed using 500 mg/g intracardiac phenobarbital following sedation with 40 mg/kg 1M phenobarbital. The nasal tip was incised through the frontonasal suture line through the midline of the nasal dorsum. The nasal bone was cut using bone scissors, the septal cartilage was incised along the nasal base, the septum was separated from all the insertion points, and the bloc was removed (Fig. 1c). Specimens were fixed in 10% neutral buffered formol solution and sent for histopathological examination.

Histopathologic study

Specimens were fixed in 10% buffered neutral formaldehyde solution for 24 hours. Following fixation, nasal septums were sliced in parallel fashion along the long axis. Sliced tissues were placed in follow-up cassettes and embedded in paraffin blocks following a routine 16-hour tissue follow-up process. After follow-up, tissues were sectioned with a microtome into 3 mm sections, which were then stained with haematoxylin-eosin (H&E) for microscopic examination. Microscopic evaluations were preformed using a binocular microscope (Olympus, BX53, Olympus Corp., Tokyo, Japan). All specimens were evaluated by the same pathologist (SBK).
The severity of inflammation in septum samples (0 = no change, 1 = mild, 2 = moderate, 3 = severe), localisation of the inflammation (E = epithelium, ES = epithelium and submucosa, ESC = epithelium, submucosa and cartilage), presence of mucosal erosion and ulceration (0 = none, 1 = visible), presence of foreign body reaction (0 = none, 1 = visible), chondrocyte necrosis and density (1-5% = 1, 6-25% = 2, 26-50% = 3, 51-100% = 4), mucosal, perichondrium and cartilage thicknesses were evaluated.
The severity of inflammation was scored as mild when a small number of inflammatory cells infiltrated the nasal septum epithelium only (Fig. 2), as moderate when more severe inflammatory cells infiltrated the epithelium and submucosa (Fig. 3) and severe when abundant inflammatory cells infiltrated septal cartilage and mucosa in full thickness (Fig. 4).
Mucosal, perichondrial and cartilage thicknesses were measured at 400x magnification using a linear micrometer (Eyepiece Graticule, Olympus Corp.). The other parameters as severity of inflammation, mucosal erosion and ulceration, chondrocyte necrosis (Fig. 5) and foreign body reaction were evaluated semi-quantitatively.

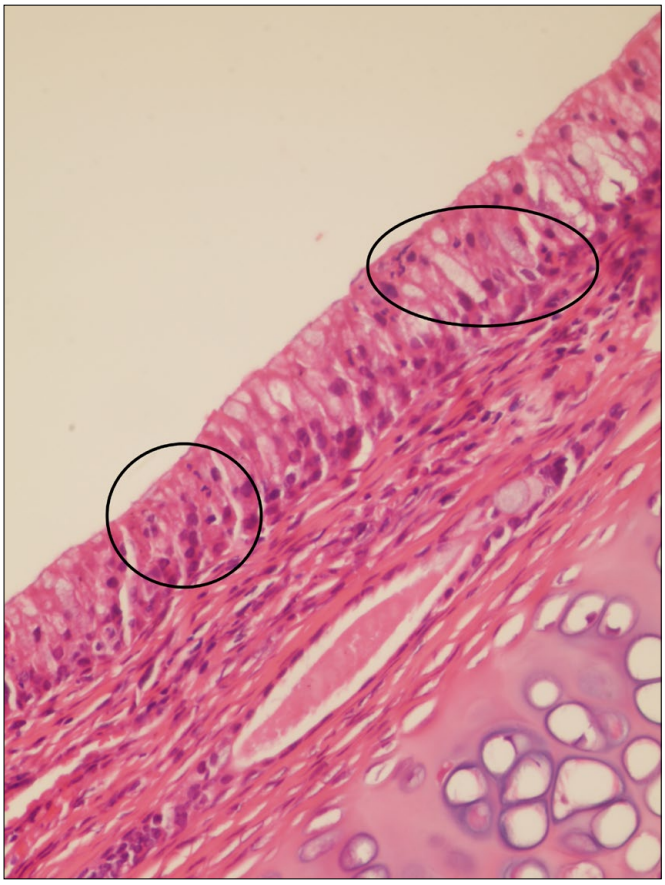


Figure 2. Inflammation limited to the mucosae (circle), Light microscopy, H-E X400. (H-E: Haematoxylin-Eosin).

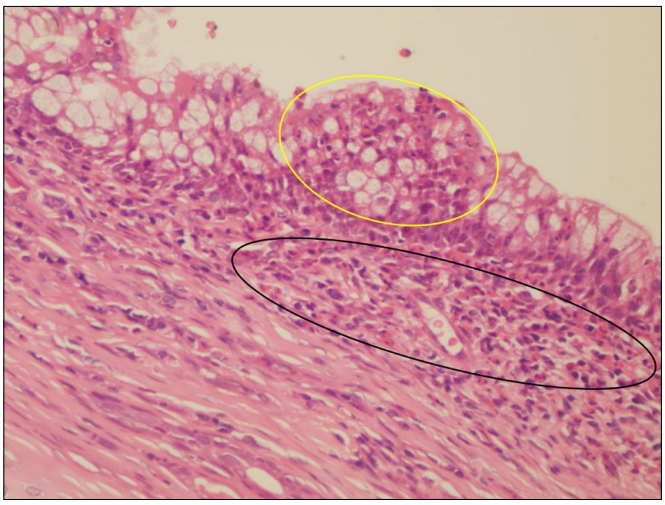


Figure 3. Severe inflammation in the mucosae (yellow circle) reached the submucosae (black circle), Light microscopy, H-E X400. (H-E: Haematoxylin-Eosin).

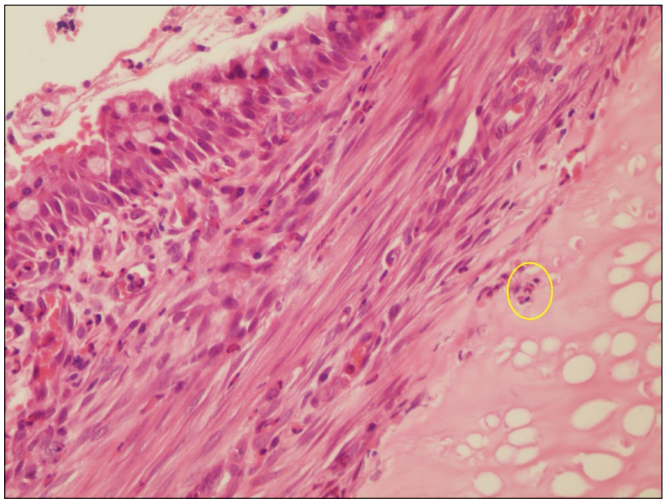


Figure 4. Cartilage affected by inflammation (circle) and chondrocyte necrosis, light microscopy, H-E X400. (H-E: Haematoxylin-Eosin).

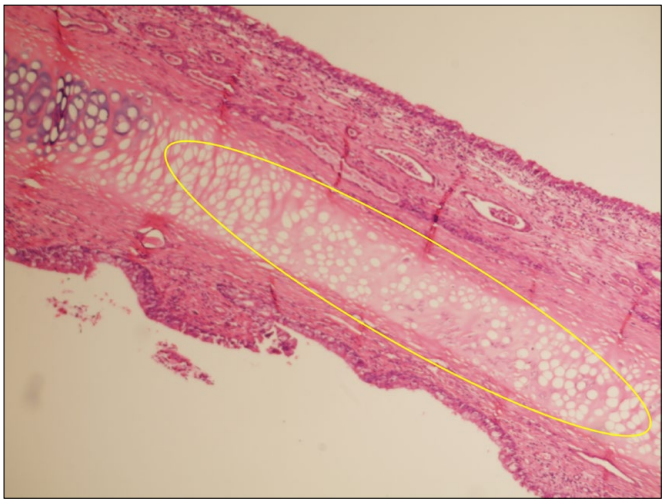


Figure 5. Chondrocyte necrosis area (yellow circle), light microscopy, H-E X400. (H-E:Haematoxylin-Eosin).

Statistical analysis

Regarding the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of the variables was measured with the Kolmogorov-Simonov test. In the anakysis of quantitative independent data, Kruskal-Wallis and Mann-Whitney U tests were used. The chi-square test was used for analysis of qualitative independent data, and Fisher's test was used when the chi-square test conditions were not met. SPSS 22.0 was used for statistical analyses.

Results

Intraoperative findings

No deaths or side effects were observed during the study. The amount of bleeding and the duration of operation were significantly higher in the saline group compared with the adrenaline + lidocaine and mesna groups ($p < 0.05$). The amount of bleeding and the duration of operation did not differ significantly between the adrenaline + lidocaine and mesna groups ($p > 0.05$) (Tab. I).

Mucosal damage was significantly greater in the saline group compared with the adrenaline + lidocaine group ($p < 0.05$). The mucosal damage in the mesna group did not differ significantly from the adrenaline + lidocaine and saline groups ($p > 0.05$) (Tab. I).

Surgical field quality was significantly poorer in the saline group compared with the adrenaline + lidocaine group ($p < 0.05$). In the mesna group, surgical site quality did not differ significantly from the adrenaline + lidocaine and saline groups ($p > 0.05$) (Tab. I).

The accessibility of the correct surgical plane score was

Table I. Amount of bleeding, operation time, surgical site quality, mucosal injury, finding the correct surgical plane for the study groups

			Adrenaline + Lidocaine		Mesna		Saline		p
Amount of bleeding (number of pads)	Med(I.Q-3.Q)/ Min-Max		1.0 (0.50-1.0)/ 0.50-1.50*		1.0 (1.0-1.0)/ 0.50-1.00*		1.5 (1.0-2.0)/ 1.00-3.50		*0.010* [K]
Operation Time (Minutes)	Med (I.Q-3.Q)/ Min-Max		4.5 (3.5-7.0)/ 3.50-8.00*		7.0 (5.0-8.0)/ 3.50-9.00*		10.5 (6.0-16.5)/ 6.00-18.50		*0.012* [K]
Surgical site quality (1-5)	Med (I.Q-3.Q)/ Min-Max		5.0 (5.0-5.0)/ 2.00-5.00		4.0 (3.0-5.0)/ 2.00-5.00		3.0 (2.0-4.0)/ 1.00-4.00		*0.027* [K]
Finding the correct surgical plane (1-5)	Med (I.Q-3.Q)/ Min-Max		5.0 (3.0-5.0)/ 2.00-5.00*		4.0 (3.0-5.0)/ 3.00-5.00*		3.0 (2.0-3.0)/ 2.00-3.00		*0.021* [K]
Mucosal Injury	None	n-%	6	85.7%*	2	28.6%	0	0.0%	
	Simple	n-%	0	0.0%	3	42.9%	5	71.4%	*p < 0.05* [X²]
	Serious	n-%	1	14.3%	2	28.6%	2	28.6%	

*[K] Kruskal-wallis (Mann-Whitney U test); [X²] Chi-square test (Fisher's exact test); * Difference with saline group p < 0.05*

significantly lower in the saline group compared with the adrenaline + lidocaine and mesna groups ($p < 0.05$). The accessibility of the correct surgical plane score did not differ significantly between the adrenaline + lidocaine and mesna groups ($p > 0.05$) (Tab. I).

Histopathological findings

The severity of inflammation, mucosal erosion and ulceration, mucosal thickness, chondrocyte necrosis and foreign body reactions did not differ significantly between the adrenaline + lidocaine, mesna and saline groups ($p > 0.05$) (Tabs. II, III).

The thickness of the perichondrium was significantly lower in the saline group compared with the adrenaline + lidocaine and mesna groups ($p < 0.05$). The thickness of the pericondrium did not differ significantly between the adrenaline + lidocaine and mesna groups ($p > 0.05$) (Tab. III).

Cartilage thickness was significantly higher in the saline group compared with the mesna group ($p < 0.05$). There was no significant difference regarding cartilage thickness in the adrenaline + lidocaine group compared with the mesna and saline groups ($p > 0.05$) (Tab. III).

Discussion

In the current study, only the amount of bleeding, operation duration and cartilage thickness were significantly higher in the saline group compared with the mesna and lidocaine+adrenaline groups, but the accessibility of the correct surgical plane score and the thickness of the perichondrium were found to be significantly lower. In terms of mucosal damage and surgical field quality, the saline group had significantly worse results compared with the adrenaline+lidocaine group. No significant difference was found between the mesna and adrenaline + lidocaine groups regarding these two parameters. Based on these findings, mesna does not appear to be superior to adrenaline. However, saline should not be the first choice in the surgical field.

There are few studies evaluating the efficacy of adrenaline in septum surgery [12,17,18]. In a clinical study, submucoperichondrial vasoconstrictor injection was compared with saline injection and was not superior to saline for intraoperative findings [11]. In another study, adrenaline and saline infiltrations were compared, and no significant difference was detected at the surgical site [12]. In contrast, adrenaline was shown to be superior to saline intraoperative findings, such as the amount of bleeding, operation duration, surgical site quality, mucosal damage and accessibility of the correct surgical plane in the current study.

Eren et al. [19] demonstrated the superiority of mesna compared with saline in terms of intraoperative findings in septal surgery. In our study, operation time and amount of bleeding were significantly higher in the saline group compared with the other groups, and these findings were similar to the study by Eren et al. However, in their study mesna was compared with saline, although a comparison with other vasoconstrictor agents was not included. In our study, saline, vasoconstrictor agents (adrenaline and lidocaine) and mesna were compared histopathologically. In this respect, the current study is different from that by Eren et al. [19].

The preservation of perichondrium integrity during septal surgery is important for prevention of scar tissue formation and cartilage viability [20-22]. The thickness of the perichondrium increases as a result of the trauma, which is caused by the elevation of the nasal mucosal flap. This increase is due to scar tissue formation because of increased fibroelastic activity and trauma-induced oedema [20]. Genç et al. [20] found an increase in perichondrium thickness in both the suture and nasal tamponade groups. In the current study, a min-

Table II. Inflammation and inflammation severity, localisation of inflammation for the study groups.

			Adrenaline + Lidocaine		Mesna		Saline		p
Inflammation	(-)	n-%	1	14.3%	1	14.3%	0	0.0%	$p > 0.05$ $^{x^2}$
	(+)	n-%	6	85.7%	6	85.7%	7	100.0%	
Inflammation severity	I	n-%	3	42.9%	2	28.6%	4	57.1%	
	II	n-%	3	42.9%	4	57.1%	2	28.6%	
	III	n-%	0	0.0%	0	0.0%	1	14.3%	
Localization of inflammation	M	n-%	1	14.3%	1	14.3%	1	14.3%	
	MS	n-%	5	71.4%	5	71.4%	5	71.4%	
	MSC	n-%	0	0.0%	0	0.0%	1	14.3%	
Inflammation severity		Med (I.Q-3.Q)/ Min-Max	1.0 (1.0-2.0)/ 1.00-2.00		2.0 (1.0-2.0)/ 1.00-2.00		1.0 (1.0-2.0)/ 1.00-3.00		0.868 ^{K}

$^{x^2}$ Chi-square test (Fisher's exact test). M: Mucosa; MS: Mucosa +Submucosa; MSC: Mucosa + Submucosa + Cartilage.

Table III. Mucosal erosion and ulceration, mucosal thickness, pericondrium thickness, cartilage thickness, chondrocyte necrosis, foreign body reaction for the study groups.

			Adrenaline + Lidocaine		Mesna		Saline		p
Mucosal erosion and ulceration	(-)	n-%	6	85.7%	4	57.1%	6	85.7%	p > 0.5 $^{x^2}$
	(+)	n-%	1	14.3%	3	42.9%	1	14.3%	
Mucosal thickness (mm)		Med (I.Q-3.Q)/ Min-Max	0.32 (0.25-0.40)/ 0.23-0.48		0.28 (0.23-0.38)/ 0.18-0.43		0.31 (0.21-0.43)/ 0.20-0.50		0.646 ^{K}
Pericondrium thickness (mm)		Med (I.Q-3.Q)/ Min-Max	0.04 (0.035-0.05)/ 0.03-0.08*		0.04 (0.03-0.045)/ 0.03-0.06*		0.03 (0.025-0.03)/ 0.02-0.03		*0.025* ^{K}
Cartilage thickness (mm)		Med (I.Q-3.Q)/ Min-Max	0.98 (0.88-1.48)/ 0.86-1.48		1.30 (1.20-1.70)/ 1.10-1.90*		0.98 (0.75-1.15)/ 0.68-1.30		*0.038* ^{K}
Chondrocyte necrosis	(-)	n-%	1	14.3%	4	57.1%	3	42.9%	p > 0.5 $^{x^2}$
	I	n-%	4	57.1%	2	28.6%	3	42.9%	
	II	n-%	2	28.6%	1	14.3%	1	14.3%	
Foreign body reaction	(-)	n-%	6	85.7%	7	100.%	7	100.0%	p > 0.5 $^{x^2}$
	(+)	n-%	1	14.3%	0	0.0%	0	0.0%	

*^{K} Kruskal-wallis (Mann-Whitney U test); X^2 Chi-square test (Fisher's exact test); * Difference with saline group p < 0.05; Min: Minimum/Max: Maximum*

iature Doyle nasal splint was placed in both nasal cavities. The perichondrium thickness was significantly lower in the saline group compared with the other groups. This leads to the question of whether the substances that are injected into the submucoperichondrial region cause chemical irritation in addition to the trauma caused by the mucoperichondrial flap elevation. Saline, which is very similar to human and animal plasma, has no irritant properties.

In the literature, numerous studies have been conducted to emphasise the need to preserve perichondrium integrity for cartilage viability [21,22]. Verwoerd et al. [21] showed that new cartilage formation started within 2 weeks after submucosal cartilage resection in young rabbits; they attributed this to the high reactivity of the perichondrium. Lee et al. [23] revealed that bilateral elevation of septal mucoperichondrium had no visible effect on chondrocyte viability, and also concluded that bilateral flap elevation caused a marked weakness in cartilage when performed with interventions to the septal cartilage.

In the current study, cartilage thickness was significantly higher and perichondrial thickness was significantly lower in the saline group compared with the mesna group, which was attributed to chemical irritation by mesna.

When comparing intraoperative parameters, we found that mesna had no significant differences compared to adrenaline + lidocaine, which is much more widely used in septum surgery than mesna. We demonstrated that mesna, which is more commonly used in otologic surgery, especially for chemically assisted dissection in ENT practice, does not create enough hydrodissection to make itself preferable in septum surgery. The perichondrium was significantly thicker and the cartilage was significantly thinner in adrenaline + lidocaine and mesna groups. However, we think that this disadvantage will not cause problems in the stability and durability of septum in the long term. In the light of all these findings, we think that adrenaline, which is widely used for submucopericondrial hydrodissection in septum surgery for many years, is preferable over mesna or saline. Because the study was performed using a small number of rabbits and because it is unethical to harvest a full-thickness septum in human studies to compare histopathological parameters with that of rabbits, these are limitations of our study.

This is the first study to compare saline, adrenaline and mesna at the same time in septal mucoperichondrial flap elevation in terms of intraoperative parameters and histopathological effects of these agents on the septum.

Conclusions

The results of this experimental study showed that using mesna instead of normal saline or lidocaine + adrenaline

in septoplasty was not more advantageous in terms of objective parameters tested, amount of bleeding, duration of operation, mucosal injuries as well as surgical field quality and accessibility of the correct surgical plane during surgery. The combination of adrenaline and lidocaine was superior to normal saline for intraoperative parameters. Mesna was not superior to normal saline in terms of mucosal damage and surgical site quality. With all these findings, we conclude that the combination of lidocaine and adrenaline might be more advantageous in septoplasty since it is inexpensive, almost always available in every operating room, much easier access worldwide and reduces bleeding due to the vasoconstriction effect of adrenaline. Further studies on a larger sample size may be beneficial to provide additional information.

Acknowledgements

Presented at the 40th Turkish National Otorhinolaryngology and Head and Neck Surgery Congress, Antalya, Turkey, 07-11 November 2018.

References

1. Spiekermann C, Savvas E, Rudack C, et al. Adaption and validation of the nasal obstruction symptom evaluation scale in German language (D-NOSE). Health Qual Life Outcomes 2018;16:172. https://doi.org/10.1186/s12955-018-1004-x
2. Clark DW, Del Signore AG, Raithatha R, et al. Nasal airway obstruction: prevalence and anatomic contributors. Ear Nose Throat J 2018;97:173-6. https://doi.org/10.1177/014556131809700615
3. Cantone E, Ricciardiello F, Oliva F, et al. Septoplasty: is it possible to identify potential "predictors" of surgical success? Acta Otorhinolaryngol Ital 2018;38:528-35. https://doi.org/10.14639/0392-100X-2072
4. Mladina R, Cujić E, Subarić M, et al. Nasal septal deformities in ear, nose, and throat patients: An international study. Am J Otolaryngol 2008;29:75-82. https://doi.org/10.1016/j.amjoto.2007.02.002
5. van Egmond MMHT, Rovers MM, Tillema AHJ, et al. Septoplasty for nasal obstruction due to a deviated nasal septum in adults: a systematic review. Rhinology 2018;56:195-208. https://doi.org/10.4193/Rhin18.016
6. van Egmond MM, Rovers MM, Hendriks CT, et al. Effectiveness of septoplasty versus non-surgical management for nasal obstruction due to a deviated nasal septum in adults: study protocol for a randomized controlled trial. Trials 2015;16:500. https://doi.org/10.1186/s13063-015-1031-4
7. Aaronson NL, Vining EM. Correction of the deviated septum: from ancient Egypt to the endoscopic era. Int Forum Allergy Rhinol 2014;4:931-6. https://doi.org/10.1002/alr.21371
8. Aksoy F, Yıldırım YS, Demirhan H, et al. Structural characteristics of septal cartilage and mucoperichondrium. J Laryngol Otol 2012;126:38-42. https://doi.org/10.1017/S0022215111002404
9. Vuyk HD, Olde Kalter P. Open septorhinoplasty. Experiences in 200 patients. Rhinology 1993;31:175-82.
10. Tahery J, Belloso A, Zarod AP. New method for raising the mucoperichondrial flap in septal surgery: microscope assisted hydrodissection technique. J Laryngol Otol 2004;118:715-6. https://doi.org/10.1258/0022215042244723
11. Gungor V, Baklaci D, Kum RO, et al. Infiltration with lidocaine and adrenaline instead of normal saline does not improve the septoplasty procedure. Eur Arch Otorhinolaryngol 2016;273:2073-7. https://doi.org/10.1007/s00405-015-3870-8
12. Vanniasegaram I. Prospective study of the use of vasoconstrictor and saline in septal surgery for infiltration. J Laryngol Otol 1991;105:638-9. https://doi.org/10.1017/s0022215100116895
13. Bogiatzi S, Pagonopoulou O, Simopoulou M, et al. The cytogenetic action of ifosfamide, mesna, and their combination on peripheral rabbit lymphocytes: an in vivo/in vitro cytogenetic study. Cytotechnology 2014;66:753-60. https://doi.org/10.1007/s10616-013-9624-9
14. Casale M, Di Martino A, Salvinelli F, et al. MESNA for chemically assisted tissue dissection. Expert Opin Investig Drugs 2010;19:699-707. https://doi.org/10.1517/13543784.2010.485192
15. Vincenti V, Magnan J, Saccardi MS, et al. Chemically assisted dissection by means of mesna in cholesteatoma surgery. Otol Neurotol 2014;35:1819-24 https://doi.org/10.1097/MAO.0000000000000514
16. Yilmaz M, Goksu N, Bayramoglu I, et al. Practical use of MESNA in atelectatic ears and adhesive otitis media. ORL J Otorhinolaryngol Relat Spec 2006;68:195-8. https://doi.org/10.1159/000091472
17. Thevasagayam M, Jindal M, Allsop P, et al. Does epinephrine infiltration in septoplasty make any difference? A double blind randomised controlled trial. Eur Arch Otorhinolaryngol 2007;264:1175-8. https://doi.org/10.1007/s00405-007-0339-4
18. McClymont LG, Crowther JA. Local anaesthetic with vasoconstrictor combinations in septal surgery. J Laryngol Otol 1988;102:793-5. https://doi.org/10.1017/s0022215100106474
19. Eren SB, Yenigun A, Tugrul S, et al. Effect of submucosal mesna application on mucoperichondrial elevation in septoplasty. J Craniofac Surg 2017;28:e94-6. https://doi.org/10.1097/SCS.0000000000003307
20. Genç E, Ergin NT, Bilezikçi B. Comparison of suture and nasal packing in rabbit noses. Laryngoscope 2004;114:639-45. https://doi.org/10.1097/00005537-200404000-00008
21. Verwoerd CDA, Verwoerd-Verhoef HL, Meeuwis CA, et al. Wound healing of the nasal septal perichondrium in young rabbits. ORL J Otorhinolaryngol Relat Spec 1990;52:180-6. https://doi.org/10.1159/000276131
22. Verwoerd-Verhoef HL, ten Koppel PG, van Osch GJV, et al. Wound healing of cartilage structures in the head and neck region. Int J Pediatr Otorhinolaryngol 1998;43:241-51. https://doi.org/10.1016/s0165-5876(98)00003-2
23. Lee DY, Kim DW, Mangoba DCS, et al. Morphological and histological changes of the septal cartilage after unilateral versus bilateral mucoperichondrial flap elevation. Am J Rhinol Allergy 2013;27:62-6. https://doi.org/10.2500/ajra.2013.27.3843

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:59-68; doi: 10.14639/0392-100X-N0915

Rhinology

Endoscopic surgical treatment of epistaxis in hereditary haemorrhagic telangiectasia: our experience

Il trattamento endoscopico dell'epistassi nella teleangectasia emorragica ereditaria: la nostra esperienza

Fabio Pagella[1,2], Alessandro Pusateri[1], Eugenia Maiorano[1,2], Giuseppe Spinozzi[1], Sara Ugolini[1,2], Roberta Lizzio[1], Rosolino Mirabella[1,2], Carmine Tinelli[3], Carla Olivieri[2,4], Elina Matti[1]

[1] Department of Otorhinolaryngology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2] University of Pavia, Italy; [3] Clinical Epidemiology and Biometric Unit, Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy; [4] General Biology and Medical Genetics, Department of Molecular Medicine, Pavia, Italy

SUMMARY

Objectives. Hereditary haemorrhagic telangiectasia (HHT) is a rare autosomal dominant disease characterised by epistaxis. Surgical procedures for epistaxis vary from diathermocoagulation to nasal closure. The aim of this paper is to report our experience in endoscopic surgical management of epistaxis in HHT patients.

Methods. This is a descriptive, longitudinal study carried out at the Otorhinolaryngology Department of IRCCS Policlinico San Matteo in Pavia, a reference centre for the treatment and diagnosis of HHT. We retrospectively evaluated HHT patients who underwent surgery for epistaxis from 1996 to 2015, including only those treated with endoscopic surgery.

Results. Among the 591 patients hospitalised and screened for HHT, 323 (54.7%) underwent endoscopic surgery for epistaxis, for a total of 679 procedures. General anaesthesia was used in 77.2% of procedures; argon plasma coagulation was the instrument of choice in the majority of patients, followed by lasers and quantum molecular resonance technology.

Conclusions. We report one of the largest cohorts undergoing endoscopic treatment of epistaxis in HHT patients. This mini-invasive surgical treatment allowed us to control epistaxis without major complications and nasal packaging and can be repeated over time. For these reasons, we recommend it as first choice in case of epistaxis in HHT patients.

KEY WORDS: hereditary haemorrhagic telangiectasia, Rendu Osler Weber disease, epistaxis, nosebleeds, endoscopy, argon plasma coagulation

RIASSUNTO

Obiettivi. *L'obiettivo di questo studio è riportare la nostra esperienza nel trattamento endoscopico dell'epistassi nei pazienti con Teleangectasia Emorragica Ereditaria (HHT).*

Metodi. *Si tratta di uno studio longitudinale retrospettivo svolto presso l'UOC di Otorinolaringoiatria della Fondazione IRCCS Policlinico San Matteo di Pavia, centro di riferimento per la diagnosi e la cura dell'HHT. Sono stati valutati i pazienti sottoposti dal 1996 al 2015 a trattamento chirurgico delle epistassi ricorrenti, includendo solo quelli trattati con tecnica endoscopica.*

Risultati. *Dei 591 pazienti ricoverati e sottoposti a screening per HHT, 323 (54.7%) sono stati sottoposti a trattamento chirurgico endoscopico per epistassi, per un totale di 679 procedure. Il 77,2% delle procedure è stato eseguito in anestesia generale; il sistema ad Argon Plasma è stato lo strumento di scelta nella maggior parte dei pazienti, seguito dai laser e dalla quantum molecular resonance.*

Conclusioni. *Riportiamo una delle più ampie casistiche nel trattamento endoscopico dell'epistassi nei pazienti con HHT. Tale approccio consente di gestire i pazienti senza necessità di tamponamento nasale, è scevro da complicanze maggiori, ripetibile nel tempo e riteniamo che debba essere preso in considerazione come trattamento di prima scelta in caso di epistassi in pazienti con HHT.*

PAROLE CHIAVE: *teleangectasia emorragica ereditaria, malattia di Rendu Osler Weber, epistassi, endoscopia, argon plasma*

Received: June 10, 2020
Accepted: October 16, 2020

Correspondence
Eugenia Maiorano
Department of Otorhinolaryngology, Fondazione IRCCS Policlinico San Matteo, piazzale Golgi 19, 27100 Pavia, Italy
E-mail: eugenia_maiorano@libero.it

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Pagella F, Pusateri A, Maiorano E, et al. Endoscopic surgical treatment of epistaxis in hereditary haemorrhagic telangiectasia: our experience. Acta Otorhinolaryngol Ital 2021;41:59-68. https://doi.org/10.14639/0392-100X-N0915

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterised by multiorgan systemic vascular dysplasia. The prevalence of the disease is estimated to be between 1:5000 and 1:8000 in the European population [1]. HHT is characterised by a highly variable phenotype and complete penetrance by the age of 40 years; vascular dysplasia leads to visceral arteriovenous malformations (AVMs) and mucosal and skin telangiectasias. Recurrent epistaxis from telangiectasias of the nasal mucosa is the most frequent symptom, which is present in more than 95% of HHT patients [1]. AVMs are frequently found in the lungs (15-50% of patients), liver (32-78%) and brain (23%) and should be recognised in these patients since they may cause severe life-threatening complications [1]. The clinical diagnosis of HHT is confirmed if three of the four diagnostic Curacao criteria (positive family history, recurrent epistaxis, mucocutaneous telangiectasias, visceral AVMs) are met. Two major genes are involved in HHT: *ENG* (OMIM #187300) and *ACVRL1* (OMIM #600376), coding for proteins involved in the TGF-β/BMP pathway [1,2].

In HHT patients, the clinical manifestations of epistaxis are variable, from rare blood spots to patients in whom nosebleed severity can require frequent blood transfusions, with a substantial worsening in quality of life. Over the years, different grading scale systems have been proposed to quantify the severity of epistaxis related to HHT. Moreover, in recent years, to enhance the visualisation of nasal vascular structures, our group developed new methods of intraoperative endoscopy based on narrow-band imaging and fluorescein-guided endoscopy [3,4]. However, epistaxis in HHT remains a clinically unsolved problem; current therapies do not lead to a definitive resolution but only to temporary control of the condition. Multiple therapeutic approaches have been proposed in the literature and can be schematically classified into the destruction of telangiectasia, reduction of blood flow, reduction of trauma, improvement of protection and control of fibrinolytic activity.

Regarding medical therapy, different approaches have been proposed and described with variable results [5-8]. From a surgical perspective, the management of epistaxis depends on clinical severity. In patients with mild nosebleeds, various forms of mini-invasive surgical techniques including bipolar cautery, argon plasma coagulation (APC), lasers and Diego-PK Shaver treatment can be indicated, while more invasive procedures, such as modified Young's procedure, are reserved for cases of severe epistaxis [9,10].

Various therapeutic approaches for epistaxis in HHT have been described, but there still is no general agreement on the best treatment. The purpose of this study was to describe our experience in the endoscopic management of epistaxis in HHT patients, focusing on mini-invasive surgical procedures.

Materials and methods

The Department of Otorhinolaryngology of I.R.C.C.S. Policlinico San Matteo in Pavia is a national reference centre for diagnosis and treatment of HHT. After Local Ethics Committee approval (Comitato Etico di Pavia, reference number 1-29/1/14), we retrospectively reviewed data of HHT patients treated from 1996 until 2015 for nosebleeds, including demographics, surgical technique, number of procedures carried out on each patient, time between each procedure, characteristics of nasal telangiectasias, presence of septal perforation and intraoperative bleeding. Patient records were stored in a Filemaker Pro Advance database (version 14.0.1, Filemaker Inc.) and extracted for this study. Molecular analyses on peripheral blood DNA were performed as described in a previous paper: 100 ng of genomic DNA was amplified in the coding regions of both *ENG* and *ACVRL1* [2].

The endoscopic endonasal mini-invasive surgical procedure was performed in the operating theatre under local or general anaesthesia. During surgery, patients were placed in a reverse Trendelenburg position. Careful preparation of the nasal cavities was undertaken: cottons soaked with xylometazoline chlorohydrate 0.1% and oxybuprocaine chlorohydrate 0.01% were placed in the nasal fossa and left in place for 5-10 min to decongest and clean the nasal mucosa. Surgery was performed under endoscopic endonasal control with a 0° rigid 4 mm optic (Karl Storz and Co., Germany) to selectively treat involved mucosa and telangiectasias located along the nasal fossae. After surgery, an antibiotic ointment was placed in the nasal cavities and no nasal packing was necessary. In some patients whose intraoperative bleeding was more severe than expected and not managed elsewhere, we applied selective bipolar cauterisation or an intranasal haemostatic matrix such as Floseal (Baxter, U.S.), Surgiflo (Ethicon, U.S.), Perclot (Cryolife, U.S.), or Haemocer (BioCer GmbH, Germany) as an adjunct to local coagulation control of haemostasis. In the postoperative period, patients were periodically evaluated (every 6–12 months) for epistaxis with medical evaluation and/or follow-up phone call. In cases in which good control of epistaxis was obtained, follow-up was continued as described; in cases of worsening of symptoms, a new surgical procedure was performed. Non-responders (31 patients) were given medical therapy with oral thalidomide and excluded from the present analysis [5].

Statistical analysis

Descriptive statistics were used for demographic characteristics for this sample of patients. The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. When quantitative variables were normally distributed, the results were expressed as mean value and standard deviation (SD), otherwise median and interquartile range (IQR; 25th -75th percentile) were reported. Qualitative variables were summarised as counts and percentages. The comparisons between gender or patients with one procedure versus patients with more than one procedure were performed with chi-square test for categorical variables and Student's t test (or Kruskall-Wallis test if data are skewed) for continuous variables. All tests were two-sided and p values < 0.05 were considered statistically significant. The data analysis was performed with the STATA statistical package (release 14.0, 2015, Stata Corporation, College Station, Texas, USA).

Results

Five hundred and ninety-one HHT patients, diagnosed according to the Curacao criteria, were hospitalised and screened at our department. Of these, 323 patients (54.7%) underwent endoscopic surgery for epistaxis, for a total of 679 procedures. Concerning mutational screening, analyses were completed on 207 patients: 152 patients (73.4%) carried a mutation in *ACVRL1*, while 55 (26.6%) carried a mutation in *ENG*.

The group consisted of 182 men (56.3%) and 141 women (43.6%), with a mean age of 56 years at first surgery (range 5–86 years); interestingly, we found a significant difference between males (mean 53 years, SD 14 years) and females (mean 57 years, SD 15 years) regarding mean age at first surgery (p = 0.0158).

General anaesthesia was used in 524 procedures (77.2%), while local anaesthesia was used in 155 (22.8%). In 175 patients (54.2%), a single surgical procedure was effective to obtain acceptable control of epistaxis (median follow-up in this group was 48 months), while 148 patients (45.8%) required more than one procedure over time, for a total number of 679 procedures (Tab. I). During the follow-up period, 25 patients (7.7%) were lost and 31 patients (9.6%) died. The mean number of surgical procedures in our group was 1.9 in females (SD 1.4), 2.3 in males (SD 1.8) and 2.1 (SD 1.6) overall. No significant difference was noted between *ACVRL1* and *ENG* patients regarding the number of surgical procedures (one surgery vs two or more; p = 0.1389). In patients with more than one surgery, the time between procedures was analysed (Tab. II; Fig. 1). Preoperative epistaxis severity was scored according to Pagella et al. and was moderate or severe in all patients [6]. Characteristics of telangiectasias were analysed before the first surgery and this data was available for 160/323 patients (49.5%): according to the description performed by Pagella et al. in 2009 [6], the most common pattern was "mixed" (90 patients, 56.3%), followed by the "large" (56 patients, 35%) and "punctate" pattern (14 patients, 8.7%) (Fig. 2). The nasal septum and lateral nasal walls were involved, respectively, in 91.9% and 91.3% of patients, and the nasal floor in 43.7% and nasal valve in 31%. Interestingly, a significant difference (p = 0.033) between males and females was found in the pattern of telangiectasias: the punctate pattern was more common in females (11 vs 3), while mixed and large patterns were more common in males (respectively 51 *vs* 39 and 33 *vs* 23).

In our sample of HHT patients treated with endoscopic endonasal mini-invasive technique, APC (Fig. 3) was the

Table I. Number of epistaxis-related surgical procedures performed in HHT patients.

Number of surgeries	No. of patients	%
1 procedure	175	54.18%
2 procedures	56	17.34%
3 procedures	43	13.31%
4 procedures	19	5.88%
5 procedures	14	4.33%
6 procedures	5	1.55%
7 procedures	7	2.16%
8 procedures	2	0.62%
9 procedures	1	0.31%
10 procedures	1	0.31%
Total	323	100%

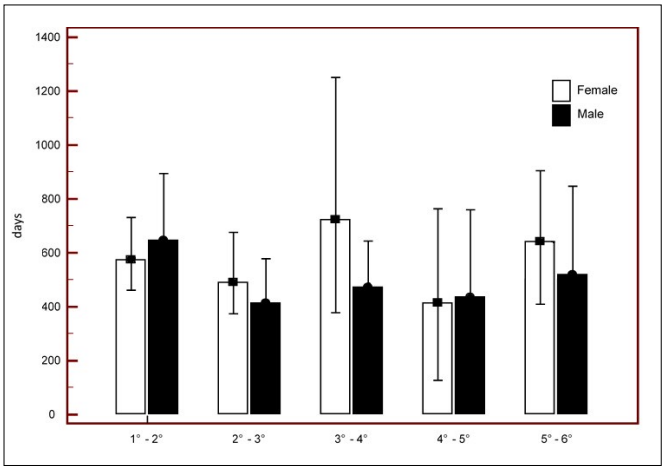


Figure 1. Plot showing the time between surgical procedures (in days) in HHT patients with more than one surgery. Columns: medians; lines: interquartile ranges. Females represented in white and males in black.

Table II. Time between surgical procedures in patients with more than one surgery. Results are reported in days, with the median of days between surgeries in each subgroup.

	No. of patients	Median	IQR (25^{th}- 75^{th})		Min	Max
First – Second	150	612	299	1225	23	4979
Second – Third	92	447	205	769	17	3810
Third – Fourth	50	540	267	917	14	2175
Fourth – Fifth	30	420	279	762	55	1820
Fifth – Sixth	16	583	278	848	19	1211
Sixth – Seventh	11	224	42	697	21	1468
Seventh – Eighth	4	322	207	647	133	930
Eighth – Ninth	2	345	311	379	311	379
Ninth – Tenth	1	261	261	261	261	261

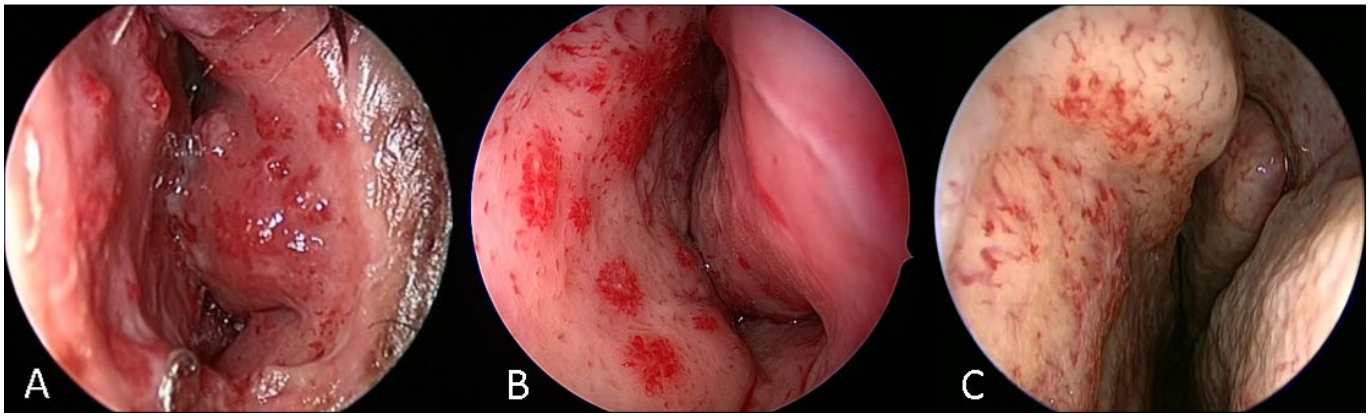


Figure 2. Nasal endoscopies in HHT patients, different patterns are shown. In (**A**), "large" pattern. In (**B**), "mixed" pattern. In (**C**), "punctate" pattern.

instrument of choice (661 procedures, 97.3%), while lasers (diode, thulium) and quantum molecular resonance technology (Figs. 4, 5) were used in 15 procedures (2.2%).

Since 2004, intranasal haemostatic matrices such as Floseal (Baxter, U.S.), Surgiflo (Ethicon, U.S.), Perclot (Cryolife, U.S.), or Haemocer (BioCer GmbH, Germany) were introduced in our clinical practice in order to permit adequate management of severe intraoperative bleeding and better visualisation of the intraoperative field. In our experience, we successfully used these devices during surgery in 83 procedures (12.2%).

Septal perforation was observed in 75 patients (23.2%). Among these, 31 patients (41.3%) had a septal perforation before our first surgery, so in these patients the complication was not related to our treatment. On the other hand, 44 patients (58.7%) developed a septal perforation during

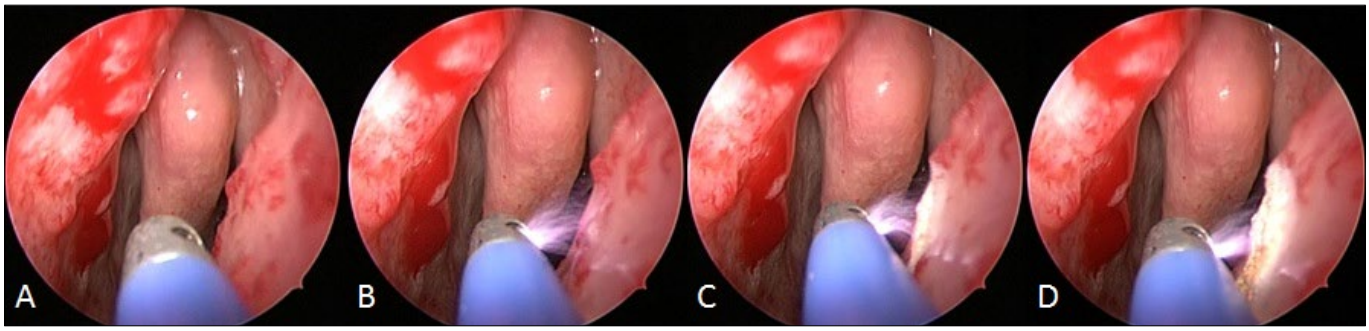


Figure 3. Intraoperative endoscopic sequence showing an APC procedure on left-side telangiectasias located on the lateral nasal wall.

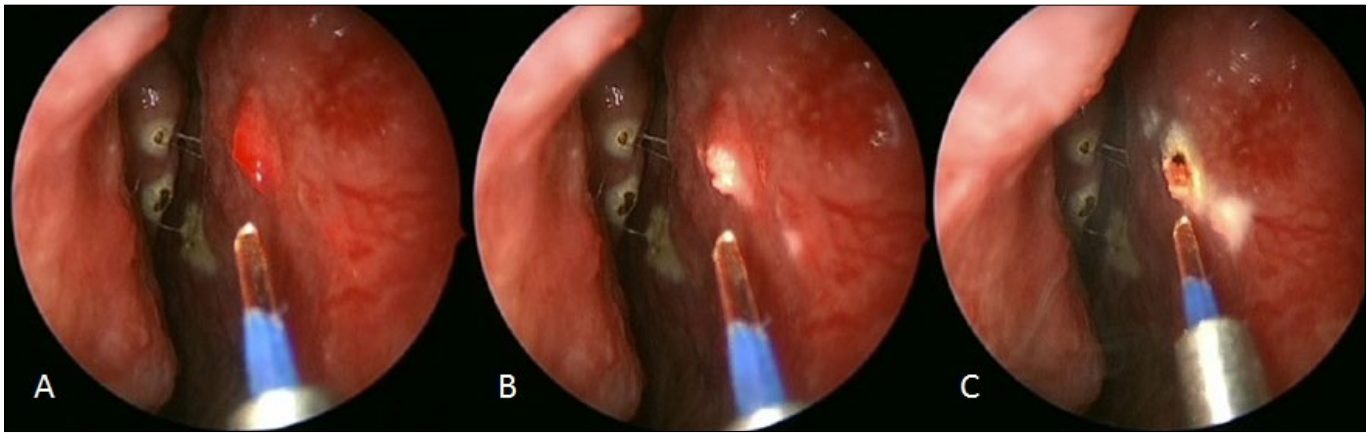


Figure 4. Intraoperative endoscopic sequence showing a thulium laser procedure on a right-side telangiectasia located on the nasal septum.

our treatment: 18 patients (40.9%) after one procedure, 8 patients (18.2%) after two procedures, 12 patients (27.3%) after three procedures, and 6 patients (13.6%) after four or more procedures. In most of these patients, previous surgery in another hospital was performed, which could explain the relatively high rate of septal perforations in our group.

Discussion

Epistaxis in HHT remains a problem with regards to definitive treatment: current therapies permit control of nosebleeds, but not complete resolution. As stated by Silva et al., first-line treatment of HHT-related nosebleeds includes hygiene of the nasal cavities and avoidance of triggering factors [7]. Different therapies, both medical and surgical, have been proposed in the literature [5,8-45]. In our opinion, endoscopic endonasal mini-invasive techniques have several advantages over other techniques, and these are represented by less morbidity, reduced trauma of nasal mucosa, low risk of septal perforation, treatment repeatability, no need for post-surgical nasal packing, the possibility of local anaesthesia and short time of hospitalisation. A review of the literature suggests that the choice of treatment should be based on the severity of nosebleeds: in cases of bleeding of mild entity, a mini-invasive technique can be proposed; on the other hand, in patients with severe epistaxis more invasive surgeries should be chosen (e.g. septodermoplasty, septectomy, closure of the nostrils) [10]. However, in 2013, our group demonstrated the efficacy and long-term benefit of a mini-invasive approach (APC) in a group of HHT patients affected by severe epistaxis with a history of blood transfusion [16].

In this paper, we report our 20-year experience in the surgical management of epistaxis in HHT, focusing on endoscopic mini-invasive techniques. The Department of Oto-rhinolaryngology at I.R.C.C.S. Policlinico San Matteo in Pavia is a reference centre for diagnosis and treatment of

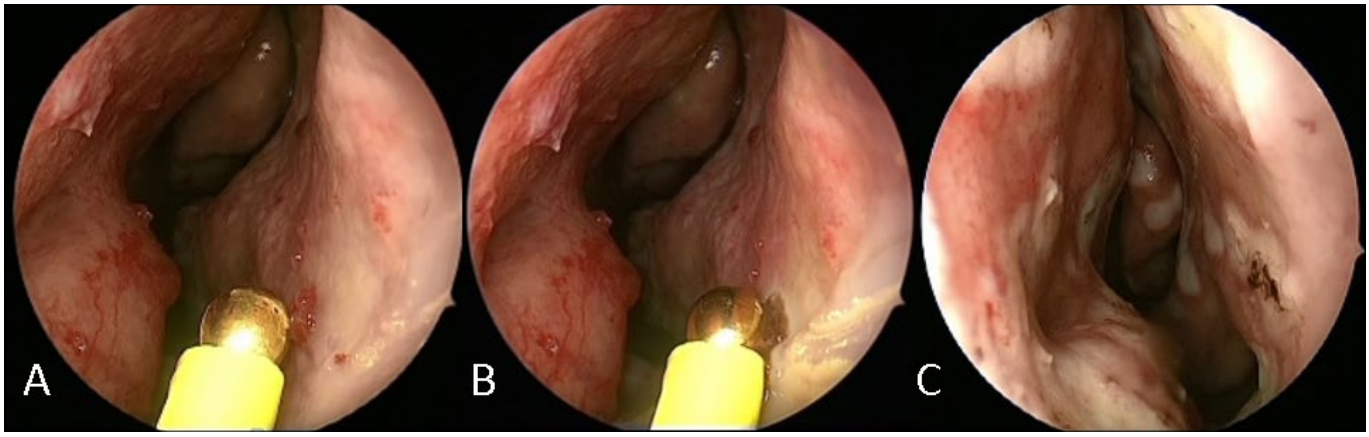


Figure 5. Intraoperative endoscopic sequence showing the quantum molecular resonance technology procedure on a left-side telangiectasia located on the inferior turbinate/nasal valve.

HHT in Italy, and, over the period analysed (1996-2015), 591 patients with a diagnosis of HHT (according to Curacao criteria) were referred to our centre. The first concept that should be stressed is that only 54.7% of these patients required surgery for control of epistaxis. This is, to the best of our knowledge, one of the most extensive reported case series on epistaxis surgical treatment in HHT. For the remaining 268 patients, although epistaxis was still present (in fact, it is usually the most common symptom that leads to diagnostic suspicion), quality of life-related to this problem was deemed acceptable and did not require further interventions. Another interesting piece of data is that in 175 patients (54.2%), a single surgical procedure was effective to obtain acceptable control of epistaxis (median follow-up: 48 months), while 148 patients (45.8%) required more than one procedure over time; even if not objective, this is a good outcome measure of patient satisfaction with epistaxis control. In our opinion, in fact, it is essential to take into consideration the personal satisfaction of each patient, given that each treatment used for epistaxis in HHT is symptomatic. According to this management strategy, Sautter and Smith also stated in 2016 that, regardless of treatment modality, HHT-related epistaxis would continue [10].

The mean number of surgical procedures in our group was 2.1 (1.9 in females and 2.3 in males, no significant difference). No significant difference was reported between *ACVRL1* and *ENG* patients regarding the number of procedures. Repetition of a mini-invasive surgical procedure, given its low risk of short-term and long-term complications (44/323 patients developed a septal perforation during treatment, most underwent previous repeated cauterisations in other hospitals) is possible when nasal bleeding returns and has a negative impact on the quality of life. A "staged" procedure should be performed when telangiectasias are present on opposing sides of the anterior nasal septum in order to avoid septal perforation. Moreover, some authors report that submucosal injections of bevacizumab associated with surgical treatment may increase the risk of perforation [10].

Regarding the characteristics of nasal telangiectasias, data was available for 160 of 323 patients (49.5%): the most common pattern was mixed (90 patients, 56.3%), followed by the large (56 patients, 35%), and punctate patterns (14 patients, 8.7%). The nasal septum and lateral nasal walls were involved, respectively, in 91.9% and 91.3% of patients, nasal floor in 43.7% and nasal valve in 31%. Wide variability can be found not only in the nasal pattern of telangiectasias, but also in the number of nasal subsites involved, even in patients with the same pattern. Furthermore, we confirmed that different subsites in nasal fossae, and even the same subsite, can present similar or different patterns. We also observed a higher incidence of mixed and large patterns in surgical candidates; this is in accordance with a previous paper in which we observed a significantly higher frequency of nosebleeds in patients presenting the large pattern [6].

Regarding surgical technique applied, APC was the instrument of choice in most of our patients (661 procedures, 97.3%), while lasers and quantum molecular resonance technology were used only in 2.7% of cases. Indeed, APC is our instrument of choice in the treatment of epistaxis in HHT patients independently of preoperative epistaxis severity, which was moderate or severe before surgery in all patients [14,16]. Bergler first described APC treatment of nosebleeds in 1999 on 12 HHT patients [17]. From a technical point of view, APC is based on high-frequency electric energy transmitted through ionised argon gas. The generator is set at 40–60 W and the argon gas flow at 1.2 L/min. Endoscopic endonasal visualisation permits selective treatment in a noncontact mode of telangiectasias located along all the nasal fossae (also in their posterior portion) and in the nasopharynx. Coagulation of tissue is limited to a 1-2 mm depth. This permits low risk of local tissue damage because the temperature is rarely over 100°C. Finally, the applicator tips can be sterilised, and the cost of argon gas is very low.

In the literature, multiple techniques have been described for endoscopic surgical treatment of nasal telangiectasias (Tab. III). Ablative therapies, such as sclerotherapy, electrosurgery and laser treatment, show good outcomes in reducing epistaxis in HHT patients. Sclerotherapy with foamed sodium tetradecyl sulfate has been shown to be effective and safe in four studies, including one randomised clinical trial [20-23]. The potential side effects are tissue necrosis, cellulitis at the site of injection and, more rarely, anaphylaxis, pulmonary embolus and permanent blindness due to central retinal artery or ophthalmic artery occlusion [24].

Bipolar electrosurgery is preferable to monopolar electrosurgery due to the lower risk of septal perforation, and Ghaheri et al. reported on the efficacy of bipolar cautery for epistaxis treatment in HHT [25].

Laser photocoagulation is also a viable option, and many different types of laser exist [18,26,29]. Lasers with higher tissue penetration that use haemoglobin as a chromophore, such as the Nd:YAG laser, are preferred over lasers with less penetration. The problem with laser use is that not all devices can be used with flexible fibres, and the manoeuverability inside nasal cavities can be limited. Moreover, increased thermal damage to surrounding tissue is a concern when using lasers.

Multiple uncontrolled series demonstrated that laser treatments are efficient in reducing epistaxis duration, frequency and severity in HHT patients [14,16-18,27-31].

Table III. Surgical techniques for epistaxis treatment in HHT patients.

Study	Study design	No. of patients	Treatment	Outcome of interest	Results
Boyer H. et al., 2011 [20]	Retrospective	7	Sclerotherapy	Epistaxis frequency and severity	100% improved
Morais D. et al., 2012 [21]	Retrospective	45	Sclerotherapy	Epistaxis frequency and severity	95% Improved
Boyer H. et al., 2015 [22]	Randomised controlled trial	17	Sclerotherapy	ESS	Improved
Esteban-Casado S. et al., 2019 [23]	Cross-sectional	38	Sclerotherapy and topical nasal propranolol	ESS, VAS, EQ-5D	Improved
Ghaheri B. et al., 2006 [25]	Retrospective	18	Bipolar cautery	Need for recurrent intervention	Recurrent intervention in 50% at a mean follow-up of 2.3 years
Bergler W. et al., 1999 [17]	Prospective	12	APC	Epistaxis frequency and intensity	Improved
Pagella F. et al., 2006 [14]	Prospective	36	APC	Reported bleeding	100% reduction at 6 months
Pagella F. et al., 2013 [16]	Retrospective	26	APC	Epistaxis score	Improved at 12 months
Jørgensen G. et al., 2011 [28]	Prospective	30	Laser	Epistaxis duration	Reduced at 1.5 and 6 months
Kuan E.C. et al., 2017 [31]	Retrospective	20	Laser	SNOT-22	Improved at 1.5 months
Fiorella M.L. et al., 2012 [18]	Retrospective	24	Diode laser	Epistaxis frequency and severity	Improved
Poje G. et al., 2017 [32]	Retrospective	17	Diode laser	Epistaxis frequency and severity	Improved
Papaspyrou G. et al., 2016 [29]	Retrospective	38	Nd:YAG laser	Need for recurrent intervention	18% recurrent intervention at a mean follow-up of 3 years
Papaspyrou G. et al., 2017 [30]	Prospective	45	Nd:YAG laser +/- APC	Need for recurrent intervention	20-33% recurrent intervention at 3-10 years
Joshi H. et al., 2011 [36]	Case series	5	Coblation	Epistaxis control	80% of patients
Mortuaire G. et al., 2013 [34]	Prospective	16	Coblation	Epistaxis frequency and duration	Reduced frequency at 6 months
Rotenberg B. et al., 2015 [35]	Retrospective	37	Coblation	ESS	Improved at 6 months
Luk L. et al., 2014 [27]	Prospective	11	Coblation vs KTP laser	ESS	No difference in mean ESS
Ishibashi T. et al., 2003 [33]	Case report	2	Harmonic Scalpel Harmonic scalpel	Frequency of epistaxis	Improved
Ichimura K. et al., 2006 [38]	Retrospective	15	Septodermoplasty	Patient satisfaction	100% satisfied
Lesnik G.T. et al., 2007 [15]	Retrospective	9	Septodermoplasty with septectomy	Epistaxis frequency, QoL, blood transfusions	100% improved QoL, blood transfusion reduced
Levine C.G. et al., 2008 [39]	Retrospective	106	Septodermoplasty	QoL	62% responded and 86% improved
Harvey R. et al., 2008 [37]	Retrospective	33	Septodermoplasty	Frequency of KTP laser	Frequency of KTP laser treatment decreased ($p = 0.012$)
Rimmer J. et al., 2014 [40]	Prospective	7	Septodermoplasty	Epistaxis frequency and severity	100% improvement
Lee J.M. et al., 2019 [44]	Prospective	7	Temporary nasal occlusion with Floseal®	ESS and clinical assessment of nasal cavity	No significant ESS improvement($p = 0.179$); clinical assessment of nasal cavity improved ($p = 0.0088$) at 1 month
Hosni A.A. et al., 1994 [13]	Case series	2	Nasal closure	Epistaxis frequency	Improved

▶

Table III. *(follows).*

Study	Study design	No. of patients	Treatment	Outcome of interest	Results
Ichimura K. et al., 2012 [41]	Prospective	7	Nasal closure	Epistaxis cessation	57% success
Richer S. et al., 2012 [42]	Retrospective	43	Nasal closure	Epistaxis cessation	84% responded and 83% success
Lund V. et al., 2017 [12]	Retrospective	100	Nasal closure	Epistaxis cessation	50% responded and 94% success
Andersen J.H. et al., 2020 [43]	Retrospective	10	Nasal closure	GBI	Overall GBI score of 38.05 with an average follow-up 66 months

ESS: Epistaxis Severiry Score; VAS: visual analoge scale; EQ-5D: EuroQol-5D scale; APC: Argon plasma coagulation; SNOT-22: Sinonasal outcome test-22; QoL: Quality of life; KTP: Potassium-titanyl-phosphate; GBI: Glasgow benefit inventory.

Ishibashi and Takamatsu described the intraoperative application of the harmonic scalpel (an ultrasonic system) in two HHT patients; highlighting the lack of damage to the surrounding mucosa, but long-term results were not reported [33].
Some authors described coblation in the treatment of HHT-related nosebleeds; this method has been shown to be a useful alternative to other surgical devices, improving nosebleed severity [33-35].
Septodermoplasty and nasal closure are considered useful in patients whose epistaxis fails to respond sufficiently to ablative therapies [35]. According to several authors, septodermoplasty improves both quality of life and epistaxis severity [37-40]. This surgical technique permits an adequate treatment of septal lesions, while it does not allow for epistaxis control in situations where bleeding originates in the lateral wall, which was involved in more than 90% of patients in our group. Worsening sinus infections, decreased sense of smell and crusting are the major complications [36].
Only a few studies have investigated nasal closure outcomes, but there is general agreement on the efficacy in controlling nose bleeds, with an epistaxis cessation rate ranging from 57 to 94% [41-43].
The major limit in comparing different surgical techniques in HHT is that there is no homogeneity among outcomes defining surgical success: some authors used epistaxis severity score as the primary outcome, while others report only patient satisfaction or quality of life (Tab. III).
A fundamental preoperative step is careful preparation of the nasal cavities before surgery with local decongestion and meticulous cleaning of crusting and blood clots. In case of profuse and uncontrollable intraoperative bleeding, we suggest a "three-hands" or even a "four-hands" procedure: two surgeons in the operative room, one holding the endoscope and the APC and the other holding the suction tube (one or two if necessary). Moreover, an intranasal haemostatic matrix can be applied during surgery to permit adequate management of severe intraoperative bleeding and better visualisation of the intraoperative field: we successfully used these devices in 83 procedures (12.2%). To the best of our knowledge, only one description of the intranasal use of a haemostatic matrix in HHT has been reported [44].
Possible drawbacks of this study include the lack of objective outcome measures, its retrospective nature and the lack of a control group treated with different procedures (e.g. APC *vs* other techniques).

Conclusions

Recurrent epistaxis from telangiectasias of the nasal mucosa is a common manifestation present in more than 95% of HHT patients. Current therapies cannot permit a definitive resolution of the symptom, but only temporary control of nosebleeds and improvement in the quality of life. Herein, we describe our 20-year experience in the endoscopic surgical treatment of epistaxis in a large group of 323 HHT patients. Endoscopic endonasal mini-invasive surgical options, and in particular APC, allowed good control of epistaxis without major complication and nasal packaging. These treatment modalities are repeatable, non-invasive and can be used as a first step even in patients with severe epistaxis. In conclusion, since no treatment could be considered definitive and the natural history of HHT-related nosebleeds is unknown, in our opinion the application of mini-invasive treatment modalities that permit preservation of nasal anatomy and physiology should be the approach of choice.

References

1 Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 2011;48:73-87. https://doi.org/10.1136/jmg.2009.069013

2 Olivieri C, Pagella F, Semino L, et al. Analysis of ENG and ACVRL1 genes in 137 HHT Italian families identifies 76 different mutations (24 novel). Comparison with other European studies. J Hum Genet 2007;52:820-9. https://doi.org/10.1007/s10038-007-0187-5

[3] Pagella F, Pusateri A, Chu F, et al. Narrow-band imaging in the endoscopic evaluation of hereditary hemorrhagic telangiectasia patients. Laryngoscope 2013;123:2967-8. https://doi.org/10.1002/lary.24338

[4] Pagella F, Pusateri A, Zaccari D, et al. Fluorescein-guided intraoperative endoscopy in patients with hereditary hemorrhagic telangiectasia: first impressions. Int Forum Allergy Rhinol 2017;7:300-3. https://doi.org/10.1002/alr.21880

[5] Invernizzi R, Quaglia F, Klersy C, et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol 2015;2:e465-e73. https://doi.org/10.1016/S2352-3026(15)00195-7

[6] Pagella F, Colombo A, Matti E, et al. Correlation of severity of epistaxis with nasal telangiectasias in hereditary hemorrhagic telangiectasia (HHT) patients. Am J Rhinol Allergy 2009;23:52-8. https://doi.org/10.2500/ajra.2009.23.3263

[7] Silva BM, Hosman AE, Devlin HL, et al. Lifestyle and dietary influences on nosebleed severity in hereditary hemorrhagic telangiectasia. Laryngoscope 2013;123:1092-9. https://doi.org/10.1002/lary.23893

[8] Gaillard S, Dupuis-Girod S, Boutitie F, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. J Thromb Haemost 2014;12:1494-502. https://doi.org/10.1111/jth.12654

[9] Dupuis-Girod S, Ambrun A, Decullier E, et al. ELLIPSE Study: a Phase 1 study evaluating the tolerance of bevacizumab nasal spray in the treatment of epistaxis in hereditary hemorrhagic telangiectasia. mAbs 2014;6:793-8. https://doi.org/10.4161/mabs.28025

[10] Sautter NB, Smith TL. Treatment of hereditary hemorrhagic telangiectasia-related epistaxis. Otolaryngol Clin North Am 2016;49:639-54. https://doi.org/10.1016/j.otc.2016.02.010

[11] Faughnan ME, Mager JJ, Hetts SW, et al. Second International Guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. Ann Intern Med 2020;173:989-1001. https://doi.org/10.7326/M20-1443

[12] Lund VJ, Darby Y, Rimmer J, et al. Nasal closure for severe hereditary haemorrhagic telangiectasia in 100 patients. The Lund modification of the Young's procedure: a 22-year experience. Rhinology 2017;55:135-41. https://doi.org/10.4193/Rhin16.315

[13] Hosni AA, Innes AJ. Hereditary haemorrhagic telangiectasia: Young's procedure in the management of epistaxis. J Laryngol Otol 1994;108:754-7. https://doi.org/10.1017/s0022215100128026

[14] Pagella F, Semino L, Olivieri C, et al. Treatment of epistaxis in hereditary hemorrhagic telangiectasia patients by argon plasma coagulation with local anesthesia. Am J Rhinol 2006;20:421-5. https://doi.org/10.2500/ajr.2006.20.2886

[15] Lesnik GT, Ross DA, Henderson KJ, et al. Septectomy and septal dermoplasty for the treatment of severe transfusion-dependent epistaxis in patients with hereditary hemorrhagic telangiectasia and septal perforation. Am J Rhinol 2007;21:312-5. https://doi.org/10.2500/ajr.2007.21.3017

[16] Pagella F, Matti E, Chu F, et al. Argon plasma coagulation is an effective treatment for hereditary hemorrhagic telangiectasia patients with severe nosebleeds. Acta Otolaryngol 2013;133:174-80. https://doi.org/10.3109/00016489.2012.718097

[17] Bergler W, Riedel F, Baker-Schreyer A, et al. Argon plasma coagulation for the treatment of hereditary hemorrhagic telangiectasia. Laryngoscope 1999;109:15-20. https://doi.org/10.1097/00005537-199901000-00004

[18] Fiorella ML, Lillo L, Fiorella R. Diode laser in the treatment of epistaxis in patients with hereditary haemorrhagic telangiectasia. Acta Otorhinolaryngol Ital 2012;32:164-9.

[19] Chin CJ, Rotenberg BW, Witterick IJ. Epistaxis in hereditary hemorrhagic telangiectasia: an evidence based review of surgical management. J Otolaryngol Head Neck Surg 2016;45:3. https://doi.org/10.1186/s40463-016-0116-8.

[20] Boyer H, Fernandes P, Duran O, et al. Office-based sclerotherapy for recurrent epistaxis due to hereditary hemorrhagic telangiectasia: a pilot study. Int Forum Allergy Rhinol 2011;1:319-23. https://doi.org/10.1002/alr.20053

[21] Morais D, Millás T, Zarrabeitia R, et al. Local sclerotherapy with polydocanol (Aethoxysklerol®) for the treatment of epistaxis in rendu-osler-weber or hereditary hemorrhagic telangiectasia (HHT): 15 years of experience. Rhinology 2012;50:80-6. https://doi.org/10.4193/Rhino11.211

[22] Boyer H, Fernandes P, Le C, et al. Prospective randomized trial of sclerotherapy vs standard treatment for epistaxis due to hereditary hemorrhagic telangiectasia. Int Forum Allergy Rhinol 2015;5:435-40. https://doi.org/10.1002/alr.21484

[23] Esteban-Casado S, Martín de Rosales Cabrera AM, Usarralde Pérez A, et al. Sclerotherapy and topical nasal propranolol: an effective and safe therapy for HHT-epistaxis. Laryngoscope 2019;129:221623. https://doi.org/10.1002/lary.27930

[24] Hanks JE, Hunter D, Goding GS Jr, et al. Complications from office sclerotherapy for epistaxis due to hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu). Int Forum Allergy Rhinol 2014;4:422-7. https://doi.org/10.1002/alr.2128

[25] Ghaheri BA, Fong KJ, Hwang PH. The utility of bipolar electrocautery in hereditary hemorrhagic telangiectasia. Otolaryngol Head Neck Surg 2006;134:1006-9. https://doi.org/10.1016/j.otohns.2005.12.019

[26] Abiri A, Goshtasbi K, Maducdoc M, et al. Laser-assisted control of epistaxis in hereditary hemorrhagic telangiectasia: a systematic review. Lasers Surg Med 2020;52:293-300. https://doi.org/10.1002/lsm.23147

[27] Luk L, Mace JC, Bhandarkar ND, et al. Comparison of electrosurgical plasma coagulation and potassium-titanyl-phosphate laser photocoagulation for treatment of hereditary hemorrhagic telangiectasia-related epistaxis. Int Forum Allergy Rhinol 2014;4:640-5. https://doi.org/10.1002/alr.21328

[28] Jørgensen G, Lange B, Wanscher JH, et al. Efficiency of laser treatment in patients with hereditary hemorrhagic telangiectasia. Eur Arch Otorhinolaryngol 2011;268:1765-70. https://doi.org/10.1007/s00405-011-1677-9

[29] Papaspyrou G, Schick B, Al Kadah B. Nd:YAG laser treatment for extranasal telangiectasias: a retrospective analysis of 38 patients with hereditary hemorrhagic telangiectasia and review of the literature. ORL J Otorhinolaryngol Relat Spec 2016;78:245-51. https://doi.org/10.1159/000447949

[30] Papaspyrou G, Hecker D, Linxweiler M, et al. Combined therapy for epistaxis by hereditary hemorrhagic teleangiectasia: a 3-year follow up study on 45 patients. J Craniomaxillofac Surg 2017;45:1179-82. https://doi.org/10.1016/j.jcms.2017.05.018

[31] Kuan EC, Peng KA, Thompson CF, et al. Sinonasal quality of life outcomes following laser treatment of epistaxis related to hereditary hemorrhagic telangiectasia. Lasers Med Sci 2017;32:527-31. https://doi.org/10.1007/s10103-017-2144-7

[32] Poje G, Kavanagh MM. Hereditary hemorrhagic telangiectasia-laser treatment of epistaxis. Ear Nose Throat J 2017;96:E10-E4.

[33] Ishibashi T, Takamatsu S. Hereditary hemorrhagic telangiectasis treated by the harmonic scalpel. Head Neck 2003;25:333-6. https://doi.org/10.1002/hed.10201

[34] Mortuaire G, Boute O, Hatron PY, et al. Pilot study of submucosal radiofrequency for epistaxis in hereditary hemorrhagic telangiectasia. Rhinology 2013;51:355-60. https://doi.org/10.4193/Rhin13.027

[35] Rotenberg B, Noyek S, Chin CJ. Radiofrequency ablation for treatment of hereditary hemorrhagic telangiectasia lesions: "How I do it". Am J Rhinol Allergy 2015;29:226-7. https://doi.org/10.2500/ajra.2015.29.4163

[36] Joshi H, Woodworth BA, Carney AS. Coblation for epistaxis management in patients with hereditary haemorrhagic telangiectasia: a multicentre case series. J Laryngol Otol 2011;125:1176-80. https://doi.org/10.1017/S0022215111001733

[37] Harvey RJ, Kanagalingam J, Lund VJ. The impact of septodermoplasty and potassium-titanyl-phosphate (KTP) laser therapy in the treatment of hereditary hemorrhagic telangiectasia-related epistaxis. Am J Rhinol 2008;22:182-7. https://doi.org/10.2500/ajr.2008.22.3145

[38] Ichimura K, Tanaka H, Yamamoto Y, et al. Nasal dermoplasty for Japanese hereditary hemorrhagic telangiectasia. Auris Nasus Larynx 2006;33:423-8. https://doi.org/10.1016/j.anl.2006.03.001

[39] Levine CG, Ross DA, Henderson KJ, et al. Long-term complications of septal dermoplasty in patients with hereditary hemorrhagic telangiectasia. Otolaryngol Head Neck Surg 2008;138:721-4. https://doi.org/10.1016/j.otohns.2008.01.005

[40] Rimmer J, Lund VJ. A modified technique for septodermoplasty in hereditary hemorrhagic telangiectasia. Laryngoscope 2014;124:67-9. https://doi.org/10.1002/lary.24303

[41] Ichimura K, Kikuchi H, Imayoshi S, et al. Are patients with severe epistaxis caused by hereditary hemorrhagic telangiectasia satisfied with nostril closure surgery? Auris Nasus Larynx 2012;39:59-64. https://doi.org/10.1016/j.anl.2011.03.003

[42] Richer SL, Geisthoff UW, Livada N, et al. The Young's procedure for severe epistaxis from hereditary hemorrhagic telangiectasia. Am J Rhinol Allergy 2012;26:401-4. https://doi.org/10.2500/ajra.2012.26.3809

[43] Andersen JH, Kjeldsen AD. Patient-recorded benefit from nasal closure in a Danish cohort of patients with hereditary haemorrhagic telangiectasia. Eur Arch Otorhinolaryngol 2020;277:791-800. https://doi.org/10.1007/s00405-019-05758-1

[44] Lee JM, Wu V, Faughnan ME, et al. Prospective pilot study of Floseal® for the treatment of anterior epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT). J Otolaryngol Head Neck Surg 2019;48:48. https://doi.org/10.1186/s40463-019-0379-y

[45] Meccariello G, Georgalas C, Montevecchi F, et al. Management of idiopathic epistaxis in adults: what's new? Acta Otorhinolaryngol Ital 2019;39:211-9. https://doi.org/10.14639/0392-100X-2155

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:69-76; doi: 10.14639/0392-100X-N1033

VESTIBOLOGY

The Video Head Impulse Test in the acute stage of posterior canal benign paroxysmal positional vertigo

Il Video Head Impulse Test nello stadio acuto della BPPV da canalolitiasi posteriore

Luigi Califano, Raffaella Iannella, Salvatore Mazzone, Francesca Salafia, Maria Grazia Melillo

San Pio Hospital, Department of Audiology and Phoniatrics, Benevento, Italy

SUMMARY

Objective. Study the high-frequency vestibulo-oculomotor reflex in posterior canal benign paroxysmal positional vertigo (BPPV) through Video Head Impulse Test (vHIT).

Methods. 150 patients suffering for the first time from posterior canal BPPV were studied. Posterior canal vestibulo ocular reflex (VOR) gain was analysed through stimulations in right anterior-left posterior and left anterior-right posterior planes before treatment, immediately after resolution of the acute stage and one month later. Results were compared with a group of 100 healthy individuals.

Results. No significant difference between the study the control groups was observed, except for normalised asymmetry ratio of the posterior canal which was significantly higher in the study group. VOR gains of both affected posterior canals and contralateral healthy posterior canals were not significantly correlated with the VOR gain of ipsilateral and contralateral anterior canals.

Conclusions. vHIT does not seem to represent an essential tool to study typical posterior canal BPPV in patients affected by this disease for the first time. Different results might be expected in relapsing forms, non-responsive forms, long lasting forms, or atypical variants in which major damage could be provoked by the persistence of otoconia in the canal or by its complete or partial jam.

KEY WORDS: posterior canal BPPV, vHIT, canalolithiasis, vestibulo-oculomotor reflex

RIASSUNTO

Obiettivo. *Valutazione del VOR del canale semicircolare posteriore in fase acuta di VPPB da canalolitiasi posteriore.*

Metodi. *Valutazione del VOR del canale affetto mediante Video-Head Impulse test in 150 pazienti per la prima volta affetti da VPPB da canalolitiasi posteriore in fase acuta dopo la diagnosi ma prima dell'esecuzione della terapia liberatoria, dopo la risoluzione della fase acuta, un mese dopo la risoluzione. I risultati sono stati confrontati con quelli di un gruppo di 100 persone sane.*

Risultati. *Non sono state riscontrate significative differenze tra gruppo di studio e gruppo di controllo per i guadagni medi del VOR dei canali semicircolari tranne che l'indice normalizzato di asimmetria risultato più alto per i canali posteriori in fase acuta nel gruppo di studio. I guadagni medi del VOR dei canali posteriori affetti e controlaterali sani non appaiono correlati con quelli dei canali anteriori ipsi e controlaterale al canale affetto.*

Conclusioni. *Il vHIT non sembra strumento indispensabile in fase acuta di canalolitiasi posteriore, almeno in una popolazione al primo episodio acuto. Risultati differenti potrebbero essere riscontrati nelle forme recidivanti, resistenti alla terapia, di lunga durata o nelle varianti atipiche in cui la recidivanza, la lunga persistenza degli otoliti nel canale o un jam canalare potrebbero determinare danni maggiori.*

PAROLE CHIAVE: *BPPV, canalolitiasi posteriore, vHIT, riflesso vestibulo-oculomotore*

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent acute vertigo, accounting for up to 25% of observations in specialist clinics [1]. The de-

Received: July 29, 2020
Accepted: November 2, 2020

Correspondence
Luigi Califano
via A. Lepore 1, 82100 Benevento, Italy
Tel. +39 082 457407. Fax +39 082 457430
E-mail: luigi.califano@tin.it

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Califano L, Iannella R, Mazzone S, et al. The Video Head Impulse Test in the acute stage of posterior canal benign paroxysmal positional vertigo. Acta Otorhinolaryngol Ital 2021;41:69-76. https://doi.org/10.14639/0392-100X-N1033

tachment of otoconia and complex membranous fragments from the macula of the utriculum and their dislocation in the semicircular canals (SC) are considered to be its most likely pathogenesis. The posterior canal (PC) is involved in 70-90% of cases, the lateral canal (LC) in 5-30% and the anterior canal (AC) in 1-5% [1]. Otoconia may remain free-floating in a canal (canalolithiasis), adhere to the cupula of a canal making it sensitive to gravity (cupulolithiasis), or entirely/partially plugging the canal lumen causing blockage of the endolymphatic flow (canal jam).

Halmagyi and Curthoys [2] introduced the head impulse test (HIT) in vestibular examination. In its clinical use, the presence of catch-up saccades after a high speed and small amplitude movement of the head is observed by the naked eye immediately after the head impulse, with a specific field of application during acute unilateral vestibular deficit. Video head impulse test (vHIT) [3,4] is the instrumental evolution of HIT.

vHIT allows clinicians to objectively measure the functional activity of all SC considering both the vestibulo ocular reflex (VOR) gain and the presence of overt or covert saccades to verify whether or not canal function is compromised. vHIT is performed through unpredictable high speed and small amplitude head thrusts in the plane of each co-planar pair of SC: horizontal plane for right and left LCs (L-L plane); LARP plane for **L**eft **A**nterior and **R**ight **P**osterior canals; RALP plane for **R**ight **A**nterior and **L**eft **P**osterior canals. In LARP and RALP stimulations, the stimulus is along vertical planes, forwards and downwards for AC, and backwards and upwards for PC [4].

The literature reports that the study of LC allows evaluation of both VOR gain and possible presence of overt or covert catch-up saccades, whereas for vertical canals clinicians usually consider only the VOR gain, as the data on the refixation saccades in LARP and RALP planes are not yet well replicable [5].

Few data on vHIT are reported in literature during the acute stage of vertical canals BPPV. Mangabeira Albernaz [6] reported that in 12/14 cases of BPPV the canal gain was normal, except for a patient with contralateral AC hypofunction, whereas in another case the interpretation was ambiguous due to the coexistence of previous otological disease. Perez-Fernandez [7] found a normal canal VOR in 12 patients with AC BPPV. Fallahnezhad [8] reported a decreased gain of the affected PC in 16/29 cases of PC BPPV. Casani [9] described 2 cases of Lindsay-Hemenway syndrome (PC BPPV arising after an acute unilateral vestibular deficit) [10], in which the gain of the PC, which is usually not affected in the case of superior vestibular nerve deficit, was decreased. Çınar [11] reported that in 24 patients with PC BPPV both the PC gain and the interaural PC gain asymmetry were normal, before and after repositioning manoeuvres, and there were no significant differences with the control population; only 2/24 patients presented a decreased VOR gain of the affected PC. Karawani [12] found that in 3/3 cases of PC BPPV *"vHIT showed injury of the posterior semicircular canal"*. Aslan [13] wrote that *"20/30 patients who were diagnosed with vertical canal BPPV… had low VOR gains in the vertical canals"*. In patients with isolated loss of the PC function, Tarnutzer [14] reported 4 cases of PC BPPV out of 52 patients with this rare condition. Castellucci [15] described 3 patients with downbeat positional nystagmus and selective deficit of the VOR gain of the affected PC. Their finding supported the hypothesis of a partial canalith jam in the non-ampullary arm of the affected PC as the cause of the positional downbeat nystagmus.

An abstract has also been presented in which BPPV patients showed a higher VOR gain asymmetry of the vertical canals compared to healthy subjects [16].

All papers report few or very few cases: the largest series were reported by Çınar [11], describing 24 cases of PC BPPV, and by Aslan [13] reporting on 30 cases of vertical canal BPPV. Furthermore, the results of these two studies are not in accordance.

The possible impairment of VOR gain of the vertical canals has also been described in cerebellar lesions, but, in this case, other signs of central suffering are present [17]. Lerchundi described a new syndrome in elderly patients termed "bilateral posterior semicircular canal dysfunction", usually idiopathic, often associated with bilateral sensorineural hearing loss which could present positional downbeat nystagmus. Chronic gait instability is the most common complaint [18]. The possible age-related reduction of PC VOR gain has been previously described by Jimenez [19].

The aim of our study is to determine if vHIT is a useful diagnostic tool during the first acute episode of typical PC BPPV, evaluating if an altered response of the ampullar receptor is present in PC lithiasis.

Materials and methods

150 patients with the first diagnosed episode of unilateral PC BPPV were included in the study between January and December 2019 to evaluate the VOR gain of the affected canal through vHIT at three time points: a) during the early acute phase of the disease, prior to treatment with physical manoeuvres; b) immediately after resolution of the acute phase; and c) at one month.

Inclusion criteria were: 1. Age > 18 years; 2. First episode of BPPV; 3. Diagnosis of unilateral PC BPPV; 4. Onset of symptoms within one week prior to the examination; 5. Absence of any relationship between the onset of the

acute positional vertigo and any trauma (also in the form of an iatrogenic microtrauma, such as dental surgery); 6. Absence of previous acute vertiginous episodes; 7. Absence of other otological/neurological pathologies (Meniere's disease, otosclerosis, VIII cranial nerve schwannoma, vestibular neuritis, significant mono or bilateral hearing loss, demyelinating and neurodegenerative diseases, other rarer diseases); 8. Not migraineurs; 9. Absence of serious visual problems; 10. Ability to complete vHIT in all the stimulation planes.

The diagnosis of PC BPPV was based on the presence of paroxysmal positional upbeat nystagmus with torsional components beating towards the lowermost ear in ipsilateral Dix-Hallpike positioning, with reversal when returning to the sitting position [1].

Immediately after diagnosis, in the sitting position, patients underwent vHIT for study of lateral and vertical semi-circular canals function through stimuli on L-L, LARP and RALP planes, using a high-frame-rate (250 frames/sec,) video-oculography device (ICS Impulse®, Natus Medical) which tests only the right eye. The head mounted camera records eye and head angular velocities: the ratio between the two values is the gain VOR for that stimulation. Twenty artifact-free impulses were considered for LC, and 10 for RALP and LARP planes. The range of velocity for accepted impulses was set at 150-210°/sec for the lateral plane, at 110-150°/sec for the vertical planes. In testing LARP and RALP planes, the horizontal gaze direction must be aligned with the canal plane being tested, otherwise the measured vertical VOR gain decrease could mimic a canal deficit [20] (Fig. 1). Normative values were obtained in a healthy population of 100 individuals: 44 males, 56 females, considered as a control group. In the case of VOR gain significantly different from the control group (for posterior canal: 0.79 ± 2 SD = 0.55, see below), the test was repeated three times, considering the highest measurement for the evaluation.

The mean VOR gain of the affected PC was compared with data from the control group and from the contralateral healthy PC. Normalised asymmetry ratio (NAR) between the gains of the affected PC and of the contralateral healthy PC was calculated using the formula: NAR = (affected canal gain-healthy canal gain)/(affected canal gain+healthy canal gain) x 100. Consequently, its value is negative when the gain of the affected canal is lower than the gain of the healthy canal, and positive in the opposite case. A difference ≥ 15% was considered significant. We also analysed the correlations between the PC gain and both ipsilateral AC and contralateral AC gains; in the first case the link could be the anatomical contiguity between the ipsilateral PC and AC, and in the second case a functional link could be identified through the push-pull stimulation in LARP and RALP planes.

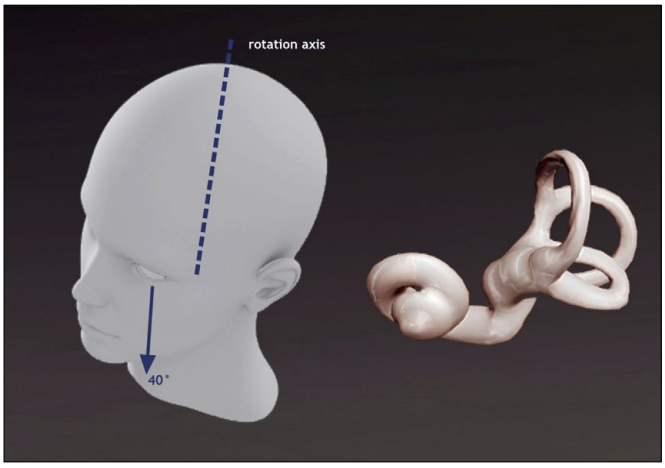


Figure 1. Coplanar orientation of gaze and vertical canals plane during a LARP stimulation (from McGarvie et al. [20], mod.).

After vHIT, patients underwent the Quick Liberatory Rotation manoeuvre (QLR) [21]. Patients were checked after 3, 7 and 10 days until a negative Dix-Hallpike test was observed. At this point, re-evaluation through vHIT was carried out in all patients. Finally, patients were scheduled for a follow-up evaluation at one month after resolution.

Statistical analysis was performed with descriptive statistics and confidence intervals of a mean, unpaired T-test, Pearson correlation test and Grubbs' test to detect an outlier, with significance level set at 0.05, 95% confidence interval, using Graph pad Quick Calcs software. The statistical power analysis was calculated both through Satorra and Saris's method - Structural Equation Model based on the Chi-squared test [22] – (good statistical power if power value ≥ 0.80) and through MacCallum's method- Structural Equation Model based on Root-Mean-Square Error of Approximation (RMSEA) [23] – (good fitting of the proposed model with RMSEA ≤ 0.8).

All procedures were in accordance with the ethical standards of the Ethics Review Board and with the 1964 Helsinki declaration and its later amendments.

Results

The control group consisted of 100 individuals, 56 females and 44 males, with a F/M ratio of 1.27 and a mean age of 58. ± 13.21 years (range 19-81 years, median 59.5 years).

vHIT assessment

LC: mean VOR gain 0.99 ± 0,113; PC: mean VOR gain 0.79 ± 0.121; AC: mean VOR gain 0.73 ± 0.094. Differences between the age classes were not significant, except for patients > 75 years. In this subgroup (8 patients), the mean

VOR gain of LC was 1.06 ± 0.051, which was significantly higher than the mean VOR gain of LC in individuals < 75 years (0.98 ± 0,101, p = 0.028). In 5 of 200 PC, the gain was between 0.56 and 0.60. No outlier was detected. Mean NAR between right and left PC was 3.8 ± 7.76. The maximum NAR was 13.1% (absolute value). The correlations between the mean VOR gain of PC and the mean VOR gains of both the ipsilateral AC and the contralateral AC were weak and not significant, for both ipsilateral PC and AC (r = 0.1235; p = 0.10561), and for PC and contralateral AC (r = 0.0987: p = 0.16754).

The study group consisted of 150 patients, 91 females and 59 males, with a F/M ratio of 1.54, and a mean age of 60.6 ± 13.16 years (range 19-91 years, median 59 years). The mean age was not significantly different from the control group (p = 0.95). Statistical power for Structural Equation Model based on Chi-squared test was 0.8, RMSEA was 0.05.

vHIT: pre-treatment assessment

The mean VOR gains were: 0.75 ± 0.152 for the affected PC; 0.81 ± 0.113 for the healthy PC; 0.71 ± 0.098 for AC; 0.98 ± 0.124 for LC. In 10/150 patients (6.7%) the VOR gain of the affected PC was ≤ 0.55 (range 0.36-0.50), i.e. two standard deviations less than the mean PC VOR gain of the control group; in two of these patients (both were > 70 years) the healthy contralateral PC VOR gain was also ≤ 0.55. Only one case among the VOR gains of the affected PC was considered as furthest from the other values, but was not a significant outlier. Mean VOR gain differences between both the affected PC and the contralateral healthy PC *vs* the control group were not significant (respectively, p = 0.33; p = 0.18). The mean VOR gain difference between the affected PCs and the healthy contralateral canals was significant (p = 0.01) due to the mild mean VOR gain increase of the non-affected PC and the mild mean VOR gain decrease of the affected PC compared to the PC mean VOR gain of the control group. The mean NAR between affected and healthy PC was -7.1 ± 9.65 (range from -38.6% to +6.9%), which was significantly different from the control group (p = 0.004). The correlation between the mean VOR gains of AC and PC was weakly positive, but not significant: for ipsilateral PC and AC, r = 0.178; p = 0.4; for LARP and RALP r = 0.24076, p = 0.1. In the study group, overt catch-up saccades in the affected PC plane were observed in six patients with the lowest observed VOR gains (Fig. 2). The mean number of liberatory manoeuvres necessary to cure PC BPPV was not significantly different between the subgroup with either normal or not far from the normal VOR gain- within 1 standard deviation (140 patients), and the subgroup of 10 patients with PC VOR gain ≤ 0.55, which was far more than 2 standard deviations from the normal value (mean: 2.04 ± 0.65 *vs* 2.06 ± 0, 74, p = 0.9).

Data of pre-treatment assessment from the control and study groups are reported in Table I.

vHIT: post-treatment assessment

The mean VOR gains were 0.77 ± 0.127 for treated PC; 0.81 ± 0.161 for healthy PC; 0.73 ± 0.144 for AC; 0.98 ± 0.212 for LC. In 9/10 cases with pre-treatment VOR gain of the affected PC ≤ 0.55, VOR gain improved but did not reach a normal level (new range: 0.57-0.64); in the lattest case the post-treatment gain was normal (0.74, pre-treatment value: 0.36). The mean VOR gain difference between pre-treatment and post-treatment values of the affected PC was not significant (0.77 *vs* 0.75, p = 0.5), whereas

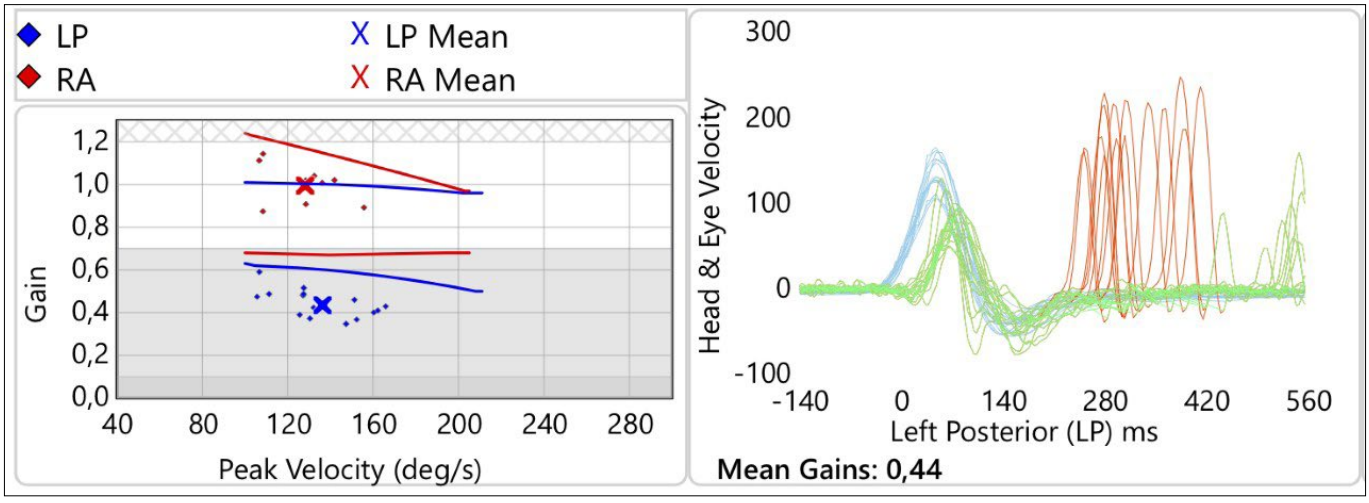


Figure 2. vHIT: a case of low VOR gain in an acute left posterior canal BPPV with overt scattered catch-up saccades.

Table I. vHIT assessment in the control and study groups (pre-treatment assessment).

	Lateral canal mean VOR gain	Affected posterior canal mean VOR gain	Healthy posterior canal mean VOR gain	Anterior canal mean VOR gain
Control group	0.99 ± 0.113	-	0.79 ± 0.121	0.73 ± 0.094
Study group	0.98 ± 0.124	0.75 ± 0.152*	0.81 ± 0.113*	0.71 ± 0.098

**Significant difference in the study group between VOR gains of affected vs. healthy posterior canals (* p = 0.01). Differences between VOR gains of all semi-circular canals in the control vs. study groups are not significant.*

the difference with the mean VOR gain of contralateral non-affected PC remained significant (0.77 vs. 0.81, p = 0.04). No outlier was detected. The mean NAR between affected and healthy PC was -5.4 ± 7.0, which was not significantly different from the pre-treatment value (p = 0.156) and not significant compared to the control group (p = 0.09).

In both the pre-treatment and post-treatment assessments, no significant difference was observed between the gains of AC and LC in the control and study, and in the VOR gain differences for age classes for vertical canals, whereas the difference was not significant for LC in the subgroup > 75 years (15 patients), in which the mean VOR gain was higher (p = 0.07).

One-month assessment

82 patients attended the scheduled examination. All were disease-free at Dix-Hallpike test; three reported mild residual dizziness. The mean VOR gains were 0.78 ± 0.215 for the treated PC; 0.80 ± 0.248 for the healthy PC; 0.73 ± 0.199 for AC; 0.98 ± 0.178 for LC. In 3 cases with pre-treatment VOR gain of the affected PC ≤ 0.55, VOR gain was normal (new range: 0.71-0.77). No outlier was detected. The difference between the mean VOR gains of affected and healthy PC was no longer significant (p = 0.58). The mean NAR between treated and healthy PC was -4.9 ± 8.4, not significantly different from the control group (p = 0.36) and from the pre-treatment value (p = 0.11). Data of PC VOR gain in the study group are summarised in Table II.

Discussion

BPPV is the most frequent acute vertigo and detachment of otoconia from the utricular macula is considered the underlying pathophysiologic mechanism. Otoconia can be either free-floating in a semicircular canal or adherent to a semicircular canal cupula; rarely they can provoke a "canal jam". Since 2001 the possible role of the canal jam in some forms of canalolithiasis has been reported [24]. Later, other authors reported the same mechanism in rare cases of positional vertigo. Luis [25] reported a case of direction-fixed nystagmus lateral canal BPPV characterised by a deficiency of the cupular-endolymph high-frequency system dynamics due to the presence of a block of the endolymphatic flow in the affected canal. The deficiency was resolved after success of the liberatory manoeuvre. Castellucci [26] described an analogous case with isolated lateral canal hypofunction, ascribed to a canal jam, that was resolved by repeated head shaking and conversion into a typical geotropic LC BPPV. Schubert [27] considered that in some cases of direction-fixed nystagmus LC BPPV, the otoconial jam acts as a "false" cupula, which causes a modification in velocity but not in the direction of the nystagmus that depends on head position. As already mentioned, Castellucci [15] described also some cases regarding the vertical canals. In these cases, the authors' interpretation was that a canal jam in the non-ampullary tract of the PC caused a partial block of the endolymphatic flow. Acting as a "low-pass filter", the jam allowed cupular activation by otoconia movements but not a good cupular response to high frequency impulses, as in vHIT. Obviously, this mechanism may be applied both to LC BPPV and to PC BPPV. Thus, the canal jam would act by modifying the endolymphatic dynamics of the affected canal.

Except in the specific case of a presumed canal jam, which is theoretically conceivable in only a small minority of cases, pathogenetic hypotheses involving mechanic factors

Table II. vHIT assessment of the posterior canal in the study group.

	Affected posterior canal Mean VOR gain	Healthy posterior canal Mean VOR gain
Pre-treatment	0.75 ± 0.152*	0.81 ± 0.113*
Post-treatment	0.77 ± 0.127**	0.81 ± 0.161**
One-month evaluation	0.78 ± 0.215***	0.80 ± 0.248***

Significant differences in the study group between VOR gains of affected vs. healthy posterior canals in pretreatment evaluation and immediate post-treatment evaluation (p = 0.01; ** p = 0.04). Not significant difference at the one-month evaluation (*** p = 0.58).*

give no immediate answer about a possible VOR gain impairment of the affected canal.

Caloric and rotatory techniques have been used to approach the problem. A transient caloric hypofunction was pointed out in the case of LC BPPV [28]. A strong cold-water caloric stimulus (24°C) had a significant inhibitory effect on the ipsilateral horizontal high-acceleration VOR-gain, assessed with vHIT, emphasising the importance of the non-linear pathway when vestibular organs are probed with high-acceleration stimuli [29]. These data were also confirmed through cold stimulation in the prone position, which has physiologic excitatory effects on LC cupula. This might occur because the cupular deviation in either direction elicits a partial mechanical and electrophysiological saturation, decreasing cupular sensitivity with respect to high acceleration stimuli [30]. In 6 patients with PC BPPV, the pendular rotation test in a head-tilted position gave a lower response of PC respect to AC [31]. In patients with BPPV, during a sinusoidal rotation VOR gains of the vertical canals were not changed in comparison with normal subjects [32].

Since 2013, the availability to test all six semi-circular canals through vHIT has allowed clinicians to evaluate the VOR gain for each of them, using specific planar stimuli: L-L plane for LC, LARP plane for Left AC and Right PC, RALP plane for Right AC and Left PC [4]. At present, vHIT is probably the most effective tool to evaluate the semi-circular canals function.

The high incidence of PC BPPV opened a window to study PC function during the acute stage of the disease with vHIT. So far, few papers have been published on this topic. As mentioned, a limited number of cases have been reported, with contrasting results about the functional impairment of PC activity. Fallahnezhad [8], Karawani [12] and Aslan [13] reported a significant lowering of PC VOR gain during the acute stage of PC BPPV. Data from Casani [9] in two cases of Lindsay-Hemenway syndrome are not easily understandable: the reported posterior canal VOR gain deficit could be due either to the previous acute vestibular neuritis as in our opinion as the Authors meant or it could be due to a secondary canalolithiasis. It is also worth mentioning the data reported by Castellucci et al. [15] about a rare variant, apogeotropic PC BPPV, in which, at least in some cases, a PC incomplete jam could be hypothesised. In their cases, vHIT was also a useful tool to discriminate between the involvement of either the PC or the contralateral AC.

In typical PC BPPV, the mechanism provoking the paroxysmal nystagmus is considered to be ampullophugal endolymphatic flow in the affected PC induced by the free floating otoconia movement away from the cupula towards the most inferior portion of the canal during Dix-Hallpike test. According to Ewald's II law, ampullophugal flow excites the PC cupular receptor to provoke specific oculomotor reflex responses through the activation of the contralateral superior rectus and ipsilateral inferior obliquus muscles, responsible for the fast phase vectors.

Does damage to the PC ampulla actually exist or should abnormal responses be considered as a result of an anomalous stimulus acting on a normal receptor? In other words, are we discussing of a purely mechanical disorder of the inner ear or does the mechanical disorder provoke either deficient or irritative responses of the ampullar receptor?

We analysed 150 patients exhibiting the first episode of typical PC-BPPV. Mean VOR gains of all semi-circular canals were not significantly different between the study and control. In particular, in the pre-treatment phase, the mean VOR gain of the affected PC was not significantly different compared to the control group ($p = 0.33$), but significantly lower than the mean VOR gain of the healthy contralateral PC ($p = 0.01$); this significant difference was also maintained in the post-treatment phase ($p = 0.04$), despite a mild increment in the mean VOR gain of the affected PC, which was not significant with respect to the pre-treatment assessment ($p = 0.5$). At the one-month evaluation, the difference between the mean VOR gains of affected and healthy PC was no longer significant ($p = 0.58$).

According to our results, PC VOR gain does not seem to be significantly affected in patients with typical PC BPPV, but in a small subgroup of 10 patients (6.7%) with a different behaviour it does exist. In these cases, the PC VOR gain was ≤ 0.55, our cut-off value for a clearly impaired PC function, within a range of 0.36-0.50, and, interestingly, after the resolution of the acute phase, it improved in all patients. It appears likely that in these cases the VOR gain deficit was directly due to the canalolithiasis effects on the ampullar receptor stimulation. In 2 patients > 70 years with bilateral PC VOR gain < 0.55, a possible age related reduction of PC VOR gain [19] was considered possible, but the successive normalisation of the values during the follow-up excluded this diagnosis.

The correlation of the mean VOR gain of AC with the mean VOR gain of the affected PC was weakly positive but not significant, as also seen in the control group. This means that both the ipsilateral AC in a possible anatomical contiguity relationship and the contralateral AC in a possible functional relationship during LARP and RALP push-pull stimulations seem to be functionally unaffected by the hydrodynamic changes induced by PC canalolithiasis.

Our data suggest that in the acute phase of PC BPPV there is usually no alteration in the canal receptor response as shown by the normality of the affected PC mean VOR gain, as in the control group. Paroxysmal positioning nystagmus, which is the primary sign of the disease, has to be inter-

preted as being due to a normal receptor response to an abnormal stimulus, and not to receptor dysfunction in terms of either canalar hyporeflexia or hyperreflexia.
However, a minority of cases (6.7%) in which the PC VOR gain was significantly reduced, it does exist, with a trend in recovery immediately after resolution of the disease through a liberatory manoeuvre. These cases did not show any difference in the quantitative and qualitative features of the diagnostic paroxysmal positioning nystagmus, as evidence of the preserved ability of the receptor to respond to the stimulus caused by the otoconial movement in the canal. It is therefore likely that in these cases the reduced response may be related to the presence of otoconia in the canal determining in a sitting position a reduction of the stimulus provided during vHIT. In fact, at post-treatment assessment an improvement of the affected PC VOR gain was observed in all cases, and in one case even its normalisation, whereas at the one-month visit all PC VOR gains were normal.
The significant difference between the mean VOR gains of the affected PC and the contralateral PC, in both pre-treatment and immediate post-treatment assessments, is not easily justifiable. The pair of PC does not respond to the same push-pull stimulus, so that a decrease of the inhibitory stimulus of a weaker affected canal cannot be hypothesised when it is in a "pull" situation during vHIT, as well as the responses of the AC of the affected side, which is the canal functionally related with the contralateral PC during LARP and RALP planes stimulations, were normal. Again, the data cannot be justified by the decrease of the inhibitory quota on the global response in either the LARP or in the RALP planes provided by a normal contralateral AC when PC is stimulated. However, even if in a numerically smaller population, the difference between affected and healthy PCs was no longer significant at the one-month control.
It should also be noted that our series relates to people suffering for the first time from acute BPPV. It cannot be excluded that in a differently selected population, i.e. subjects with multiple recurrence of the disease, the situation of the canal receptor may be different. We believe that future clinical series should take this potential diversity into account.

Conclusions

vHIT appears to play an ancillary role in the clinical management of patients suffering from acute PC BPPV. However, vHIT can provide useful data for better understanding of the pathology, identify possible otological comorbidities, help to identify the affected canal, and can have forensic value in highlighting possible persistent canal damage.
Keeping in mind these considerations, its routine performance in acute PC BPPV does not appear to be clinically essential, recalling, however, the selected population of our study and the current limit that there are still very limited data in the literature regarding vHIT results in frequently recurrent forms, in long-term forms, in non-responsive forms, in atypical variants, which are specific issues in which this test could have relevance. In these cases, hypothetically, otoconia could be either partially entrapped or embedded in some narrow portion of the affected canal causing their anomalous evolution. Interesting and perhaps different data could be obtained in forms we could label as "cupulolithiasis" in which the PC receptor could be more directly affected. The scientific method is based on hypotheses and their demonstration: all hypotheses need objective data to be supported. Ad hoc studies in those subgroups are thus required. Nonetheless, even in typical PC BPPV, the information provided by vHIT is definitely useful for a more complete assessment of the vertiginous patient.

References

1 Von Brevern M, Bertholon P, Brandt T, et al. Benign paroxysmal positional vertigo: diagnostic criteria. Consensus document of the Committee for the Classification of Vestibular Disorders of the Bárány Society. J Vestib Res 2015;25;105-17. https://doi.org/10.3233/VES-150553

2 Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. Arch Neurol 1988;45:737-9. https://doi.org/10.1001/archneur.1988.00520310043015

3 MacDougall HG, Weber KP, McGarvie LA, et al. The video head impulse test diagnostic accuracy in peripheral vestibulopathy. Neurology 2009;73:1134-41. https://doi.org/10.1212/WNL.0b013e3181bacf85

4 MacDougall HG, McGarvie LA, Halmagyi GM, et al. Application of the video head impulse test to detect vertical semicircular canal dysfunction. Otol Neurotol 2013;34:974-9. https://doi.org/10.1097/MAO.0b013e31828d676d

5 Singh NK, Govindaswamy R, Jagadish NV. Test-retest reliability of video head impulse test in healthy individuals and individuals with dizziness. J Am Acad Audiol 2019;30:744-52. https://doi.org/10.3766/jaaa.17080

6 Mangabeira Albernaz PL, Zuma E Maia FC. The video head impulse test. Acta Otolaryngol 2014;134:1245-50. https://doi.org/10.3109/00016489.2014.942439

7 Perez-Fernandez N, Martinez-Lopez M, Manrique-Huarte R. Vestibulo-ocular reflex in patients with superior semicircular canal benign paroxysmal positional vertigo (BPPV). Acta Oto-Laryngologica 2014;134:485-90. https://doi.org/10.3109/00016489.2013.871750.

8 Fallahnezhad T, Ghahraman MA, Farahani S, et al. Vestibulo-ocular reflex abnormalities in posterior semicircular canal benign paroxysmal positional vertigo: a pilot study. Iran J Otorhinolaryngol 2017;29:269-74.

9 Casani AP, Cerchiai N, Navari E. Paroxysmal positional vertigo despite complete vestibular impairment: the role of instrumental assessment. Acta Otorhinolaryngol Ital 2018;38:563-8. https://doi.org/10.14639/0392-100X-1549

10 Hemenway W, Lindsay J. Postural vertigo due to unilateral sudden partial loss of vestibular function. Ann Otol Rhinol Laryngol 1956;65:692-706. https://doi.org/10.1177/000348945606500311

11 Çınar Y, Bayram A, Culfa R, et al. Analyses with the video head

impulse test during the canalith repositioning maneuver in patients with isolated posterior semicircular canal benign paroxysmal positional vertigo. Turk Arch Otorhinolaryngol 2018;56:81-4. https://doi.org/10.5152/tao.2018.3166

[12] Karawani K, Bielińska M, Nowosielska-Grygiel J, et al. Comparative evaluation of the diagnostic value of the VHIT and Dix-Hallpike test in patients with balance system disorders in out-patient healthcare practice and expertise preparation. Otolaryngol Pol 2018;72:36-42. https://doi.org/10.5604/01.3001.0012.5421

[13] Aslan H, Pınar E, Aladağ İ, et al. Our results of VHIT on BPPV. Eur J Rhinol Allergy 2018;1:12-4. https://doi.org/10.5152/ejra.2018.56708

[14] Tarnutzer AA, Bockisch CJ, Buffone E, et al. Association of posterior semicircular canal hypofunction on video-head-impulse testing with other vestibulo-cochlear deficits. Clin Neurophysiol 2017;128:1532-41. https://doi.org/10.1016/j.clinph.2017.04.029

[15] Castellucci A, Malara P, Delmonte S, et al. A possible role of video-head impulse test in detecting canal involvement in benign paroxysmal positional vertigo presenting with positional downbeat nystagmus. Otol Neurotol 2020;41:386-91. https://doi.org/10.1097/MAO.0000000000002500

[16] Guan Q, Zhang L, Hong W, et al. Video head impulse test for evaluation of vestibular function in patients with vestibular neuritis and benign paroxysmal positional vertigo. J Zhejiang Univ (Med Sci) 2017;46:52-8.

[17] Choi J-Y, Kim H-J, Kim J-S. Recent advances in head impulse test findings in central vestibular disorders. Neurology 2018;90:602-12. https://doi.org/10.1212/WNL.0000000000005206

[18] Lerchundi F, Laffue AH, Olivier M, et al. Bilateral posterior semicircular canal dysfunction: a new finding with video head impulse test. J Neurol 2020;267:2347-52. https://doi.org/10.1007/s00415-020-09793-5

[19] Jiménez GG, Pérez Fernandez N. Reducción de la ganancia del canal semicircular posterior en el test del impulso cefálico con la edad. Estudio observacional. Acta Otorrinolaringol Esp 2016;67:15-22. https://doi.org/10.1016/j.otorri.2014.12.002

[20] McGarvie LA, Martinez-Lopez M, Burgess AM, et al. Horizontal eye position affects measured vertical VOR gain on the video head impulse test. Front Neurol 2015;6:58. https://doi.org/10.3389/fneur.2015.00058

[21] Califano L, Capparuccia PGG, Di Maria D, et al. Treatment of benign paroxysmal positional vertigo of posterior semicircular canal by "Quick Liberatory Rotation Manoeuvre". Acta Otorhinolaryngol Ital 2003;23:161-7.

[22] Satorra A, Saris WE. Power of the likelihood ratio test in covariance structure analysis. Psychometrika 1985;50:83-90. https://doi.org/10.1007/BF02294150

[23] MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. Psychol Methods 1996;1:130-49. https://doi.org/10.1037/1082-989X.1.2.130

[24] von Brevern M, Clarke AH, Lempert T. Continuous vertigo and spontaneous nystagmus due to canalolithiasis of the horizontal canal. Neurology 2001;56:684-6. https://doi.org/10.1212/wnl.56.5.684

[25] Luis L, Costa J, Vaz Garcia F, et al. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials. Otol Neurotol 2013;34:743-7. https://doi.org/10.1097/MAO.0b013e318287f343

[26] Castellucci A, Malara P, Brandolini C, et al. Isolated horizontal canal hypofunction differentiating a canalith jam from an acute peripheral vestibular loss. Am J Otolaryngol 2019;40:319-22. https://doi.org/10.1016/j.amjoto.2018.12.005

[27] Schubert MC, Helminski J, Zee DS, et al. Horizontal semicircular canal jam: two new cases and possible mechanisms. Laryngoscope Investig Otolaryngol 2020;5:163-7. https://doi.org/10.1002/lio2.352

[28] Domènech Campos E, Armengol Canceller M, Barona de Guzman R. Vértigo posicional paroxístico benigno del canal horizontal. Acta Otorinolaringol Esp 2006;57:446-9. https://doi.org/10.1016/s0001-6519(06)78746-5

[29] Tamás LT, Weber KP, Bockisch CJ, et al. Cold thermal irrigation decreases the ipsilateral gain of the vestibulo-ocular reflex. Ear Hear 2017;38:e193-e9. https://doi.org/10.1097/AUD.0000000000000398

[30] Tamás LT, Obrist D, Avan P, et al. Biasing the semicircular canal cupula in excitatory direction decreases the gain of the vestibulo-ocular reflex for head impulses. J Vestib Res 2019;29:281-6. https://doi.org/10.3233/VES-190681

[31] IIda M, Igarashi M, Naitoh A, et al. Evaluation of the vertical canal function by the pendular rotation test: a study on patients with benign paroxysmal positional vertigo. ORL J Otorhinolaryngol Suppl 1997;59:269-71. https://doi.org/10.1159/000276951

[32] Sekine K, Imai T, Morita M, et al. Vertical canal function in normal subjects and patients with benign paroxysmal positional vertigo. Acta Otolaryngol 2004;124:1046-52. https://doi.org/10.1080/00016480410018061

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:77-83; doi: 10.14639/0392-100X-N0502

VESTIBOLOGY

Recurring paroxysmal positional vertigo: evaluation of the vascular factor

La valutazione del fattore vascolare nella vertigine parossistica ricorrente

Giampiero Neri[1], Giulio Romano Filograna Pignatelli[1], Alessandro Pacella[1], Rocco Ortore[2], Laith Khasawneh[3]

[1] *Department of Neurosciences Imaging and Clinical Sciences, University Gabriele D'Annunzio of Chieti-Pescara, Italy*
[2] *Department of Otolaryngology (ENT), IRCCS Hospital Home for the Relief of Suffering, San Giovanni Rotondo, Italy*
[3] *Department of General and Special Surgery, Hashemite University of Jordan, Zarqa, Jordan*

SUMMARY

To evaluate the effective incidence of vascular factor in the recurrence of benign paroxysmal positional vertigo (BPPV), we studied 50 subjects, 32 affected by idiopathic recurrent BPPV (study group) and 18 healthy subjects (control group). All subjects underwent complete otoneurological balance and haemodynamic evaluation by extracranial colour-coded duplex sonography (ECCS) of vertebral arteries (VA) with indication of arterial flow in ml/min, and retinal fluorangiography (FAG). The ECCS of 19 patients (59.3%) within the study group presented a reduction in vertebral arterial flow, exceeding the limits established by normative values (< 100 ml/min). In all cases, the same side was affected by BPPV, emphasised by vertebral hypoperfusion. The remaining 13 patients (40.6%) showed an arterial vertebral flow entirely within the normative values. The FAG excluded qualitative alterations of the cerebral microcirculation. The ECCS demonstrated that 59.3% of the study group showed a significant reduction in vertebral arterial flow ipsilateral to the semicircular canal affected by BPPV. This increased to 68.75% when the flow difference (D) between both the vertebral arteries were considered and reached 71.8% when vascular risk factors were evaluated. We conclude that reduced perfusion of the vestibular structures makes an already critical situation even more difficult, which can eventually develop into labyrinth suffering. The absence of fluorangiographic signs suggests that the labyrinthine neuroepithelium is much more sensitive to hypoperfusion than the retina. We hypothesise that this ischaemic situation could degenerate utricular macula, otolith detachment, leading to the development of recurrent BPPV. This risk situation for the labyrinth can also be revealed by the evaluation of three parameters: presence of vascular risk factors, reduction of vertebral flow < 100 ml/min and the difference in flow between the 2 vertebral arteries > 29 ml/min.

KEY WORDS: BPPV, cerebral blood flow, EcoColorCodedSonography, ECCS, vertebral flow, vascular vertigo, retinal fluorangiography

RIASSUNTO

La vascolarizzazione dell'orecchio interno è termino-terminale, questo espone il labirinto a danni da ipossia o ipossia-rivascolarizzazione. Riduzioni ulteriori di flusso ematico potrebbero essere alla base non solo della insorgenza, ma anche della maggiore frequenza di recidive della vertigine parossistica. Allo scopo di valutare l'incidenza di questi fattori abbiamo studiato 50 pazienti, 32 con VPPB ricorrenti e 18 soggetti sani. Tutti i soggetti sono stati sottoposti a esame otoneurologico completo, a valutazione emodinamica con ecocolordoppler (ECD) delle arterie vertebrali con indicazione del flusso in ml/min e a fluorangiografia retinica (FAG). Nel gruppo di studio 19 pazienti (59,3%) all'ECD hanno presentato una riduzione del flusso vertebrale rispetto ai valori di normalità (< 100 ml/min). In tutti i casi il lato con maggiore ipoafflusso era lo stesso affetto da VPPB. I restanti 13 pazienti (40,6%) avevano valori ECD nella norma. La FAG non ha evidenziato alterazioni vascolari del microcircolo. L'esame ultrasonografico ha dimostrato quindi che il 59% dei soggetti con VPPB ricorrenti ha una riduzione significativa nel flusso vertebrale omolaterale al lato affetto e che questo valore aumenta al 68,75% se la differenza del flusso tra le due arterie vertebrali è maggiore del valore soglia riscontrato nei soggetti normali e al 71,8%, se viene considerata anche la presenza di fattori di rischio. In conclusione, lo

Received: October 11, 2019
Accepted: April 13, 2020

Correspondence
Giampiero Neri
Department of Neurosciences Imaging and Clinical Sciences, University Gabriele D'Annunzio of Chieti-Pescara, Italy, 136-65125
Fax +39 0871 358550
E-mail: giampiero.neri@unich.it

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Neri G, Filograna Pignatelli GR, Pacella A, et al. Recurring paroxysmal positional vertigo: evaluation of the vascular factor. Acta Otorhinolaryngol Ital 2021;41:77-83. https://doi.org/10.14639/0392-100X-N0502

studio evidenzia che il labirinto è molto più sensibile della retina all'insulto ischemico. Infatti, anche in assenza di segni retinici di alterazione del microcircolo, una ridotta perfusione labirintica, precipitando la già precaria irrorazione del labirinto, può determinare la degenerazione della macula utricolare portando al distacco otoconiale e al conseguente sviluppo della VPPB ricorrente. Questa situazione di rischio per il labirinto inoltre può essere svelata dalla valutazione di tre parametri: la presenza di fattori di rischio vascolare, la riduzione del flusso vertebrale < 100 ml/min. e la differenza di flusso tra le 2 arterie vertebrali > 29 ml/min.

KEY WORDS: *VPPB, flusso ematico cerebrale, ecocolordoppler, flusso vertebrale, vertigine vascolare*

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent cause of vertigo [1]. The number of relapses is variable, but it has been observed that 27% of patients suffer from at least one new episode and of these 14% have one episode, 10% two relapses and about 3% of patients have 3 episodes per year [2]. In 50% of cases, relapses occur within the first 6 months from the onset of the disease. The strong social impact of BPPV has encouraged continuous clinical research that has revealed many aspects of this pathological condition. However, the reasons for the frequent recurrence of idiopathic BPPV, without apparent cause, are yet to be clarified [3].

A new vertigo episode after a pause almost two months must be interpreted as a new event, where an unknown "facilitating factor" has a relevant role [4].

At present, there are no diagnostic exams that allow us to observe this "facilitating factor", but when the recurrence is verified, we are normally oriented towards a hypothetical vascular cause [5].

According to Baloh [6], vertigo is often caused by vertebrobasilar insufficiency, and is present in many diseases caused by vascular damage, such as cerebellar infarct, lateral medullary infarct, and labyrinth and pons-medullar tract infarct. In two cases, hearing loss was associated with vertigo and caused by either vessel occlusion or simple reduction of vascular flux [7,8].

The vascularisation of the inner ear depends on the internal auditory artery, a branch of the basilar artery or anterior inferior cerebellar artery, which is a terminal vessel and make the labyrinth sensitive to ischaemic phenomena [9].

The experimental study on blood flow distribution in the Circle of Willis [10,11] showed that reductions in cerebral capillary arterial flow in the posterior circulation are directly proportional to reductions in the vertebral arteries flow. Extracranial colour-coded duplex sonography of vertebral arteries (ECCSVA) can be a useful and low-cost screening tool for the evaluation of posterior cerebral circulation [12]. It has been demonstrated, furthermore, that the blood that comes from the two vertebral arteries, after having engaged in the basilar artery, flows separately and is divided from a central zone where the flux is absent, defined "dead point" [13]. This indicates that the perfusion of the labyrinth is not only proportional to the vertebral blood flow, but can also depend on the side in which the flow is reduced.

It is well known that common variations of size and flow capacity between the two vertebral arteries exist, which may range from a slight asymmetry to marked hypoplasia of one side, with prevalence of unilateral vertebral artery hypoplasia between 2 to 25% [14]. This has also been observed in patients with vertebrobasilar insufficiency [15] and Seidel [16] and Jeng [17] reported that the vertebral artery flow is considered pathological when it is lower than 100 ml/min.

The aim of our study is to evaluate the incidence of the vascular factor in recurring BPPV with quantitative analysis of vertebral flow using ECCSVA and the analysis of cerebral microcirculation using retinal fluorangiography (FAG) [18].

Materials and methods

Fifty consecutive samples were recruited from January 2016 to December 2017 in our Audiovestibology Unit of the ENT Department in the University Hospital SS Annunziata in Chieti. Of these, 32 patients were affected by recurring idiopathic BPPV with a frequency of recurrence not less than 3 episodes/year, and the remaining 18 subjects were enlisted as the control group.

The exclusion criteria were a recurrence frequency of < 3 episodes/year; labyrinthine disease different from BPPV, age 70 years and over; a history of trauma or cervico-facial district contusion; and degenerative neurological pathologies.

All patients were informed about the study in detail, which adhered to the Declaration of Helsinki and ICH-GCP, GU 184/2003. Written informed consent was obtained from all patients.

All subjects underwent physical ENT examination, pure tone audiometry, vestibular spontaneous and positional testing using videonystagmoscopy and bithermal caloric evaluation according to Fitzgerald-Hallpike.

The haemodynamic quantitative analysis of vertebral artery flow, expressed in ml/min, was obtained by the same operator using ECCS Mindray DC-70 through the acoustic windows from the transverse processes of the vertebrae in one segment (or more) of the V2 section. The Doppler waveforms and flux were obtained with an angle of insonation of 60° or less. On the basis of the literature [17], we considered

that a vertebral artery flow of < 100 ml/min was valid indicator of vertebral artery hypoperfusion.
Evaluation of cerebral microcirculation was investigated using retinal fluorescein angiography (FAG).
Finally, we evaluated in each person of both groups the flow difference between the vertebral arteries (D) considering as normal the highest difference found in the control group (29 ml/min) (Tab. I). Statistical analysis was performed using independent-samples t-test for $P \leq 0.05$ to determine if a difference exists between two means of two independent groups on continuous dependent variables.

Results

Fifty subjects, 36 females (72%) and 14 males (28%), were included in this study; 32 patients (study group) had recurring BPPV and 18 subjects (control group) had no vertigo or vascular pathologies. Audiometry results showed age-related disorders in all 50 subjects.
The study population was composed of 22 females (69%) and 10 males (31%) with age ranged between 24 and 70 years (average age 52 years). In this sample, 12 patients (37.5%) presented a documented pathological vascular risk (Tab. I) while in 20 cases (62.5%), BPPV was idiopathic. The most common vascular risk factors were hypertension (28%), diabetes (18.7%) and hyperlipidaemia (15.6%). Types of BPPV were found to be distributed as right posterior in 11 (34%), right lateral in 6 (18.7%), left posterior in 10 (31%) and left lateral canal in 5 (15%).
In the study group, on bithermal caloric testing 14 patients (43%) were found to have labyrinthine hypofunction of the affected side.
Ultrasonography in the control group showed normal vertebral flow in all subjects with values between 104 and 218 ml/min (average 149.6) in the right side, 109 and 195 ml/min (150.3) in the left side end with a D between 2 and 29 ml/min. The ECCSVA in the study group presented in 19 patients (59.3%) a reduction in arterial vertebral flow, exceeding the normal range (< 100 ml/min) between 26 and 96 ml/min, 13 patients (40.6%) demonstrated hypoperfusion on only one side, and 6 patients (18.75%) presented a reduction on both sides. In all pathological cases (64%), BPPV was present on the side where the blood flow was most decreased. The remaining 13 patients (40.6%) had a normal VA flow (> 100 ml/min) (Tabs. II, III).
In the 12 patients (37.5%) with vascular risk, we detected hypoperfusion in 9 subjects (75%): unilateral in 4 subjects and bilateral in 5.
The hypoperfusion in the 20 patients (62.5%) with idiopathic BPPV was unilateral in 8 (25%) and bilateral in 2 subjects.
In the study group, the D between the two VAs observed in each patient was superior to the normality range in 21 cases (65.6%): 9 patients (28.1%) with vascular risk and 12 patients (37.5%) with idiopathic BPPV.
FAG exam in all patients excluded qualitative and dynamic alterations of the retinal situation that could explain the eventual damage at the microcirculatory level.
The results of the control group are shown in Table I.

Table I. Vertebral flow in ml/min in the control group. We hypothesised that the highest difference in flow between the two arteries (Δ = 29 ml/min) was the normal limit.

Patient	Age	Right Vert. A. (ml/min)	Left Vert. A. (ml/min)	Δ
C.G.	56	143	132	11
C.V.	24	108	125	-17
D.A.	47	165	176	-11
D.R.M.	34	104	115	-11
D.F.T	43	115	110	5
P.T.	62	160	188	-28
D.R.	49	172	170	2
G.A.	63	151	129	22
G.L.	26	104	109	-5
L.E.	65	168	157	11
G.S.	68	166	160	6
P.R.	45	149	165	-16
R.M.	50	115	131	-16
S.F.	61	157	186	-29
S.L.	46	170	154	16
M.O.	67	165	158	7
T.A.	60	163	145	18
V.M.	52	218	195	23
	Mean	Mean	Mean	D
	51	149.6	150.3	23
		Standard Deviation		
		28.2		

Discussion

BPPV is a recurring pathological condition. While a clear clinical diagnosis is available in 86% of cases [19], the frequency of relapses depends on unknown causes. Since instrumental exams and imaging are often not capable of demonstrating evident alterations, it is possible that the frequency of relapses may have a facilitating factor that remains unknown.
When it is not possible to identify a definite cause of BPPV, a vascular cause is suspected. The main cause of vascular aetiology is vertebrobasilar ischaemia, generated by pa-

Table II. Vertebral flow in ml/min in BPPV group with vascular risk.

Patient	Age	Risk factors	Right VA (ml/min)	Left VA (ml/min)	BPPV	Δ
F.P.	50	Hypertension	140	164	R PSC	24
D.P.M.	68	Diabetes	81	45	L LSC	36
D.L.G.	64	Hypertension dyslipidaemia	63	198	R PSC	135
C.F.	65	Hypertension dyslipideamia	86	24	L PSC	62
C.S.	57	Hypertension diabetes	49	137	R LSC	88
S.Z.	50	Hypertension diabetes	96	25	L PSC	70
L.D.C.	63	Hypertension dyslipidaemia	59	182	R PSC	123
M.V.	58	Hypertension dyslipidaemia	76	44	L LSC	32
F.C.	68	Diabetes	52	140	R LSC	88
G.S.	66	Hypertension diabetes	145	155	R PSC	10
PP	62	Diabetes	77	56	L PSC	21
M.C.	51	Hypertension dyslipidaemia	130	160	L PSC	30

R PSC: Right Posterior Semicircular Canal; R LSC: Right Lateral Semicircular Canal; L LSC: Left Lateral Semicircular Canal; L PSC: Left Posterior Semicircular Canal

Table III. Vertebral flow in ml/min in BPPV group without vascular risk.

Patient	Age	Right VA (ml/min)	Left VA (ml/min)	BPPV	Δ
C.F.	56	64	119	R PSC	-55
D.L.	45	160	189	R PSC	-29
D.A.	45	89	154	R LSC	-65
D.AR.	51	195	129	L PSC	66
M.F.	70	128	66	L PSC	62
T.M.	64	164	179	L PSC	-15
T.R.	52	128	129	R LSC	-1
T.A.	70	66	33	L LSC	33
L.M.	58	140	149	L LSC	-9
V.L.	53	188	160	R PSC	28
C.R.	57	72	128	R PSC	-56
F.G.	58	34	135	R PSC	-101
DA.P.	49	170	113	L PSC	57
M.M	51	198	228	R PSC	-30
D.P.E.	35	133	143	R PSC	-10
C.S.	57	49	136	R LSC	-87
D'A.P.	36	93	82	L PSC	11
C.P	56	141	148	L LSC	-7
M.M.	47	75	110	L PSC	-35
C.C.	55	87	140	R LSC	-53

R PSC: Right Posterior Semicircular Canal; R LSC: Right Lateral Semicircular Canal; L LSC: Left Lateral Semicircular Canal; L PSC: Left Posterior Semicircular Canal

thologies such as atherosclerosis, congenital or acquired arterial malformation, cervical arthrosis and peripheral microangiopathy [4,20].

It has been hypothesised that otolith detachment in idiopathic BPPV could be secondary to microvascular problems [20,21], without necessarily being accompanied by the most important vascular pathologies (myocardial infarction, heart failure, ictus). The reduction in vertebral arterial flow, moreover, might not be significant for organs like the brain or cerebellum, which are endowed with a remarkable compensatory capacity [22], but can have a significant role in compromising the perfusion of organs supplied by a terminal-type circulation [23]. For example, it might affect the utricular macula or semicircular canals, and this ischaemia of their neuroepithelium can facilitate its degeneration with consequent detachment of otoliths [24].

In this study, we tried to understand whether the use of tests that specifically explore the vascular district, namely retinal FAG for microcirculation and ECCS for the vertebral artery, may be useful for diagnosis in patients with recurring BPPV. A normal vertebral flow upper to 100 ml/min was considered. This is in agreement with Jang [17] who reported a normal limit of vertebral hypoperfusion < 100 ml/min.

The results showed that the retinal FAG is inadequate for indirect evaluation of vestibular microcirculation because patients, even those with verified reduction in vertebral arterial flow, did not present alterations in retinal microcirculation. This result is possibly due to differences between the diameters of the central retinal artery (0.16 mm) [25] and internal auditory artery (0.05 mm) [26] which makes the labyrinth more susceptible to ischaemia than the eye.

Using ECCS, we found that 59.3% of subjects in the study group presented a significant reduction in VA flow (< 100 ml/min) compared to the control group. Our data is in agreement with the study by Seidel et al. [16,17]. In these subjects, the pathology of the semicircular canal was found to be ipsilateral to the vertebral artery with haemodynamic insufficiency. In 6 cases, where both vertebral arteries had a reduced flow with compared to the mean, the pathology of

the semicircular canal was ipsilateral to the side most hypo perfused (Tabs. II, III).

The predominance of the VA compared to the one on the contralateral side is physiologically normal. Hence, our study, using statistical analysis on the control group, highlighted that such a prevalence does not exceed the limits of normality (Tab. III).

Our study demonstrated that the reduction of the VA flow, unilateral to the injured side, was present in 59.3% of patients with recurring BPPV. In particular, it was observed in 10 patients with idiopathic recurring BPPV (31.2%) and 9 patients (28.1%) with recurring BPPV and documented vascular risk.

These results confirm the absolute dependence of the vestibular system of one side to the ipsilateral VA flow, as demonstrated by studies of circulatory physiology of the Circle of Willis by Mc Donald and Potter (1951) and Carney (1981) [13]. These studies demonstrated that, inside the basilar artery (BA), the blood flow merger by the two vertebral arteries remains distinct and separated by a zone defined as the "dead point," where the value of vertebral flow is zero. Consequently, the pressure of the flow in the vertebral vessels, measured by ECCS in ml/min (Fig. 1), was found to be directly proportional to the flow of the ipsilateral internal auditory artery.

Another parameter considered is D which represents the highest difference in flow values registered between the two vertebral arteries (Tabs. II, III). In the healthy subjects of our case series (Tab. I), this value is 29 ml/min. In the study group, this parameter was greater than 29 ml/min in 21 patients (65.6%), and most precisely 12 of them (37.5%) among those without vascular risk and 9 (28.1%) with reported vascular risk.

Notably, the results of the two parameters (D and flow in ml/min) are comparable and documented independently from each other, along with the validity of the methodology and their extreme correlation with the onset of recurring BPPV.

The study of blood flow distribution on experimental models of the Circle of Willis, constructed by David in 2002 [10] showed that blood confluence from the vertebral arteries into the basilar artery is almost diverted into the larger artery like the posterior cerebral artery. It was also demonstrated that only a moderate quantity of blood is distributed in smaller vessels, like the posterior cerebellar artery, and above all, the internal auditory artery. In other words, the labyrinth is physiologically less supplied.

In this situation, further reduction in perfusion can precipitate an already critical condition that can translate into labyrinthine suffering.

However, ischaemia cannot be compensated by the flow of the opposite vertebral artery because, as previously mentioned, the flow of the two vertebral arteries remains separated inside the basilar artery. This can be translated into degeneration of the utricular macula with repeated detachment of otolith material and consequent BPPV [27]. Therefore, we can legitimately hypothesise that the influence of general factors, like the vascular factors during persistent ischaemic states in the vertebrobasilar area lead to secondary distress of neuroepithelial structures of the macula, which can be followed by detachments of the otoconial membrane [28]. This could also be the cause of the subclinical labyrinthine hypofunction revealed by the bithermal caloric tests in 40% of our sample.

Deterioration of the circulation in the vertebral artery, which is already hypofunctional, can result in the alteration of the endothelial wall, which might even be insignificant and not

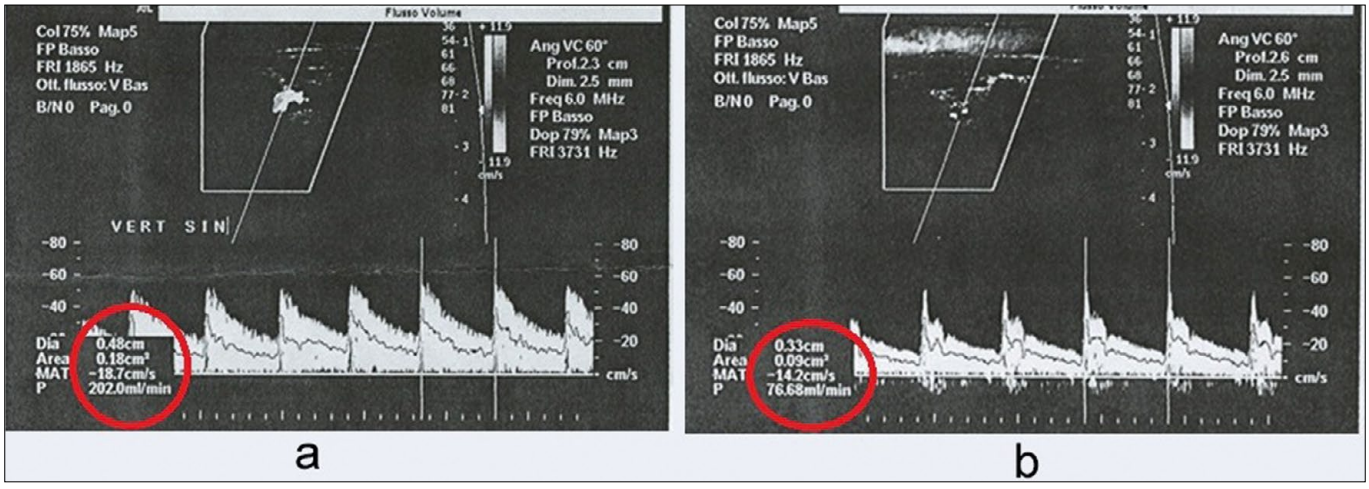


Figure 1. ECCS of the vascular vertebral left (A) and right (B) arteries fFlow value in ml/min is circled in red).

appreciable with any diagnostic technique. As demonstrated by Fischer in 2002, in carotid circulation the presence of stenosis, atherosclerosis, or flow obstruction can generate turbulence capable of further stenosis and worsened altered circulation [23]. This could also explain why BPPV is related to future ischaemic strokes regardless of age [29].

Conclusions

A correct interpretation of vascular vertigo is of extreme prognostic importance because isolated and repeated episodes of vertigo can precede stroke in a relevant number of cases. In 25% of patients with basilar artery obstruction, recurring vertigo was revealed to be the symptom in 50% of patients during autopsy, while in 60-70% of subjects who subsequently developed a vascular deficit, vertigo is the principal symptom. A brief episode of vertigo frequently occurs during the three days immediately preceding the stroke, or during the last six weeks. These observations suggest that when diagnosing BPPV it is very useful to utilise other diagnostic, and not vestibological, tools, such as ECCS of the VA, which gives information directly on labyrinthic vascular flow. It is possible to consider the results of this exam as a new risk factor for recurrent BPPV and vascular risk.

In conclusion, from our results, we confirm that ultrasound examination of the vertebral arteries represents a method of choice in the diagnosis of recurring vascular vertigo, provided that the vertebral artery flow is specifically measured in ml/min and not in cm/sec as normally occurs in ultrasound laboratories. This value, in fact, does not indicate the flow rate of blood, but rather the speed relative to the caliber of the artery, an observation therefore only indirect and in our opinion not very significant. The absence of fluorangiographic signs suggests that the labyrinthine neuroepithelium is much more sensitive to hypoperfusion than the retina. For this reason, the labyrinth could be considered to be a more reliable sentinel than the retina to intercept microcirculatory vascular disorders even earlier. BPPV, especially if recurrent, should always be evaluated with ECCS to reveal possible signs of hypoperfusion. The vascular risk situation for the labyrinth can also be better revealed by evaluation of all three parameters: presence of vascular risk factors, reduction of vertebral flow < 100 ml/min and the difference in flow between the 2 vertebral arteries > 29 ml/min. Moreover, this data is confirmed empirically by the reduction in recurring vertigo subsequent to the use of drugs that activate the microcirculation like betahistine [27], mesoglycan, or sulodexide [30].

References

1 von Brevern M, Radtke A, Lezius F, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry 2007;78:710-5. https://doi.org/10.1136/jnnp.2006.100420

2 Pérez P, Franco V, Cuesta P, et al. Recurrence of benign paroxysmal positional vertigo. Otol Neurotol 2012;33:437-43. https://doi:10.1097/MAO.0b013e3182487f78

3 Casani A, La Vertigine Ricorrente: una sfida per l'otoneurologo. Acta Otorhinolaryngol Ital 2003;75:6-18.

4 Nuti D, Gaudini E, Salerni L. Vertigini ricorrenti a eziologia vascolare. Acta Otorhinolaryngol Ital 2003;75:33-8

5 Kashimada A, Machida K, Honda N, et al. Measurement of cerebral blood flow with two-dimensional cine phase-contrast MR imaging: evaluation of normal subjects and patient with vertigo. Radiat Med 1995;13:95-102.

6 Baloh RW, Vertebrobasilar insufficiency and stroke. Otolaryngol Head Neck Surg 1995;112:114-7. https://doi.org/10.1016/s0194-5998(95)70309-8

7 Doyle KJ, Fowler C, Starr A. Audiologic findings in unilateral deafness resulting from contralateral pontine infarct. Otolaryngol Head Neck Surg 1996;114:482-6. https://doi.org/10.1016/s0194-5998(96)70224-3

8 Yamasoba T, Kikuchi S, O'Uchi T, et al. Magnetic resonance angiographic patients with slow vertebrobasilar blood flow. Acta Otolaryngol 1995(Suppl);115:153-6. https://doi.org/10.3109/00016489509125215

9 Seo T, Tominaga S, Sagakami M. Relationship between neurological asymptomatic vertigo and vertebrobasilar system as revealed by MR-angiography. ORL J Otorhinolaryngol Relat Spec 2000;62:63-7. https://doi.org/10.1159/000027719

10 David T, Ferrandez A, Brown M. Computational model of blood flow in the Circle of Willis. Comput Methods Biomech Biomed Engin 2000;4:1-26. https://doi.org/10.1080/10255840008907996

11 Šutalo ID, Bui AV, Ahmed S, et al. Modeling of flow through the Circle of Willis and cerebral vasculature to assess the effects of changes in the peripheral small cerebral vasculature on the inflows. Engineering Applications of Computational Fluid Mechanics 2014;8:4, 60922. https://doi.org/10.1080/19942060.2014.11083311

12 Nazerian P, Bigiarini S, Pecci R, et al. Duplex sonography of vertebral arteries for evaluation of patients with acute vertigo. Ultrasound Med Biol 2017;44:584-92. https://doi.org/10.1016/j.ultrasmedbio.2017.11.002

13 Carney AL. Vertebral artery surgery: historical development, basic concepts of brain hemodynamic, and clinical experience of 102 cases. Adv Neurol 1981;30:249-82.

14 Park JH, Kim JM, Roh JK. Hypoplastic vertebral artery: frequency and associations with ischemic stroke territory. J Neurol Neurosurg Psychiatry 2007;78:954-8. https://doi.org/10.1136/jnnp.2006.105767

15 Miura M, Naito Y, Naito E, et al. Usefulness of magnetic resonance imaging in diagnosing vertebrobasilar insufficiency. Acta Otolaryngol Suppl 1997;528:91-3.

16 Seidel E, Eicke BM, Tettenborn B, et al. Reference values for vertebral artery flow volume by duplex sonography in young and elderly adults. Stroke 1999;30:2692-6. https://doi.org/10.1161/01.str.30.12.2692

17 Jeng JS, Yip PK. Evaluation of vertebral artery hypoplasia and asymmetry by color-coded duplex ultrasonography. Ultrasound Med Biol 2004;30:605-9. https://doi.org/10.1016/j.ultrasmedbio.2004.03.004

18 Menchini U, D'Ettorre M, Mondelli M, et al, The use of retinal fluorangiography tecniques in the study of cerebral circulation. Cephalgia 1985;2:59-63. https://doi.org/10.1177/03331024850050s210

19 Nuti D, Caruso G, Salerni L, et al. Epidemiologia e caratteristiche cliniche della vertigine parossistica posizionale benigna: 10 anni di esperienza. Arq Otorrinolaringol 2003;7.

[20] Barbieri M, Mora R, Barbieri A. Eziologia della vertigine parossistica posizionale. In: Nuti D, Pagnini P, Vicini C, editors. Revisione critica di venti anni di vertigine parossistica posizionale benigna (VPPB). Milano: Comitato Simposi Scientifici Formenti 1999, pp. 55-8.

[21] Guidetti G. Diagnosi e terapia dei disturbi dell'equilibrio. Roma: Marrapese Editore 1997.

[22] Gutmann R, Wollemberg B, Krampert B, et al. Incidence of Doppler ultrasound detectable stenoses of cervical arteries in patients with cochlear-vestibular symptoms. Laryngorhinootologie 1993;72:502-5. https://doi.org/10.1055/s-2007-997945

[23] Katsanos AH, Kosmidou A, Kyritsis AP, et al. Is vertebral artery hypoplasia a predisposing factor for posterior circulation cerebral ischemic events? A comprehensive review. Eur Neurol 2013;70:78-83. https://doi.org/10.1159/000351786

[24] Casani AP, Dallan I, Marchetti M, Ruolo dei potenziali evocati vestibolari miogenici nella diagnostica vestibolare. Acta Otorhinolaryngol Ital 2003;23(Suppl 75)5:113-9.

[25] Dorner GT, Polska E, Garhöfer G, et al. L Calculation of the diameter of the central retinal artery from noninvasive measurements in humans. Curr Eye Res 2002;25:341-5. https://doi:10.1076/ceyr.25.6.341.14231

[26] Haidara A, Peltier J, Zunon-Kipre Y, et al. Microsurgical anatomy of the labyrinthine artery and clinical relevance. Turk Neurosurg 2015;25:539-43. https://doi:10.5137/1019-5149.JTN.9136-13

[27] Toupet M. Betahistine and vestibular function. Unexpected therapeutical implications. In: Aggiornamenti di vestibologia 2° ed. Atti congressuali. Milano: Energy editions, Energy S.r.l. 2005, pp. 77-82.

[28] Faralli M, Ricci G, Frenguelli A, et al. Paroxysmal positional vertigo: the role of possible vascular factors in etiology. Mediterr J Otol 2006;2:63-9.

[29] Kao CL, ChengYY, Leu HB, et al. Increased risk of ischemic stroke in patients with benign paroxysmal positional vertigo: a 9-year follow-up Nationwide Population Study in Taiwan. Front Aging Neurosci 2014;108:1-7. https://doi.org/10.3389/fnagi.2014.00108

[30] Neri G, Marcelli V, Califano L, et al. Assessment of the effect of mesoglycan in the treatment of audiovestibular disorders of vascular origin. Int J Immunopathol Pharmacol 2018;32:2058738418773833. https://doi:10.1177/2058738418773833

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:84-90; doi: 10.14639/0392-100X-N0213

Otology

Is the Carhart notch a predictive factor of hearing results after stapedectomy?

La tacca di Carhart è un fattore predittivo dei risultati uditivi dopo stapedectomia?

Elea Lamblin[1], Alexandre Karkas[2], Jérôme Jund[3], Sébastien Schmerber[1]

[1] Department of Otolaryngology-Head and Neck Surgery, Grenoble University Hospital, Grenoble Cedex 9, France; [2] Department of Otolaryngology-Head and Neck Surgery, Saint Etienne University Hospital, CHU de Saint-Étienne Hôpital Nord, Saint Etienne Cedex 2, France; [3] Department of Research and Clinical Investigation, Annecy Hospital, Metz - Tessy, Pringy Cedex, France

SUMMARY

The Carhart notch (CN) is a depression in the bone-conduction audiogram of patients with clinical otosclerosis. The middle frequencies from 0.5 to 2 kHz, which correspond to the resonance frequency of the middle ear, can be substantially improved upon following successful stapes surgery. This retrospective audiometric database and chart review in a tertiary referral centre was performed with the aim of assessing whether the presence of a CN could be predictive of results after stapes surgery in otosclerosis, through improvement in bone conduction (BC) thresholds. Nine hundred and thirty-one cases of stapes surgery over a period of 25 years benefitted from audiological assessment before and 4 months after surgery. A CN was considered present when the BC threshold at the notch frequency (0.5, 1 or 2 kHz) exceeded the mean thresholds at higher and lower adjacent frequencies by at least 7.5 dB. BC threshold improvement was better at 2 kHz (+14.1 ± 12.5 dB *vs* +12 ± 13.2 dB) and lower at 4 kHz (+3.6 ± 13.5 dB *vs* +11 ± 14.7 dB) for the CN+ group compared to the CN- group. Moreover, sensorineural hearing loss was more frequent in the CN+ group than in the CN- group. These results indicate that a CN on preoperative audiogram should alert the clinician to lesser postoperative BC improvement at 4 kHz related to a preoperative sensorineural hearing loss or to a higher incidence of postoperative sensorineural hearing loss.

KEY WORDS: otosclerosis, stapedectomy, hearing, Carhart notch, bone conduction

RIASSUNTO

La tacca di Carhart è una depressione della via ossea nell'audiogramma dei pazienti con otosclerosi clinica. Le frequenze medie da 0,5 a 2 kHz, che corrispondono alla frequenza di risonanza dell'orecchio medio, possono essere efficacemente migliorate mediante un intervento chirurgico di stapedectomia. Sono state eseguite la valutazione di un database audiometrico retrospettivo e la revisione delle cartelle cliniche dei pazienti afferenti in un centro terziario con l'obiettivo di valutare se la presenza di una tacca di Carhart (CN) potesse essere predittiva dei risultati dopo la chirurgia della staffa nell'otosclerosi, attraverso il miglioramento delle soglie di conduzione ossea (BC). Novecentotrentuno pazienti sottoposti a chirurgia della staffa trattati in un periodo di 25 anni sono stati sottoposti a valutazione audiologica prima e 4 mesi dopo l'intervento. Una CN è stata considerata presente quando la soglia BC alla frequenza del notch (0,5, 1 o 2 kHz) ha superato le soglie medie delle frequenze vicine superiori e inferiori di almeno 7,5 dB. Il miglioramento della soglia BC è risultato migliore a 2 kHz (+ 14,1 ± 12,5 dB contro +12 ± 13,2 dB) e inferiore a 4 kHz (+3,6 ± 13,5 dB contro +11 ± 14,7 dB) per il gruppo CN + rispetto al gruppo CN-. Inoltre, la perdita neurosensoriale dell'udito era più frequente nel gruppo CN + rispetto al gruppo CN-. Questi risultati indicano che una CN sull'audiogramma preoperatorio dovrebbe essere predittiva di un minore miglioramento postoperatorio della BC a 4 kHz correlato a una perdita dell'udito neurosensoriale preoperatoria o a una maggiore incidenza di ipoacusia neurosensoriale postoperatoria.

PAROLE CHIAVE: *otosclerosi, stapedectomia, udito, tacca di Carhart, conduzione ossea*

Received: March 26, 2019
Accepted: November 26, 2020

Correspondence
Sébastien Schmerber
Department of Otolaryngology-Head and Neck Surgery, Grenoble University Hospital, 1 avenue du marquis du Grésivaudan, 38043 Grenoble Cedex 9, France
Tel. +33 4 76 76 56 62. Fax +33 4 76 76 51 20
E-mail: SSchmerber@chu-grenoble.fr

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Lamblin E, Karkas A, Jund J, et al. Is the Carhart notch a predictive factor of hearing results after stapedectomy? Acta Otorhinolaryngol Ital 2021;41:84-90. https://doi.org/10.14639/0392-100X-N0213

Introduction

Patients with a middle ear pathology have increased air conduction (AC) thresholds. There is often also an accompanying depression of the bone conduction (BC) thresholds. The increase in BC thresholds for otosclerosis, maximal at 2 kHz, is called the "Carhart notch" (CN) [1]. This effect may be explained by BC mechanisms. The inertial component seems to be the most important factor contributing to BC hearing [2]. The ossicular and inner ear fluid inertia are less efficient due to the higher impedance of the fixed stapes footplate in otosclerosis and an increase in BC thresholds is observed. The middle ear inertia is the most effective in the mid frequencies close to the resonance frequency vibration which is 1.5 kHz [3]. In a model simulation of BC excitation of the inner ear, Stenfelt et al. [3] hypothesised that the CN close to 2 kHz could be simulated as a result of increasing the impedance at the oval window seen from inside the inner ear. This explains the predominant presence of CN around 2 kHz in otosclerosis.

Definite criteria for the detection of a CN are unclear and previous studies were conducted with different definitions [4-8]. Hence, the reported CN prevalence in otosclerosis varies considerably among authors, ranging from 31% to 80%. We propose a new definition of CN in order to standardise the reporting of audiometry results in future studies. In 1950, Carhart [1] was the first to observe that BC thresholds were improved following successful fenestration surgery for otosclerosis: this BC improvement is called "overclosure" [9]. Although the initial diagnosis of sensorineural hearing loss (SNHL) is usually made on the basis of abnormal BC hearing thresholds, this apparent BC loss is not a true indicator of the inner ear function, since it could improve following successful surgery; it reflects the successful reestablishment of the former impedance of the oval window by surgery [10]. Thus, the term overclosure, while widely used, remains confusing. We prefer to use BC improvement.

Bone lesions in otosclerosis were reported to affect intracochlear structures and also cause SNHL [11]. In some cases the audiogram is unusual and may be attributed to sensorineural impairment: this could be the case if the BC curve shows a notch which is duplicated on the air conduction (AC) curve; this AC-notch is usually called a "cookie bite" [12]. Indeed, the question of BC improvement is particularly pertinent in patients with mixed hearing loss to determine the influence of preexisting SNHL. We aimed to determine whether different types of AC curve impacted BC threshold improvement.

Audiological predictive factors of successful surgery are well known [13], but few authors have focused on preoperative tools predicting BC threshold improvement [5,12]. The main goal of our study was to determine whether preoperative audiological assessment as the presence of a CN were predictive factors for postoperative hearing results such as BC threshold improvement.

Materials and methods

Patients

All patients treated for otosclerosis were included in this retrospective consecutive case-series study. Patients were operated on by the same senior surgeon over a period of 25 years in our tertiary referral centre. The surgical procedure consisted of a stapedotomy with interposition of either a perichondrium or a vein graft, and placement of a Causse-type Teflon stapes 0.4 mm diameter prosthesis [14], the loop of which was anchored to the long process of the incus.

Audiological assessment

Assessment of hearing status was performed before and after surgery (at 4 months and at 1 year). The audiological assessment included the preoperative and postoperative AC and BC thresholds. We used a 4-frequency pure-tone average (PTA) for AC and BC thresholds (0.5, 1, 2 and 4 kHz). The thresholds at 3 kHz were not available in the database at its implemention and were replaced in all cases with those at 4 kHz.

Only AC and BC results that were obtained at the same time postoperatively were used for calculation of the postoperative air-bone gap (ABG). Audiometry was assessed according to the American Academy of Otolaryngology Head and Neck Surgery guidelines [9], except for thresholds at 3 kHz which were substituted in all cases with those at 4 kHz. This was necessary because 3 kHz measurements were not performed at the beginning of this study.

Carhart notch definition

Choosing relevant factors for a precise definition of a CN was necessary (Fig. 1). First, we identified a CN at various frequencies from 0.5 to 2 kHz. To avoid underestimation, we determined that the minimum differences between the CN frequency and the adjacent frequencies was 7.5 dB and not 10 dB as reported in other studies [4], otherwise some audiograms (e.g. type B in Figure 1) were not defined as including a CN pattern. Finally, to avoid overestimation, the CN frequency had to be higher than the adjacent frequencies, or other audiograms (e.g. type A in Figure 1) were considered as including a CN pattern [6-8]. Indeed, a CN was defined by BC threshold at the notch frequency (0.5, 1 or 2 kHz) ≥ 7.5 dB above the mean of thresholds at higher and lower adjacent frequencies. Another criterion was that the

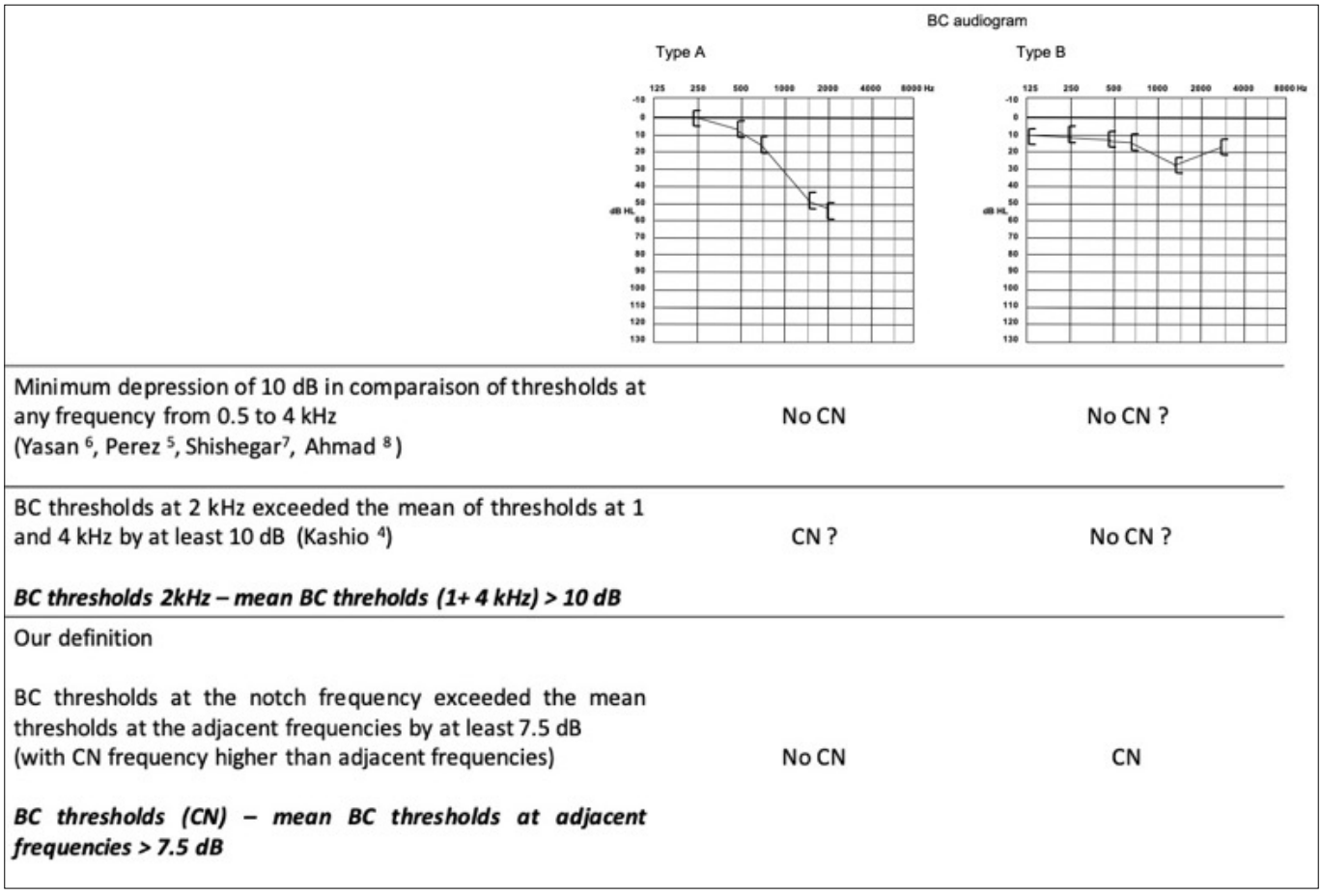


Figure 1. CN considered present or not on various type of BC curves according to previous CN definitions and according to our definition (example of right ear).

CN frequency threshold had to be higher than the adjacent frequency thresholds.

Hearing outcomes

BC threshold improvement was measured by the preoperative minus the postoperative pure-tone BC average following successful surgery. Various AC curve types were described to determine whether preoperative AC thresholds impact postoperative BC thresholds (Fig. 2): 1) a flat AC curve; 2) a downward AC curve (defined by high frequency AC hearing loss > 2 kHz); 3) an AC-notch or "cookie bite" (defined by a notch in the AC threshold along with the CN at 2 kHz). The success rate in stapes surgery was defined in two ways. Firstly, an AC PTA < 30 dB as primary criterion alone. Secondly, combined criteria of this primary assessment with 2 additional criteria: absence of postoperative sensorineural hearing loss (SNHL defined by a 4 kHz BC threshold postoperative increase > 10 dB) and a postoperative ABG < 10 dB.

Statistical analyses

We used SPSS software (*V13.0; SPSS Inc., Chicago, IL, USA*). Quantitative data were expressed as mean and standard deviation. We used the Chi-square and Fisher's exact test for the analysis. Univariate analysis was used to identify a CN as a possible predictive factor for hearing outcome. A P value < 0.05 was considered significant.

Results

Population studied

This retrospective study was conducted on 1,029 patients who underwent 1,250 stapes surgeries for otosclerosis in our tertiary referral centre. Seven hundred and ninety-nine patients (931 surgical cases) were followed at 4 months after surgery and 355 patients (415 surgical cases) at 1 year.

Preoperative data: Carhart notch description

A CN was observed in 495 (53.1%) of the 931 surgical cases in the preoperative audiogram according to our defi-

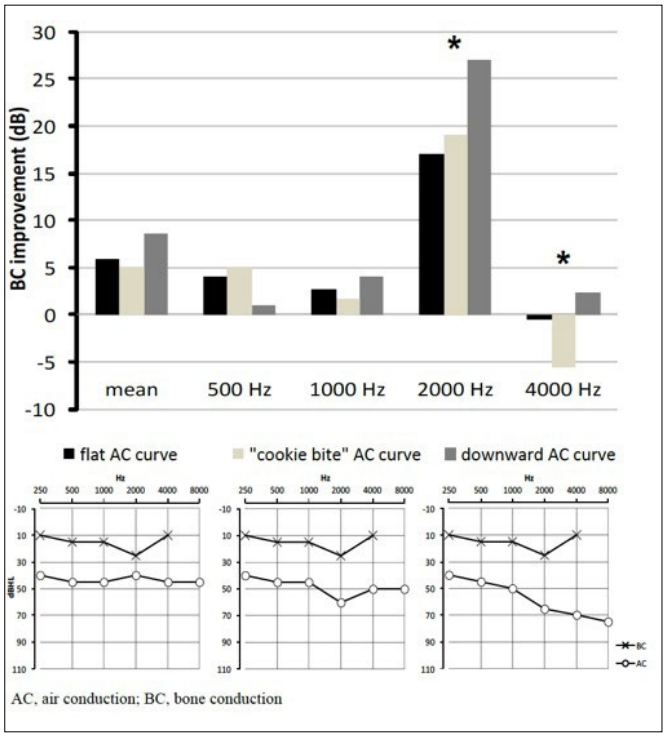


Figure 2. BC improvement for cases with a 2 kHz CN preoperatively depending on the AC curve type (a flat AC curve; a "cookie-bite" AC curve defined by "CN duplication" on an AC curve 4 months after surgery (*: $p < 0.05$, Anova).

nition. Notches were distributed according to the peak frequency as follows: 273 (29.2%) surgical cases at 2 kHz, 44 (4.7%) at 1 kHz and 178 (19.1%) at 0.5 kHz. The CN dip means (corresponding to the difference of mean adjacent thresholds minus CN threshold) were: 13 ± 4.7 dB for 2 kHz CN, 11.3 ± 4.4 dB for 1 kHz CN, and 11.5 ± 4.7 dB for 0.5 kHz CN.

Postoperative data: BC threshold improvement

Table 1 is a list of BC threshold improvement using primary successful surgery criteria from 931 cases and 415 cases respectively, 4 months and 1 year after stapes surgery. The mean BC threshold improvement for cases with successful surgery at 4 months of follow-up was: +5.4 dB at 0.5 kHz, +3.8 dB at 1 kHz, +13.8 dB at 2 kHz and +8.5 dB at 4 kHz. The mean BC threshold improvement decreased in cases of failed hearing restoration but remained in positive values. The results were stable at 1 year after surgery.

Preoperative audiological predictive factors affecting audiological results

Improvement of BC thresholds 4 months after surgery were significantly different if a CN was observed on preoperative audiogram (495 cases with CN: CN+ group) or not (436 cases without CN: CN- group). BC thresholds improvement for the CN+ group were better at 0.5 and 2 kHz (+7.1 ± 11 dB *vs* +3.8 ± 10.3 dB, p = 0.00015, Anova; +14.1 ± 12.5 dB *vs* +12 ± 13.2 dB, p = 0.017, Anova) and lower at 4 kHz (+3.6 ± 13.5 dB *vs* +11 ± 14.7 dB, p = 0.00019, Anova) compared to the CN- group (Fig. 3). We measured the likelihood of a > 10 dB BC thresholds improvement and found it to be greater in the CN+ group at 0.5 kHz (odds ratio = 2; 95% CI = 1.5-2.7; p = 0.029) and at 2 kHz (odds ratio = 1.6; 95% CI = 1.3-2.1; p = 0.035). The likelihood of a > 10 dB BC thresholds improvement was lower at 4 kHz (odds ratio = 0.4; 95% CI = 0.3-0.5; p = 0.022).

Figure 3 shows that if a CN was observed at 2 kHz in the preoperative audiogram there is no BC threshold improvement (negative overclosure) at 4 kHz if the AC thresholds presented a corresponding notch. The likelihood of a > 10 dB BC threshold improvement was significantly lower (odds ratio = 0.08; 95% CI = 0.01-0.6; p = 0.016). On the other hand, in the event of a "downward" AC curve, BC threshold improvement at 2 kHz was significantly better (p = 0.0001, Anova). The likelihood of a > 10 dB BC threshold improvement was significantly higher (odds ratio = 3.6; 95% CI = 1.1-10.1; p = 0.0013).

The univariate analysis did not allow any significant relationship to be determined between the presence of a preoperative CN and successful surgery, considering the primary

Table I. BC threshold improvement according to surgical results after stapes surgery.

			BC threshold improvement (dB)			
Follow-up		**n (%)**	**500 Hz**	**1000 Hz**	**2000 Hz**	**4000 Hz**
4 months	Total	931	5.6	2.6	13.2	7.1
	Successful surgery (AC PTA < 30dB)	609 (65%)	5.4	3.8	13.8	8.5
	Failed hearing restoration	322 (35%)	6	0.4	12	4.3
1 year	Total	415	5.1	2.3	13	6.5
	Successful surgery	263 (63%)	4.8	3.5	14.2	9.2
	Failed hearing restoration	152 (37%)	5.5	0.2	11.1	1.8

AC PTA: air conduction threshold pure tone average.

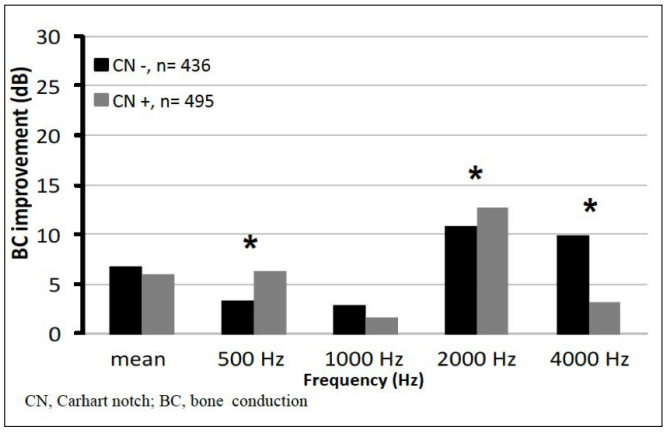


Figure 3. BC improvement according to the presence of a CN, 4 months after surgery (*: $p < 0.05$, Anova).

criterion alone or the 3 associated criteria (Tab. II). However, SNHL if considered separately, was more frequent in the CN+ group than in the CN- group at 4 months (odds ratio = 3.1; 95% CI = 1.7-5.7; p = 0.00016) and at 1 year of follow up (odds rati = 2.6; 95% CI = 1.3-5.4; p = 0.0013).

Discussion

In our study, a CN was observed according to our definition in 53.1% of the 931 preoperative audiograms, mainly at 2 kHz. Definite criteria for the detection of a CN were not yet clearly established, and the authors of previous studies used different definitions. The definition that we propose describes CN at various frequencies (0.5, 1 and 2 kHz), whereas some authors suggested defining CN only at 2 kHz. In addition, as shown in Figure 1, some definitions used previously to define the presence of a CN were inadequate, leading to over- or underestimation. The definition we propose helps to describe with accuracy if a CN is present or not, but it does not account for notches with broader spectrum.

CN was renamed "the Carhart effect" by Gatehouse [15] since increases in bone conduction thresholds are reported from 0.5 to 4 kHz. This increase of BC thresholds are not an indicator of the inner ear function since BC thresholds were demonstrated to improve after surgery [1]. The Carhart effect is due to the lack of excitation mainly from the inertial component of the ossicles close to a resonance frequency of 1.5 kHz, and to a lesser extent from the inertia of the cochlear fluid for lower frequencies [3]. Indeed, the presence of a CN in a patient with conductive hearing loss cannot be used for the specific diagnosis of otosclerosis [4] because the CN can also be due to other disorders of the middle ear that reduce the movement of ossicles, such as otitis media with effusion, tympanosclerosis, or ossicular malformations [4,6-8]. The mean BC improvement in our series was +5.4 dB at 0.5 kHz, +3.8 dB at 1 kHz, +13.8 dB at 2 kHz, and +8.5 dB at 4 kHz. The authors of previous studies confirmed the finding of largest BC improvement at 2 kHz [5,15-17]. The values of BC improvement in our study correlated with those of Gatehouse [15] who also assessed the magnitude of the Carhart effect in his series from precise criteria of successful surgery (ABG < 10 dB, mean BC thresholds not worsened by > 5 dB, AC improved by > 10 dB). BC improvement varies considerably according to the author, but Gatehouse demonstrated that discrepancies were markedly reduced when the appropriate selection criteria were used. Thus BC improvement can be underestimated with other methods such as comparing BC thresholds of patients with BC in an age-matched healthy population, or including only patients whose BC improved [15]. Gatehouse also demonstrated that BC values before and after surgery underes-

Table II. Hearing results at 4 months and 1 year after surgery according to the presence of a CN (Chi 2 Pearson).

		CN-		CN +		
		n	%	n	%	*p*
4 months after surgery	Total, n	436		495		
	PTA AC< 30 dB:1 criterion	276	63.3%	333	67.3%	0.204
	3 criteria	246	56.4%	290	58.6%	0.505
	ABG < 10	376	76.0%	316	72.0%	0.225
	SNHL	14	3.2%	46	9.3%	0.00016
1 year after surgery	Total, n	201		214		
	PTA AC < 30 dB :1 criterion	121	60.0%	142	66.4%	0.193
	3 criteria	111	55.2%	118	55.1%	0.986
	ABG < 10	135	67.2%	164	76.6%	0.032
	SNHL	11	5.4%	28	13.1%	0.013

CN-: absence of Carhart notch; CN+: presence of a Carhart notch; PTA AC: air conduction threshold pure tone average; ABG: air bone gap; SNHL: sensorineural hearing loss.

timated the Carhart effect for low frequencies compared to theoretical considerations, with an experimental model in which pressure changes were applied to the external canal to simulate the Carhart effect. Indeed, our results could be underestimated for low frequencies.

We found that a CN observed at 2 kHz with a corresponding AC-notch in the preoperative audiogram was correlated to lesser BC thresholds improvement at 4 kHz (negative overclosure). Therefore, an AC-notch on preoperative audiogram is a warning sign for the lack of postoperative BC improvement related to a preoperative SNHL or to a higher incidence of postoperative SNHL. The assessment of whether SNHL was preoperative or postoperative is difficult to know as postoperative BC thresholds were the result of a combination of improvement by adequate impedance change and loss by surgical trauma. Cook et al. [18] described a method allowing changes in BC to be predicted according to air conduction at any frequency by a linear regression. In Cook's model, changes in BC other than those expected could be attributed to other causes than the Carhart effect, and help assess the degree of SNHL in the presence of conductive hearing loss. Our findings using our new definitions have never been described.

We did not find any relationship between the presence of a CN and successful surgery rate, according to our criteria. However, postoperative SNHL tended to be more frequent when a CN was present.

These results must be balanced by the fact that our study was monocentric and retrospective. In addition, only audiological data were considered: patient characteristics, imaging features, or intraoperative data were not assessed. It has been demonstrated that a larger diameter piston (0.6 *vs* 0.4 mm) allows a higher AC gain [19,20]. In our study, only type of 0.4 mm diameter prosthesis was used. Hearing results may differ according to the radiological otosclerosis classification [21]. Marx et al. [21] reported according to CT-scan analyses that AC and BC thresholds were increased in cases of extensive otosclerosis: BC thresholds were significantly higher when the disease involved the pericochlea, the cochlear endosteum, or the round window. Furthermore, they found that SNHL was at higher risk of aggravation in case of extensive otosclerosis. Most authors have confirmed that CT-scan is a sensitive diagnostic method and a useful tool for differential diagnosis of otosclerosis [21,22]. However, diagnosis relies on clinical observation and imaging is not always mentioned in national guidelines [23]. Our consecutive case series of 931 stapes surgery should be large enough to cover all CT-scan grades with a distribution similar to that of Veillon [24]. This classification was based on more than 2,000 CT scans of otosclerosis according to the size and topography of foci with the following distribution: type Ia 14%, Ib 8%, II 52%, III 10% and IV 12% [25]. Age was not considered in our study since functional results do not vary according to age group [26]. Likewise, there was no difference in initial or late postoperative hearing outcome, depending on vein or tragal perichondrium interposition [27].

Conclusions

CN or more appropriately the Carhart effect was observed at a wide range of frequencies, predominantly at 2 kHz. It is illustrated by the improvement in BC thresholds, which is predominant at 2 kHz, but that is not an indicator of successful surgery. We identified preoperative audiological factors influencing BC improvement: 4 kHz BC improvement was significantly lower in case of preoperative CN or in presence of an AC–notch at 2 kHz. These findings should alert the clinician to mixed hearing loss with preoperative SNHL or to an incidence of postoperative SNHL.

Acknowledgements

We are grateful to Pierre-Emmanuel Colle, University Grenoble Alpes, for copy editing.

References

1 Carhart R. Clinical application of bone conduction audiometry. Arch Otolaryngol 1950;51:798-808.

2 Tonndorf J. Bone conduction. Studies in experimental animals. Acta Otolaryngol 1966:Suppl 213:1+.

3 Stenfelt S. Inner ear contribution to bone conduction hearing in the human. Hear Res 2015;329:41-51. https://doi.org/10.1016/j.heares.2014.12.003

4 Kashio A, Ito K, Kakigi A, et al. Carhart notch 2-kHz bone conduction threshold dip: a nondefinitive predictor of stapes fixation in conductive hearing loss with normal tympanic membrane. Arch Otolaryngol Head Neck Surg 2011;137:236-40. https://doi.org/10.1001/archoto.2011.14

5 Perez R, de Almeida J, Nedzelski JM, et al. Variations in the "Carhart notch" and overclosure after laser-assisted stapedotomy in otosclerosis. Otol Neurotol 2009;30:1033-6. https://doi.org/10.1097/MAO.0b013e31818edf00

6 Yasan H. Predictive role of Carhart's notch in pre-operative assessment for middle-ear surgery. J Laryngol Otol 2007;121:219-21. https://doi.org/10.1017/S0022215106003343

7 Shishegar M, Faramarzi A, Esmaili N, et al. Is Carhart notch an accurate predictor of otitis media with effusion? Int J Pediatr Otorhinolaryngol 2009;73:1799-802. https://doi.org/10.1016/j.ijporl.2009.09.040

8 Ahmad I, Pahor AL. Carhart's notch: a finding in otitis media with effusion. Int J Pediatr Otorhinolaryngol 2002;64:165-70.

9 Committee on Hearing and Equilibrium guidelines for the evaluation of results of treatment of conductive hearing loss. American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc. Otolaryngol Head Neck Surg 1995;113:186-7. https://doi.org/10.1016/S0194-5998(95)70103-6

10 Arnold A, Fawzy T, Steinhoff HJ, et al. Influence of a totally open oval window on bone conduction in otosclerosis. Audiol Neurootol 2011;16:23-8. https://doi.org/10.1159/000308302

[11] Topsakal V, Fransen E, Schmerber S, et al. Audiometric analyses confirm a cochlear component, disproportional to age, in stapedial otosclerosis. Otol Neurotol 2006;27:781-7. https://doi.org/10.1097/01.mao.0000231500.46534.79

[12] Beal C, Poncet-Wallet C, Frachet B, et al. A propos de l'effet Carhart, étude de l'évolution post-opératoire de 47 otospongioses opérées [Carhart's effect; a study of postoperative outcome of 47 surgically treated cases of otosclerosis]. Ann Otolaryngol Chir Cervicofac 1992;109:76-9.

[13] Kishimoto M, Ueda H, Uchida Y, et al. Factors affecting postoperative outcome in otosclerosis patients: predictive role of audiological and clinical features. Auris Nasus Larynx 2015;42:369-73. https://doi.org/10.1016/j.anl.2015.03.001

[14] Causse J, Causse JB. Eighteen-year report on stapedectomy. II. Postoperative therapy. Clin Otolaryngol Allied Sci 1980;5:329-37.

[15] Gatehouse S, Browning GG. A re-examination of the Carhart effect. Br J Audiol 1982;16:215-20.

[16] Garcia-Iza L, Navarro JJ, Goiburu M, et al. Study of the improvement in bone conduction threshold after stapedectomy. Acta Otorrinolaringol Esp 2016;67:268-74. https://doi.org/10.1016/j.otorri.2015.11.003

[17] Sabbe A, Verhaert N, Joossen I, et al. Otosclerosis: shift in bone conduction after stapedotomy. B-ENT 2015;11:183-9.

[18] Cook JA, Krishnan S, Fagan PA. Quantifying the Carhart effect in otosclerosis. Clin Otolaryngol Allied Sci 1995;20:258-61.

[19] Bernardeschi D, De Seta D, Canu G, et al. Does the diameter of the stapes prosthesis really matter? A prospective clinical study. Laryngoscope 2018;128:1922-6. https://doi.org/10.1002/lary.27021

[20] Quaranta N, Piccininni K, Romanello M, et al. The impact of intraoperative factors in otosclerosis outcomes: retrospective study in a tertiary centre. Acta Otorhinolaryngol Ital 2019;39:197-204. https://doi.org/10.14639/0392-100X-2004

[21] Marx M, Lagleyre S, Escude B, et al. Correlations between CT scan findings and hearing thresholds in otosclerosis. Acta Otolaryngol 2011;131:351-7. https://doi.org/10.3109/00016489.2010.549841

[22] Revesz P, Liktor B, Liktor B, et al. Comparative analysis of preoperative diagnostic values of HRCT and CBCT in patients with histologically diagnosed otosclerotic stapes footplates. Eur Arch Otorhinolaryngol 2016;273:63-72. https://doi.org/10.1007/s00405-015-3490-3

[23] Purohit B, Hermans R, Op de Beeck K. Imaging in otosclerosis: a pictorial review. Insights Imaging 2014;5:245-52. https://doi.org/10.1007/s13244-014-0313-9

[24] Veillon F, Stierle JL, Dussaix J, et al. Imagerie de l'otospongiose: confrontation clinique et imagerie [Otosclerosis imaging: matching clinical and imaging data]. J Radiol 2006;87:1756-64.

[25] Veillon F, Casselman YW. Imagerie de l'oreille et de l'os temporal. In: Nahum H, editor. Traumatologie, urgences, otospongiose. Volume 3. Paris: Lavoisier; 2013. p. 298.

[26] Vincent R, Sperling NM, Oates J, et al. Surgical findings and long-term hearing results in 3,050 stapedotomies for primary otosclerosis: a prospective study with the otology-neurotology database. Otol Neurotol 2006;27:S25-47. https://doi.org/10.1097/01.mao.0000235311.80066.df

[27] Schmerber S, Cuisnier O, Charachon R, et al. Vein versus tragal perichondrium in stapedotomy. Otol Neurotol 2004;25:694-8.

ACTA OTORHINOLARYNGOLOGICA ITALICA 2021;41:91-99; doi: 10.14639/0392-100X-N0609

Otology

Retrosigmoidal placement of an active transcutaneous bone conduction implant: surgical and audiological perspectives in a multicentre study

Posizionamento retrosigmoideo di una protesi transcutanea attiva a conduzione ossea: prospettive chirurgiche e audiologiche in uno studio multicentrico

Pietro Canzi[1*], Irene Avato[1,2*], Millo Beltrame[1*], Giovanni Bianchin[3], Marco Perotti[4], Lorenzo Tribi[3], Barbara Gioia[4], Federico Aprile[1], Stefano Malpede[1], Andrea Scribante[5], Marco Manfrin[1], Marco Benazzo[1]

[1] Department of Otorhinolaryngology, University of Pavia, Foundation IRCCS Policlinico "San Matteo", Pavia, Italy; [2] PhD in Experimental Medicine, University of Pavia, Italy; [3] Department of Otolaryngology and Audiology, Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy; [4] Otorhinolaryngology Unit, Ospedale Civile "SS Antonio Biagio and C. Arrigo", Alessandria, Italy; [5] Unit of Orthodontics and Paediatric Dentistry-Section of Dentistry-Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy

** P. Canzi, I. Avato and M. Beltrame contributed equally to this work*

SUMMARY

Introduction. The retrosigmoidal (RS) placement of the Bonebridge system (BB) has been advocated for cases of unfavourable anatomical or clinical conditions which contraindicate transmastoid-presigmoidal positioning. However, these disadvantageous conditions, combined with the considerable dimensions of the implant, may represent a challenge, especially for surgeons with no skull base experience. Moreover, the literature reports only limited experience concerning RS implantation of the BB system.

Methods. A multicentre, retrospective study was conducted to analyse the surgical and functional outcomes of a wide population of patients undergoing RS placement of the BB system by means of a surgical technique specifically developed to overcome the intraoperative issues related to this surgery. Twenty patients with conductive or mixed hearing loss and single sided deafness were submitted to RS implantation of the BB system.

Results. Audiological assessment concerning the measurement of the functional and effective gain by pure-tone audiometry (28 dB HL and -12.25 dB HL, respectively) and speech audiometry (24.7 dB HL and -21 dB HL, respectively) was conducted. A high overall subjective improvement of quality of life was recorded with the Glasgow Benefit Inventory questionnaire. No major complications, such as device extrusions or other conditions requiring revision surgery, were reported during the follow-up period (median: 42 months).

Conclusions. In our study, which has one of the largest cohort of patients reported in the literature, RS placement of the BB system was safe and effective. Our functional results showed comparable hearing outcomes with presigmoidal placement. The effective gain, rarely investigated in this field, may be the object of further research to improve our understanding of bone conduction mechanisms exploited by bone conduction hearing implants.

KEY WORDS: bone conduction hearing implant, Bonebridge, transcutaneous, retrosigmoidal, surgical technique

RIASSUNTO

***Introduzione**. Il posizionamento retrosigmoideo del sistema Bonebridge (BB) è stato introdotto per ovviare alla presenza di condizioni anatomiche e cliniche che controindichino l'alloggiamento del device in regione presigmoidea. Tuttavia, queste condizioni sfavorevoli, associate alle considerevoli dimensioni dell'impianto, possono costituire un ostacolo per i chirurghi senza esperienza nell'ambito del basi-cranio. Inoltre, in letteratura sono pochi gli studi riguardanti il posizionamento retrosigmoideo del sistema BB.*

***Metodi**. Abbiamo svolto uno studio retrospettivo e multicentrico con lo scopo di analizzare i risultati chirurgici e funzionali di un'ampia popolazione di pazienti sottoposti a posizionamento retrosigmoideo del sistema BB tramite una specifica tecnica chirurgica che è stata*

Received: January 15, 2020
Accepted: April 10, 2020

Correspondence
Pietro Canzi
University of Pavia, Department of Otorhinolaryngology, IRCCS Policlinico San Matteo Foundation, viale C. Golgi 19, 27100 Pavia, Italy
Fax +39 0382 528184
E-mail: pietro.canzi@unipv.it

Funding
None.

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Canzi P, Avato I, Beltrame M, et al. Retrosigmoidal placement of an active transcutaneous bone conduction implant: surgical and audiological perspectives in a multicentre study. Acta Otorhinolaryngol Ital 2021;41:91-99. https://doi.org/10.14639/0392-100X-N0609

sviluppata con lo scopo di superare i problemi intraoperatori relativi a questa chirurgia. Venti pazienti con ipoacusia di trasmissione o mista e affetti da sordità monolaterale sono stati sottoposti a impianto retrosigmoideo del sistema BB.
Risultati. *La valutazione audiologica ha riguardato la misurazione del guadagno funzionale ed effettivo in audiometria tonale (rispettivamente pari a 28 dB HL e -12.25 dB HL) e audiometria vocale (rispettivamente pari a 24.7 dB HL e -21 dB HL). Globalmente è stato riportato un significativo miglioramento soggettivo della qualità della vita rispetto alla condizione preoperatoria, quantificato mediante la compilazione del questionario Glasgow Benefit Inventory. Non sono state riscontrate gravi complicanze o condizioni necessitanti una chirurgia di revisione durante il periodo di follow-up (mediana: 42 mesi).*
Conclusioni. *Nell'ambito della nostra esperienza, risultata tra le più ampie mai riportate in letteratura, il posizionamento retrosigmoideo del sistema BB si è dimostrato sicuro ed efficace. I nostri risultati funzionali hanno mostrato dati uditivi comparabili con il posizionamento presigmoideo. Il guadagno effettivo, raramente indagato in questo campo della letteratura, potrebbe essere oggetto di future ricerche al fine di migliorare la nostra comprensione dei meccanismi di conduzione ossea impiegati da questa tipologia di protesi impiantabili.*

PAROLE CHIAVE: *protesi impiantabile a conduzione ossea, Bonebridge, transcutaneo, retrosigmoideo, tecnica chirurgica*

Introduction

In the 16th century, Girolamo Cardano first described the transmission of sounds by bone conduction (BC) as an effective way to produce the sense of hearing [1]. Based on audiological principles described many centuries ago, current BC hearing implants (BCHIs) result from the impressive advances of the modern hearing industry and are used for different types of hearing impairment: conductive or mixed forms of hearing loss and single sided deafness (SSD) [2,3]. BCHIs are mainly divided into two different categories: skin-drive BCHIs and direct-drive BCHIs. For the first type of device, the vibrations are transmitted through intact skin, while in direct-drive BCHIs the vibrations are sent directly to the bone via a screw attached to the skull (percutaneous BCHI) or an active transducer implanted into the bone (transcutaneous BCHI) [2]. The active transcutaneous direct-drive systems have been developed to overcome the limits of percutaneous devices (skin irritation or infections around the screw, fixture extrusion), and to avoid the skin attenuation effects of skin-drive BCHIs. Nowadays, the Bonebridge® (Med-El, Innsbruck, Austria) (BB) is the only active transcutaneous BCHI available on the market, although another device has been in development since 2013 and is currently under regulatory review [4,5]. Three types of surgical placements are currently being performed for the BB housing. The most commonly used is transmastoid-presigmoid placement, in which the internal part is placed in the mastoid portion of the temporal bone (sinodural angle) [6,7]. The suprameatal-middle fossa placement has been proposed in patients with aural atresia and requires the drilling of the parietal bone with complete exposure of the meninges. The lack of research on direct and long-term vibrations on the dura is in alignment with the authors's recommendations for long-term follow-ups [8]. Retrosigmoidal (RS) placement has proven to be useful in all patients in whom anatomical or clinical conditions contraindicate a presigmoidal position [9]. The literature reports only limited experience concerning RS implantation of the BB system, for which surgical decision making faces many intraoperative challenges, mainly related to the device dimensions [2,3,6-10]. The purpose of our study was to analyse surgical and functional outcomes in a wide population of patients undergoing RS placement of the BB system by means of a surgical technique specifically developed to overcome the intraoperative issues related to this surgery.

Materials and methods

Study design and participants

A multicentre, retrospective case series study was conducted on BCHI recipients who underwent RS placement of the BB system at three Otolaryngology tertiary referral centres between January 2013 and September 2019. Approval from the local ethics committees was obtained and all patients signed informed consent agreements before treatment. All patients met the audiological criteria suggested by the manufacturer: mild to moderate conductive hearing loss (CHL) or mixed hearing loss (MHL) with pure tone average (PTA) BC threshold (0.5, 1, 2, 3 and 4 kHz) ≤ 45 dB HL and minimum PTA air bone gap (ABG) of 30 dB, or SSD with a better ear PTA air conduction (AC) threshold ≤ 20 dB HL. Moreover, enrolment criteria involved:

- conditions that contraindicate a presigmoid-transmastoid approach:
  - anatomical (protruding sigmoid sinus, low-lying middle fossa dura, contracted mastoid bone);
  - clinical (chronical wet middle ear and mastoid cavity, previous canal wall down mastoidectomy, aural atresia scheduled for external ear reconstruction);
  - failure of previous hearing rehabilitation surgery (e.g. stapedotomy, tympanoplasty);
  - inadequate hearing rehabilitation with conventional hearing aids.

The preoperative assessment included a temporal bone CT scan and a brain MRI aimed at planning the surgical approach and excluding comorbidities that may contraindi-

cate surgery or require radiological follow-up. All audiometric tests were performed with an Inventis Piano Plus® audiometer. Preoperatively, pure-tone AC threshold from 0.125 to 8.0 kHz and pure-tone BC threshold from 0.25 to 4.0 kHz were measured and the PTA (0.5, 1, 2, 4 kHz) was calculated. The speech reception threshold (SRT), at which 50% of the presented disyllabic words are recognised, was recorded in quiet conditions for both AC and BC. Postoperatively, a pure tone audiometry and a speech audiometry with disyllabic words in free field and quiet conditions were performed in both unaided (BB-OFF) and aided conditions (BB-ON). A noise masker by means of insert (at the non-test ear) was adopted to prevent cross hearing when necessary. As audiological outcomes, the functional gain (i.e. the difference between the postoperative unaided and aided threshold) and the effective gain (i.e. the difference between the BC threshold and the aided threshold) were evaluated by pure-tone audiometry and speech audiometry. The first fitting was planned about 1 month after surgery. Audiological follow-ups were scheduled at 3, 6, and 12 months and then yearly. The Glasgow Benefit Inventory (GBI) questionnaire was administered to each patient to evaluate items regarding the quality of life after the surgery. It consists of 18 questions, 12 of which apply to general health, 3 to physical health and 3 to social health. For each question, 5 possible answers are available (scores ranging from 1 to 5). Through a mathematical formula, four scores are then obtained: a total score and three partial scores (general health, physical health and social health). Each score ranging from -100 (worsening after surgery) through 0 (no change) to + 100 (improvement after surgery) [11].

Surgical technique

All the surgical procedures employed the same technique, the steps of which are described below.

The conventional RS anatomical landmarks were identified to allow the positioning of the internal implanted unit (the BC floating mass transducer or BC-FMT) posteriorly to the sigmoid sinus and superiorly to the digastric fossa, where a regular bony surface was usually identified as the ideal location for the BC-FMT.

A retro-auricular reversed C-shaped incision was made (4 cm-long incision) and an anteriorly pedicled C-shaped muscular-periosteal flap was harvested to enable access to the bony area located above the digastric fossa and to create a natural anatomical division between the mastoid cavity and the BB housing. The subperiosteal pouch for the location of the coil and the magnet was obtained under the flap. The probe (T-sizer) of the device was used to identify a suitable area for the BC-FMT placement. In the centre of the marked area, the cortical bone was removed by shaping a circular hole which diameter was smaller than the actual BC-FMT diameter (Fig. 1a,b).

A diamond burr was used to drill in the undercut position to safely explore the circumference of the surgical site. Careful drilling was needed close to the sigmoid sinus. If the sigmoid sinus was encountered, the circumference was enlarged step by step in a safer direction with the intent of obtaining the diameter required (Fig. 1c,d). The emissary mastoid vein was closed if intercepted.

A bony island between the BC-FMT and the dura mater was shaped in order to reach a suitable depth for the BC-FMT housing when necessary. Once the bone layer was obtained, it was separated from the underlying dura mater using a freer dissector. The resulting surface could be depressed, allowing complete lodging of the BC-FMT. (Fig. 1e,f).

The T-sizer was used to verify the correct positioning of the BC-FMT, and the device was inserted and fixed with two self-tapping cortical screws. The anterior pedicle muscle-periosteal flap was reconstructed with resorbable sutures and the subcutaneous layer and the skin were then closed.

Statistical analysis

Statistical analysis were performed with R software (R version 3.1.3, R Development Core Team, R Foundation for Statistical Computing, Wien, Austria). Descriptive statistics were calculated for all groups (the mean, standard deviation, median, minimum and maximum values). Normality of distributions was assessed with the Kolmogorov and Smirnov tests. An ANOVA test was ran to determine whether significant differences existed among the groups. The Tukey test was used post-hoc. The Kruskal Wallis test was used to assess the statistical significance of each GBI subscore. Significance for all statistical tests was predetermined at $p < 0.05$.

Results

A total of 20 patients (11 males, 9 females, median age of 47.2 years) were included in the study. 13 patients were implanted on the right side and 7 on the left side. The aetiology, type of hearing loss, and previous otologic and surgical history were investigated (Tab. I).

Preoperative audiological assessment

10 patients with CHL (50%), 8 patients with MHL (40%) and 2 patients with SSD (10%) were identified; these latter two were not included in the statistical analysis of audiological outcomes because surgery was performed to obtain a contralateral routing of signal. Mean PTA (18 out of 20 patients) of the implant candidate's ear was 61.5 dB HL

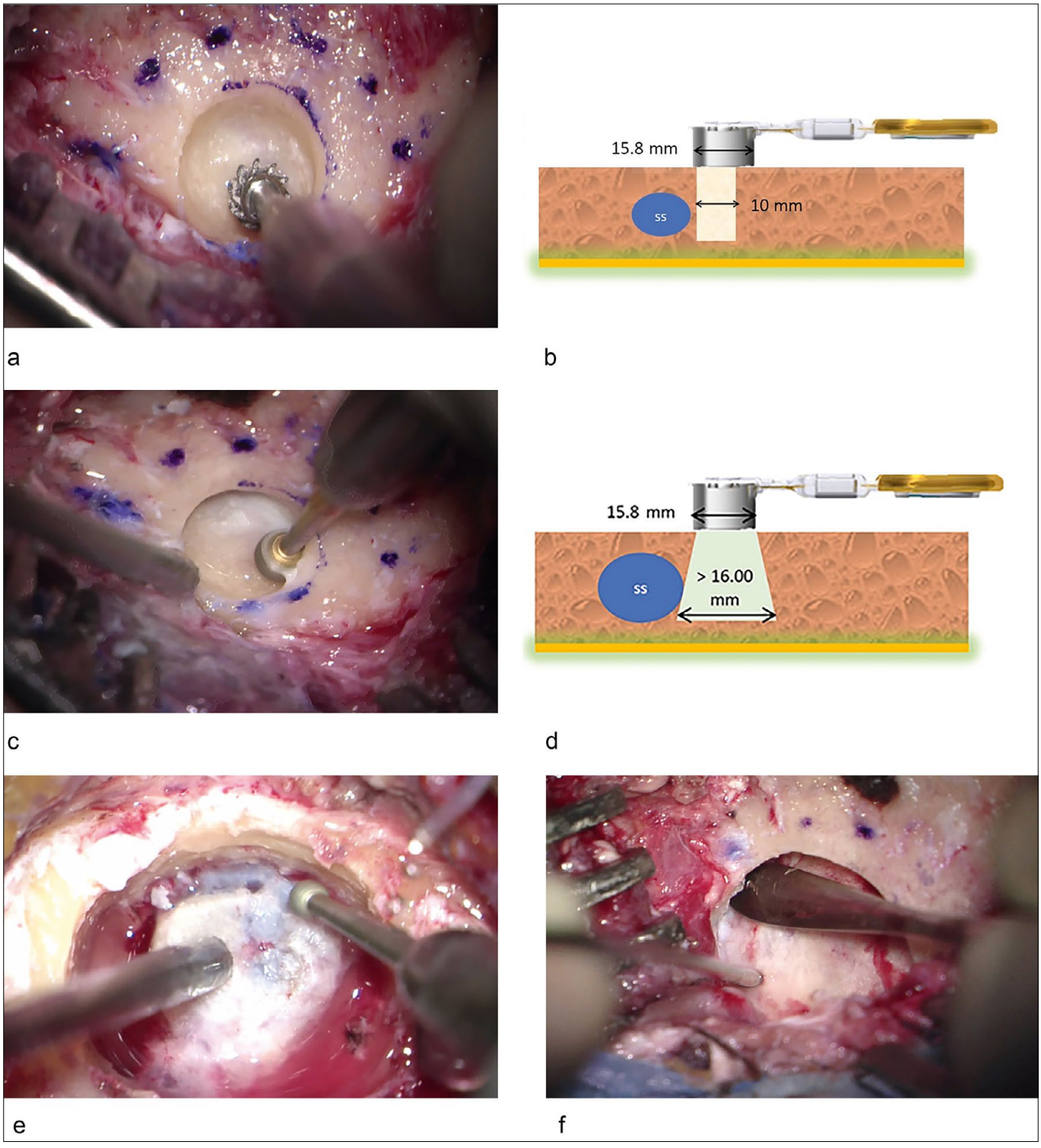


Figure 1. Intraoperative images of the surgical steps and schematic representations. A cutting burr is used for the initial drilling (**a**), its diameter is smaller than the actual diameter of the transducer as shown by the dotted line (**a, b**). An undercut drilling by means of a diamond burr is then executed to safely explore the circumference of the surgical site and to create the housing for the device (**c**), this process is schematically represented (SS: sigmoid sinus) (**d**). A bony island is sculpted to obtain a suitable depth for the housing of the device (**e**) and the dural layer is then detached by means of a freer dissector (**f**) to create a compressible surface.

Table I. Demographic data and otologic history.

Patient	Sex	Age	Hearing loss	Pathology	Previous surgery (BB side)	Implanted side	Bony island
1	M	47	Bilateral MHL	Bilateral cholesteatoma	CWD TPL	Right	Not required
2	M	60	Bilateral MHL	Bilateral cholesteatoma	CWD TPL	Right	Yes
3	M	23	Bilateral CHL	Atresia auris (BB side) + cholesteatoma	None	Left	Yes
4	M	46	Bilateral MHL	Bilateral COM	CWU TPL	Right	Yes
5	F	52	Bilateral CHL	Bilateral cholesteatoma	CWD TPL	Left	Yes
6	F	45	SSD	Cholesteatoma	CWD TPL	Right	Yes
7	F	31	Bilateral CHL	Bilateral atresia auris	None	Left	Yes
8	F	49	Bilateral MHL	Cholesteatoma (BB side) + COM	CWD TPL	Right	Yes
9	M	47	SSD	Cholesteatoma	CWD TPL	Right	Yes
10	F	61	Bilateral MHL	Bilateral cholesteatoma	CWD TPL	Left	Yes
11	M	64	Bilateral MHL	Bilateral COM	CWU TPL	Right	Not required
12	M	76	MHL (BB side) + SNHL	Cholesteatoma	Lateral petrosectomy	Right	Yes
13	F	67	Bilateral MHL	Bilateral cholesteatoma	CWD TPL	Right	Yes
14	F	14	Unilateral CHL	Cholesteatoma	CWD TPL	Right	Yes
15	M	37	Bilateral CHL	Bilateral cholesteatoma	Lateral petrosectomy	Left	Yes
16	F	33	Bilateral CHL	Bilateral otosclerosis	Stapedotomy	Right	Yes
17	M	39	Unilateral CHL	Cholesteatoma (BB side) + COM	Lateral petrosectomy	Right	Yes
18	F	47	CHL (BB side) + MHL	Cholesteatoma (BB side) + COM	CWD TPL	Right	Yes
19	M	57	CHL (BB side) + SNHL	Cholesteatoma (BB side)	CWD TPL	Left	Yes
20	M	48	CHL	Cholesteatoma	CWU TPL	Left	No (lifts 2 mm)

M: male; F: female; CHL: conductive hearing loss; MHL: mixed hearing loss; SNHL: sensorineural hearing loss; SSD: single sided deafness; BB: Bonebridge; COM: chronic otitis media; CWD: canal wall down; CWU: canal wall up; TPL: tympanoplasty

(range 41.25-83.75 dB HL, SD: ± 13.07) for AC, 20.5 dB HL (range 6.25-33.75 dB HL, SD: ± 8.72) for BC. The ABG calculated on the PTA was 41 dB HL (range 28.75-56.25 dB HL, SD: ± 7.58). Regarding speech audiometry on the implant candidate's ear, the mean AC SRT was 67.85 dB HL (range 55-90 dB HL, SD: ± 13.4); BC SRT was 20.35 dB HL (range 10-40 dB HL, SD: ± 9.49). The ABG SRT for the implanted side was 47.5 dB HL (range 30-70 dB HL, SD ± 10.51) (Fig. 2).

Postoperative audiological assessment

Postoperatively, in the BB-OFF setting, AC PTA was 60.8 dB HL (range 41.25-83.75 dB HL, SD: ± 12.22). The PTA threshold improved to 32.75 dB HL in the BB-ON setting (range 11.25-45 dB HL, SD: ± 8.29). The mean functional gain on pure-tone audiometry was 28 dB HL (range 13.75-45 dB HL, SD: ± 10.54). Concerning speech audiometry, the mean BB-OFF SRT was 66 dB HL (range 40-90 dB HL, SD: ± 13.32) improving up to 41.35 dB HL in the BB-ON setting (range 30-65 dB HL, SD: ± 9.54). The mean functional gain as analysed via speech audiometry was 24.7 dB HL (range 10-36 dB HL, SD: ± 8.74 – Fig. 3). The mean pure-tone effective gain (i.e. the mean difference between the BC PTA and the BB-ON PTA) was -12.25 dB HL (range -27.5-0 dB HL, SD: ± 8.82) (Fig. 3). The effective gain distribution was also selectively analysed at low (0.25, 0.5 kHz), mid (1, 2 kHz) and high frequencies (4 kHz) and resulted in -26.25 dB HL (SD: ± 5.8), -4.29 dB HL (SD: ± 6.56) and -18.57 dB HL (SD: ± 9.07) respectively. The mean effective gain calculated via speech audiometry was -21 dB HL (range -30-0 dB HL, SD: ± 8). During the follow-up (median: 42 months; range: 11-72 months) no worsening of the BC threshold occurred. About 3 months after the first fitting, a stability of the audiological gain values was observed and then confirmed at subsequent evaluations. The ANOVA and Tukey tests were ran to determine the presence of significant differences ($p < 0.05$) between BB-ON thresholds and BB-OFF thresholds (functional gain) and between BB-ON thresholds and BC thresholds (effective gain). Specifically, pure-tone BB-ON and BB-OFF thresholds were compared considering all frequencies between 0.25 kHz and 4 kHz. A significant difference was found for each frequency tested ($p < 0.05$). Functional gain was found significant ($p < 0.05$) by speech audiometry when BB-ON SRTs were compared with BB-OFF SRTs. Focusing on the effective gain analysed via pure-tone audiometry, a significant difference ($p < 0.05$) was seen

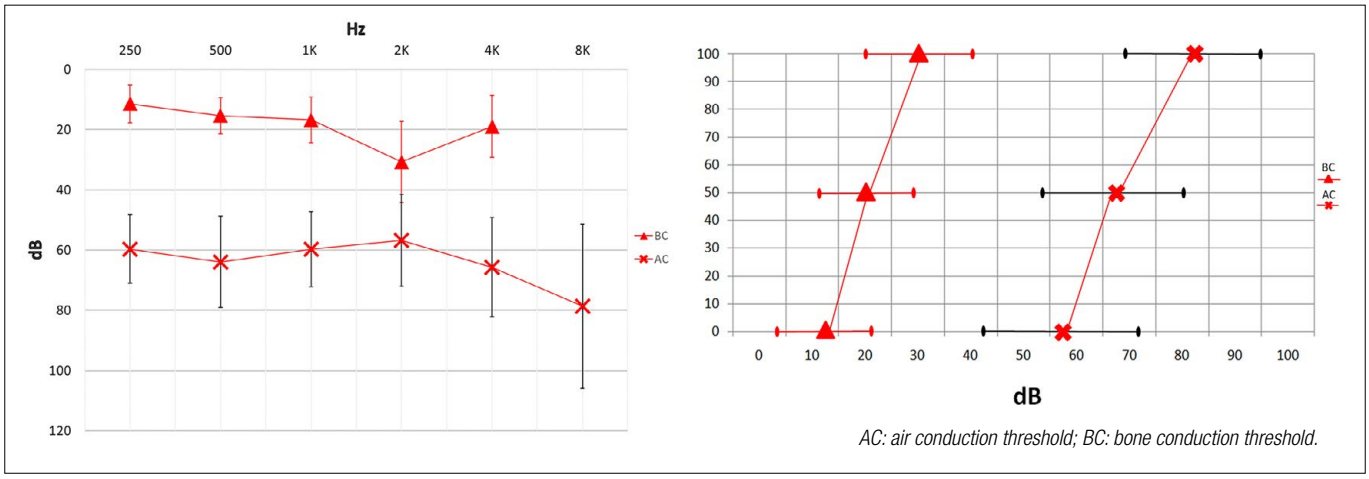


Figure 2. Preoperative mean audiograms of implant candidate's ear: pure-tone audiometry (vertical bars: standard deviation) and speech audiometry (horizontal bars: standard deviation).

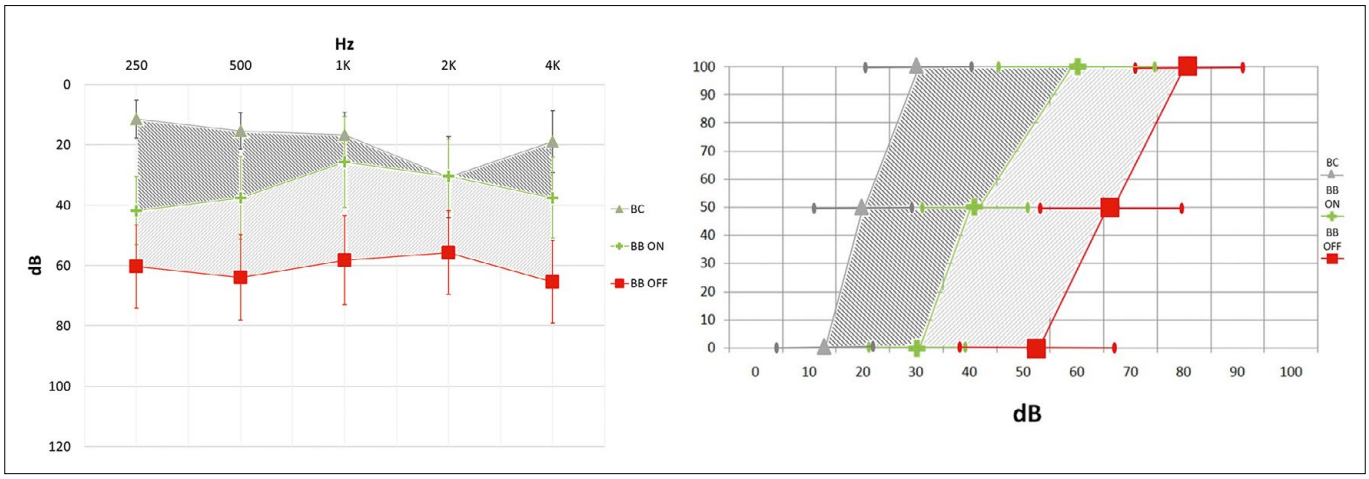


Figure 3. Mean free field aided threshold (BB-ON) compared with the free field unaided threshold (BB-OFF): pure-tone audiometry (vertical bars: standard deviation) and speech audiometry (horizontal bars: standard deviation). BC: bone conduction threshold. Light grey highlighted area: mean functional gain (i.e. the difference between the postoperative unaided and aided threshold). Dark grey highlighted area: mean effective gain (i.e. the difference between the BC threshold and the aided threshold). A noise masker by means of insert (at the contralateral ear) was adopted when necessary.

between BB-ON thresholds and BC thresholds at 0.25, 0.5 and 4 kHz (Fig. 4a,c). Conversely, a significant difference was not found at 1 and 2 kHz ($p > 0.05$) (Fig. 4b). An overall statistically significant difference ($p < 0.05$) was found when BB-ON SRTs were compared with BC thresholds (Fig. 4d).

Surgery and complications

The device was correctly placed in the designated RS surgical area in all patients and it was possible to fix the implant with both screws. Specifically, a bony island was sculpted in 17 patients (85%) and lifts were used in 1 patient (5%), while the implant was directly lodged in 2 patients (10%). No major complications were observed. Minor complications included a single case of dural dehiscence that was repaired with autologous fascia. Postoperative sensorineural hearing worsening or vestibular symptoms were never observed. At the time of follow-up, none of the BB recipients experienced device extrusions or other conditions requiring revision surgery.

Quality of life assessment

Concerning the GBI questionnaire, descriptive statistics are showed in Table II. Patients showed general, physical and social health gain ($p < 0.05$; Fig. 5) and no significant differences were reported among the various subcategories ($p > 0.05$).

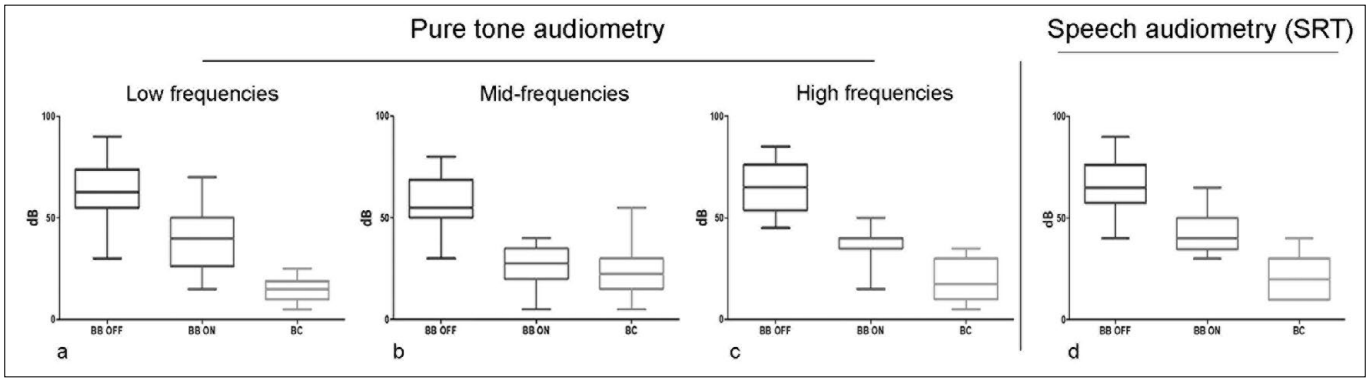


Figure 4. ANOVA test applied to compare the free field aided thresholds (BB-ON) with the free field unaided thresholds (BB-OFF) and with bone conduction (BC) thresholds. a) Pure-tone audiometry – low frequencies b) Pure-tone audiometry – mid frequencies; c) Pure-tone audiometry – high frequencies; d) Speech audiometry – speech recognition threshold (SRT). All graphs show a significant difference ($p < 0.05$) when the BB-ON thresholds are compared with the BB-OFF thresholds. All graphs show a significant difference ($p < 0.05$) when the BB-ON thresholds are compared with the BC thresholds with the exception of the mid-frequencies graph. Vertical bars: standard deviation.

Table II. Glasgow Benefit Inventory descriptive statistics.

	Mean	SD	Min	Median	Max
Total score	49.40	19.54	10	55.5	83
General health	55.65	17.88	15	58.5	92
Physical health	41.70	27.63	-15	42	84
Social health	34.60	32.09	-33	50	80

SD: standard deviation.

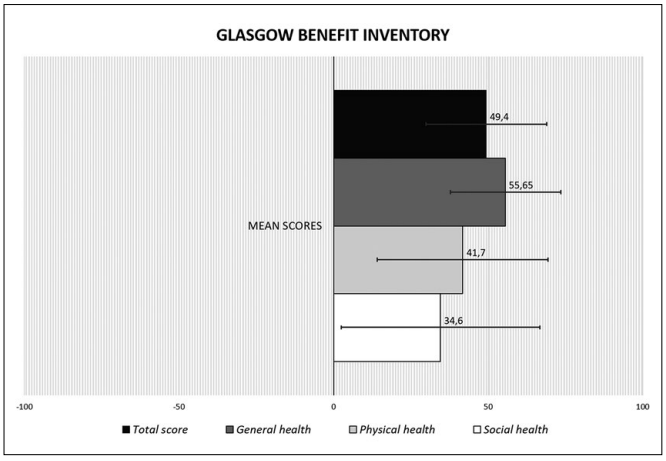


Figure 5. Results of the Glasgow Benefit Inventory (GBI) questionnaire. The histogram provides a graphic representation of the quality of life after surgery reporting the mean GBI total and partial scores (horizontal bars: standard deviation). Scores can range from – 100 (worsening after surgery) through 0 (no change) to + 100 (improvement after surgery). A significant improvement ($p < 0.05$) is shown for each GBI score and no significant differences are reported among the various subcategories ($p > 0.05$).

Discussion

Our study presents one of the largest samples of patients submitted to RS implantation of the BB system reported in literature. The sample is highly homogeneous in terms of surgical technique and audiological assessment. First described by Sprinzl et al. in a European multicentre study [12], RS placement has been advocated in case of unfavourable anatomical or clinical conditions which contraindicate the presigmoidal position [9,13,14]. However, these disadvantageous conditions combined with the considerable dimensions of the internal implanted unit (8.7 mm in thickness and 15.8 mm in diameter) and with the topography of the anatomical area addressed to the BC-FMT housing, make this surgical procedure challenging [7,15-17]. In alignment with data from the literature, medical history of previous middle ear surgery represented the main eligibility criteria for a RS position [9] in our study. The harvesting of an anteriorly pedicled muscular-periosteal flap was developed to prevent possible contaminations from the mastoid cavity and middle ear towards the site of implantation. The surgical technique was designed to obtain an adequate bony bed for the BC-FMT housing, while avoiding hazardous drilling (especially close to the sigmoid sinus). It also prevents over-extension of the drilling surface which could compromise fixation of screws. In all BB recipients, the surgical procedure was successfully performed with a complete lodging of the BC-FMT and with its fixation with two self-tapping screws. None of the patients required revision surgery or BB explantation. A bony island was sculpted in 85% of patients, allowing adequate BC-FMT housing and concurrent protection of the dura from major complications both intra- and postoperatively. Brkic et al. [18] recently reported one of the largest studies of patients submitted to BB implantation, analysed over a 6-year follow-up period. In

their experience, the authors observed an overall complication rate of 9.4% including 5 cases of explantation. Interestingly, 3 of these implants were positioned in a radical cavity, which was subsequently compromised by postoperative infections. According to the authors, a presigmoidal approach is to be preferred even in patients with history of previous radical cavities because of anatomical factors limiting RS placement. Furthermore, the same tertiary referral centre published a previous study of 19 patients in which the BC-FMT was directly coupled to the dura or sinus (7 RS placements, 12 presigmoidal/middle fossa placements). Although no adverse events were reported, the authors clarified that the risks of direct sinus/dura compression are not yet clear [19].

In our experience, the surgical technique was designed to overcome the abovementioned issues and to reduce the possibility of revision surgery or long-term untoward events. Considering audiological findings, all patients enrolled met the preoperative recommended criteria: specifically, mean BC PTA was 20.5 dB, almost 25 dB lower than the manufacturer's indications. The effectiveness of BCHI was investigated by means of two audiological measurements: functional and effective gain. The mean PTA functional gain was found to be 28 dB HL, consistent with the results reported in the two largest series of RS implanted patients (28.9 dB and 28 dB in Ihler et al. [20] and Loader et al. [14] respectively). With regards to presigmoidal placement, our data did not reveal a significant difference in terms of mean functional gain (Gerdes et al. [21] 27.5 dB; Riss et al. [22] 28.8 dB). Although debated in literature, superior audiological effectiveness cannot be assessed using currently published data when the two BC-FMT surgical placements are compared [14,19,23,24]. The effective gain is considered expression of the relationship between the threshold in aided condition and the patient's cochlear reserve. Defined as the difference between the BC threshold and the aided threshold, the effective gain may result in negative values and if positive, indicates ABG overclosure. This parameter was previously measured by Donnelly et al. [25] to evaluate the effectiveness of different types of active middle ear implants and by van Barneveld et al. [26] to define fitting ranges for BC devices. To the best of our knowledge, only one study has reported this parameter in BCHI recipients [18], although it was not object of further analysis. In our experience, the mean pure-tone effective gain was -12.25 dB HL, although it showed a different statistical distribution when selectively analysed at low, mid and high frequencies. In particular, the highest values were measured at 1-2 kHz (-4.29 dB HL) where a significant difference between the BB-ON thresholds and the BC thresholds was not found. These observations, apparently, do not relate to power output issues. What seems to limit the BB fitting range on certain frequencies are unpleasant sound distortions and annoying vibratory perceptions [26]. The RS placement itself, does not seem to be related to these findings, since our audiological results have shown to be comparable with current literature data for presigmoid positioning. Furthermore, a significant improvement in the quality of life was recorded in all patients as suggested by the total and partial GBI scores. We are, nonetheless, aware that some concerns regarding our study may arise. The retrospective and multicentric nature of the study may be considered a limitation in terms of heterogeneity of the series. However, the adoption of common enrolment criteria and a standardised surgical technique and the uniformity of data analysis minimise this bias. Additionally, the introduction of an uncommonly used audiological measurement such as the effective gain may preclude comparison with the current literature.

Conclusions

RS placement of the BB system was seen to be safe and effective, thus constituting in a valid surgical alternative when the presigmoidal position is not advised. However, it may represent a challenge, especially for surgeons with no skull base experience. The surgical technique introduced was developed to define the main surgical steps of RS placement in order to obtain a complete lodging of the internal implanted unit, avoiding untoward events both intra- and postoperatively, even after long-term follow-up. Our functional results show comparable hearing outcomes with presigmoidal placement, in contrast to authors who argue a greater efficacy of one of the two positions. The effective gain, rarely investigated in this field of literature, may be object of future research to improve our understanding of BC mechanisms exploited by the BCHIs.

References

1 Berger KW. Early bone conduction hearing aid devices. Arch Otolaryngol 1976;102:315-8. https://doi.org/10.1001/archotol.1976.00780100101017

2 Reinfeldt S, Håkansson B, Taghavi H, et al. New developments in bone-conduction hearing implants: a review. Med Devices (Auckl) 2015;8:79-93. https://doi.org/10.2147/MDER.S39691

3 Canale A, Boggio V, Albera A, et al. A new bone conduction hearing aid to predict hearing outcome with an active implanted device. Eur Arch Otorhinolaryngol 2019;276:2165-70. https://doi.org/10.1007/s00405-019-05450-4

4 Eeg-Olofsson M, Håkansson B, Reinfeldt S, et al. The bone conduction implant – first implantation, surgical and audiologic aspects. Otol Neurotol 2013;35:679-85. https://doi.org/10.1097/MAO.0000000000000203

5 Håkansson B, Reinfeldt S, Persson AC, et al. The bone conduction

implant – a review and 1-year follow-up. Int J Audiol 2019;58:945-55. https://doi.org/10.1080/14992027.2019.1657243

6 Sprinzl GM, Wolf-Magele A. The Bonebridge Bone Conduction Hearing Implant: indication criteria, surgery and a systematic review of the literature. Clin Otolaryngol 2016;41:131-43. https://doi.org/10.1111/coa.12484

7 Wimmer W, Gerber N, Guignard J, et al. Topographic bone thickness maps for Bonebridge implantations. Eur Arch Otorhinolaryngol 2015;272:1651-8. https://doi.org/10.1007/s00405-014-2976-8

8 Der C, Bravo-Torres S, Pons N. Active transcutaneous bone conduction implant: middle fossa placement technique in children with bilateral microtia and external auditory canal atresia. Otol Neurotol 2018;39:342-8. https://doi.org/10.1097/MAO.0000000000001809

9 Lassaletta L, Sanchez-Cuadrado I, Muñoz E, et al. Retrosigmoid implantation of an active bone conduction stimulator in a patient with chronic otitis media. Auris Nasus Larynx 2014;41:84-7. https://doi.org/10.1016/j.anl.2013.04.004

10 Barbara M, Perotti M, Gioia B, et al. Transcutaneous bone-conduction hearing device: audiological and surgical aspects in a first series of patients with mixed hearing loss. Acta Otolaryngol 2013;133:1058-64. https://doi.org/10.3109/00016489.2013.799293

11 Robinson K, Gatehouse S, Browning GG. Measuring patient benefit from otorhinolaryngological surgery and therapy. Ann Otol Rhinol Laryngol 1996;105:415-22. https://doi.org/10.1177/000348949610500601

12 Sprinzl G, Lenarz T, Ernst A, et al. First European multicenter results with a new transcutaneous bone conduction hearing implant system: short-term safety and efficacy. Otol Neurotol 2013;34:1076-83. https://doi.org/10.1097/MAO.0b013e31828bb541

13 Lassaletta L, Calvino M, Zernotti M, et al. Postoperative pain in patients undergoing a transcutaneous active bone conduction implant (Bonebridge). Eur Arch Otorhinolaryngol 2016;273:4103-10. https://doi.org/10.1007/s00405-016-3972-y

14 Loader B, Sterrer E, Reichmayr C, et al. Direct comparison of mastoidal and retrosigmoidal placement of a transcutaneous bone conduction device after canal wall down tympanoplasty. Clin Otolaryngol 2018;43:1603-6. https://doi.org/10.1111/coa.13187

15 Bianchin G, Bonali M, Russo M, et al. Active bone conduction system: outcomes with the Bonebridge transcutaneous device. ORL 2015;77:17-26. https://doi.org/10.1159/000371425

16 Canzi P, Marconi S, Manfrin M, et al. From CT scanning to 3D printing technology: a new method for the preoperative planning of a transcutaneous bone-conduction hearing device. Acta Otorhinolaryngol Ital 2018;38:251-6. https://doi.org/10.14639/0392-100X-1625

17 Law EKC, Bhatia KSS, Tsang WSS, et al. CT pre-operative planning of a new semi-implantable bone conduction hearing device. Eur Radiol 2016;26:1686-95. https://doi.org/10.1007/s00330-015-3983-x

18 Brkic FF, Riss D, Scheuba K, et al. Medical, technical and audiological outcomes of hearing rehabilitation with the bonebridge transcutaneous bone-conduction implant: a single-center experience. J Clin Med 2019;8:1614. https://doi.org/10.3390/jcm8101614

19 Vyskocil E, Riss D, Arnoldner C, et al. Dura and sinus compression with a transcutaneous bone conduction device – hearing outcomes and safety in 38 patients. Clin Otolaryngol 2017;42:1033-8. https://doi.org/10.1111/coa.12793

20 Ihler F, Blum J, Berger MU, et al. The prediction of speech recognition in noise with a semi-implantable bone conduction hearing system by external bone conduction stimulation with headband: a prospective study. Trends Hear 2016;20:1-12. https://doi.org/10.1177/2331216516669330

21 Gerdes T, Salcher RB, Schwab B, et al. Comparison of audiological results between a transcutaneous and a percutaneous bone conduction instrument in conductive hearing loss. Otol Neurotol 2016;37:685-91. https://doi.org/10.1097/MAO.0000000000001010

22 Riss D, Arnoldner C, Baumgartner WD, et al. Indication criteria and outcomes with the Bonebridge transcutaneous bone-conduction implant. Laryngoscope 2014;124:2802-6. https://doi.org/10.1002/lary.24832

23 Salcher R, Zimmermann D, Giere T, et al. Audiological results in SSD with an active transcutaneous bone conduction implant at a retrosigmoidal position. Otol Neurotol 2017;38:642-7. https://doi.org/10.1097/MAO.0000000000001394

24 Schmerber S, Deguine O, Marx M, et al. Safety and effectiveness of the Bonebridge transcutaneous active direct-drive bone-conduction hearing implant at 1-year device use. Eur Arch Otorhinolaryngol 2017;274:1835-51. https://doi.org/10.1007/s00405-016-4228-6

25 Donnelly NP, Pennings RJE. Hearing rehabilitation with active middle ear implants. Adv Otorhinolaryngol 2018;81:43-56. https://doi.org/10.1159/000485529

26 Van Barneveld DCPBM, Kok HJW, Noten JFP, et al. Determining fitting ranges of various bone conduction hearing aids. Clin Otolaryngol 2018;43:68-75. https://doi.org/10.1111/coa.12901

In Memoriam of

Mario Mantovani

Mario Mantovani suddenly passed away on July 3, 2020. He was born in Como on January 19, 1946. After carrying out classical studies (Liceo Classico A. Volta, Como), he graduated in Medicine at the University of Pavia (1970). He specialised in ENT (1975), Ophtalmology (1977), Reconstructive Plastic Surgery (1981) and Maxillo-Facial Surgery (1986) at the University of Milan. His entire clinic career took place at the Department of Otolaryngology-Head and Neck Surgery at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan. He started as Assistant (1974) under the guidance of Prof. Ettore Bocca who awarded him the position of Adjunct Professor. In 2000 he was appointed as Head of the Department (2000-2001). He continued to collaborate with the Department (directed by Prof. Lorenzo Pignataro) with care and teaching assignments (until 2020).

He was a learned gentleman, brilliant inventor, skillful surgeon, passionate about his profession, good skier, lover of life and his family.

He developed a completely innovative surgical approach for Obstructive Sleep Apnea: the "Modular Barbed Snoring & OSAHS Surgery", being the first to use barbed sutures for pharyngoplasties: it was a revolution that changed the current surgical management of sleep apnea all over the world.

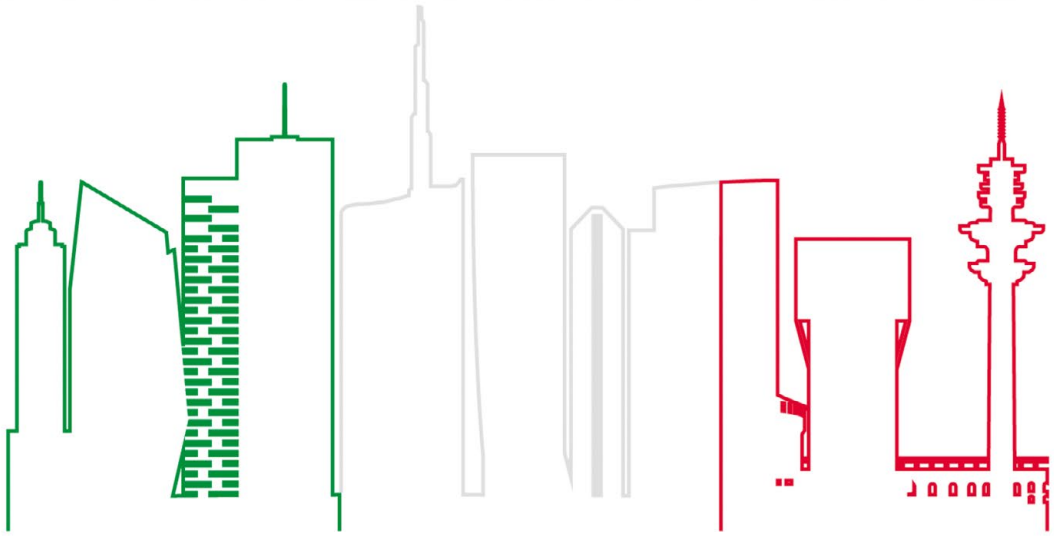
In the field of rhinology he was inventor of new surgical techniques such as the "Back and Forth Septoplasty" and new devices such as the "Guastella-Mantovani septal-valve splint". He was a pioneer in the field of odontogenic sinusitis, contributing to the definition of ENT contraindications to Sinus Lift and inventing "the Antral Retriever" for foreign bodies removal from the maxillary sinus. There are many other inventions and not only in the field of otolaryngology, some even very peculiar like a device to turn his motorcycle into a snow bike. He was the author of numerous scientific papers published in peer reviewed journals, as well as many book chapters.

For all of us it was a sad and immense loss. He still had so much to discover and to teach. He will remain in the memory and in the heart of all those who had the privilege of knowing him. He is survived by his wife Elena and by his daughter Camilla.

We will miss you Mario and we will do our best to carry out your innovative ideas and your projects.

Vittorio Rinaldi, Lorenzo Pignataro

Otorinolaringoiatria Italiana
Il Congresso che celebra Evoluzione e Futuro di una grande Società



107° SIO

MILANO MiCo 26.05/29.05 2021

SOCIETÁ ITALIANA DI OTORINOLARINGOIATRIA E CHIRURGIA CERVICO-FACCIALE

Presidente del Congresso **MARIO BUSSI** Presidente Onorario **ANTONINO ANTONELLI**

SIO
Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale
Presidente Gaetano Paludetti

Presidente del Congresso

Mario Bussi
bussi.mario@sio2021.com
Direttore U.O. Universitaria ORL
Ospedale San Raffaele
Via Olgettina 60
20132 Milano I Italy

Segreteria Scientifica

COORDINAMENTO
Davide Di Santo, Andrea Galli
segreteriascientifica@sio2021.com
U.O. Universitaria ORL
Ospedale San Raffaele
Via Olgettina 60
20132 Milano I Italy

Segreteria Organizzativa

Nord Est Congressi
Piazza di Pietra 63
00186 Roma I Italy
Via Portanuova 3
33100 Udine I Italy
mail@nordestcongressi.it
www.nordestcongressi.it