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

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Managing Editor
M. Ansarin

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Review

Changing trends in otorhinolaryngology publishing

Trend in cambiamento nell'ambito delle pubblicazioni scientifiche otorinolaringoiatriche

Kadir Cagdas Kazikdas[1], Murat Tanik[2], Ahmet Ural[3]

[1] Department of Otorhinolaryngology, Near East University, Faculty of Medicine, Nicosia, Cyprus; [2] Department of Econometrics, Faculty of Economics, Dokuz Eylul University, Izmir, Turkey; [3] Department of Otorhinolaryngology, Abant Izzet BaysalUniversity, Faculty of Medicine, Bolu, Turkey

SUMMARY

The aim of this study is to compare the changes in impact factors and citation numbers of Open Access (OA) vs subscription-based (SB) journals between 1999 and 2016 and to explore the changing trends in ORL publishing. All data extracted from SCImago Journal and Country ranking (SJR) website have been used as input for statistical analysis. The chi-square test of independency was applied in order to understand whether the ratio of number of OA journals of ORL category have dramatically changed between years 1999 and 2016. Also, the years and impact factors of journals belonging to the OA and SB journals have been graphed separately and the changes of annual SJR ranks of both journal types have been compared using one-way Z-test. There was a significant difference as the proportion of OA Journals were not equal to the proportion of SB Journals throughout the years 1999 and 2016, and it showed the tendency to increase greater compared to SB Journals ($p < 0.01$). Although the overall level of impact factors of SB journals was generally high, by comparing two regression models, it was obvious that the level of increase of the impact factors of OA journals were significantly higher ($p < 0.01$). When choosing where to publish, it is important to consider the journal's visibility, cost of publication, IF or SJR of the journal and speed of publication as well as changing trends in medical publishing nourished by the Web of Science.

KEY WORDS: open access, SCImago journal rank indicator, impact factor, journal metrics, scientific publishing

RIASSUNTO

Lo scopo di questo lavoro è valutare i cambiamenti dell'impact factor e numeri delle citazioni delle riviste scientifiche Open Access (OA) versus riviste con sottoscrizione di contratto (SB) dal 1999 al 2016 ed esplorare i cambiamenti della tipologia di articoli ORL pubblicati. È stato utilizzato il test del chi quadrato a campioni indipendenti per valutare se il numero di riviste OA è sostanzialmente cambiato fra il 1999 ed il 2016. Gli anni e gli impact factor delle riviste OA e SB sono stati analizzati separatamente ed è stato utilizzato lo Z-test ad una via per comparare l'indice SJR di entrambe le tipologie di rivista. È stata dimostrata una differenza statisticamente significativa fra la proporzione delle riviste OA e SB dal 1999 al 2016. Intuitivamente l'aumento di impact factor delle riviste OA è risultato maggiore rispetto alle riviste SB. A tal proposito, la scelta della rivista su cui pubblicare un articolo deve tenere conto della visitbilità della rivista stessa, costi di pubblicazione, impact factor/SJR, velocità di pubblicazione e trend di interesse scientifico suggeriti da web of science.

PAROLE CHIAVE: *open access, SCImago journal rank, impact factor, parametri di valutazione, pubblicazioni scientifiche*

Introduction

Open access (OA) means unrestricted, free access to all scientific information, although its significance and impact are yet not fully understood. With the transformation from analogue, printed to digital electronic media for dissemination of scientific information in the last decade, the concept of OA

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Correspondence
Kadir Cagdas Kazikdas
Department of Otorhinolaryngology, Near East University, Faculty of Medicine, Near East Blv, via Mersin 10, 99138 Nicosia, Cyprus
E-mail: ckazikdas@gmail.com

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publishing has become even more prominent and the market for scientific publications is currently more global and heterogeneous. The potential of technical reproduction and dissemination worldwide provided by the Web of Science have enabled new business models for scientific publishers, where anyone with internet access can read OA articles, and the required resources to operate such medical journals are supplied by means other than charging readers [1]. Thus, OA is not only a single unambiguous term, but rather a set of possible strategies for distributing unrestricted scientific information accessible to all with various publishing modalities such as green, gold, platinum etc.

The idea of a journal that is fully accessible to the public, with no financial barriers, seems theoretically great, but when it is time for publication and journal selection, many researchers may find difficulty in making a decision between an OA or a traditional subscription-based (SB) journal. In the early days, OA journals were fraught with doubts and scepticism about the reliability and peer-reviewing quality, thus publishing in such journals was evaluated as a "quick fix" for academic promotions. However, over the years, major reliable publishers such as PLoS and BioMed Central have taken up this type of publishing modality and OA publishing started to gain repute and began to be indexed in quality databases [2]. A study in 2012 scientifically showed that OA journals began to reach same scientific quality and impact just like their SB equivalents, and the average citation rates were only 30% higher for subscription journals at the time of publication [1]. A recent study has shown that ORL journals with active social media accounts such as Twitter had much better visibility and significantly higher academic influence and H-index [3]. In a similar manner, since 2012, it is our personal observation that there is even a greater increase of citation numbers for the ORL articles published in OA journals, which can be attributed to the widespread usage of the internet and smartphones globally after this date. The aim of this current study is to test this hypothesis and compare the changes in impact factors and citation numbers of OA vs SB journals over years, thus exploring the changing trends in ORL publishing.

Materials and methods

In this study, two statistical methods are used to evaluate the changing trends in publishing in ORL journals. All data extracted from SCImago journal and country ranking (SJR) website have been used as input for statistical analysis. Initially, we applied the chi-square test of independency to understand whether the ratio of number of OA journals of ORL category listed inside SJR website have dramatically changed between years 1999 and 2016. As a second analysis, data of yearly impact factors of each ORL journal have been taken from the same website as presented on 20 December 2017 and listed separately for OA and SB journals using MINITAB Statistical Software (Release 17, Minitab Inc. State College, PA, USA). The years have been taken as a discrete factor variable for each journal and the annual SJR have been taken as response variables. By using a statistical package, the years and SJR of journals belonging to the OA and SB journals have been graphed separately and the ranking trends of both journal types have been compared. This comparison has been done by comparing the slopes of the two lines that are fitted to the two different data sets by least square method. The slopes of the two regression lines have been compared by a one-way Z-test and statistical significance of the difference of the trends was analysed.

Results

As of 1999 among 82 ORL journals, only 3 were OA journals. However, in 2016, 105 journals were published on the SJR website and 18 were OA. The increase of proportions may be shown by a chi-square of independency. When we arrange Table I regarding the expected values of for the procedure, Table I becomes:

The hypothesis should be:

- $H_0 = p_1 = p_2$ (the proportion of the number of OA and SB journals are the same through years 1999-2016);
- $H_1 = p_1 \neq p_2$ (the proportion of the number of OA and SB journals are not the same through years 1999-2016). When we calculate the chi square test statistic

$$\chi^2 = \frac{(3-9{,}21)^2}{9{,}21} + \frac{(79-72{,}79)^2}{72{,}79} + \frac{(18-11{,}79)^2}{11{,}79} + \frac{(87-93{,}21)^2}{93{,}21} = 8{,}4$$

The critical χ^2 table value for $\alpha\hat{E}$= 0,05 for (2-1) x (2-1) = 1 degree of freedom is equal to 3.841. Thus, we can conclude that: the hypothesis that says the proportions of number of OA journals through years are equal to the proportion of the number of SB journals can be rejected. Thus, there is a statistical significance that the proportion of the number of OA Journals are not equal to the proportion of SB Journals through 1999 and 2016. The proportion of OA Journals show a tendency to increase more compared to SB Journals ($p < 0.01$).

In addition, the changes of annual SJR of two types of journals shows a different trend through years between 1999 and 2016. For each year, the data have been split into two categories as SJR of OA journals and non-OA journals. Starting from 1999 to 2016, the impact factor of all journals

Table I. Contingency table of OA and SB journals.

	No. of OA journals	No. of SB journals	Total
1999	3 (9.21%)	79 (72.79%)	82
2016	18 (11.79%)	87 (93.21%)	105
Total	21	166	187

p < 0.01.

was entered into MINITAB and two separate graphs were drawn (Fig. 1A, B).

Although the general level of impact factors of SB journals is generally high, by comparing the two graphs it can be seen that the level of increase of the impact factors of OA journals are significantly higher. Although the increase of the impact factors of OA journals seems better, a one-way Z test was performed to compare the trends. The blue lines that passes through the data are the regression models that are fit to the data by the least square method. The slope coefficient of the first model that represent the subscription-based journals is 0.01126 and the second representing the OA journals is 0.02104. The standard error of the slope coefficient of the first model is $s_{b1} = 0.00202$ and the standard error of the slope coefficient of the second model is $s_{b2} = 0.00311$. The equality of the two slopes may be tested by the following one-way Z test.

$H_0: \beta_1 = \beta_2$ The slopes of the models are equal

$H_1: \beta_1 \neq \beta_2$ The slopes of the models are not equal

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{SE_{\beta 1}^2 + SE_{\beta 2}^2}}$$

Z=2.66

Since z value is higher than the critical value for which is equal to 2.33 for a one way z-test, which means the prob value is lower than 0.01 ($p < 0.01$) the null hypothesis may be rejected with a confidence level of 99%. The slopes of the two lines formed by the least square regression model are significantly different. The slope of the model that shows the increasing trend of OA journals is greater than the slope of the line that is fitted by the subscription based journal data. The slopes of the two lines are significantly different. It can be seen that the SJR of OA journals are tending to increase more rapidly, especially in the recent years.

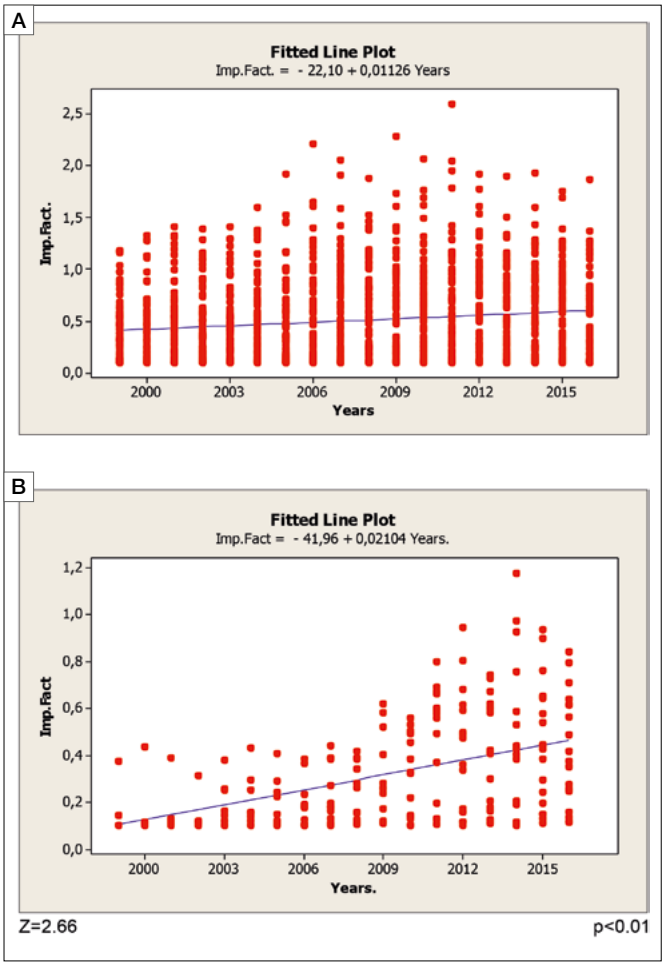

Figure 1. (A) The SJR of SB Journals of ORL during 1999-2016; (B) The SJR of OA Journals of ORL during 1999-2016.

Discussion

Since the publication of the first scientific journal, the Philosophical Transactions of the Royal Society, in 1665, today's journal publication landscape has exploded to more than 28,000 active scholarly peer-reviewed English-language journals, sharing the scientific discoveries of seven to nine million scientists in academia and industry. As of 2013, the scientific publication niche has been defined as a "bottomless pot of gold", with an estimated 110,000 employees globally and $ 25 billion annual revenue from public sources (via SB journals) and from the authors themselves (via OA journals). The market was predicted to grow at about 4% annually through 2017 [4]. This is not an astonishing fact, given that scientific effort has never diminished, and with the fierce competition for academic positions, scientific publication rates are likely to increase further. However, this last decade has seen the growth of OA journals

that offer a slightly different concept of peer-reviewed scientific publication to more traditional SB journals [5].

The "h-index", a new indicator proposed by Jorge E. Hirsch in 2005, is being widely used today to evaluate scientists' research performance, rather than just the number of articles they produce, and measures productivity of the researcher and the quality of that productivity taken together. In order to have a high h-index, it is necessary to publish a significant number of articles and each should have high citation numbers. At this stage, easy accessibility and high visibility of a printed article plays a major role in achieving the desired high number of citations. Although OA journals are fulfilling these criteria in an appropriate manner, they have been criticised for having a lower impact factor and poor peer review quality for many years. However, the results of this study show that these determinations have begun to change with an increasing ratio of OA journals in scientific indexes.

The "Impact Factor" (IF) is the major indicator of scientific importance of journals, calculated annually by Institute for Scientific Information (ISI) and by definition in any given year is the ratio of the number of articles cited all citable documents published in the two previous years to all citable documents in the same period of time [6]. The SCImago journal rank (SJR) indicator is a novel alternative index of scientific influence of the academical journals using the Scopus database. The SJR is defined as a size-independent prestige indicator that ranks journals by their "average prestige per article". It is an assessment of scientific influence of journals that accounts for both the number of citations received by a journal and the importance or "prestige" of the journals where such citations come from SCImago journal and country ranking website [7]. Based on the comparisons made by Falagas et al. [8], the SJR index might be a serious alternative to the well-established journal IF, based upon its OA nature, larger source database and assessment of the quality of citations, and it is recommended that the authors should consider all of these indices rather than just IF alone in assessing the influence and importance of medical journals in their respective disciplines [9]. In the present study, otorhinolaryngology journals were selected from the journal ranking section of SCImago journal and country ranking website [7], where they are grouped as quartiles (Q1-4) and as a result of the regression model applied; it was obvious that the level of increase of the impact factors of OA journals were significantly higher than SB ones. As of 2016 SJR listings, we have started to encounter more OA journals in the indexes and this observation was also statistically significant.

Conclusions

When choosing between OA and traditional journals, it is important to consider the journal's visibility, cost of publication, IF or SJR of the journal and speed of publication. To the best of our knowledge, this is the first study in the English literature to compare the OA and SB journals in the ORL field, demonstrating novel trends in medical publishing between 1999-2016. Nevertheless, it is still recommended to consider all the pros and cons of both journal types to achieve the desired high-citation numbers.

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Review

Head and neck cutaneous basal cell carcinoma: what should the otorhinolaryngology head and neck surgeon care about?

Carcinoma basocellulare della cute del distretto testa e collo: cosa dovrebbe valutare il chirurgo otorinolaringoiatra e cervico-facciale?

António Castanheira[1,2*], Paula Boaventura[2,3,4*], Manuel Pais Clemente[2], Paula Soares[2,3,4], Alberto Mota[2,5], José Manuel Lopes[2,3,4]

[1] Department of Otorhinolaryngology, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal; [2] FMUP-Faculty of Medicine; [3] IPATIMUP - Institute of Molecular Pathology and Immunology of the University of Porto, Portugal; [4] i3S - Instituto de Investigação e Inovação em Saúde, University of Porto, Portugal; [5] Department of Dermatology of Centro Hospitalar São João, Porto, Portugal

** A. Castanheira and P. Boaventura contributed equally to this work.*

SUMMARY

Cutaneous basal cell carcinoma (cBCC) is the most common malignancy diagnosed in the human population. cBCC presents an increasing incidence which, in the near future, will be higher than all other cancers combined. The majority of cBCC are located in the head and the neck. A diversity of management modalities is currently available; nonetheless, surgical excision remains the main modality of treatment. cBCC rarely metastasises and presents a low mortality rate. cBCC morbidity is influenced by local invasion and destruction, especially in the face, where function and aesthetics are major issues. Easy accessibility to the face and skin on the neck makes cBCC an important issue for otorhinolaryngology head and neck surgeons who must be aware and committed in its management, as the main modality of treatment continues to be surgical. The aim of this review is to present a brief and practical overview of head and neck cBCC management for ear, nose and throat (ENT) surgeons, discussing key issues about its epidemiology, risk factors, diagnosis and pathogenesis.

KEY WORDS: basal cell carcinoma, head and neck, ENT surgery, review

RIASSUNTO

Il carcinoma basocellulare cutaneo (cBCC) è la neoplasia maligna più comunemente diagnosticata nella popolazione umana. La sua incidenza è in aumento e sarà in futuro anche maggiore rispetto alle altre neoplasie. La maggior parte di questi tumori è localizzata a livello del distretto testa e collo. Al momento esistono diverse modalità di trattamento tuttavia la chirurgia rappresenta l'opzione primaria. cBCC tende raramente a metastatizzare ed ha una bassa mortalità, influenzata dal grado di invasione locale. A livello del volto la chirurgia del cBCC deve essere attentamento ponderata da parte del chirurgo per il suo importante impatto a livello estetico e funzionale. Lo scopo di questa review è quello di fornire una concisa e pratica overview della letteratura per il chirurgo otorinolaringoiatra e cervico facciale, sottolineando i keypoints dall'epidemiologia sino ai fattori di rischio, diagnosi e patogenesi del cBCC.

PAROLE CHIAVE: *carcinoma basocellulare, head and neck, otorinolaringoiatria, review*

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Correspondence
Paula Boaventura
i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, rua Alfredo Allen 208, 4200-135 Porto, Portugal
E-mail: mboaventura@ipatimup.pt

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Introduction

Otorhinolaryngology head and neck (ear, nose and throat - ENT) surgeons are often challenged in their daily practice with patients presenting cutaneous cancer. Cutaneous basal cell carcinoma (cBCC) is the most common cancer diagnosed in humans, accounting for 70-80% of all skin malignancies in fair-skin people, with 80% occurring in the head and the neck [1-3].

A logarithmic relationship between age and cBCC development risk is well established [4]. Life expectancy has been increasing over the past decades, and thus an increasing cBCC incidence is expected in the near future and estimated to be higher than the incidence of all other cancers combined [3-6]. cBCC is a slow growing and locally invasive malignant tumour, which rarely metastasises and presents an extremely low mortality rate. cBCC can be easily treated by surgical excision, particularly when diagnosed early; its morbidity is influenced by local invasion and destruction, especially in the face and the neck, where function and aesthetics are major issues [7]. The increasing longevity of the human population entails the polarisation of pathologies usually managed by ENT surgeons: presbycusis and cancer (particularly face, head and neck cutaneous cancer). Substantial numbers of elderly patients presenting a cBCC risk profile present to ENT outpatient consultation. Hence, the high cBCC prevalence in the face and neck skin of elderly people demands appropriate expertise by ENT surgeons concerning adequate diagnostic and management practices for patients presenting with this cutaneous cancer.

Epidemiology

New cases of skin cancer surpass the combined incidence of breast, prostate, lung and colon cancer each year [1]. Cutaneous cancer includes two main groups: malignant melanoma (MM) and non-melanoma skin cancer (NMSC). NMSC comprises two main groups: cBCC and cutaneous squamous cell carcinoma (cSCC) which are the most common malignancies worldwide and are increasing in incidence [8]. NMSC accounts for more than 95% of the new cases of cutaneous cancer [1]. In USA, 5.4 million NMSC cases were estimated to occur during 2012, and were diagnosed in 3.3 million people [1]. Lifetime risk of developing cBCC in the USA is estimated to be greater than 30% for Caucasians [8]. After an index cBCC case is diagnosed, the incidence of subsequent cases among such patients increases by a factor of 10 compared with the general population [9]. cBCC are usually not recorded in cancer registries due to their low mortality, and often only the first case is registered, but not the subsequent multiple cBCC in the same patient [5,10,11].

There is a striking variation in the geographical incidence of cBCC, with the highest values in Australia (726 to 884/100,000 person-year) and the lowest in some parts of Africa (less than 1/100,000 person-year) [2,5,7]. In Scotland, Ireland, Wales, England, Finland, Germany, Switzerland, Italy, France and Spain intermediate values have been reported, ranging from 44.6/100,000 to 128/100,000 person-year [5,12]. In Portugal, a study comprising a large series of 3,493 skin malignancies revealed a consistent and gradual increase of 5.0% per year in cBCC [13]. Ethnicity differences as well as skin phenotype may explain different distributions in cBCC incidence, which is higher in fair skinned populations, in a single country or region, and or between countries at the same latitude [5].

Male gender and age are independent risk factors for cBCC [8]. cBCC incidence is higher in men than in women (1.5-2:1), probably due to professional environments [10,14,15]. cBCC is a malignancy of the elderly, and more than 50% occur in patients between 50 and 80 years of age [2]. The incidence of cBCC in a USA population younger than 40 years of age, particularly women, appears to be increasing. cBCC is rare in children and young adults [16].

cBCC usually develops in chronically sun-exposed skin in the head and the neck (64.5-95.9%), followed by the trunk (15-25%), arms and legs. It has also been reported in other locations such as the axillae, breasts, perianal area, genitalia, palms and soles [2,17]. In the head and the neck, the nose is the most affected area (26-33.4%), followed by the cheek/perioral (14.2-23.9%), forehead/temple (11.2-16.1%), eyelids (4.7-8.2%), ears, pre-auricular region (6.84-10%) and neck (12.4%) [10,17,18].

Risk factors

After age and gender, sunlight exposure is the main risk factor for cBCC, but its pathogenesis remains to be completely understood. cBCC are more frequent in sun-exposed body sites of patients with a strong history of actinic exposure, such as farmers or fishermen [2,19-21]. The main five facial cutaneous anatomical sites (nose, cheek, eye area, forehead and ears) affected by cBCC correspond closely to the subsites having the greatest UV exposure [22]. cBCC frequency may be reduced by sun exposure protection measures, but sunscreen use is not clearly associated with decrease of cBCC incidence [23]. Recreational intermittent sun exposure during childhood and adolescence is associated with an increased risk to develop cBCC, showing the importance of some life periods of sun exposure for later life cBCC risk. This association is stronger among sun-sensitive phenotypes with propensity to burn rather than tan [24]. It seems that cBCC develops following a period of 10 to 50 years after sun exposure causing skin damage [15]. cBCC incidence rates are in-

versely associated with latitude. These differences may be explained by greater UV radiation vulnerability of patients in lower latitudes than in higher latitudes [5,25]. The use of tanning beds is reported to be strongly associated with the risk of cBCC development in a dose-response manner [26].
Patients with distinct phenotypic UV susceptibility traits have different cBCC incidence rates [2,21]. In fact, cBCC development is more frequent in light phototypes I and II (Fitzpatrick classification), namely patients with light skin, eyes and hair [3,17,27]. Beyond these constitutional risk factors, other markers of UV susceptibility comprise freckles in childhood, and especially severe sun burns with blistering during childhood [28,29]. Light-skinned people have a probability to develop cBCC that is 10 to 20 times higher than dark-skinned individuals, even when they cohabit in the same region [2,28,29]. cBCC is uncommon in Blacks, dark-skinned people and the Oriental population [5].
Genome-wide association studies have highlighted some UV radiation susceptibility traits associated with cBCC that are controlled by common low-penetrance susceptibility alleles in genes related to skin pigmentation, such as *ASIP*, *TYR*, *OCA2*, *MC1R* and *SLC45A2* [30,31].
Psoralen and ultraviolet A (PUVA) therapy have been related with a moderate risk of cBCC [32]. Radiotherapy for acne and tinea capitis, a treatment modality no longer used, was associated with a high cBCC risk [33,34]. In organ transplant recipients submitted to immunosuppression, the incidence of cBCC increases 5- to 16-fold compared with the general population [3,35].
Chronic arsenic exposure has been reported to be related with an increased risk of cBCC [36]. Photosensitising drugs in a long-term use, such as tetracycline, deoxycline, sulfonamides, fluoroquinolones, phenothiazines, thiazide diuretics [37], nonsteroidal anti-inflammatory drugs (NSAIDs) and retinoids have been associated with a higher risk of cBCC [38].

Diagnosis and staging

Identifying suspicious head and neck cutaneous lesions to establish a precise diagnosis is of utmost importance because cBCC has no known precursor lesion and can present as distinct intricate forms [39]. Lesions with one to several cm, presenting with typical clinical features, can be accurately diagnosed in a regular and fast physical examination. Typical cBCC presents as a pearly pink or flesh coloured nodule with sharp contour, smooth margin and telangiectasia on the surface. Lesions may be translucent or slightly erythematous with a roller border, occasionally together with scaling, crusting, bleeding or ulceration (Fig. 1A). Most cBCC present as a single lesion, although multiple and simultaneously lesions are not uncommon [40]. The biological behaviour of cBCC usually fits the features of a slow growing non-aggressive tumour, taking more than 6 months to achieve one cm in its largest diameter [41,42]. Median time period between lesion onset and diagnosis is estimated at 37.1 months [17].
The staging of cBCC is based on the largest lesion diameter, spreading or infiltration pattern of the surrounding tissues and systemic dissemination (Tab. I) [39,43].

Table I. Dermatoscopy criteria for cBCC.

Dermatoscopy findings	
Arborising blood vessels	In-focus dots
Superficial fine telangiectasia	Maple leaf-like areas
Shiny white-red structureless areas	Concentric structures
Short white streaks	Spoke wheel areas
Multiple blue-grey nodules	Multiple small erosions
Blue-grey ovoid nests	Ulceration

from Lallas et al., 2014 [52]; Altamura et al., 2010 [55], mod.

Clinical subtypes

cBCC may be classified in three main clinical subtypes: nodular, superficial, and morpheaform. In the same surgical specimen a combination of these subtypes may occur [7,44].
Nodular cBCC corresponds to the most common subtype, representing 38.4-86.9% of all subtypes, and usually presents the typical features of cBCC (Fig. 1A, B) [17,40,45-47]. The head or the face harbour 90% of this clinical subtype, particularly the nasolabial folds, cheeks, forehead and eyelids [46]. The differential diagnosis comprises a variety of skin lesions such as molluscum contagiosum, sebaceous hyperplasia, amelanotic melanoma, intradermal melanocytic nevus, Merkel cell carcinoma, fibrous papule of the nose, trichoepithelioma and other adnexal neoplasms, SCC, keratoacanthoma and inflamed seborrheic keratosis [48].
Superficial cBCC is the second most frequent subtype, representing from 0.6% to 50.7% of cases [17,45-47]. It is one of the less aggressive cBCC subtypes, usually appearing as well-circumscribed and scarcely infiltrating erythematous-scally plaque, macule, patch or a thin papule (Fig. 1C) [40,49]. Sun protected trunk and extremities are the main locations for these lesions which may be multiple [17,40]. The differential diagnosis includes inflammatory dermatoses such as psoriasis and nummular dermatitis, dermatophytosis, eczema, lichenoid keratosis, actinic keratosis, extra mammary Paget's disease, Bowen's disease and early amelanotic melanoma [48].
Morpheaform BCC is the least frequent subtype, comprising 3.1-12.5% of cases [17,45-47]. Lesions appear as indurated pink-to-ivory-white, shiny, smooth, scar like plaque of morphea, localised scleroderma, or depressions with ill-defined borders; skin atrophy is frequently associated (Fig.

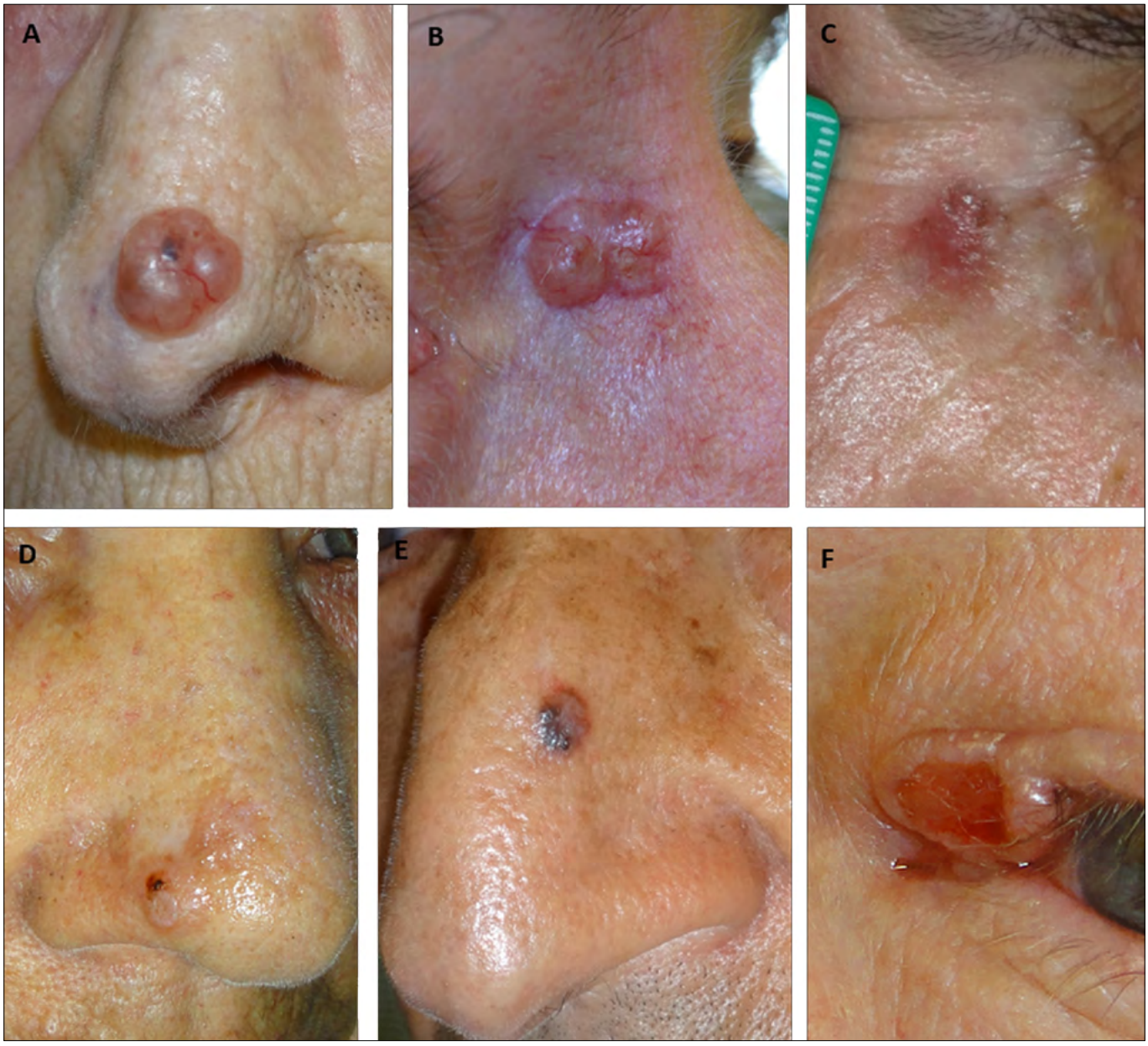

Figure 1. Clinical features of cBCC. A) Nodular; B) Nodular; C) Superficial; D) Morpheaform; E) Pigmented; F) Ulcerated.

1D) [40]. The clinical presentation and evolution are monotonous and subtle, leading to late diagnosis. It usually occurs in the face and the neck, is more aggressive than nodular or superficial cBCC and portends worse prognosis, higher risk of infiltration and recurrence [40,49,51,52]. The differential diagnosis includes scars, particularly white scar-like lesions (e.g. desmoplastic trichoblastoma), morphea (localised scleroderma), dermatofibrosarcoma protuberans, Merkel cell carcinoma, amelanotic melanoma, microcystic adnexal carcinoma and other adnexal neoplasms [48].

Other clinical subtypes

The rare cBCC with abundant pigment – pigmented cBCC – is more frequent in darker skin patients and mostly associated with nodular subtypes. They present as elevated and translucent lesions varying from black to blue colour with a pearly white border (Fig. 1E) [40,51-53]. The differential diagnosis includes melanocytic nevi, melanoma and pigmented seborrheic keratosis [54]. The ulcerated cBCC – "rodent ulcer" – occurs as a lesion with a rolled translucent, pearly, firm and smooth border with telangiectasia, often

Table II. cBCC staging.

Stage	Features
Stage I	Lesions smaller than 2 cm and limited to the skin with no metastasis
Sage II	Lesions larger than 2 cm and limited to the skin and subcutaneous tissue with no metastasis
Stage III	Lesions of any size invading adjacent structures (e.g. muscle, cartilage, and bone) such as the orbit, maxilla, mandible and temporal bone or one lymph node measuring less than 3 cm is involved
Stage IV	Lesions with direct or perineural invasion of the skull base, or more than one lymph node involved or associated with dissemination to distant organs (e.g. lung, pleura, liver and bone)

BCC staging according to the American Joint Commission on Cancer (AJCC), Cancer Staging Manual. 7th Edition. (from Edge et al., 2010 [43], mod.).

covered with crust, which may result from ulceration of any cBCC subtype. The differential diagnosis includes painless ulcers (Fig. 1F) [40].

Dermatoscopy

After direct visual examination, clinicians can perform dermatoscopy, which is particularly useful in uncertain or suspicious lesions, supporting accuracy in diagnosis and differential diagnosis. Dermatoscopy is based on magnification under polarised light for skin inspection, and allows reliable and safe identification of cBCC features (Tab. I). It provides additional information for guiding cBCC management, although meaningful differences in specificity and predictive value have been reported [52,55].

Biopsy

Definitive and precise diagnosis of cBCC can be achieved only by histology. Biopsy can confirm clinical diagnosis and aims towards subtype identification of cBCC. Importantly, histological examination of the whole lesion is often essential not only for accurate diagnosis of cBCC subtype, but also to ascertain the risk of recurrence after treatment [7]. Biopsy techniques include punch biopsy, shave biopsy, incisional biopsy and excisional biopsy. Punch and shave biopsies have been reported to have almost equal accuracy in the cBCC subtype diagnosis, approximately 80% [56]. They are simple and easy to perform, but occasionally may not be precise as only a portion of the entire lesion may be represented [56]. The punch biopsy has an overall diagnostic accuracy of 69%, which is higher in single-subtype cBCC (83%) and superficial cBCC (84%), and lower in mixed-subtype cBCC (37%) and micronodular cBCC (38%) [57]. Excision biopsy may be sufficient for concomitant diagnosis and treatment of small cBCC which do not present high recurrence risk features or cosmetic concerns [7].

Recurrent and metastatic BCC

cBCC may be classified as low- or high-risk for recurrence and metastasis, according to their location, size and histopathological features of aggressiveness [7,49,58]. High risk features for single cBCC recurrence are summarised in Table III [49,58,59].

Recurrence may be due to incomplete tumour excision and the risk increases with tumour size, particularly if the diameter is > 2 cm. The latency period between surgery and onset of recurrence ranges from 2 months to 2 years, although cBCC recurs mostly in the first six months [2]. Perineural invasion is a high-risk feature present in about 1% of cases. It is frequent in aggressive histopathological subtypes such as infiltrating, morpheaform and basosquamous, particularly in large cBCC of the face [60,61]. Recurrence is higher in cBCC arising in previous radiation therapy locations [33,34]. Recurrent cBCC have a worse prognosis than primary lesions as the relationship between tumoural stroma and surrounding tissue may be changed during previous treatment procedures leading to easy spread [62]. Moreover, a

Table III. Major predictors for cBCC recurrence.

Tumour and patient features	High risk features
Size/ location	≥ 6 mm diameter in high-risk locations (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular, ears, postauricular, and temples) > 10 mm diameter in intermediate-risk locations of the head (cheeks, forehead, and scalp) and neck > 20 mm diameter in low-risk areas such as the trunk and the extremities
Borders	Poorly defined
Primary vs recurrent	Recurrent
Site of prior radiotherapy	Yes
Immunosupression	Present
Aggressive histopathological features	Morpheaform, sclerosing or mixed infiltrative pattern component in any single lesion Micronodular pattern component in any single lesion Basosquamous (metatypical) Perineural invasion

from Bichakjian et al., 2016 [59], mod.

first failed treatment approach may lead to recurrent cBCC with increasing potential of spreading [15,62].

Lymphatic and haematogenous metastases may occur and are associated with a poor prognosis of cBCC. Incidence of cBCC metastases varies from 0.0028 to 0.55% with a few hundred cases reported [63-65]. Median survival for metastatic cBCC was reported to be 24 months in patients with distant metastases, and 87 months in patients with regional metastases [65]. They are mostly present in regional lymph nodes which are affected in 68% of cases, but can affect the lungs, pleura, liver and bone [41,64]. Features of cBCC associated with increased risk of metastases are primary cBCC in high-risk locations, large and locally invasive or recurrent cBCC, male gender, and cBCC in immunocompromised patients [64,66].

Extensive subclinical cBCC spread

Some cBCC presenting with a high risk of subclinical infiltration need more complex and aggressive management. A risk scale for predicting the cBCC risk of subclinical spread may assist in patient management (Tab. IV) [67].

Table IV. Major predictors of extensive subclinical cBCC spread.

Basosquamous, morpheaform, nodular and recurrent cBCC on the nose
Morpheaform cBCC on the cheek
Recurrent and nodular cBCC on the nose
Location on the ear helix, the eyelid and the temple
Location on the neck in men
Recurrent cBCC in men
Preoperative size >10 mm

from Batra et al., 2002 [67], mod.

Table V. WHO histological classification of keratinocytic cutaneous tumours.

Keratinocytic tumours
Basal cell carcinoma
Superficial basal cell carcinoma
Nodular (solid) basal cell carcinoma
Micronodular basal cell carcinoma
Infiltrating basal cell carcinoma
Fibroepithelial basal cell carcinoma (Pinkus tumour or fibroepithelioma of Pinkus)
Basal cell carcinoma with adnexal differentiation
Basosquamous carcinoma
Keratotic basal cell carcinoma

from Kossard et al., 2006 [39], mod.

Histopathology

cBCC is a malignant epithelial tumour originated in the interfollicular epidermis or follicular epithelium [68,69]. Most histological classifications subdivide cBCC as nodular, micronodular, superficial, infiltrative and morpheaform, but mixed histology is frequent. The WHO histological classification was adopted in this review (Tab. V) [39]. cBCC can be grouped in two broad categories according to growth features of aggressiveness: indolent-growth subtypes (nodular and superficial) and aggressive-growth subtypes (morpheaform, infiltrative, micronodular, and basosquamous carcinoma) [7]. Aggressive-growth cBCC subtypes display local invasive behaviour and high recurrence rates [7].

In micronodular cBCC, tumoural nests extend deeper into the reticular dermis or subcutis and perineural extension can be present. Surgical margins may be underestimated. Superficial cBCC typically shows discontinuous tumoural aggregations giving rise to a multifocal pattern and raising difficulties in the surgical margins assessment [39]. Infiltrative and morpheaform cBCC show dermal or dermal-hypodermal infiltration with frequent mitotic activity and individual tumoural cell necrosis. Perineural invasion is particularly seen in the infiltrative subtype, as well as invasion of subcutis and other adjacent structures, such as muscle [39]. Mixed cBCC comprises 38.5% of all cases and may be classified according to the most unfavourable subtype [7,39,49,68]. The metatypical cBCC (basosquamous carcinoma) is clinically similar to cBCC, sharing histologic features of cBCC and cSCC. It shows more aggressive growing features and metastasises more frequently [39,67,68].

Immunohistochemistry may assist in the differential diagnosis with other malignant skin tumours such as cSCC. Expression of BerEP4 (a monoclonal antibody which recognises two glycopolypeptides expressed in most human epithelial cells) and CD10 (a neutral endopeptidase) is frequent in cBCC, while the expression of epithelial membrane antigen is rare [69].

Molecular pathogenesis

cBCC development and progression is the outcome of a multi-step and complex process, resulting from the interaction between genes endowing susceptible traits, genetic mutations and environmental factors, such as UV exposure. Reported genetic changes in Sonic hedgehog (SHH) pathway are considered sufficient to generate the main features of cBCC, although other genetic changes have been reported [70].

SHH pathway in sporadic BCC and genetic syndromes associated with BCC

SHH pathway is a main signal transduction pathway in embryologic development. In adults, it influences the skin stem-cell population maintenance, regulation of hair follicles and sebaceous gland development, and plays a role in carcinogenesis of many tumours in humans. The SHH pathway is usually inactivated (in a "turn-off" state) in adult

cells, and its abnormal activation is associated with the development of several tumours, namely cBCC (Fig. 2) [71] (for more detail see Fig. 2). Mutations in the *PTCH* gene are associated with the development of cBCC in 30-75% of sporadic cases and almost all cases of basal cell nevus syndrome (BCNS) [72]. *SMO* gene mutations are present in 10-21% of sporadic cBCC.

Several genetic syndromes should be suspected when multiple cBCC are present, especially at younger ages. Although rare, the most common syndrome is BCNS, also known as Gorlin syndrome, which is an inherited autosomal dominant disorder associated with mutations in the SHH pathway, and specifically in the *PTCH1*, *PTCH2*, and SUFU genes [73]. Constitutive activation of the SHH pathway may act synergistically with changes in the p53 pathway. Mutations in the *TP53* gene were reported in up to 50% of cBCC, and with overexpression in the most aggressive cBCC subtypes; more than two-thirds are UV-induced mutations.

Other genetic changes interacting with environmental fac-

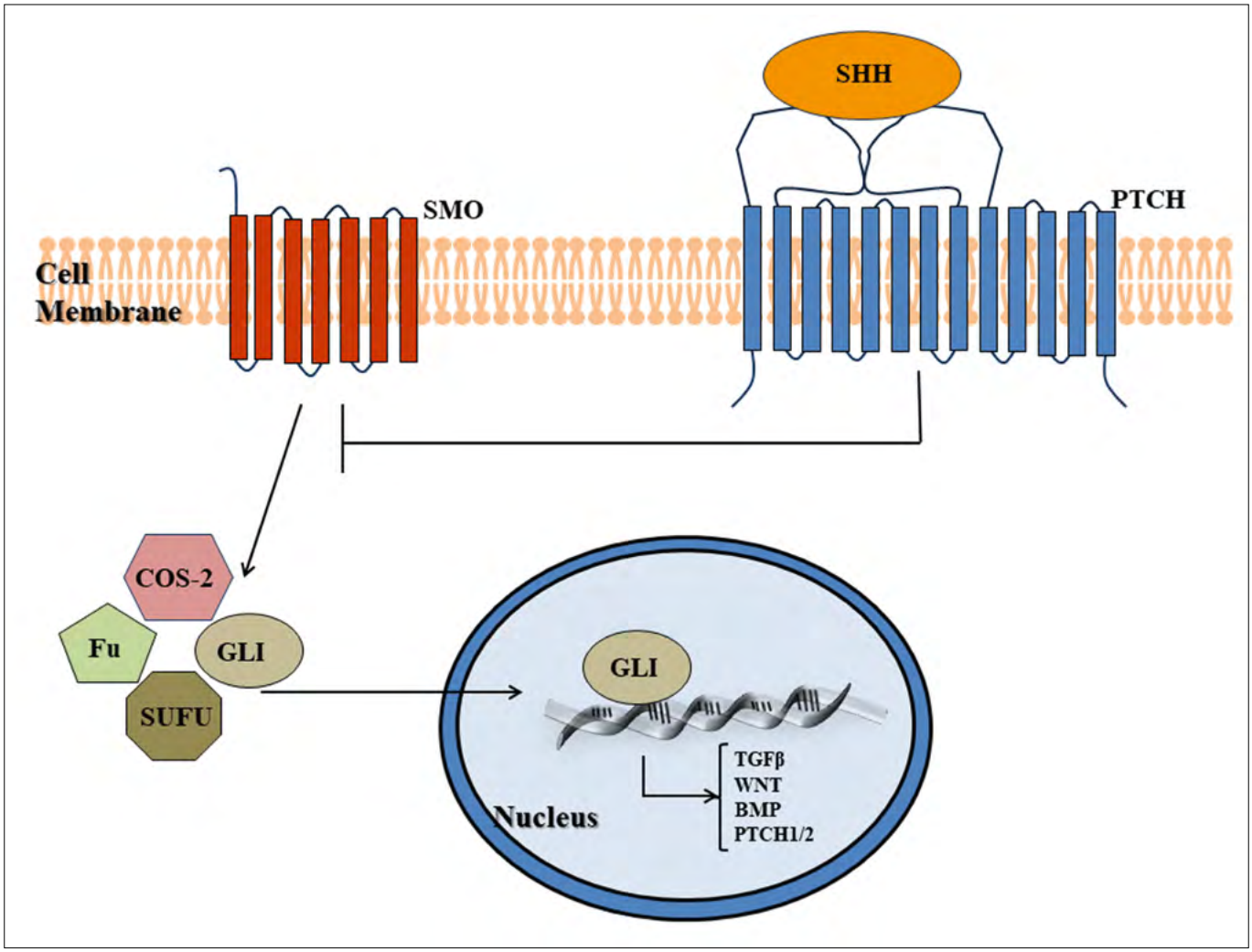

Figure 2. Sonic hedgehog (SHH) pathway. The *PTCH1* gene encodes for a receptor protein of the SHH pathway, the Patched1 (*PTCH1*) receptor. *PTCH1* receptor is allocated in the cell plasma membrane and functions as a receptor for ligands of the SHH proteins. *PTCH1* receptor constitutively inhibits the next step in SHH pathway. The protein SHH ligand binds to *PTCH1* receptor, resulting in a complex in which *PTCH1* receptor becomes inhibited releasing the downstream signalling pathway. *PTCH1* gene is a tumour suppressor gene as *PTCH1* receptor inhibits smoothened (*SMO*), a seven-transmembrane G-coupled protein receptor expressed by the *SMO* gene located in chromosome 7q32, which acts as signal transducer of SHH pathway. *SMO* behaviour is consistent with a proto-oncogene. Activated *SMO* internalises from plasma membrane and releases GLI proteins from *SUFU* inhibition which is expressed by *SUFU* gene located in chromosome 10q24-q25. GLI proteins comprise the transcription factors GLI1, GLI2 and GLI3 which are brought into the cell nucleus. GLI1 protein is a transcriptional activator, while GLI2 and GLI3 proteins may function as activators or as repressors. They have DNA-binding zinc-fingers and activate target genes involved in cell growth and proliferation (*PDGFRA, Fox family genes, MYC, cyclins, CTNNB1-,* β*-catenin-* and *RUNX3*) (from Madan et al., 2010 [35], mod.).

tors can be associated to cBCC development, a topic that is beyond the scope of this review [74]. The most recently reported ones are the *TERT* promoter mutations which are highly prevalent, ranging from 39% to 74% in sporadic cBCC (detailed elsewhere) [75-77].

Management

The key goal of cBCC management is definitive tumour removal, with radical surgery at first attempt, if possible with preservation of function and aesthetics [59,78]. Low-risk cBCC should not be overtreated, avoiding unnecessary morbidity for the patient and increased costs for the health system. Conversely, aggressive and high-risk cBCC should not be undertreated in order to avoid recurrence, metastases and further needless high morbidity treatments [7]. Likewise, personal preferences, psychological, social, economic, logistic and health patient conditions must be taken into account, as well as surgeon/physician preferences [59]. Overall, treatment options may comprise surgical and non-surgical therapies.

Surgical therapies

Standard surgical excision (SSE) with or without reconstruction, Mohs micrographic surgery (MMS), electrosurgery (electro dissection and curettage - ED&C), carbon-dioxide laser surgery, and cryosurgery are possible alternatives to be considered in each case [78].

SSE. Surgical removal of the entire lesion with clear margins is standard treatment for cBCC. Surgical excision is followed by primary closure or reconstruction with tissue flaps, skin grafts, or healing by secondary intention [59]. In some patients, the surgical wound is closed after definitive histopathological diagnosis.

Primary cBCC in the head and the neck have a variable recurrence rate related to size, 3-5% for tumours < 6 mm [79,80], 8% for tumours 6-9 mm size [79] and 9-23% for tumours > 10 mm in diameter [79,80]. The highest recurrence rates after surgical excision are reported in the nose, periocular, paranasal and scalp areas [7]. The incidence of incompletely excised cBCC varies among different reports and seems to be influenced by the surgeon's experience, anatomical location (higher in the head and the neck) and histological subtype (higher in the mixed and sclerosing subtypes) [7]. Most cBCC with positive margins are disease-free after 5 years and will not recur, probably as a consequence of tumour remnants destruction during cicatrisation [81]. Nonetheless, a mean recurrence rate of 26-27% is reported in these cBCC [81,82], a value that may be underestimated as many patients with a relapse after incomplete excision do not return to the previous surgeon, being treated in another centre.

Management of incompletely excised cBCC has no consensus until today. When incompletely excised at the deep margin, a high-risk cBCC with aggressive clinical/histopathological features should be re-excised, preferentially by MMS [7]. Recurrent cBCC managed with surgical excision display recurrence rates of 11-17% during 5-year follow-up, which indicates that they should be treated by MMS [79,83].

Adequate width for surgical margins clearance assuring maximal cure rate of cBCC is usually decided taking into account several factors: the clinical presentation of the primary tumour, recurrent or incompletely excised tumour, anatomical site and local features, clinical and histopathological subtype and subclinical tumour extension. Physician choices based on personal experience also support decisions concerning the width of surgical margins [7,59,82]. Nodular cBCC on the face should be excised with standard 4 mm margins to ensure best cure rates [84]. Nevertheless, 4 mm margins are not always feasible and desirable on the face, where functional and aesthetic issues should be considered. In these cBCC, a 3 mm margin may be effective, attaining a 95% cure rate [82] when performed according to the three-dimensional growing of the tumour.

Alternatively, MMS may be performed for complete tumour excision and tissue sparing, taking into account tumour size and location, as well as the aggressiveness of the cBCC [84]. A feasible and pragmatic algorithm for surgical management of primary and recurrent cBCC is presented in Figure 3 [85,86].

Surgical excision is fast, inexpensive and well accepted, and usually has good long-term functional and aesthetic outcomes. It is often a straightforward office-based procedure, performed under local anaesthesia, and provides information about surgical margins. Its disadvantages encompass longer time spent in reconstructive cases, higher costs than cryosurgery and ED&C, invasiveness issues and loss of potential healthy tissue associated to poorer functional/cosmetic results [7,82]. The main limitation of this technique is the failure to accurately detect cBCC in surgical margins (under diagnosis), conceding lower cure rates than MMS in high-risk cBCC [87]. An active collaboration between a surgeon and pathologist is desirable, but not always achievable when the resection is an office-based procedure.

MMS. Mosh micrographically controlled surgery or histopathological controlled excision comprises a sequence of steps combining surgical excisions with frozen section histopathological evaluations of complete, or almost complete, epidermal and deeper surgical margins. The cycle excision/histologic evaluation may be repeated according to the histopathological results until clear and safe margins are achieved [88,89] (Fig. 4). The MMS recurrence rate for primary cBCC has been reported to be 1.4% in a 5-year period of follow-up, whereas for

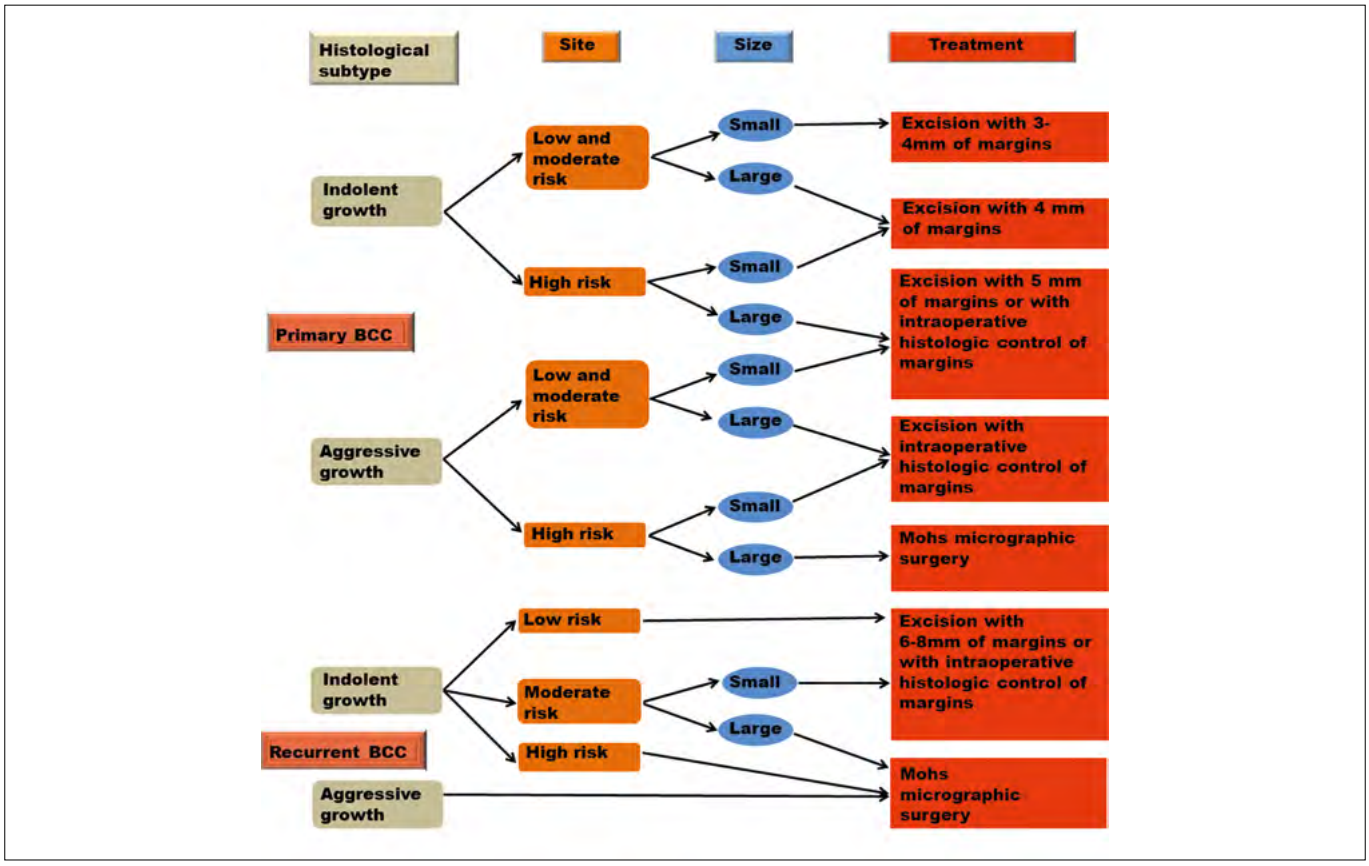

Figure 3. Algorithm for surgical management of primary and recurrent cBCC. Indolent: nodular and superficial. Aggressive: infiltrative, sclerosing and metatypical. Low risk: trunk and extremity. Intermediate risk: scalp, neck, forehead and cheek. High risk: centrofacial, nose, temple, periocular region, perioral and ears. Large lesions: larger than 1cm in high-risk areas; larger than 2 cm in intermediate-risk areas; larger than 4 cm in low-risk areas (from Luz et al., 2016 [85]; Luz et al., 2015 [86], mod.).

recurrent tumours 4% was reported in the same period [88], establishing MMS as a treatment of choice not only for primary, but mainly for recurrent cBCC [83].

MMS is suitable for the treatment of high risk or aggressive-growth histologic cBCC subtypes allowing intra-operative margin control in a short period of time (minutes to few hours) and in an outpatient setting under local anaesthesia [88,90]. In these cases, radical excision may be associated with good function and cosmetic outcomes, as sparing ability of surrounding tissue by MMS allows smaller defect areas comparing with SSE [7]. Its disadvantages comprise invasiveness, financial cost and special techniques requiring more time, laboratory equipment, microscope and specialised pathologists for intra-operatory procedures [7,59,87].

Electrodessication and curettage (ED&C)

This technique combines a superficial ablation by electrodissection and surgical scraping of the affected skin with a curette. Classically ED&C is performed in two or three rounds of electrodissection and curettage [80]. ED&C is fast, easy to perform, and well tolerated. It is indicated in primary low-risk cBCC, specifically in the trunk and limbs, where it achieves low recurrence rates. In tumours demanding more than one cycle of electro fulguration and curettage, excision (SSE or MMS) should be the preferred method, allowing a reliable histological assessment [59]. The most common adverse effect is a hypopigmented scar, which makes ED&C less reasonable in the face [80].

Cryosurgery. This technique consists of the use of liquid nitrogen to destroy tumour tissue by freezing. It is rarely applied with a curative intent due to the high recurrence rate. It does not allow histological evaluation, and can lead to a hypopigmented scar [7,59]. Nevertheless, in patients who refuse surgery or without conditions for other invasive procedures (elderly, high-risk surgical patients, patients with a coagulopathy or a pacemaker), cryosurgery may be an option. Performed in outpatient setting, this procedure is inexpensive, fast and usually safe [59].

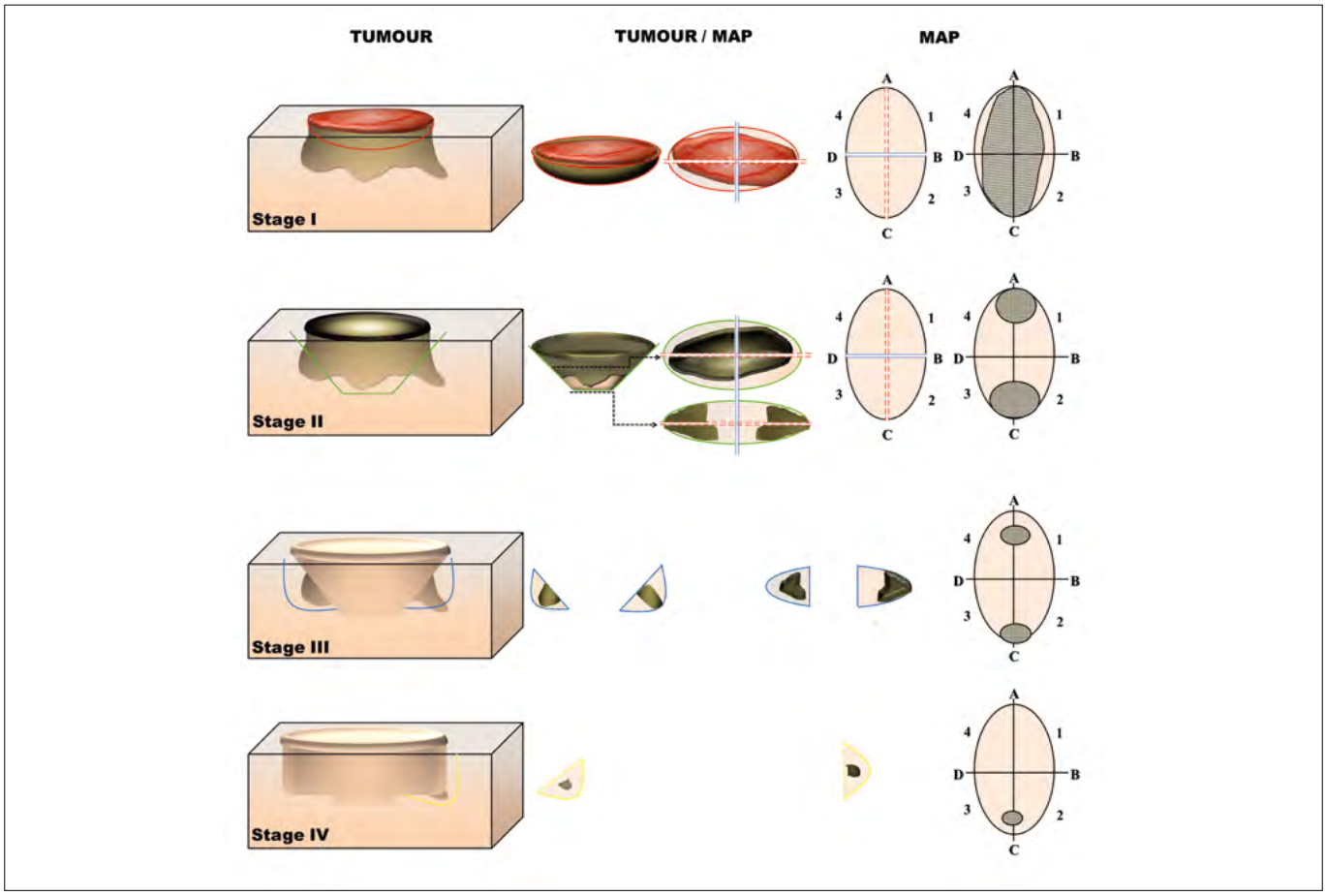

Figure 4. Mohs micrographic surgery (MMS) (from Finley et al., 2003 [89]; ACMS, 2017 [97]; The Skin Cancer Foundation 2017 [98], mod.).

Carbon-dioxide (CO2) laser surgery. Although an uncommon treatment option, CO2 laser surgery can be used to remove cBCC, and is useful in patients with coagulopathy because it accomplishes a bloodless surgical field. Minimal postoperative pain and discomfort, as well as good long term functional and aesthetic results, are reported. The disadvantages, beyond financial and logistics issues, are the wide range of recurrences rates [7].

Topical medical therapies

Imiquimod is a toll-like receptor (TLR) 7 and 8 agonist that activates the nuclear factor kappa B (NFKB), inducing interferon and other cytokines. It is assumed to promote T-cell-mediated apoptosis of tumour cells, tricking survival mechanisms [7]. Imiquimod, as topical imiquimod 5% cream, was approved by the FDA for superficial cBCC in low-risk locations and is indicated for the treatment of primary tumours in which recurrence and subsequent treatment does not carry relevant functional and cosmetic morbidity [7].

Topical 5-flurouracil (5-FU) (5% formulation) causes cytotoxicity through inhibition of thymidylate synthase interfering with DNA replication and repair [91]. 5-FU was approved by the FDA for superficial cBCC in low-risk locations, and may be an alternative to imiquimod, although it has been now replaced by imiquimod. It is well-tolerated, offering a generally good cosmetic outcome and high levels of patient satisfaction [59,92].

Topical medical therapies are easy to self-apply and are thus options in small and multiple low-risk localisations of cBCC for patients lacking the conditions for SSE. Conversely, local adverse effects may cause more annoying and unfavourable reactions and outcomes in facial lesions compared to MMS [93].

Other therapies

In *photodynamic therapy* (PDT), a combination of light and porphyrins is used for cBCC ablation. Illumination in the red light narrow band at 570-670 nm (75 J/cm^2) is regularly used. The prodrugs applied are 5-aminolaevulinic acid (ALA) and its lipophilic methyl ester, methyl aminolae-

vulinate (MAL). PDT was approved for cBCC treatment in many countries in Europe [7]. Superficial cBCC are the major subtypes indicated for this modality with overall cure rates varying from 70% to 90% [59]. Adverse effects include pain or burning sensation at administration, erythema, itching, epithelial exfoliation and pustules [7,59].

Radiotherapy (RT) is not indicated as a first line treatment for cBCC unless surgery is contraindicated. RT displays a low recurrence rate in cBCC treatment, 7.4% for primary and 9.5% for recurrent cBCC [94]. Common adverse effects, such as permanent skin hypopigmentation or hyperpigmentation, dryness, epidermal atrophy, telangiectasia and dermal fibrosis are reported in 37% of patients with cBCC [94]. Chronic radiation dermatitis, alopecia and radiation-induced skin malignancies limit the indications for radiotherapy, making it more suitable for patients with more than 60 years of age in whom surgery is not possible or not desired [94].

Chemotherapy (platinum-based therapy) has been used for management of uncontrolled local and metastatic cBCC. However, the patient's comorbidities must be considered: proper kidney function is required and bone marrow toxicity may occur [7].

Targeted medical therapies

In some cBCC complete surgical resection may be impossible without compromising not only aesthetics, but also vital or functional important structures. Additionally, radiotherapy may be ineffective or contraindicated. Local advanced and metastatic cBCC have been a challenging issue, emphasising the importance of the new emerging medical therapies, such as the anti-*SMO* agents.

Vismodegib, an inhibitor of the *SMO* receptor in the hedgehog pathway, is a new systemic therapeutic option for advanced cBCC. This drug was approved by the FDA in 2012 for the treatment of locally advanced and metastatic cBCC [95]. Sekulic et al. reported objective responses in 43% of patients with locally advanced cBCC and in 30% of patients with metastatic cBCC treated with Vismodegib [96]. Its common adverse events comprise muscle spasms, alopecia, taste disturbance, weight loss and fatigue [95,96].

Ingenol mebutate gel has been reported to have promising results in clinical trials, with a stated histological clearance between 38% and 63%. On the other hand, its main indication is the treatment of actinic keratosis and not cBCC. Adverse events include erythema, flaking and scaling, pain and headache [7].

Surgical modalities often achieve cure of cBCC with good oncological, functional and cosmetic efficiency. Low-risk cBCC can be treated with ED&C or mainly with SSE. High-risk and recurrent cBCC should undergo aggressive management. In this setting, MMS is considered the gold standard treatment of choice, providing the highest cure rates and best aesthetic outcomes [7,59].

Prognosis and prevention

Overall, prognosis of cBCC is good and defined by the likelihood of cure or risk of recurrence. During follow-up two major issues must be taken into account: the risk of local invasion and recurrence, and although very rare, the management of metastatic cBCC [78].

The main prevention strategy should consist of measures addressing protection from UV exposure during childhood and adolescence, especially in fair skin people. Despite being a controversial issue, the regular use of sunscreens with a solar protector factor (SPF) of 15 has been associated with a reduction in the lifetime incidence of cBCC [7,23]. The use of sunscreen can be advised as it may prevent melanoma and may have a role in cBCC prevention, especially in organ transplant recipients [7]. Self-skin examination of susceptible patients in a routine-based practice, and outpatient consultation referral when suspicious lesions are present, are of utmost importance in early detection and diagnosis of cBCC.

Conclusions

cBCC is, and will continue to be, a major public health problem because of its growing incidence, causing an increased financial burden to healthcare systems [8]. Hence, it is very important that physicians assisting patients with high risk of developing cBCC attain clinical competence on this common oncological topic. cBCC are mainly located on the head and the neck, making these lesions a significant issue for ENT surgeons who must be aware and committed to take part in its management since the main treatment modality is surgery.

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HEAD AND NECK

An innovative and safe way to train novice ear nose and throat residents through simulation: the SimORL experience

Didattica innovativa per specializzandi in otorinolaringoiatria: l'esperienza di SimORL

Valeria Dell'Era[1], Massimiliano Garzaro[1], Luca Carenzo[2], Pier Luigi Ingrassia[2], Paolo Aluffi Valletti[1]

[1] ENT Division, University of Eastern Piedmont, Novara, Italy; [2] SIMNOVA, Centro Interdipartimentale di Didattica Innovativa e di Simulazione in Medicina e Professioni Sanitarie, Università del Piemonte Orientale, Novara, Italy

SUMMARY

Medical simulation enables trainees to learn procedural skills in a tailored, non-threatening, controlled environment that can provide feedback and educational experiences. The goals of this study are to describe the set-up and execution of an educational intervention (SimORL) in Ear Nose and Throat (ENT) simulation, to report confidence in performing basic ENT procedures before and after the event and investigate whether participants would find it useful and educationally effective. SimORL was a two-day formative event held at SIMNOVA - Eastern Piedmont Simulation Centre, Italy. The event was open to ENT trainees from any Italian ENT training program; participants were divided into 5 teams and rotated around 10 different simulation stations over two days. Stations included: high-fidelity, skill trainer, computer based, wet lab and dissection. Stations were: virtual otoscopy (OtoSim®), simulated clinical cases with high-fidelity mannequin (e.g. epistaxis) or standardised patients (e.g. vestibular neuronitis), robotic surgery (Da Vinci®), human anatomy (zSPACE AIO®), surgical tracheostomy (wet model), cadaveric sino-nasal endoscopy (wet model), crisis resource management (team exercise), surgical sutures (Limbs&Things SkinPad®), surgical set station and team building exercises. Participants were asked to complete a pre- and post-test that queried previous experience and confidence using 10-item unanchored semantic scales. Results are presented as median (25-75 percentile). Satisfaction was assessed by a validated 5-item Likert Simulation Experience Scale (SSES). Twenty-three ENT trainees attended SimORL 2018. Only 3 participants reported limited previous simulation experience. Pre-post confidence significantly improved between before and after the event. Overall satisfaction with Simulation Experience Scale (SSES) was very high with a median of 4.5 of 5. Regarding simulation evaluation, the most appreciated station was nasal endoscopy (10/10), while the least appreciated was otoscopy (6/10). SimORL proved to be a highly rated and useful educational tool to improve junior ENT trainees' confidence in performing basic ENT procedures.

KEY WORDS: medical simulation, ENT residents training, wet lab, educational ENT program

RIASSUNTO

La simulazione in ambito medico è uno strumento didattico efficace e validato. In letteratura emerge chiaramente come un'esperienza riproducibile ed un contesto sicuro favoriscano l'apprendimento. Obiettivo dello studio è di descrivere un' esperienza di simulazione rivolta a specializzandi in Otorinolaringoiatria (SimORL) indagando come vari la sicurezza dei partecipanti nell'eseguire procedure otorinolaringoiatriche di base ed indagandone il gradimento in termini didattici (efficacia formativa). SimORL è un evento di due giorni, svoltosi presso il centro di simulazione SIMNOVA dell'Università del Piemonte Orientale - Novara. Il corso era rivolto a specializzandi ORL di tutt'Italia: i partecipanti erano divisi in 5 gruppi e ruotavano all'interno delle 10 stazioni allestite (5 il primo giorno, 5 il secondo). La simulazione si avvaleva di scenari ad alta fedeltà, diagnostica endoscopica su cadavere, simulatori "umidi", simulazione basata su computer e simulazione guidata dall'esperto. Le stazioni erano le seguenti: otoscopia diagnostica virtuale (OtoSim®), casi clinici simulati con l'ausilio di manichini ad alta fedeltà (HAL®) o pazienti standardizzati (tra cui ad esempio un caso di epistassi posteriore ed

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Correspondence
Valeria Dell'Era
ENT Division, University of Eastern Piedmont,
c.so Mazzini 18, 28100 Novara, Italy
Tel. +39 0321 3733403
E-mail: valeria.dellera@gmail.com

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uno di vertigine vestibolare), studio anatomico 3D della laringe (zSPACE AIO®), endoscopia naso-sinusale su cadavere, tracheostomia chirurgica su simulatori umidi, suture chirurgiche (Limbs&Things SkinPad®), stazione di familiarizzazione con la strumentazione chirurgica otorinolaringoiatrica ed esercizi di team building. Ai partecipanti è stato chiesto di compilare un questionario prima e dopo il corso per indagare eventuali precedenti esperienze e la sicurezza nell'eseguire procedure specifiche mediante una scala di valutazione numerica con punteggio da 1 a 5. I risultati sono stati espressi come mediana (25-75 percentile). Il livello di soddisfazione tra i partecipanti è stato misurato mediante l'impiego di una scala di gradimento a 5 campi validata per le esperienze di simulazione (Satisfaction Simulation Experience Scale - SSES). All'evento hanno partecipato 23 specializzandi ORL e di questi solo 3 riferivano una precedente e limitata esperienza nell'ambito della simulazione. La sicurezza nell'eseguire le procedure oggetto del corso è stata registrata con un post-test, risultando significativamente migliorata rispetto a quella emersa nei pre-test, così come elevato è stato l'indice globale di gradimento (SSES = 4,5/5). SimORL si è rivelato uno strumento didattico valido e gradito per specializzandi ORL nello svolgimento di procedure di base.

PAROLE CHIAVE: *simulazione in medicina, formazione degli specializzandi ORL, simulatori "umidi", corso di formazione in otorinolaringoiatria*

Introduction

Post-graduate specialist education is a progressive process. Studies show a variable range of competences as junior doctors enter their specialist clinical training [1,2]. Many junior residents are initially not comfortable with the clinical setting as it is perceived as a stressful environment, something that is only experienced to a degree during medical school [3]. It would be advisable, however, that junior trainees entering the clinics are equipped with a homogenous skill-set and clinical competences that allow them to safely approach the first on-calls.

In Italy, most Ear Nose and Throat (ENT) training programs use apprenticeship as their main teaching model (time-based education), where junior trainees learn from direct observation and trial from senior residents and attending physicians. This is a very common model in the medical sciences, and is particularly rooted in surgical disciplines [4]. This model has some limitations, however, as case and procedure exposure for observation and practice will be dependent on a specific institution's characteristics, mentors personal subspecialty or preference and case-mix available at any given time. An alternative or integration to time-based education is competency based medical education. Competency-based medical education allows trainees to progress through their training based on competency, rather than fulfillment of a pre-defined amount of time [5,6].

Medical simulation offers an excellent tool to supplement this model by offering a safe and repeatable learning environment to integrate specific cases and procedures that can be tailored to the resident's competency needs. Simulation allows the creation of custom-made learning programs that are able to provide junior trainees with basic tools to approach safely, among others, the first year of training and associated on-call duties.

The field of otorhinolaryngology is not new to the use of simulation and much literature is available, especially regarding simulation of specific surgical approaches [7-11]. Recently, some centres have launched short educational events aimed at introducing junior residents to the duties of being a new resident, the so-called boot camp. Almost all published boot-camps in ENT are from North America, are one day long, use simulation as a main teaching tool and focus predominantly on training about common ENT emergencies [12-17]. These events are designed with the goal of developing the cognitive, communication and procedural skills necessary for otolaryngology residency [18].

The aim of this work is to present and describe the model of SimORL – a two-day simulation event in ENT dedicated to junior residents – and investigate whether participants found the event beneficial to their professional development. We hypothesised that SimORL would increase participants confidence and be perceived as useful and educationally effective in teaching basic ENT topics of interest to the junior trainee.

Methods

SimORL (Simulation in Otolaryngology) is a two-day intensive, focused, training course that covers multiple topics of interest to the junior trainee. SimORL uses simulation as the main educational strategy, including different modalities ranging from cadaver models to high fidelity mannequins.

The first SimORL took place in 2018 at the SIMNOVA Healthcare Simulation Centre, Università del Piemonte Orientale, Novara, Italy.

Participants

SimORL was open to any junior ENT resident across the country. Invitees included novice otolaryngology - head and neck surgery trainees (postgraduate year one and/or two). The event was also advertised through social media channels.

Participants were divided into 5-person teams leveled out by training year. Participants signed an on-line written informed consent as part of their registration process for the event.

Curriculum design and content

The core curriculum of the event was developed to meet the following educational goals: 1) recognise and treat com-

mon ENT presentations; 2) perform simple instrumental diagnostics; 3) perform basic surgical interventions (tracheostomy was chosen as the surgical intervention); and 4) communicate effectively with teams and relatives. Over the two days a total of 9 + 1 educational stations were delivered (five per day) in three teaching categories. More information about the stations are reported in Table I. Each group rotated through all of the stations. All stations included debriefing and no assessment was carried out to grade participants in their actions.

Program evaluation

Self-assessment data was collected from participants using anonymous pre-course and post-course surveys. Prior to attending the event, participants were asked to complete a survey on demographics and pre-course simulation experience, as well as confidence levels in performing the skills involved in the event. Post-event surveys assessed participants' post-training confidence level with each of the skills and abilities presented. Moreover, participants completed a satisfaction questionnaire and expressed an educational effectiveness rating for each of the event stations. The previously validated Satisfaction with Simulation Experience Scale (SSES, a 5-item Likert scale) was used to assess satisfaction [19]. For the other sections, responders were asked to reply using an unanchored semantic scale ranging from "1 - strongly disagree/not confident at all" to "10 - strongly agree/very confident". Residents were also given the opportunity to include free-text comment about the event, the stations and suggestions for improvement of the event.

Table I. Type, goals and simulators used for each station during the two days of SimORL.

Educational station		Skill	Educational goals	Teaching cathegories	Equipment
1	**Diagnostic nasal endoscopy**	Diagnostic nasal fibre optic examination on prepared (prepared with ethmoidectomy-medial meatotomy-sphenoidotomy)/ not prepared nostrils	Perform simple instrumental nasal diagnostics	Task trainers and manual abilities	Cadaveric model, Olympus 4K technology
2	**Diagnostic otoscopy**	Virtual otoscopy	Perform simple instrumental otologic diagnostics Recognise and treat common ENT presentations	Task trainers and manual abilities	OtoSim®
3	**Sutures**	Principles of skin sutures (with silk, vicryl and prolene stitches)	Perform basic surgical interventions	Task trainers and manual abilities	Limbs and Things® Skin Pad
4	**Surgical 3D anatomy**	Human anatomy of head and neck	Perform simple instrumental diagnostics Recognise and treat common ENT presentations	Task trainers and manual abilities	3D virtual simulator, zSPACE AIO®
5	**Surgical tracheostomy**	Surgical tracheostomy	Perform basic surgical interventions	Task trainers and manual abilities	High-fidelity wet part-task trainer
6-7	**Common ENT conditions, high-fidelity scenarios**	4 high-fidelity scenario (posterior epistaxis and neuronitis on day 1, laryngeal respiratory distress due to glottic cancer and neck swelling in a retro-parapharyngeal abscess on day 2)	Perform basic surgical interventions Recognise and treat common ENT presentations Communicate effectively with teams and relatives	High-fidelity simulation	Gaumard HAL human patient simulator or standardised patient
8	**Non-technical skills**	Team building exercise	Communicate effectively with teams and relatives	Interactive discussions, non-technical skills	N/A
9	**Surgical skills**	Become familiar with ENT surgical instruments	Perform basic surgical interventions	Interactive discussions, non-technical skills	ENT surgical kits
10	**Robotic surgery**	Competitive robotic surgery station	Perform basic surgical interventions	Gamification	Robotic surgery DaVinci® XI simulator trainer

Data analysis

Data was collected on paper-based forms and later transformed into digital spreadsheets. Descriptive statistics were summarised using median and percentiles. Pre-post-event differences in self-perception regarding confidence were tested using the Wilcoxon signed-rank test.

Results

Twenty-three ENT residents from eight different training programs around the country participated in the first SimORL; all completed the pre- and post-event questionnaires. The post graduate year (PGY) levels of the 23 participants were: 11 (48%) PGY-1, 6 (26%) PGY-2, 5 (22%) PGY-3, and 1 (4%) PGY-4. 15 (65%) were female. Only 3 (13%) individuals reported limited previous experience with simulation and the remaining 20 (87%) reported no experience with simulation. No individuals were excluded from the analysis.

Confidence

Post-event confidence levels demonstrated significant increases in all six stations. Confidence in performing diagnostic otoscopy improved from 6 (5-7) to 7 (6-8) ($p = 0.021$); in performing diagnostic nasal endoscopy from 6 (5-7) to 8 (6-8) ($p = 0.0003$); confidence with surgical anatomy from 4 (3-6) to 7 (6-8) ($p < 0.0001$); confidence managing common ENT conditions from 6 (5-7) to 7 (6-8) ($p = 0.036$); confidence performing a surgical tracheostomy from 5 (2-6) to 7 (5-8) ($p < 0.0001$) and finally confidence in suturing from 6 (5-7) to 8 (7-8) ($p = 0.0011$). Variations of confidence pre-post including min-max scores per station are presented in Figure 1.

Participant's satisfaction with the event and the simulation experience

Overall participants found SimORL a useful learning experience, rating it 10 (9-10) of 10 for global satisfaction and educational value. The majority of participants highly rated each of the learning stations for educational effectiveness (Tab. II). The most appreciated station was diagnostic nasal endoscopy, while the least appreciated was the otoscopy station.

Overall, the global SSES rating was very high with a median of 4.5 of 5 (4-5). All satisfaction measures are reported in Table III.

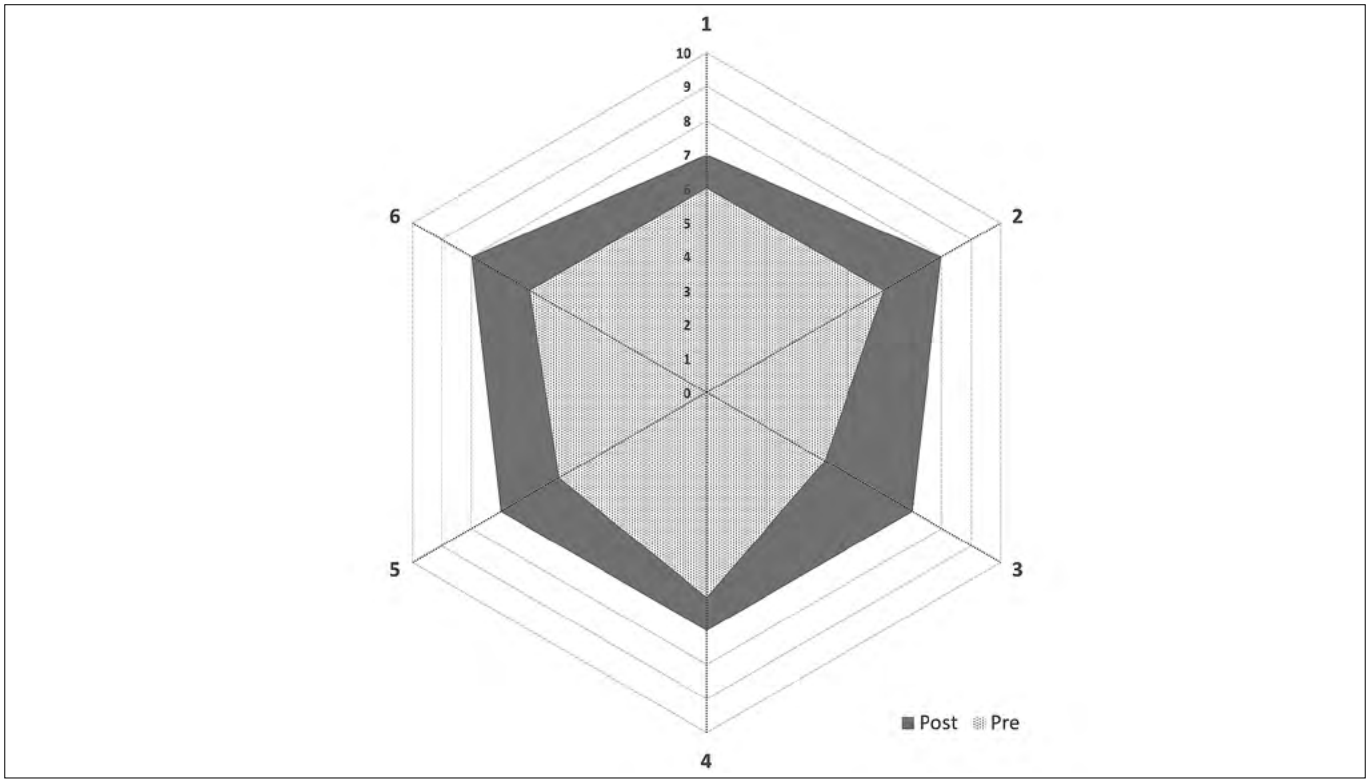

Figure 1. Radar chart presenting median self-confidence perception level before (dotted white) and after (grey) the event. Apexes of polygon represent each simulation station (1: diagnostic otoscopy; 2: diagnostic nasal endoscopy; 3: surgical anatomy; 4: common ENT management scenarios; 5: surgical tracheostomy; and finally 6: suturing). Axes in each radar chart represent the 10-points semantic unanchored scale.

Discussion

The results of our study suggest that SimORL can be a valuable tool to provide didactic, hands-on and confidence building experiences for junior otorhinolaryngology trainees. After completing the SimORL curriculum, participants referred significant improvement in self-confidence in several areas, including improvements in the diagnostics process (otoscopy and nasal endoscopy), general knowledge (anatomy), surgical procedures (suturing and tracheostomy) and complex clinical reasoning (management of common ENT emergencies).

Previous studies suggest a correlation between actual proficiency and self-perceived competence [20-22].

The high rating in the SSES likely reflects a high-quality formative process including well-delivered expert debriefing with non-judgmental constructive approaches throughout the entire event and the application of theoretical reinforcements of key teaching points by tutors.

The entire program was designed with the concepts of deliberate practice in mind. Based on the Ericsson research on skill acquisition, significant improvements in performance can be realised when individuals are: a) given a task with a well defined goal; b) motivated to improve; c) provided with feedback; and d) provided with opportunities for repetition [23].

SimORL allowed residents to increase their confidence by practice, trial-and-error and help from supervisors and teachers. A key aspect of the practice of surgical disciplines is the ability to perform practical procedures efficiently and

Table II. Educational effectiveness of each simulation scenario/topic as rated by participants using a 10-point unanchored semantic scale. Results are presented as median and 25-75 percentile.

Skill	Rating
Diagnosic otoscopy	6 (6-8)
Surgical 3D anatomy	8 (6.75-10)
Suture	8 (7-10)
Diagnostic nasal endoscopy	10 (8.75-10)
Surgical tracheostomy	9 (8.75-10)
Common ENT conditions high fidelity scenarios - day 1	8 (7.75-9.25)
Common ENT conditions high fidelity scenarios - day 2	9 (8-10)
Non-technical skills	8 (7-9)
Surgical skills	7.5 (6.75-8)
Robotic surgery	9.5 (8.75-10)

Table III. The Table reported all satisfaction measures: responders were asked to reply using a -point unanchored semantic scale ranging from "strongly disagree/not confident at all" to "strongly agree/very confident".

	Strongly disagree (%)	Disagree (%)	Unsure (%)	Agree (%)	Strongly agree (%)
Debrief and reflection					
The facilitator provided constructive criticism during the debriefing	0	0	4	17	78
The facilitator summarised important issues during the debriefing	4	0	4	22	70
I had the opportunity to reflect on and discuss my performance during the debriefing	0	0	13	13	74
The debriefing provided an opportunity to ask questions	0	0	4	30	65
The facilitator provided feedback that helped me to develop my clinical reasoning skills	0	0	4	22	74
Reflecting on and discussing the simulation enhanced my learning	0	0	9	26	65
The facilitator's questions helped me to learn	0	0	9	30	61
I received feedback during the debriefing that helped me to learn	0	0	9	17	74
The facilitator made me feel comfortable and at ease during the debriefing	0	0	4	9	83
I had the opportunity to reflect on and discuss my performance during the debriefing	0	0	4	17	78
Clinical reasoning					
The simulation developed my clinical reasoning skills	0	0	4	35	61
The simulation developed my clinical decision-making ability	0	0	17	26	57
The simulation enabled me to demonstrate my clinical reasoning skills	0	9	9	35	48
This was a valuable learning experience	0	0	4	26	70
Clinical learning					
The simulation caused me to reflect on my clinical ability	0	0	4	26	70
The simulation tested my clinical ability	0	0	13	30	57
The simulation helped me to apply what I learned from the case study	0	4	9	35	52
The simulation helped me to recognise my clinical strengths and weaknesses	0	0	9	26	65

safely. Patient safety, malpractice and increased mortality rates caused by human errors have increased the importance of medical simulation sessions for undergraduate and postgraduate training programs [24]. Simulation-based training offers well-described advantages as an educational tool. It provides many opportunities to practice both technical and non-technical skills in a safe environment, learning from achievements and errors without the consequences that may result from mistakes [25].

According to Italian training standards for the ENT residency program, at the end of the training period, residents becoming specialists should have proficiently mastered all the different regions and systems pertaining to the head and neck, including surgery. Other residency programs (such as Anesthesia or Emergency Medicine) include the option to use simulation as a complementary simulation tool in their national training requirements. SimORL could offer the opportunity to safely improve fields of training.

There are previously published studies with similar methodologies. Our results are in line with that of other similar events both in the field of otorhinolaryngology as well as in other medical specialties [26,27].

Recently, Dean et al. conducted a cross-sectional survey of all otolaryngology residency program directors in the United States and Puerto Rico: based on the participants' answers, the authors concluded that simulation-based boot camps can be a significant and valuable component of residency training [28].

International data have shown that current training paradigms may fail to adequately prepare surgeons for independent practice [29]. Restrictions on trainee working hours, new patient safety initiatives and pressures for increased operating room efficiency have significantly reduced the number and quality of learning opportunities for surgical trainees [5,30].

This is, to our best knowledge, the first nationwide simulation event in the field of otorhinolaryngology in Italy. SimORL aims to be a stimulus for the integration of training with simulation, an approach to competency-based post-graduate medical education and, hopefully, provides a small contribution to the improvement of patient care.

There are several limitations to this study. The sample size was small and may not be representative of the overall trainee population. There was no summative assessment of skills and performance, as this was excluded to preserve the psychological safety of trainees who are new to the concept of simulation and debriefing, which, however, limits the ability to document improvement objectively.

There was no follow-up over time: this study presents immediate results, when the signals are stronger and no long-term follow-up of confidence self-perception has been performed nor did we assess for knowledge retention over time. Although longer than most ENT simulation events reported in literature, the length is still significantly shorter than other specialty boot camps than can span from one week to one month. The ideal program length is yet to be clarified.

Conclusions

The SimORL experience demonstrated that simulation for ENT residents can be a valid educational tool to improve confidence in performing specific ENT procedures, showing a very high overall global satisfaction rate. Further studies are needed to confirm these encouraging results.

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HEAD AND NECK

Impact of a dedicated radiologist as a member of the head and neck tumour board: a single-institution experience

Impatto della presenza di un radiologo dedicato nella gestione multidisciplinare dei pazienti con tumori del distretto testa collo: l'esperienza di un singolo centro

Daniela Alterio[1], Lorenzo Preda[2,3], Stefania Volpe[1,4], Caterina Giannitto[5], Giulia Riva[1,4], Frank Arthur Kamga Pounou[1,4], Murat Atac[6], Gioacchino Giugliano[6], Roberto Bruschini[6], Annamaria Ferrari[1], Giulia Marvaso[1], Maria Cossu Rocca[7], Elena Verri[7], Duccio Rossi[8], Massimo Bellomi[4,5], Barbara Alicja Jereczek-Fossa[1,4], Roberto Orecchia[9], Mohssen Ansarin[6]

[1] Department of Radiation Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2] Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy; [3] Diagnostic Imaging Unit, National Center of Oncological Hadron Therapy (CNAO), Pavia, Italy; [4] Department of Oncology and Hemato-Oncology, University of Milan, Italy; [5] Department of Radiology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [6] Department of Head and Neck Surgery, IEO, European Institute of Oncology IRCCS, Milan, Italy; [7] Department of Head and Neck and Urogenital Medical Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [8] Postgraduate School of Radiology, University of Milan, Italy; [9] Scientific Directorate, IEO, European Institute of Oncology IRCCS, Milan, Italy

SUMMARY

The aim of this study was to quantify the impact of radiologic image review performed by experienced radiologists in a multidisciplinary team (MDT) for head and neck cancers (HNCs). We performed a retrospective review of cases discussed at MDT meetings from April 2014 to March 2017 for which radiologic review was required. All changes in the former radiologic report were collected and classified as follows: 1) modifications of radiological reports (patients for whom the treatment strategy had not been defined at the moment of MDT meeting) and 2) modifications in treatment strategy (patients for whom treatment strategy had previously been defined and subsequently modified according to the outcome of radiologic revision). The latter subgroup was further categorised as "major changes" and as "minor changes". A total of 540 cases were retrieved. Imaging review was required at the time of tumour diagnosis in 310 (57.4%) cases. Most patients (69%) had advanced stage tumours (III and IV). In 262 (48%) cases, no change of the initial radiologic report was made. In a total of 144 (27%) cases, the available imaging was not considered sufficient for a final indication to treatment and further imaging was required. In the remaining 134 (25%) cases, radiologic review led to a modification of either tumour staging (55%) or treatment strategy (45%). Specifically, major and minor modifications were applied in 44 (13%) and 17 (11%) of the cases considered, respectively. Among 134 patients for whom the radiologic review led to stage/treatment modification, follow-up was available for 118. In all but one patient, we could confirm the original reports were correctly modified per MDT discussion results. Our data strongly support the importance of including an experienced radiologist as a core member of the MDT for HNCs.

KEY WORDS: head and neck cancer, multidisciplinary management, imaging, radiology

RIASSUNTO

Scopo del lavoro è stato quello di quantificare l'impatto della revisione radiologica condotta da radiologi esperti nell'ambito di un gruppo di lavoro multidisciplinare nella gestione dei tumori del distretto testa collo. È stata condotta un'analisi retrospettiva dei casi discussi nelle riunioni multidisciplinari svoltesi tra i mesi di aprile 2014 e marzo 2017, per i quali è stata richiesta una revisione radiologica. Le modifiche apportate ai referti radiologici originari sono state classificate come segue: 1) variazioni dello stadio tumorale e 2) cambiamenti alla strategia terapeutica, di seguito classificati come "rilevanti" e come "non rilevanti". La revisione radiologica si è resa necessaria in 540 casi, in 310 (57,4%) si trattava di pazienti in prima diagnosi. La maggior parte dei pazienti (69%) presentava

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Correspondence
Lorenzo Preda
Fondazione CNAO, strada Campeggi 53, 27100 Pavia, Italy
Tel. +39 0382 078613. Fax +39 0382 078901
E-mail: lorenzo.preda@cnao.it

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tumori in stadio avanzato (III e IV). In 262 casi (48%) non è stato apportato alcun cambiamento rispetto alla valutazione radiologica iniziale. In 144 casi (27%), le immagini disponibili non sono state considerate sufficienti per una adeguata pianificazione terapeutica e sono state richieste ulteriori indagini diagnostiche. Nei rimanenti 134 casi (25%), la revisione radiologica ha portato a modificare lo stadio della malattia (55%) o la strategia terapeutica (44%). In particolare, variazioni "rilevanti" e "non rilevanti" alla strategia terapeutica sono state applicate rispettivamente in 44 (13%) e in 17 (11%) dei casi considerati. In 118 di tali pazienti erano disponibili i successivi controlli nel tempo. In tutti i casi, tranne uno, è stato possibile confermare che la modifica apportata ai referti originari in sede di discussione multidisciplinare era corretta. I nostri dati confermano l'importanza di includere un radiologo esperto come componente fondamentale dei gruppi di lavoro multidisciplinari per la gestione dei tumori del distretto testa-collo.

PAROLE CHIAVI: *neoplasie laringologiche, gestione multidisciplinare, diagnostica per immagini, radiologia*

Introduction

Head and neck cancers (HNCs) are a heterogeneous group of malignancies, which may arise in multiple subsites of an anatomically complex region. Despite the fact that national and international guidelines have led to a progressive standardisation of indications for treatment, the availability of different equipment and expertise (e.g. transoral robotic surgery) may vary between single institutions, thus influencing treatment strategies. Moreover, as multimodality treatments have become the standard of care in locally advanced-stage disease, integrated management between different medical specialties has become paramount [1,2].

Multidisciplinary care has been shown to bring several advantages to patient management, including but not limited to shorter diagnosis-treatment time, greater adherence to clinical guidelines and optimisation of diagnostic and treatment procedures [3-5]. Arguably, the combined effect of these factors may account for the better oncological outcomes of patients managed by multidisciplinary teams (MDTs) compared to those treated by a single referring physician [6-9]. These data have encouraged the incorporation of multidisciplinary management into national and international guidelines on treatment of HNCs [10,11].

In agreement with this statement, in 2000 our institution established an ongoing MDT program to coordinate the different phases of HN patient management ranging from diagnosis to supportive care. MDT meetings are arranged according to a weekly schedule and involve radiation oncologists, radiologists, ear-nose-throat (ENT) surgeons and medical oncologists with well-recognised clinical and scientific expertise in the field. Additional professionals have gradually entered the core of the MDT, including pathologists, dental surgeons, endocrinologists, speech therapists and dieticians. Due to the increasing availability of both morphological and functional imaging in HN patient workup [12-14], the role of the radiologist has become paramount in every step of the clinical pathway.

Starting from these observations, the aim of the present study is to quantify the impact of inserting a radiologic image review into the pattern of care of HNC patients and to verify whether such an imaging-based indication was adequately tailored based on the analysis of subsequent follow-up.

Materials and methods

At our institution, radiologists with specific expertise in HNC have become steady core members of the MDT starting from 2010. Routinely, imaging may be reviewed both in the diagnostic setting and follow-up period for patients eligible either for surgical or a non-surgical approach. In the diagnostic setting, imaging reviews are performed to: 1) discriminate between benign and malignant lesions, 2) to refine tumour staging, and 3) to define the optimal treatment strategy, especially where radiological and clinical findings conflict. Conversely, if imaging review is required during the course of follow-up, the radiologist may be required to address at least one diagnostic issue from among the following: 1) disease persistence after a non-surgical strategy; 2) loco-regional recurrence and/or distant metastatic progression; 3) second primary tumour of the HN region; 4) surgical and/or radiotherapy sequelae (including osteoradionecrosis). Imaging review may be required either for examinations performed at our institution (if evaluated by a non-dedicated HN radiologist) or as a referral/second opinion for patients treated in other centres (with radiologic images evaluated by general radiologists). In those latter cases, reports from outside hospitals were available in the majority of cases. Whenever radiologic image review is required, both clinical information and DICOM (Digital Imaging and COmmunications in Medicine) files (CT and/or MR) are provided to the radiologist at least one day before the MDT discussion for primary assessment. For the aim of the current analysis, we retrospectively reviewed all cases discussed at MDT meetings from April 2014 to March 2017. Of those, we selected only cases for whom a radiologic review of CT and/or MR was performed by two experienced radiologists.

The radiologists involved in the image review process were LP and CG. Although there are no precise criteria to define radiologist "expertise" on evaluating radiologic images of

head and neck cancers, different parameters are generally considered: years of work on the topic, number of radiologic images examined, availability of modern radiologic equipment, the expertise of the centre (high volume centres), availability of certification endorsed by scientific societies and involvement in multidisciplinary discussions. LP has 15 years'experience in executing and reporting CT and MR HN examinations. Moreover, in 2013 he acquired the subspecialisation in Head and Neck Radiology endorsed by the European Society of Radiology. This qualification attests a standard of in-depth knowledge in the field of head and neck radiology. CG has 5 years' experience in executing and reporting CT and MR HN examinations. During the period considered, their referral Department was the Department of Diagnostic Imaging of the European Institute of Oncology which performs about 2600 HN radiologic exams per year including approximately 220 MRs per year, 150 CTs per year and 2300 ultrasounds per year. LP and CG followed about 80% of the HN TC and MR exams of the Department. Both radiologists were fully involved in the MDT discussion of all cases requiring radiologic images revision. The study investigators were independent of the MDT radiologists.

Inclusion criteria were as follows: 1) clinical and/or radiological suspicion or histologically-proven diagnosis of HNC; 2) availability of a written medical record of the MDT discussion and final radiological report; 3) follow-up length of at least 12 months; 4) willingness and ability to sign a written informed consent for the use of personal data for educational and scientific purposes. Both malignant and benign tumour cases were included. Only CT and MR imaging were considered; data on positron emission tomography (PET) were also collected. Patients who were discussed regarding adjuvant treatment (i.e. radiation treatment alone or in association with systemic treatment) and/or diagnosis of thyroid cancers were excluded.

The aim of the study was to quantify the impact of radiologic image review performed during MDT weekly discussion. Therefore, for each case, the original radiological report was compared to the result from the imaging reviewing process. The following descriptors were considered: 1) any changes in radiological reports in patients for whom treatment strategy had not been previously defined (Tumour Node Metastasis (TNM) staging system 7th ed. in cases of staging modification); 2) any changes in treatment strategy. The latter were categorised as either "major modifications" (i.e. MDT non-indication to surgery in favour of radiotherapy ± systemic therapy, and vice versa) or "minor modifications" (i.e. MDT indication to an alternative approach: open versus than minimally-invasive surgery, and

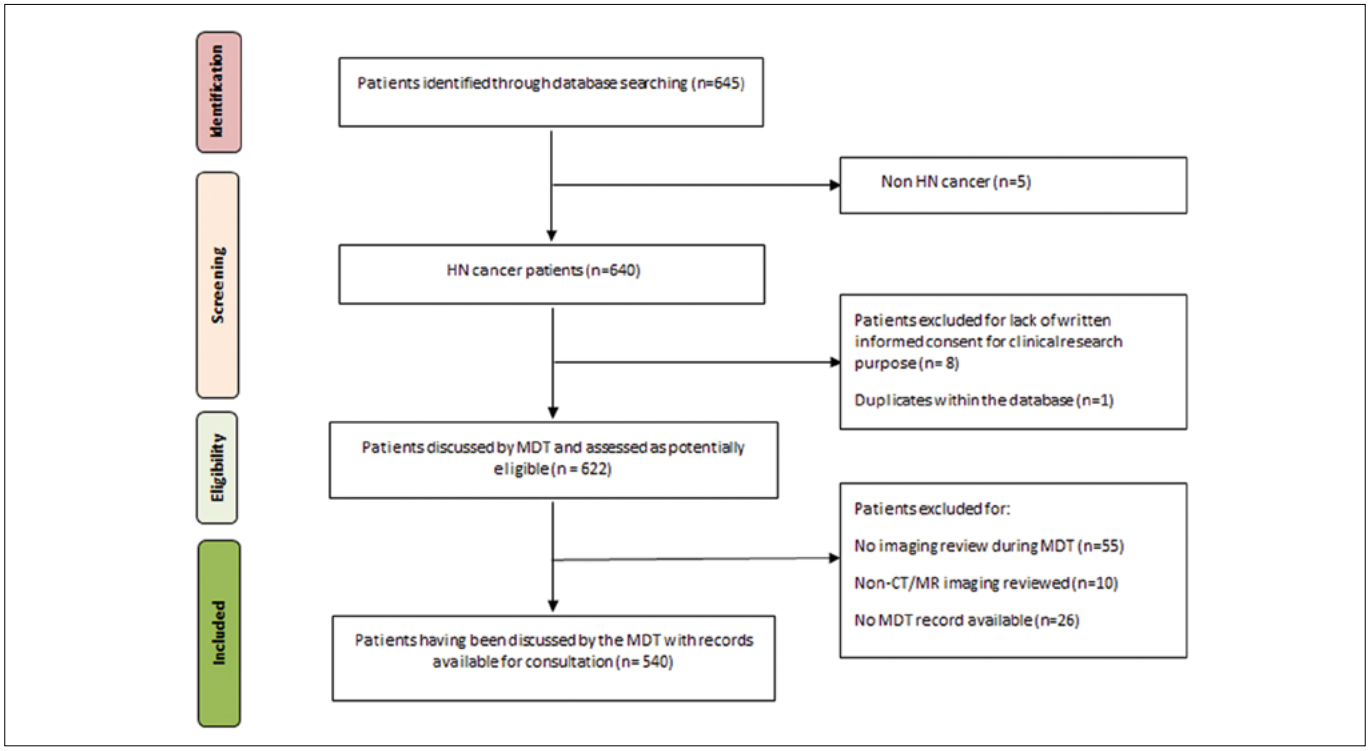

Figure 1. Consolidated Standards for Reporting Trials (CONSORT) diagram.

vice versa). Additionally, MDT final decision and accuracy of MDT indication-to-treatment (as evaluated by histological confirmation and/or follow-up data) were collected.
Patient- and disease-related characteristics were retrieved from electronic medical records. DICOM files were retrospectively reviewed for verification of complex cases (LP, CG).
Descriptive statistical analysis was performed with the SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC).

Results

A total of 2445 cases were discussed during the institutional MDT meetings over the period considered. Radiologic imaging review was required in 649 (26%) cases; of those, 540 met inclusion criteria for the current analysis and constituted the final patient cohort. Details of case selection are provided by the CONSORT diagram depicted in Figure 1. Patients were predominantly male (66%), median age was 63 (interquartile range, IQR: 52.9-71.6) years. The most represented HN subsite was the oropharynx (28%), followed by the larynx (19%) and oral cavity (18%). Further patient demographics and disease-related details are provided in Table I.
Imaging review was required at the time of tumour diagnosis in 310 (57.4%) cases. Most patients (69%) had advanced stage (III and IV) tumours. The remaining 230 (42.6%) patients were discussed during the course of follow-up, mainly because of suspected loco-regional recurrence (131 cases, 57%). Among all cases discussed, 124 (23%) represented the second opinion of patients referred from another centres. Specifics on the setting of imaging review are summarised in Table II.
Considering imaging modality, CT and MR were almost equally represented in our cohort, with 234 (43%) and 249 (46%) of cases, respectively, as illustrated in Table III. Patient stratification according to MDT decision following radiologic imaging review is summarised in Figure 2.
Details of the miscellaneous group (patients for whom radiologic revision did not lead to any amendment in treatment strategy) are as follows:

- Patients with prior indication to surgery for whom the TNM staging modification did not translate into a modification of the treatment strategy (56 patients 77%). The accuracy of staging modification could be verified through the pathological report, which confirmed adequacy in all cases.
- Patients for whom the diagnostic question was to differentiate between benign and malignant lesions (11 patients, 14%). Of these, 6 patients (59%) underwent further assessment through fine needle aspiration or biopsy, while 3 patients (25%) received an indication for clinical and/or radiological follow-up. For these 9 patients, modification of the radiologic report proved to be correct in all cases. As the remaining 2 patients (16%) were lost to follow-up, it was not possible to verify the appropriateness of the radiologic report modification.
- Patients for whom the diagnostic question was to differentiate between recurrent/persistent disease and treatment-related sequelae (i.e. local recurrence vs post-RT osteoradionecrosis) (6 patients, 9%). Pathological confirmation was required in 4 cases, and the modification

Table I. Patient and disease characteristics.

	Number of patients (%)
Total number of patients	540
Gender	
M	358 (66)
F	182 (34)
Age (at the time of multidisciplinary discussion)	
Mean (range) year	61.8 (20-90)
Median (IQR) year	63.0 (52.9-71.6)
Head and Neck sites	
Oral cavity	98 (18)
Oropharynx	152 (28)
Hypopharynx	24 (4)
Larynx	100 (19)
Salivary glands	60 (11)
Skin	17 (3)
Nasal cavity and paranasal sinuses	16 (3)
Lymph node metastasis from unknown primary	12 (2)
Recurrences of nasopharyngeal tumours	5 (1)
Other head and neck sites	56 (11)
Histology	
Squamous cell carcinoma	391 (72)
Adenocarcinoma	15 (3)
Adenoid cystic carcinoma	23 (4)
Pleomorphic adenoma	17 (3)
Mucoepidermoid tumours	6 (1)
Sarcoma	9 (2)
Schwannoma	2 (0.5)
Paraganglioma	2 (0.5)
Neuroendocrine tumours	3 (0.6)
Benign histology	9 (2)
Other histology	17 (3)
N.A. at the time of discussion	46 (9)

CUP: cancer of the unknown primary; HNC: head and neck cancer; IQR: interquartile range; N.A.: not available; SCC: squamous cell carcinoma.

Table II. Aim of the radiologic image revision, sorted by first-diagnosis and follow-up settings.

Setting of radiologic revision	Number of patients (%)	
Diagnosis		310 (57.4)
	Malignant tumours: early-stage disease	59 (19)
	Malignant tumours: advanced-stage disease	216 (70)
	Benign tumours	35 (11)
Follow-up		**230 (42.6)**
	Suspected persistent disease	23 (10)
	Suspected loco-regional recurrence	130 (57)
	Suspected distant metastasis	19 (8)
	Suspected loco-regional recurrence and distant metastasis	12 (5)
	Suspected second primary tumour	28 (12)
	Suspected surgical or radiation-sequelae (including osteoradionecrosis)	8 (3)
	Surgical- or radiation sequelae versus locoregional recurrence	3 (2)
	Other	7 (3)

Table III. Type of images reviewed by the multidisciplinary team.

Imaging modality	No. of patients (%)
CT	234 (43)
MR	249 (46)
CT+MR	25 (4.5)
CT+PET	14 (3)
MR+PET	15 (3)
CT+MR+PET	3 (0.5)

CT: computed tomography; MR: magnetic resonance; PET: positron emission tomography

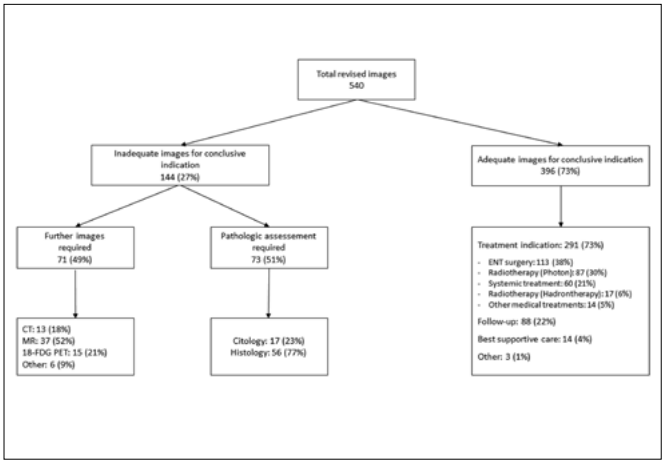

Figure 2. Schematic representation of cases stratification according to MDT decisions (tumour staging and indication-to-treatment).

of the initial radiologic report was proven to be accurate in all but one case (the detailed description of this case is provided later in the section). Of the remaining 2 cases, modification of the radiologic report was confirmed by subsequent imaging in one case, while the other case could not be verified as the patient was lost to follow-up. Missing follow-up data represented 21% (13/61) for patients for whom radiologic image revision led to a modification in treatment strategy.

Overall, considering the whole cohort of 540 patients, imaging review led to modification of radiologic reports (miscellaneous group) or in treatment strategy in 73 (13%) and 61 (11%) of cases, respectively.

Follow-up was available for 118 (86%) of the 134 patients for whom the radiological report was edited following the MDT meeting. Forty-five (37%) patients were submitted to subsequent surgery or cytohistologic sampling (specifically, 50% underwent surgical specimen examination, 35% were biopsied and 15% received a fine-needle biopsy). For the remaining 73 patients, the adequacy of radiologic indication was verified through further imaging and/or clinical examination during the follow up period.

Finally, among patients with available follow up (134 cases) in 117 (87%) we could confirm that modification of the original reports as defined during the MDT discussion was correct.

In only one case was the modification of initial radiological chart not confirmed by subsequent histologic specimen examination. This was the case of a 70-year-old man with a diagnosis of early stage (cT2cN0M0) glottic cancer treated with curative radiotherapy followed by laser surgery for persistent disease. One year after the end of radiotherapy, a CT scan showed a partially necrotic tissue in the right residual larynx with transglottic extension. The finding was considered to be radiologically stable compared with two previous exams and was therefore considered as a radiation-related sequela. Nevertheless, because of worsening symptoms and clinical evidence of cricoid cartilage expo-

sure, after a second MDT discussion, the patient was indicated for a total laryngectomy. The laryngectomy specimen revealed the presence of persistent malignancy.

The management of cases presented for radiological review is depicted in Figure 3. In particular, available imaging could be deemed inadequate and/or insufficient for appropriate evaluation either due to technical issues (such as low-quality image) or to the need for integrated morpho-functional information. In these cases, continuation of the diagnostic workup or cytohistologic assessment was required. Conversely, when the available data were considered adequate, patients were referred for either treatment, follow-up, or best supportive care according to the MDT decision.

A time-trend analysis documented an increase in the absolute number of cases presented to the MDT for radiologic consultation during the period under consideration (Tab. IV).

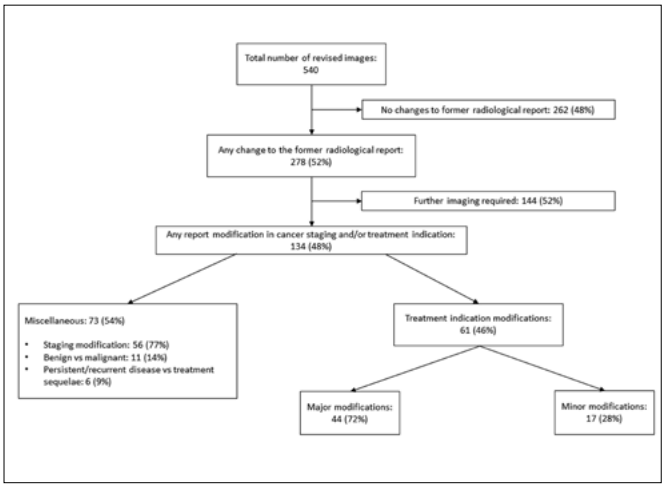

Figure 3. Schematic representation of MDT decision outline.

Discussion

The results of this retrospective analysis show that HN image review performed in a multidisciplinary context has a significant influence on clinical management as it gave rise to a modification of the initial radiologic report in one out of four cases, and led to a change in tumour treatment strategy in 11% of cases. Moreover, our work highlights the high quality of the image review provided, since the majority of the suggested modifications were confirmed by subsequent follow up and/or pathologic specimen examination.

The importance of radiologists at the core of the MDT has been progressively advocated [3,5,15,16]. Not only has the availability of radiologic imaging grown, but recent technological advances in imaging acquisition and post-processing elaboration also require an increasing level of expertise. In the era of precision medicine, the definition of tumour volume and extent is of paramount importance to define the best treatment approach and to avoid geographically missing the target lesion (i.e. mini-invasive surgery, intensity-modulated and stereotactic body radiation therapy). Moreover, the availability of radiologic imaging with higher sensitivity and specificity during follow-up could result in selecting patients whose loco-regional recurrences are being diagnosed at an early stage, thus making them potentially good candidates for curative-intent salvage treatments (surgery and/or re-irradiation). Bergamini et al. [3] found that MDT evaluation led to staging refinement or modifications of the original treatment plan in approximately 60% of HNC cases; of those, 49% were indications to further diagnostic imaging, pathology assessment and/or molecular analyses. Our results are in line with these observations. Accordingly, a recent systematic review of 27 studies by Pillay et al. [6] has shown that the MDT discussion led to changes in former diagnostic reports in 4% to 45% of cases, with the significant limitation that only one of the included studies was dedicated to HNC. The results of our analysis are in line with those observations since accurate review of the radiologic images led to a modification of tumour staging and/or treatment strategy in 13% and 11% of patients, respectively.

Friedland et al. [7] reported that patients seen by the MDT were more likely to present with advanced stage disease compared to those evaluated by individual specialists. Interestingly, the investigators demonstrated a statistically significant benefit for stage IV patients discussed by the MDT, as they were more frequently eligible for multimodality treatment and therefore could achieve better 5-year survival compared with non-MDT patients. This observation is confirmed by our series in which the majority of cases requiring a radiologic image review had advanced stage tumours (69% stage III and IV), corroborating that

Table IV. Number of cases discussed with radiologic image revision compared to the total of patient discussed during the multidisciplinary team meetings, temporal trend/year.

Considered period	No. of patients discussed	Radiologic image revision (% of patients discussed)
April 2014 - March 2015	735	113 (15)
April 2015 - March 2016	804	195 (24)
April 2016 - March 2017	906	21 (23)

the multidisciplinary approach is mostly required in cases for which a multimodality treatment strategy is mandatory. Since we did not have a comparative group of patients managed by a single specialist, we were not able to quantify the impact of MDT management on patients' outcome.
A previously published report by Loevner et al. analysed issues similar to those analysed in the present paper for head and neck cancer patients. In this retrospective study, authors showed that in 56 of 136 cases (41%) the original reports were modified after re-evaluation by an expert radiologist with a significant impact on subsequent patient management [17]. Of note, the study involved patients treated in the 2000s. Despite the significant technical advances in radiologic imaging in recent decades, the role of a dedicated radiologist in a MDT has been strongly confirmed by the present study including a larger cohort, since a comparable proportion of radiologic reports (48%) have been changed after the image review given by an expert head and neck radiologist. All these data highlight the importance of having an expert radiologist present during multidisciplinary discussions, suggesting that radiologic images of every patient should be reviewed in order to optimise the treatment strategy.

Conclusions

We are well aware of the limitations of our study, including: 1) the retrospective nature of the analysis, 2) the exclusion of FDG-PET images from the radiologic revision in some patients, and 3) the unblinded evaluation of the initial radiologic report. Moreover, each MDT discussion also took into account other findings such as clinical examination, symptoms and clinical history. The final MDT decision was, therefore, a multidimensional process in which the radiologic images review represented only one, albeit fundamental, step. Nevertheless, we strongly believe our analysis may convey useful information not only towards the full integration of expert radiologists in the core of MDT for HNCs, but also towards a stronger standardisation of radiologic imaging acquisition and reporting. Although retrospective in nature, the strength of our work resides in the prospective collection of data related to all MDT decision. Moreover, as a tertiary care centre, follow-up information was available for the vast majority of cases, thus permitting the adequacy of the radiologic image review to be verified. In conclusion, in one of four cases in our cohort radiology review led to modification of staging/treatment strategy. This finding strongly supports the importance of including a dedicated HN radiologist as a core member of the MDT. Further efforts of prospective nature are warranted in order to assess whether imaging review in the setting of MDTs translates into improved oncological outcomes.

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Thyroid

Can preoperative serum thyroglobulin levels predict the risk of malignancy? Results from prospective analysis of biochemical predictors of malignancy in thyroid nodules

Valore predittivo dei livelli sierici di tiroeglobulina nei tumori maligni della tiroide. Risultati di un'analisi prospettica in pazienti con noduli tiroidei

Narendra Hulikal[1], Azhagamuthu RE[1], Manilal Banoth[1], Amith Kumar Chowhan[2], Mutheswaraiah Yutla[3], Alok Sachan[4]

[1] Department of Surgical Oncology, [2] Department of Pathology, [3] Department of General Surgery, [4] Department of Endocrinology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Chittoor district, Andhra Pradesh, India

SUMMARY

Although thyroid nodule is a common presentation, malignancy is rare. The present study investigated biochemical predictors of malignancy in enlarged thyroid. This is a prospective study of all willing patients 18 to 70 years presenting with a complaint of thyroid swelling and who underwent definitive surgery over a period of 19 months. All subjects were initially evaluated with detailed history, physical examination, ultrasonography of neck and fine needle aspiration cytology (FNAC). Preoperative estimation of serum thyroid stimulating hormone (TSH), thyroglobulin (Tg) and anti-thyroglobulin (anti Tg) antibody was obtained. The treatment plan was based on FNAC results and included hemi- or total thyroidectomy. During the study period, 110 patients underwent thyroidectomy, and met the selection criteria, of which 47 patients had malignancy on final histopathology. The majority were females, 30 to 60 years old. Median serum Tg, TSH and anti Tg levels in the benign group were, respectively 29 ng/ml, 1,6 mIU/L and 1,1 IU/ml, whereas in malignant nodules they were 162 ng/ml. 1,7 mIU/L and 0,9 IU/ml. On receiver operating characteristic curve analysis, a Tg cut off value of 53 ng/ml predicted malignancy risk with a sensitivity and specificity of 72% and 73%, respectively ($p < 0.001$). Our study showed the utility of preoperative Tg in predicting risk of malignancy. Its role should be further explored especially in the backdrop of indeterminate cytology through a larger study.

KEY WORDS: head and neck cancer, thyroid neoplasms, thyroglobulin, thyrotropin, thyroidectomy

RIASSUNTO

Nonostante i noduli tiroidei siano frequenti, i tumori maligni della tiroide sono rari. Questo studio indaga il valore predittivo di malignità di markers biochimici plasmatici in caso di noduli tiroidei. Sono stati analizzati pazienti di età compresa fra i 18 e 70 anni, affetti da struma tiroideo e sottoposti a chirurgia in un periodo di 19 mesi. Tutti i pazienti sono stati sottoposti ad anamnesi, visita clinica, ecografia del collo e agoaspirato tiroideo. Sono stati effettuati prelievi per il dosaggio del TSH, tireoglobulina ed anticorpi antitireoglobulina. La chirurgia ha incluso l'emitiroidectomia o la tiroidectomia totale sulla base dello FNAC. 110 pazienti sono stati sottoposti a chirurgia di cui 47 con diagnosi istopatologica finale di malignità, principalmente di sesso femminile, di età compresa fra i 30 e 60 anni. I livelli sierologici medi di Tg, TSH ed anticorpi antiTG nei pazienti con noduli benigni sono stati ripettivamente 29 ng/ml, 1,6 mIU/L e 1,1 IU/ml, mentre nei noduli maligni erano 162 ng/ml. 1,7 mIU/L e 0,9 IU/ml. Il valore cut off della tireoglobulina predittivo di malignità è stato 53 ng/ml con una sensibilità e specificità del 72% and 73%, ($p < 0,001$). Il nostro studio ha mostrato l'utilità dei valori di tireoglobulina come marker predittivo di malignità. Tali risultati vanno meglio approfonditi, in gruppi più ampi e specialmente in quei pazienti il cui FNAC risulta non diagnostico.

PAROLE CHIAVE: *tumori testa e collo, neoplasie tiroidee, tireoglobulina, tireotropina, tiroidectomia*

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Correspondence
Narendra Hulikal
Department of Surgical Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Chittoor district, Andhra Pradesh, India-517507
Tel. +91 7382629699
E-mail: drnarendrah@yahoo.co.in

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Conflict of interest
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Introduction

Thyroid nodule is a common presentation and requires a structured diagnostic approach to ascertain the risk of malignancy and determine appropriate management. With a 5-10% lifetime risk of developing a palpable thyroid nodule, they can be detected by palpation in 10% of women and 2% of men [1]. However, with high resolution ultrasound they can be detected in a 19-68% of the randomly selected population [2]. The risk of thyroid malignancy in a nodule depends on various factors attributable to the patient's history as well as clinical, sonological and metabolic features of the nodule, and is roughly estimated to be 3-15% [3,4]. Their accuracy in predicting the presence of malignancy is debatable. The clinical significance rests mainly on the need to exclude thyroid cancer, especially in so called incidentalomas or non-palpable lesions. Most guidelines recommend evaluation of only nodules greater than 1 cm owing to the greater potential to be clinically significant cancers. Occasionally, there may be nodules smaller than 1 cm that require evaluation because of suspicious sonological features or metabolic activity, associated lymphadenopathy, history of head and neck irradiation, or family history of thyroid cancer [4].

Though patients with multiple nodules have the same risk of malignancy as those with a single nodule [5], one large study found that a solitary nodule had a higher likelihood of malignancy than did a non-solitary nodule although the risk of malignancy per patient was the same and independent of the number of nodules [6]. Furthermore, the nodular gland may be secreting hormones normally, subnormally or supranormally. At present, any suspicious nodule on sonography is subjected to guided fine needle aspiration cytology (FNAC), the result of which decides the need for surgery. In about 15 to 30% of patients, the aspirate can be indeterminate [7], which is associated with more than a 20% risk of malignancy. Hence, it is reasonable to conclude that a significant number of patients with nodules need surgery to exclude malignancy with the antecedent risk of recurrent laryngeal injury and permanent hypoparathyroidism.

While there is exhaustive literature on clinical and sonological cancer predicting risk factors in a nodule, recent area of research has been on biomarkers such as serum thyroid stimulating hormone (TSH), thyroglobulin (Tg) and antithyroglobulin (anti-Tg) antibody. Thus, the present study was planned to evaluate the potential role of these biochemical factors as preoperative indicators of thyroid malignancy.

Materials and methods

A prospective study of all eligible, willing patients presenting with thyroid swelling from May 2015 to December 2016 was planned and institutional ethical committee approval was given for the protocol. To be eligible, patients were to be 18 to 70 years old and willing to participate in the study. Patients with recurrent disease, diffuse thyroid enlargement, clinical hypothyroidism, thyrotoxicosis, proven extrathyroidal disease, poorly differentiated cytology, lymphoma or metastasis from elsewhere were excluded.

All study subjects were evaluated clinically with detailed history, physical examination, neck sonography, thyroid profile consisting of serum TSH, triiodothyronine and thyroxine, Tg, anti-Tg antibody and fine needle aspiration cytology. The size of the nodule as measured using a 10 mHz high frequency ultrasonographic probe. Based on the FNAC report, a treatment plan was made. A decision of hemi- or total thyroidectomy was made primarily on the FNAC report and secondarily on the presenting clinical scenario. The nodules where the preoperative FNAC was inconclusive (either suspicious or indeterminate), the hemithyroidectomy specimen were sent for frozen section analysis. Data on age and sex of subjects, voice change, number and size of the nodule/largest nodule, FNAC, frozen section and final histopathology findings along with the preoperative biomarker information such as serum levels of TSH, Tg and anti-Tg antibody were collected. Any further treatment and follow-up were done as per our standard practice.

Lesions were grouped as benign or malignant based on final histopathology, and based on this information, receiver operating characteristic curves (ROC) were plotted for serum Tg, Anti-Tg antibody and TSH levels.

Laboratory methods

Serum thyroglobulin, anti-thyroglobulin and thyroid stimulating hormone were determined using chemiluminescence immunoassay (CLIA), and processed using a Beckman Access-2 analyser (Beckman Coulter Access, GMI Inc, Germany).

Results

During the study period, 110 patients presented with thyroid nodules, of which 18 were excluded. The majority of patients were women (72 of 92) and were 30 to 60 years old (51 of 92, Tab. I). On final histopathology, 47 patients harboured malignancy (Tab. I). The sensitivity, specificity, positive predictive value and negative predictive value for FNAC and frozen sections were 77%, 71%, 73%, 74% and 70%, 100%, 100% and 68%, respectively. The accuracy of FNAC was 71% and for frozen section was 73%.

Table I. Clinicopathological profile of the study subjects.

Characteristic	Benign	Malignant	P value
Age (years)			
45 or less	23	23	0.83
> 45	22	24	
Sex			
Female	38	34	0.13
Male	07	13	
Size of nodule			
2 cm or less	18	23	0.38
> 2 cm	27	24	
Biomarkers (mean value)			
TSH (IU/L)	1.94	2.16	
Tg (ng/ml)	72.55	215.05	
Anti-Tg antibody (IU/ml)	2.84	6.99	
FNAC			
Benign (n = 34)	27	07	
Borderline (n = 9)	04	05	
Suspicious (n = 24)	08	16	
Malignant (n = 25)	05	20	
Frozen section			
Benign (n = 16)	11	05	
Malignant (n = 12)	00	12	

Serum biomarkers

Serum thyroglobulin (Tg): the levels of Tg varied from 0.1 to 500 ng/ml with a median of 29 ng/ml in patients with benign nodules compared to 0.3 to 816 ng/ml with a median of 162 ng/ml among malignant nodules (Fig. 1). A ROC curve was plotted as shown in Figure 2. Using ROC analysis, we obtained a cut-off of 53 ng/ml, with a sensitivity of 72%, specificity of 73% and a *p* value of < 0.001 (Fishers exact test, Fig. 2, Tab. II).

Serum anti-thyroglobulin (anti-Tg) antibody: in the present study, mean serum anti-Tg antibody levels in benign and malignant nodules were 2.25 and 7.27 IU/ml, respectively, (Fig. 3) with median values of 1.1 and 0.9 IU/ml. On ROC analysis, there was no statistically significant association of anti-Tg antibody levels with risk of malignancy (P value = 0.34, Fischer exact test).

Serum thyroid stimulating hormone (TSH): mean TSH in benign and malignant nodules were 1.94 and 2.15 mIU/L with a median of 1.6 mIU/L and 1.7 mIU/L, respectively (Fig. 4). On ROC analysis, there was no significant correlation with risk of malignancy (P value = 0.54, Fisher exact test).

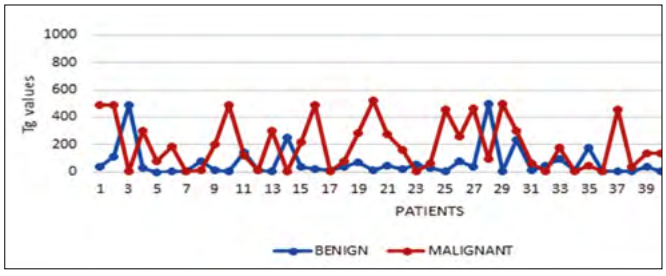

Figure 1. Distribution of serum Tg values in benign and malignant groups.

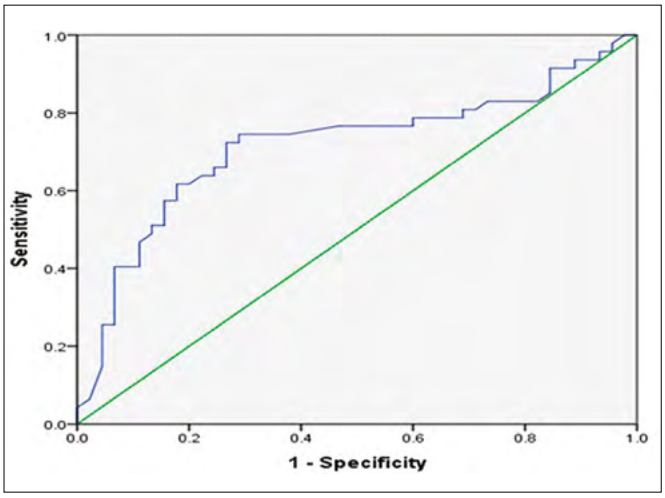

Figure 2. ROC Curve of serum Tg values.

Table II. Analysis of ROC curve and Chi-square test of Tg.

Area under the curve	0.716
ROC P value	0.001
Sensitivity	72.3%
Specificity	73.3%
Cut-off	53 ng/ml
p value (Fischer exact test)	< 0.001

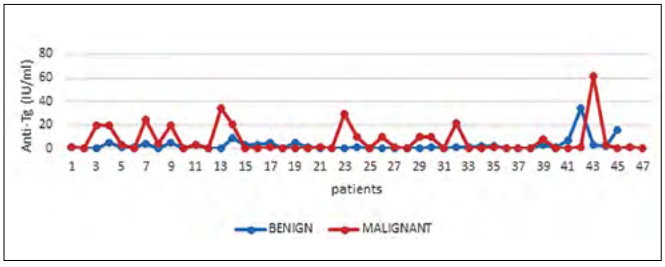

Figure 3. Distribution of serum anti-Tg antibody levels in benign and malignant groups.

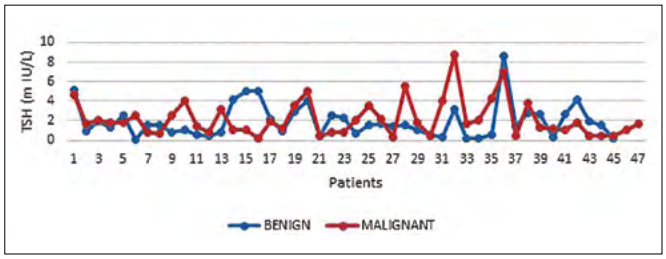

Figure 4. Distribution of serum TSH among benign and malignant nodules.

Discussion

Even if thyroid nodule is a common presentation, cancer is rare, representing 1% of all cancers. Accordingly, it requires a structured diagnostic approach to ascertain the risk of malignancy and determine appropriate management. Increasing incidence of thyroid nodules partly owing to incidental detection mandates us to improve our understanding on the risk factors and biomarkers that might help in guiding their management. While FNAC is a cost-effective, simple, outpatient procedure, its accuracy depends on the experience of the cytopathologist. The reported sensitivity and specificity of FNAC varies from 65 to 98% and 73-100% respectively [7]. The major reason for such a wide variation among studies are differences in categorisation of follicular neoplasms, suspicious of malignancy and atypical cell of unknown significance/ follicular lesion of unknown significance. Common factors for false negatives are inadequate sampling due to calcified nodules, unguided FNAC, difference in inclusion of Bethesda categories under benign and malignant lesions and interobserver variability among reporting cytopathologists. While guided FNAC was not strictly mandated in our study, its sensitivity and specificity in diagnosing malignant nodules are comparable to other studies.

Currently, serum Tg is used in the follow-up of patients with well differentiated thyroid cancer (WDTC) to monitor disease recurrence. The diagnostic value of preoperative serum Tg is still an area of intense debate. Sands et al. in a retrospective study on 861 patients, of whom nearly 35% had indeterminate cytology, 81% with both indeterminate cytology and preoperative Tg ≥ 75 ng/ml had well-differentiated cancer on final pathology compared to 58% with indeterminate cytology alone (p = 0.014, RR = 1.4). They concluded that a combination of indeterminate cytology and preoperative Tg ≥ 75 ng/ml increased diagnostic efficacy compared to indeterminate cytology alone [8]. In another retrospective study of 164 patients with indeterminate cytology undergoing surgery, Lee et al. reported that a cut off Tg more than 70ng/ml predicted cancer risk in nodules more than 1.7 cm with a sensitivity and specificity of 67.7% and 60.7%, respectively. When the size of the nodule was ignored, a serum Tg value of more than 100 ng/ml predicted increased risk [9]. Another study of 97 follicular neoplasm by Lee et al. reported that preoperative serum Tg levels of 75 ng/ml or more and presence of calcification on ultrasonography predicted malignant risk [10]. Similarly, in our prospective study of 92 patients (of which 33 had indeterminate cytology), 76% of patients (13 of 17) with both indeterminate cytology and preoperative Tg > 53 ng/ml had well differentiated cancer on final histopathology compared to 60% (20 of 33) of patients with indeterminate cytology alone. We also conclude that combination of indeterminate cytology and preoperative Tg > 53 ng/ml increased diagnostic efficacy compared to indeterminate cytology alone. While indeterminate cytology was only 35% of our study population, a larger prospective study in this subset would answer whether serum Tg levels could predict risk of malignancy to guide surgery. Some authors have reported higher levels of preoperative serum Tg levels for diagnosing risk of malignancy [11-14] .

It has been reported that the prevalence of WDTC is higher in patients with elevated anti-Tg antibody levels compared with the general population. The association between autoimmune thyroiditis and thyroid cancer is still not clear. A retrospective study of 1638 subjects by Kim et al. using multivariate regression analysis concluded that elevated anti-Tg antibody (odds ratio = 1.61; 95% CI: 1.21-2.23) and elevated serum TSH (odds ratio = 1.72; 95% CI: 1.12-2.63) were significantly associated with malignancy [15]. Another retrospective study of 854 patients by Vasileiadis et al. also concluded that tumour size > 10 mm ($p < 0.001$) and preoperative anti-Tg antibody levels ($p = 0.003$) were independent risk factors of malignancy [16]. A study on 108 patients reported that preoperative serum TSH level may be useful in predicting cancer in thyroid nodules. In that study, mean serum TSH in malignant vs benign nodules were 1.94 vs 1.16 mIU/L ($p < 0.005$) [17]. Similarly, in a study of 63 patients, mean serum TSH in malignant and benign groups were 5.5 vs 1.4 mIU/L ($p = 0.001$) [18]. In the present study, we could not find no association of malignancy with either preoperative serum anti-Tg antibody or serum TSH levels in contrast with other studies [19-25].

Conclusions

Preoperative serum Tg may be a useful biomarker in differentiating benign from malignant thyroid nodules when a cut-off more than 53 ng/ml is used. Hence, we feel that preoperative Tg levels could be incorporated in counselling patients for surgery as well as the need for surgery. Its role in the background of indeterminate cytology needs further

exploration through a large prospective study. We could not demonstrate any association between preoperative levels of serum anti-Tg or TSH with risk of malignancy.

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Laryngology

The correlation between pharyngeal residue, penetration/aspiration and nutritional modality: a cross-sectional study in patients with neurogenic dysphagia

Correlazione tra residui faringei, penetrazione/aspirazione e modalità nutrizionali: uno studio cross-sectional in pazienti con disfagia neurogena

Sara Nordio, Arianna Di Stadio, Isabella Koch, Paola Stritoni, Francesca Meneghello, Katie Palmer

Fondazione Ospedale San Camillo IRCCS, Venice, Italy

SUMMARY

Aspiration risk has a substantial influence on clinical management of swallowing disorders, and can be associated with pharyngeal residue. The aims of this cross-sectional study are to examine the correlation between the presence of pharyngeal residue and penetration-aspiration during fiberoptic endoscopic evaluation of swallowing (FEES), examine the correlation between objective data and Functional Oral Intake Scale (FOIS) and determine whether using objective assessment (Pooling score and Penetration Aspiration Scale-PAS) to categorise patients as pathological or not identifies the same patients identified by FOIS. Fifty-five patients with neurogenic dysphagia were evaluated during FEES by using the Pooling Score scale and PAS. They underwent an assessment of nutritional modalities using FOIS. There was a significant positive correlation between Pooling score and PAS scores for semisolid bolus (Pearson = 0.305; p = 0.024) and liquids (Pearson = 0.841; p = 0.000). The semi-solid bolus Pooling score had a negative correlation with FOIS (Pearson =- 0.355; p = 0.008), but there were no other significant correlations for FOIS with Pooling score or PAS. There were significant differences between objective assessments (P-score/PAS) and functional measure (FOIS) for identifying patients as pathological; although the positive predictive values were high, the negative predictive values were very low. Although pharyngeal residues are significantly associated with the presence of penetration-aspiration during endoscopy, the real intake modalities are not correlated with objective assessments of swallowing disorders. Therefore, clinicians need to implement a comprehensive approach to assess dysphagia.

KEY WORDS: deglutition disorders, residues, penetration, aspiration

RIASSUNTO

Il rischio di aspirazione ha una sostanziale influenza nella gestione dei disturbi della deglutizione, e può essere associato a residui faringei. Gli scopi di questo studio cross-sectional sono di indagare la correlazione tra la presenza di residui faringei e penetrazione/aspirazione durante la fiberoptic endoscopic evaluation of swallowing (FEES), indagare la correlazione tra i dati oggettivi e la Functional Oral Intake Scale (FOIS); verificare se la valutazione oggettiva (Pooling score e Penetration Aspiration Scale-PAS) per dividere i pazienti tra patologici e non patologici, identifica gli stessi pazienti identificati dalla FOIS. 55 pazienti con disfagia neurogena sono stati valutati durante la FEES utilizzando la Pooling Score e la PAS, poi sono state valutate le modalità nutrizionali utilizzando la FOIS. C'è una significativa correlazione positiva tra i punteggi della Pooling Score e della PAS per i boli semisolidi (Pearson = 0,305; p = 0,024) e liquidi (Pearson = 0,841; p = 0,000). I punteggi della Pooling score riguardanti i boli semi-solidi mostrano una correlazione negativa con la FOIS (Pearson =- 0,355; p = 0,008), ma non ci sono altre correlazioni significative per la FOIS confrontata con la Pooling score o la PAS. Ci sono differenze significative tra le valutazioni oggettive (P-score e PAS) e la misurazione funzionale (FOIS) per identificare i pazienti come patologici; sebbene i valori predittivi positivi siano alti, i valori predittivi

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Correspondence
Sara Nordio
Fondazione Ospedale San Camillo IRCCS, via Alberoni 70, 30126 Venice, Italy
Tel. +39 041 2207189. Fax +39 041 731330
E-mail: sara.nordio@ospedalesancamillo.net

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Conflict of interest
The Authors declare no conflict of interest.

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negativi sono molto bassi. Nonostante i residui faringei siano significativamente associati alla presenza di penetrazione-aspirazione durante l'esame endoscopico, le reali modalità di nutrizione non sono correlate con le valutazioni oggettive dei disturbi di deglutizione. Quindi, i clinici necessitano di implementare un approccio globale per valutare la disfagia.

PAROLE CHIAVE: *disturbi deglutitori, residui, penetrazione, aspirazione*

Introduction

Oropharyngeal dysphagia is a symptom that negatively affects swallowing dynamics, involving the oral, pharyngeal, or oesophageal phases [1]. Oropharyngeal dysphagia is commonly associated with neurologic disease, as well as other acute and chronic conditions. Prevalence rates of oropharyngeal dysphagia are 37% and 78% in the acute and chronic phases of stroke, respectively [2]. Patients affected by neurodegenerative diseases have high prevalence of this symptom; in fact, 82% of patients with Parkinson's Disease [3] and 25% of patients with amyotrophic lateral sclerosis [4] are symptomatic for oropharyngeal dysphagia. The presence of dysphagia is associated with increased risk of pulmonary complications, increased hospital length of stay, dehydration, malnutrition and mortality [5].

Aspiration risk is one of the primary factors that influences the clinical management of swallowing disorders [6]. We define "aspiration" as the passage of material below the level of the vocal folds, while penetration is defined as the passage of material into the larynx that does not pass below the vocal folds [7]. From a clinical point of view, the amount of the material and the depth of the aspiration acquired is also highly relevant, influencing the rehabilitation process and clinical outcomes. Patients who aspirate food and liquids into the airway are at increased risk of developing pneumonia [8]. Factors associated with increased aspiration risk include salivary pooling [9], impaired sensation [10], reduced airway protection [11] and pharyngeal residue [12,13]. Murray et al. reported a significant association between accumulated secretions and aspiration of food and/or drink, observed during endoscopic evaluation of older individuals, including patients with mixed aetiology and healthy persons [9].

Pharyngeal residue suggests an underlying impairment of oropharyngeal bolus driving forces [14] and reduced swallow efficiency [15]. In neurogenic dysphagia, residue consists in the result of incomplete bolus clearance caused by poor propulsion, weak pharyngeal muscles activity and/or impaired upper oesophageal sphincter relaxation [12,16]. Pharyngeal bolus residue is most commonly located in the valleculae and/or the pyriform sinuses [17].

Clinical judgment and some previous studies[18-20] suggest that pharyngeal residue can influence aspiration risk, as it can be seen during instrumental swallowing examinations [6]. Videofluoroscopic swallowing study and fibreoptic endoscopic evaluation of swallowing (FEES) are considered the gold standards for detecting dysphagia and aspiration [21] and both provide images of post-swallow pharyngeal residue. They can be considered complementary, and both are needed to make a correct diagnosis of dysphagia. However, a recent study by Kelly et al. [6] suggests that pharyngeal residue and aspiration are better identified by FEES rather than videofluoroscopy. This superior sensitivity is most likely related to the axial, direct view of the surface anatomy within the laryngopharynx [22]. The only protocol for assessing the presence and amount of pharyngeal residues that has been validated in Italy is the Pooling Score scale by Farneti et al. [23,24].

The first aim of this study is to verify a correlation between the presence and amount of pharyngeal residues and penetration-aspiration measured during FEES, assessed with the Pooling Score [23,24] and Penetration Aspiration Scale-(PAS) [7]. The second aim is to verify the correlation and relationship between the degree of severity of dysphagia considering objective data as pharyngeal residue and penetration/aspiration and Functional Oral Intake Scale (FOIS) [25]. In addition, as a third aim, we examine if currently available assessments (Pooling Score, PS, FOIS) have the same specificity and sensitivity for identifying dysphagic patients.

Materials and methods

We analysed in a prospective study 55 patients with neurogenic dysphagia hospitalised at San Camillo Hospital IRCCS, Venice, Italy from February 2017 until August 2017. The study was approved by the Ethics Committee of IRCCS San Camillo Foundation, and research was conducted in accordance to the Declaration of Helsinki. All participants signed informed consent before being included in the study. Patients were referred for a FEES after a bedside clinical swallowing examination performed by an expert speech and language pathologist reporting dysphagia.

The FEES was performed by a trained otorhinolaryngologist, assisted by a speech and language pathologist, using a Storz endoscope. No topical anaesthetic was used; a water-soluble lubricant was used to minimise patient discomfort. First, 5-mL yogurt for pureed [26] food was used, followed by 5-mL water for liquid food. They were mixed with one drop of blue dye in each milliliter, to improve visualisation during endoscopy and avoid confounding food with salivary

secretion. We did not test solids because of the discomfort to patients after the other two trials. All fluids were given at fridge temperature to minimise the risk of aspiration. We avoided testing liquids in patients who had a compromised ability to swallow their own saliva and aspiration during pureed to minimise the possibility of aspiration during FEES. In this case (n = 7), the lowest score for each assessment scale was given to patients who could not assume liquid bolus during the evaluation. The entire clinical procedure was recorded on video, and the videotape of the procedure was analysed by an otolaryngologist (P.S.) and a speech and language pathologist (I.K.). For each bolus ingested, a pooling score according to Farneti's Scale [23] was given, where pooling of materials is considered as any material in the containment cavities of the hypopharynx and larynx before and/or after the act of swallowing [23]. Two different parameters were assessed. First, the pooling-score considers the location (identified by anatomical landmarks), amount of pooling materials and management (ability of the patient to clear the residue). Second, data from Pooling-Sensation Collaboration Age score (P-SCA) combines this information with additional data, such as sensation of the pharynx, patient collaboration and age. Both are continuous variables, with a minimum score corresponding to no dysphagia, and a high score to severe dysphagia. Scores range from 4-11 for the Pooling-score and 3-16 for the Pooling-SCA score.

Penetration-aspiration status was evaluated using the eight-point PAS Scale [7], where a score of 1 indicates no airway invasion and a score of 8 indicates silent aspiration below the level of the vocal cords.

The speech and language therapist completed the FOIS, which is an ordinal scale where level 1 corresponds to "nothing by mouth" and 7 is a "total oral diet without restrictions".

Demographic data (age and sex), clinical presentation (aetiology, presence of tracheostomy, tube feeding, presence of cognitive deficits) were documented by a neurologist. Data are shown in Table I.

For data analysis, we used two-tailed Pearson correlation to examine the correlation between the presence and magnitude of pharyngeal residues (Pooling score and Pooling-SCA) and penetration-aspiration of materials in the airways (PAS), for both semisolid and liquid bolus. Second, Pearson correlations were calculated to identify the correlations between the level of dysphagia expressed by presence and amount of residues (Pooling score) or penetration-aspiration (PAS) and the clinical assessment of dysphagia based on nutritional modalities (FOIS). We choose to not consider the P-SCA score in statistical analysis due to inclusion of clinical characteristics in the scale. Third, to investigate whether using the objective scales during FEES (Pooling score and PAS) to dichotomously categorise patients as dysphagic or non-dysphagic, could identify the same patients as the nutritional modalities assessment (FOIS). Pooling-score scores of less than six were considered not pathological, and scores of six or more as pathological. For PAS, scores of two or more were considered pathological. A score of less than 7 was considered pathological for FOIS. Chi square was used to assess whether there was a difference in the categorisation of patients as pathological or not by Pooling-score or PAS compared to FOIS. We also report the positive and negative predictive values and specificity and sensitivity values. Significance was set at $p < 0.05$. All statistical analyses were conducted using IBM SPSS Statistics version 20.

Table I. Patient characteristics.

	Mean	SD*
Age (year)	62.6	14.6
Time since onset (months)	41	116.5
Aetiology	**Frequency**	
Ischaemic stroke	8	
Cerebellar stroke	2	
Haemorrhagic stroke	19	
Subarachnoid haemorrhage	4	
Traumatic brain Injury	4	
Amyotrophic lateral sclerosis	4	
Wallemberg syndrome	3	
Parkinson's disease	1	
Multiple sclerosis	1	
Anoxia	4	
Arnold Chiari malformation	2	
Bleeding after arteriovenous malformation rupture	1	
Spinal cord injury	4	
Cerebellar ataxia	1	
Tracheal tube	39	
Tube feeding	44	
Cognitive impairment	45	

**: standard deviation.*

Results

We recruited 55 patients, 41 males and 14 females. Patient age ranged from 20 to 84 (mean age = 62.6 years; SD = 14.6), the mean disease onset at time of evaluation was 41.0 (SD = 116.5) and the most common diagnosis was haemorrhagic stroke (Tab. I). 39 had tracheal tube and 44 tube feeding; 45 had cognitive impairment (Tab. I). Mean scores on the different assessment scales are reported in Table II.

Correlations between the presence and amount of pharyngeal residues measured by Pooling Score [23] and the penetration-aspiration of materials in the airway assessed with PAS [7] are shown in Table III.

Table II. Mean scores on the battery of tests.

	Minimum	Maximum	Mean	SD[3]
Pooling-score semisolids	2	8	6.0	1.6
Pooling-SCA semisolids	3	15	6.6	2.5
PAS[1] semisolids	1	8	2.3	2.0
Pooling-score fluids	4	11	6.6	2.3
Pooling SCA fluids	3	16	7.8	4.2
PAS[1] fluids	1	8	3.1	2.4
FOIS[2]	0	7	3.5	1.7

[1]: penetration aspiration scale; [2]: functional oral intake scale; [3]: standard deviation.

There was a significant positive correlation between Pooling-score and PAS scores for both semisolid and liquid bolus. Significant positive correlations were also seen for Pooling-SCA and PAS scores, for both semisolid and liquid bolus.

The correlation between Pooling score or PAS with FOIS is reported in Table IV. All correlations were in a negative direction but none were significant, except that Pooling-score for semisolid bolus was negatively correlated with FOIS ($p = 0.008$).

The third aim was to examine whether using the scores from objective evaluation (Pooling score and PAS) to dichotomously categorise patients as pathological or not identified the same patients as the functional/symptomatic scale (FOIS). There were no significant differences between the instruments (P-score/PAS) and clinical functional measure (FOIS) in identifying patients as pathological. We separately evaluated the specificity and sensitivity of the assessment for liquid and semisolid. FOIS, compared with PAS for identifying dysphagia for liquids, had a sensitivity of 6.3% and a specificity of 94.9%. For semisolids, the sensitivity was 6.1% and specificity was 95.5%. The sensitivity of FOIS, when compared with P-score for identifying dysphagia in swallowing liquids, was 10% and specificity was 97.1%. For semisolids the sensitivity and specificity were 13.6% and 100%, respectively. Negative and positive predictive values are shown in Table V.

Table III. Correlation between pooling score and penetration aspiration scale.

	Penetration aspiration scale (PAS)	
	Pearson	P value
Semisolids pooling-score	0.305	0.024*
Semisolids pooling-SCA[1]	0.373	0.005*
Liquids pooling-score	0.841	0.000*
Liquids pooling-SCA[1]	0.852	0.000*

*[1]: sensibility, collaboration, age; *: $p < 0.05$.*

Table IV. Correlation between pooling score/PAS and the functional oral intake scale.

	FOIS[2]	
	Pearson	P value
Semisolids pooling-score	– 0.355	0.008*
Semisolids pooling-SCA[3]	– 0.134	0.330
Semisolids PAS[1]	– 0.201	0.140
Liquids pooling-score	– 0.180	0.189
Liquids pooling-SCA[3]	– 0.122	0.375
Liquids PAS[1]	– 0.218	0.110

*[1]: penetration aspiration scale; [2]: functional oral intake scale; [3]: sensibility, collaboration, age; *: $p < 0.05$.*

Discussion

Our study identified three main findings. First, Pooling-score, Pooling-SCA and PAS scores are positively correlated for both semisolid and liquid bolus. Second, there were no significant correlations between Pooling-score/PAS and FOIS, except for semisolid pooling score compared with FOIS. There were differences between the objective assessments (Pooling-score/PAS) and the functional measure (FOIS) in identifying pathological dysphagia; in fact, although the sensitivity of Pooling/PAS is high, the specificity is lower than FOIS.

The correlation between the objective assessment shows that the presence, position and quantity of pharyngeal residue is related to an increased risk of penetration and/or aspiration in neurogenic dysphagia. These results are in accordance with the data by other authors [9,12,27].

The accumulation of residue in neurological is due to a reduction in tongue thrust strength, impaired pharyngeal constriction, or failure to release of upper oesophageal sphincter. Furthermore, the incomplete elevation of hyo-laryngeal complex, impaired motility of vocal cords and incomplete epyglottidis tilting increase the risk of penetration-aspiration events.

The deficit function of trigeminal (III), glossopharyngeal (IX), vagus (X) and hypoglossal (XII) nerves modifies the

Table V. Positive predictive values for pathological categorisation of the pooling-score and penetration-aspiration scale (PAS) compared to the functional oral intake scale (FOIS).

	Negative predictive value for FOIS[2]	Positive predictive value for FOIS[2]	P value[1]
Semi-solid pooling-score	13.6	100.0	0.590
Semi-solid penetration-aspiration scale	6.1	95.5	0.807
Liquid pooling-score	10.0	97.1	0.546
Liquid penetration-aspiration scale	6.3	94.9	0.869

[1]: calculated with chi square; [2]: functional oral intake scale.

swallowing process by acting at different levels, both in the oropharyngeal and in the oesophageal phases. Specifically, the association between residues and penetration-aspiration can be explained by considering the main role of cranial nerve X and the consequences of its damage, because it allows pharyngeal propulsion and cough reflex. Thus, it is relevant to evaluate its function to predict the increased risk in patients with neurogenic dysphagia.

In our results, all correlations between Pooling score or PAS with FOIS were in a negative direction and only Pooling-score values for semisolid bolus was negatively correlated with FOIS. This latter scale documents the functional level of oral intake food and liquid, also considering the use of enteral nutrition.

In neurological patients, enteral nutrition may be necessary to avoid malnutrition in cases of severe dysphagia [28].

Our results showed that there was no correlation between FOIS and scores that describe pooling and penetration-aspiration level, for both semisolids and fluids. Therefore, objective evaluation describes fundamental aspects of dysphagia, but, especially in neurological patients, clinical outcome can be influenced by other important parameters, for example, awareness, collaboration, cognitive abilities, presence of apraxia, or speech impairment like aphasia, which can compromise the ability to understand language. The presence of these types of impairments in neurological disorders [29-32] can add further difficulties in the deglutition process, even more if specific or complex postures and manoeuvres are requested to swallow safely, and may reduce the success rate of swallowing treatment. It is important to highlight that more than 80% of our sample had cognitive impairment, which may explain the discrepancies observed in the results of penetration-aspiration assessment and FOIS.

Swallowing is a complex behaviour that requires dynamic neural coordination at both the cerebral and brainstem levels [31]. The primary sensory and motor cortex, supplementary motor area, prefrontal and inferior frontal cortex, cingulate cortex, insula, basal ganglia, thalamus and cerebellum [32] (cortical and sub-cortical structures) need to have perfect functionality to produce an effective swallowing process. The analysis of the comparison between dichotomised pathological values is consistent with the other results of this study; in fact, the sensitivity was low for all the comparisons made, and therefore only a small number of patients non-pathological on the P-score or PAS scale were equally non-pathological according to FOIS.

Overall, our results support the idea that the three scales used provide diverse information about different aspects of dysphagia, and thus all three are necessary to perform accurate diagnosis and adapt the rehabilitation path to the specific dysphagia characteristics of each patient by designing a sort of "personal therapy".

There are several limitations in this study. First, the sample size was small and there was a heterogeneity in the patient aetiologies. We made the swallowing test with one bolus only of semisolid and one of fluid. We did not have access to information about whether residue remains over time. Finally, in the third aim of the study, we used specific cut-offs to dichotomise the scores into pathological or not pathological categories. The results of the study may differ if different cut-offs were used, and this would be an interesting avenue for future research to adjust the cut-offs to find an optimum way of assessing the objective and clinical aspects.

Future research would be necessary to evaluate possible differences in the aspect of dysphagia in specific neurological population (stroke, traumatic brain injury etc.), to evaluate if by swallowing several boluses there is an improvement or a worsening of dysphagia and to study if the position of residue may be relevant for evaluating the increased risk of penetration-aspiration over time.

Conclusions

In conclusion, in this study we have shown that pharyngeal residues, measured through Farneti's protocol, are significantly associated with the presence of penetration-aspiration on swallowing semisolid and liquid bolus during endoscopic evaluation in neurological patients, reported by PAS. Moreover, the tool that documents the functional impact of dysphagia of oral intake of food and liquid (FOIS)

is not correlated to the objective assessment of dysphagia. Therefore, each scale measures different significant aspects and the use of all three assessment is necessary for an accurate diagnosis of the disorder. In our opinion, it is necessary to implement a comprehensive approach to assess neurogenic dysphagia, including evaluation of presence and amount of pharyngeal residues, penetration-aspiration and effective nutritional modalities, in order to plan the proper treatment and monitor changes in swallowing efficacy and impact on functional feeding abilities.

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RHINOLOGY

Endoscopic treatment of choanal atresia and use of balloon dilation: our experience

Il trattamento endoscopico dell'atresia coanale e utilizzo delle dilatazioni mediante balloon: nostra esperienza

Giovanni Carlo De Vincentiis[1], Maria Laura Panatta[1], Eugenio De Corso[2], Giulia Marini[1], Alessandra Bianchi[1], Monica Giuliani[1], Emanuela Sitzia[1], Filippo Maria Tucci[1]

[1] UOC di Otorinolaringoiatria, Ospedale Pediatrico Bambino Gesù IRCCS Rome, Italy; [2] UOC di Otorinolaringoiatria, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY

The aim of this study is to report our experience in surgical treatment of unilateral and bilateral choanal atresia. We describe the endoscopic surgical technique for creation of neo-choanes and following repeating balloon dilation after surgery to stabilise the results. The study was carried out from December 2014 to December 2018, enrolling 46 patients who underwent surgery for choanal atresia at the Otolaryngology Unit of the Paediatric hospital Bambino Gesù: 17 with bilateral choanal atresia (Group A) and 29 with unilateral choanal atresia (Group B). All patients underwent transnasal endoscopic surgery. The incision of the mucosa was made with a cold and hot system (laser diode). The elimination of atresic plaque was possible thanks to the use of a drill; the calibration of the neo-choanes was carried out with the help of balloon dilation. No stent was used, and no patient underwent treatment with topical mitomycin. The first endoscopic follow-up was made 7 days after surgery with surgical curettage and a second balloon dilation 15 days after surgery to stabilise the new choanes. Further check-ups were suggested at 1 month after surgery and later based on individual progress. In group A, the average age for the first treatment was 10.4 days, and atresia was associated with other anomalies in 64% of cases. The therapeutic protocol led to a successful outcome in 82% of cases, with an average of 4.6 procedures per patient (range: 3-11). In group B, the average age for the first treatment was 36.6 months, association with other anomalies was 27% of cases and the prevalent side was the right (11:6). We obtained surgical success in 85.7% of cases and the average number of endoscopic dilations was 3.5 (range: 3-7). Transnasal endoscopic surgery is now considered the therapeutic gold-standard for both unilateral and bilateral atresia. Even if still used, post-surgery stenting can be avoided in our opinion; relapse is reduced with the use of balloon dilation, which, in our experience, is a valid aid in both primary atresia treatment and in cases of relapse.

KEY WORDS: choanal atresia, endoscopic sino-nasal surgery, balloon dilation

RIASSUNTO

Scopo di questo studio è quello di descrivere i risultati della nostra esperienza nel trattamento chirurgico endoscopico della atresia coanale e di illustrare in particolare il nostro protocollo che per mantenere pervio lo spazio coanale non prevede l'applicazione di uno stent ma dilatazioni endoscopiche mediante balloon ripetute nel post-operatorio al fine di stabilizzare il risultato chirurgico. Nel periodo compreso fra dicembre 2014 e dicembre 2018, abbiamo arruolato 46 pazienti affetti da atresia coanale e sottoposti a trattamento chirurgico presso l'Unità di Otorinolaringoiatria dell'Ospedale Pediatrico Bambino Gesù (17 con atresia coanale bilaterale e 29 con atresia coanale monolaterale), Tutti i pazienti sono stati sottoposti a chirurgia endoscopica transnasale. L'incisione della mucosa è stata realizzata con strumentazione a freddo e a caldo (laser a diodi). L'eliminazione della componente ossea è stata possibile mediante l'utilizzo di frese; la calibrazione delle neo-coane è stata eseguita con la tecnica di dilatazione mediante balloon. Nessuno stent è stato utilizzato e nessun paziente ha ricevuto trattamento topico con mitomicina. Il primo controllo endoscopico post-operatorio con eventuale dilatazione è stato eseguito 7 giorni dopo la procedura chirurgica. Una seconda valutazione endoscopica con medicazione e dilatazio-

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Correspondence
Maria Laura Panatta
UOC di Otorinolaringoiatria, Ospedale Pediatrico Bambino Gesù IRCCS, via Torre di Palidoro snc, Fiumicino, Rome, Italy.
E-mail: marialaura.panatta@opbg.net

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ne è stata effettuata 15 giorni al fine di stabilizzare il risultato chirurgico. Ulteriori controlli sono stati pianificati ad un mese dall'intervento e i successivi sulla base dei progressi del singolo paziente. In nessuno dei 46 pazienti trattati abbiamo osservato complicanze dopo i trattamenti endoscopici. L'età media dei 17 pazienti con atresia coanale bilaterale è stata di 10,4 giorni al momento del primo trattamento; nel 64% dei casi l'atresia era associata ad altre anomalie. Il protocollo terapeutico ha garantito il raggiungimento di outcome soddisfacenti nell'82% dei casi, con una media di 4.6 procedure realizzate per ogni paziente (range: 3-11). I 29 pazienti affetti da atresia monolaterale presentavano un'età media di 36,6 mesi al primo trattamento, una prevalenza di atresia monolaterale destra (11:6), un'associazione con ulteriori anomalie nel 27% dei casi. Abbiamo ottenuto una percentuale di successo dell'85,7% con una media di 3,5 procedure per paziente (range: 3-7). La chirurgia endoscopica transnasale è attualmente considerata il gold standard terapeutico, sia per l'atresia monolaterale che bilaterale. A nostro parere, andrebbe evitato l'utilizzo di stent post-intervento, anche se ancora oggi vengono utilizzati; la recidiva è ridotta dall'utilizzo della dilatazione mediante balloon che, nella nostra esperienza, è un valido aiuto sia nel trattamento dell'atresia primaria che delle recidive.

PAROLE CHIAVE: *atresia coanale, chirurgia con balloon*

Introduction

Choanal atresia is a rare congenital malformation characterised by the lack of patency of communication between the third postero-inferior of the nasal cavity and nasopharynx. It can be unilateral or bilateral; its prevalence in the population is one in 5000-8000 live births with an incidence that is twice as high in females and with a predominance of the right side in unilateral atresia [1-3].

Atresia may be associated with other congenital anomalies in over 50% of cases. The most common condition is the CHARGE syndrome, where the acronym is indicative of the association of coloboma with cardiac malformations (heart disease), atresia of the choanes, retard in development, alterations of the genital-urinary district and deafness and some other ear dysmorphism. Other associated congenital anomalies may be Crouzon and Di George syndromes, Treacher-Collins syndrome, Down syndrome and finally malformations which involve the mid-line of the face such as cleft palate, hypertelorism, development of meningocele, or encephalomeningocele [4].

To date, its aetiology is unknown, even if Lee et al. found a significant association between the presence of bilateral choanal atresia and low levels of thyroxine serum [5]. Many embryological theories have tried to explain the genesis of this congenital malformation; the most accepted theory refers to the persistence of Hochstetter's nose and mouth membrane, as this membrane is re-adsorbed at the fifth-sixth week of pregnancy to allow the choanal openings to develop, and its non-reabsorption favours the growth of an atresic plaque. Other theories suggest that this could be due to the anomalous persistence of mesodermic tissue, which results in an anomalous adhesion as well as anomalous migration of cells, also due to the presence of some local growth factors [6].

Usually, 65-75% of cases show unilateral atresia, whereas bilateral atresia is less common [7]. The atresic plaque is completely osseous in 30% of cases and is mixed, osteo-membranous in the remaining 70%. The bone surface is usually positioned at the back of the nasal cavity at the end of the septum bone, but the anatomic deformity is usually more complex, and the nasal cavity is reduced and funnel-shaped due to the presence of a medial procidentia of the pterygoid wing, whereas the widening of the vomer enhances an obstruction in the medial portion of the nasal cavity [8].

In this manuscript, we report our experience on surgical treatment of bilateral and monolateral choanal atresia. We propose an endoscopic approach without using stents and suggest optimisation and stabilisation of the new choanes through the innovative use of balloon dilation. This approach was made possible by using sinuplasty balloon, which offers several advantages such as reduction of trauma in the surrounding tissues with minor complications, reduction of surgical time in the following revisions, an advantageous post-operation recovery and reduced hospitalisation of patients.

Materials and methods

Study population and study design

This is an observational study of 46 patients who were treated for choanal atresia at the "Ospedale Pediatrico Bambino Gesù" and who were followed for at least 12 months at our institution. Patients were enrolled between December 2014 and December 2018; 17 of 46 (36%) had bilateral atresia (group A), and 29 of 46 (64%) had unilateral atresia (group B). In group A (mean age: 10.4 days; range: 6-21 days; 7 male 7, 9 female), choanal atresia was associated with other syndromes in 64% of cases (11 of 17) and specifically: 2 Down syndrome, 2 Franceschetti's syndrome, 3 CHARGE syndrome, 1 osteopetrosis, 1 deletion of chromosome 9, 1 Rapp-Hodkging syndrome and 1 patient with deletion of chromosome 8. In group B (mean age: 2.6 yrs.; range 2-12 yrs., 12 male, 17 female) complex malformations were observed in 7 of 29 patients (24%) and specifically: 5 Down syndromes, 1 costo-mandibular syndrome and 1 Di George syndrome.

At pre-operative evaluation all patients underwent nasal endoscopy and CT scan (Fig. 1) of the facial bone to confirm the presence of atresia and define the anatomic characteris-

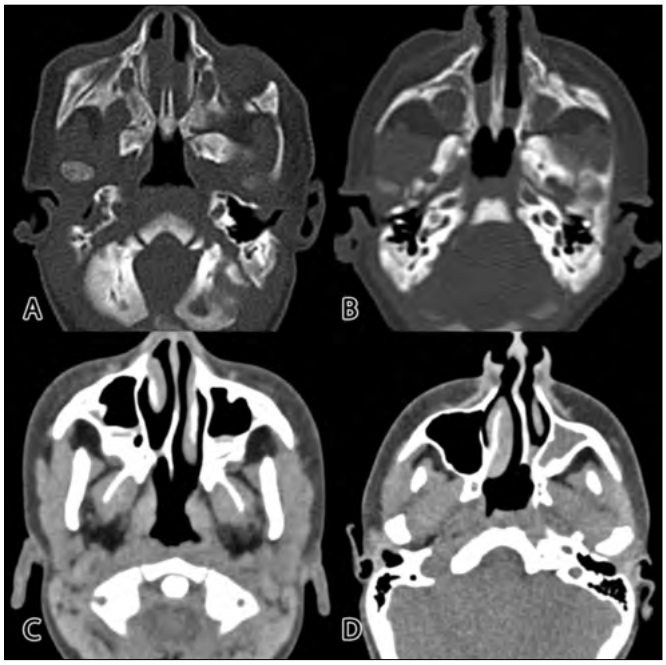

Figure 1. CT scan of bilateral (A-B) and unilateral choanal atresia (C-D).

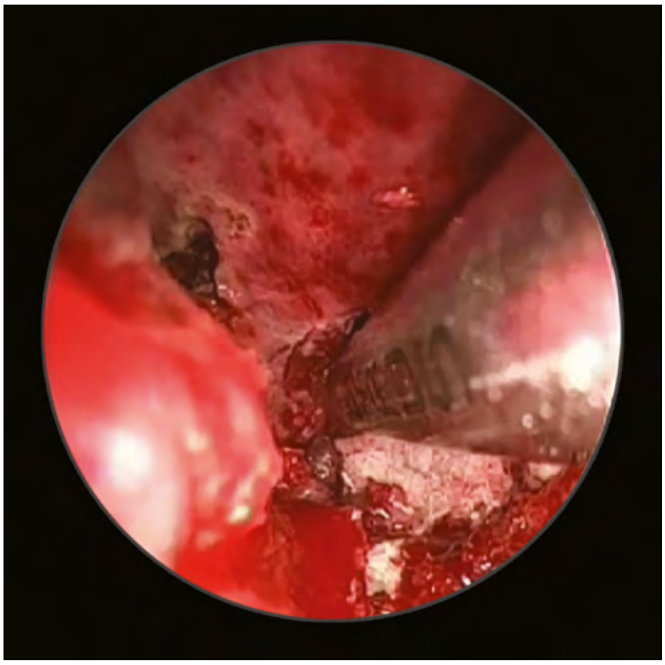

Figure 2. Elimination of choanal athresic plaque using a micro-drill.

tics of the malformation of the nasal cavities, as well as the nature of the atresic plaque and possible association with other anomalies.

Surgical technique

All patients underwent surgery under general anaesthesia with oral-tracheal ventilatory intubation. Inspection of the nasal cavities was done using a 0° endoscope, with diameters from 2.7 to 4 mm (according to the patient's age), after nasal mucosa was decongested with cotton ball soaked in xylocaine 1% and 1:1000 adrenaline. All patients had osseous or osteo-membranous atresic plaques, whereas no case showed pure membranous forms. Access to the vomer was possible through definition of side hinge mucosal flaps, cut with or without the use of a laser diode, whereas elimination of the plaque was possible using a micro drill, by associating, in some cases, elimination of part of the vomer bone with forceps, so as to ensure a wider choanal caliber (Fig. 2).

In order to stabilise the neo-choanes obtained, they were dilated with the aid of balloon catheter (Acclarent Relieva Ballon Inflation Device), with a calibre from 7 to 10 mm (according to the patient's age) and with a length of 16 mm. The catheters were applied in each nasal cavity for 20 seconds, after being floated with saline solution, to 10-12 atmospheres by also positioning Hegar dilators of the fit calibre in the other cavity in order to avoid possible misplacement while carrying out the operation (Fig. 3).

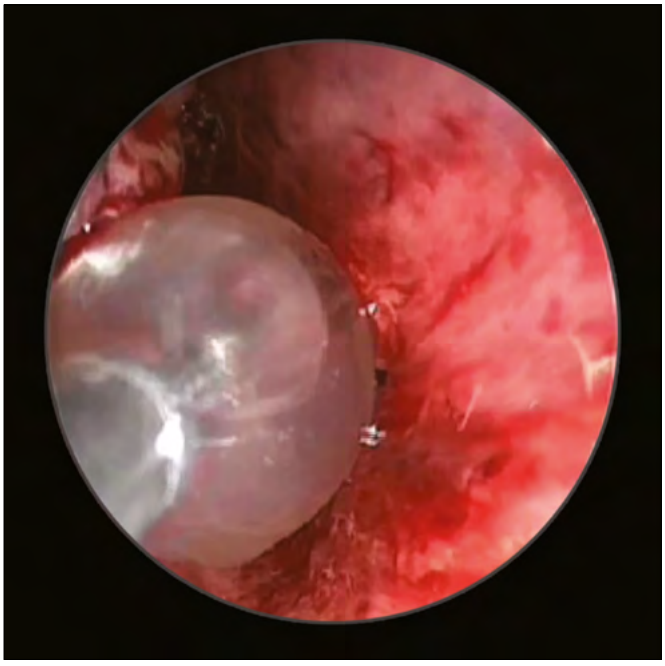

Figure 3. Endoscopic view of choanal balloon dilation.

No stent was applied and no nasal packing was necessary to control haemorrhage. All parents were instructed to perform several daily nasal irrigations during the post-surgical period, as well as topic inhalation of mometasone furoate, once daily, with 0.05 mg for each cavity with nasal spray.

After surgery two endoscopic follow-ups were planned under general anaesthesia at one and two weeks after surgery; granulation tissue was removed, whereas the presence of stenosis for excessive scarring was treated with new dilations, with radial drainage incisions made with cold systems so as to break the circular field lines which condition the restenosis. Nasal irrigations and topic inhalation were prescribed post-operatively for one month.
Further check-ups were planned at one month after surgery and later if required. The analysis of results is based on post-operative endoscopic check-ups. We assumed restenosis of the choane if a 50% reduction of the neo-choanal space was observed. The minimum follow-up was 6 months and patients were observed for at least 12 months.

Results

In total, we treated 46 patients. Bilateral choanal atresia was most frequently associated with other syndromes than unilateral atresia, respectively 64% and 24 % with a significant difference ($p < 0.05$). In group A, average age at the first treatment was of 10.4 days of life (range 6 to 21 days). Surgery was safe in all cases; none of the patients needed post-surgery intensive care. Packing of the nasal cavity was not performed and stents were not applied. Topic steroids were prescribed for the following 30 days, associated with nasal irrigations with isotonic saline solution. All patients performed the planned endoscopic dilations in the first post-operative month. Surgery was successful in 82% of cases (14 of 17), and none had re-stenosis during follow-up. In three of 17 (18%) patients we observed an early post-operative re-stenosis of choanal space that was evident at the first endoscopic follow-up at one month after surgery. In all cases the re-stenosis exceeded 50% of the neo-choanal space. In these cases, we performed monthly dilation until success was obtained (in 2 of 3 cases). In these specific cases we performed from 3 to 11 dilations. The average of the dilation treatments in all series was 4.6 per patient, including the most difficult cases.
Following we provide a brief description of two of the challenging cases that failed in group A. The first was a patient suffering from Rapp-Hodgkin syndrome, which resulted in a higher number of procedures (11 treatments). This form of uncommon ectodermic dysplasia, due to a mutation in heterozygosity of the TP63 gene on chromosome3q28, is characterised by abnormal development of the adnexal structures of ectodermic derivations (hair, teeth). The patient had large tendency towards post-surgery cicatricial stenosis that was inexplicable and for this reason we performed a genetic investigation that lead to the definition of the syndrome. The second case was suffering from osteopetrosis and was particularly difficult to treat. In this case, even after 10 treatments, we observed relapse of the stenosis due to abnormal re-ossification. Furthermore, the patient post-operatively developed severe anaemia that was not related to intra-operative blood loss. Post-operative clinical investigation revealed severe myelodysplasia requiring a bone marrow transplant that was effective.
Patients with unilateral atresia (group B) had better therapeutic outcomes, probably age-related, as the medium age for first treatment was 36.6 months. The average number of treatments per patient was 3.5. Surgery was successful in 93% of cases (27 patients of 29); none of these had re-stenosis during follow-up. In 2 of 29 (7%) patients, both with an associated syndrome, the vomer bone had to be removed with construction of a monochoane. In particular, one of the patients suffered from a cerebro-costo-mandibular syndrome associated with a non-defined syndromic condition related to deletion of chromosome 10q26 with associated micro-duplication of chromosome 22q26.

Discussion

Choanal atresia was identified as nosological entity in the 18th century, and the first surgical treatment was described in the literature by Emmert in 1851, through the use of a transnasal technique which, through a mere injection made by a provided trocar, assured patency of the choanal region. As can be imagined, the method was associated with a high percentage of restenosis [9]. From a clinical point of view, bilateral choanal atresia represents a specific medical rather than surgical emergency. A newborn has to breath through the nose, and this explains the so-called condition of "paradoxical cyanosis" that during a baby's cry is unexpectedly resolved thanks to momentary oral breathing, physiologically unknown to these patients. Considering such peculiarities, intensive care may be necessary, and surgery needs to be planned as soon as the clinical conditions of the patient allow for it. Patients with unilateral atresia have a different progress, diagnosis is often late and it is mostly related to the persistence of mono-lateral rhinorrhoea that is not responsive to therapy. Surgery has to be adequately planned to ensure correct cranial-facial development, thus preventing the recurrence of phlogosis in the rhino-sinus district. According to literature data, in our series we observed that bilateral choanal atresia was most frequently associated with other syndromes than monolateral choanal atresia (64% versus 24%; $p < 0.05$). Furthermore, in our series the diagnosis and age at first treatment were earlier in group A than in group B: 10.4 days versus 36.6 months, respectively.
The surgical approach for treatment of choanal atresia

has always considered the use of transnasal, transseptal, transpalatal techniques, each of which has advantages and disadvantages, especially in relation to the patient's age and the complexity of the associated malformation. The aim of each intervention is to create patency of the choanal region in the most conservative way possible in order to avoid useless injuries to nearby structures whatever the approach. The transpalatal approach has undoubted advantages, especially in surgery, by offering a better visualisation of anatomic structures and consequently a lower risk of disorientation by the operator. Furthermore, it guarantees a lesser frequency of endocranial complications compared to a transnasal approach. This procedure, however, can modify the patterns of growth of the hard palate, the alveolar process of the maxillary and the bone and fleshy structures of the mid-line of the face; it can result in a higher risk of bleeding during surgery, other than in a changing incidence of lesions of the soft palate as explained in the literature [10].
The use of endoscopic techniques has radically changed surgery for choanal atresia, even if the rarity of this malformation and the random cases encountered explain why there is no standardised protocol for surgical technique, application of transchoanal stents and duration of such application [11]. Many advantages were brought with the application of endoscopic instruments, created to treat rhino-sinus inflammatory pathologies, when this instrument was used for diagnosis and treatment of choanal atresia, as this method represents a genuine revolution. It is a mini-invasive technique, much less traumatic, with the clear advantage that it provides high optimisation of the operative field, minimizing the risk of bleeding. This technique allows for correct inspection of these patients' noses, not only during surgery, but also after surgery, and is therefore commonly accepted as the preferred surgical method. Nevertheless, surgeons have to deal in the post-operative period with a high risk of re-stenosis due to local inflammation which promotes granulation tissue and scarring. For this reason, post-operative medications are very important to guarantee maintenance of the neo-choanal space over the months.
Some authors have suggested to use stents against the tendency of re-stenosis; choanal stents, in fact, are made of non-reactive material to allow stable and enduring surgical outcomes. Nevertheless, the need for postoperative stents has been debated for years. Riepl et al. [12] supported the use of stents, describing a brief series of six cases of bilateral choanal atresia that underwent a transnasal endoscopic technique supported by balloon dilation. The balloon dilator was used to dilate the neochoanae and prevent restenosis. Nevertheless, they suggested the use of bilateral stents for 6 weeks after surgery, especially in very young patients, as a prerequisite to prevent early restenosis. In a recent TRIO Best Practice monograph [13], the authors recommended against the routine use of stents to avoid complications of stenting such as alar injury or infection. The review demonstrated that endoscopic transnasal repair of choanal atresia is a safe and effective surgery and that outcomes are good regardless of whether postoperative stents are used. Furthermore, the authors concluded that repair without stenting reduces the intensity of postoperative management and avoids the potential for stent-related complications.
The balloon dilation technique has been recently proposed as an alternative option to the use of stents. Balloon dilations with floatable catheters have been applied in many fields of our discipline, offering a good aid both in endoscopic functional surgery of the paranasal sinus and in the treatment of non-uniform sub-glottal and tracheal stenosis. The advantage of these devices is to apply radial strength, thus avoiding non-uniform solicitations on the stenotic surface, as well as the possibility to approach even very small diameters thanks to the presence of a guided system with minimum obstruction. Supporting the use of balloon dilation, Bedwell et al. [14] described a series of 5 patients who underwent balloon dilation repair of choanal atresia or stenosis in conjunction with a transnasal endoscopic approach. All patients demonstrated choanal patency on last follow-up.
In this manuscript, we present our personal experience on endoscopic transnasal treatment of choanal atresia supported by balloon postoperative dilations. This is one of the largest series in literature conducted at a single centre. In a recent systematic review of the literature, Murray et al. [15] demonstrated that there were significantly higher rates of treatment failure in patients who underwent delayed surgery for bilateral choanal atresia. Accordingly, in line with this supposition, in our series patients with bilateral choanal atresia were treated at an average age of 10.4 days, whereas those with a unilateral defect were treated at a mean age of 36.6 months. We further differentiate our results based on unilateral or bilateral involvement of stenosis. Treatment of monolateral choanal atresia usually may reach the best surgical outcome compared with bilateral involvement. In our protocol, an endoscopic approach plus repeated balloon dilation was successful in 82% of cases with bilateral atresia and in 93% of monolateral defects, with a statistically significant difference. Furthermore, the average number of treatments per patient was higher in bilateral choanal atresia than those with monolateral disease.
In conclusion, it is our opinion that this new approach to atresia represents a very good option in the surgical treatment of this pathology. Parents should be counselled that long-term success of choanal atresia repair may require revision surgeries to remove granulation tissue, inspect the

choana and additional dilation. We sustain an approach that does not foresee the use of endonasal devices aimed at assuring the patency of the choanal area, since the inflammatory condition produced on the mucosa enhances cicatricial stenosis. We believe, therefore, that the use of stents is not motivated if not in exceptional cases.

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OSAHS

Description of the relationship between NOHL classification in drug-induced sleep endoscopy and initial AHI in patients with moderate to severe OSAS, and evaluation of the results obtained with oral appliance therapy

Descrizione della relazione tra classificazione NOHL definita durante la drug-induced sleep endoscopy e AHI iniziale in pazienti con OSAS da moderato a grave, e valutazione dei risultati ottenuti con dispositivi orali

Claudio Vicini[1], Valentina Colabianchi[2], Gianluca Giorgio Marrano[1], Francesca Barbanti[1], Giorgio Alfredo Spedicato[3], Luca Lombardo[2], Giuseppe Siciliani[2]

[1] Department of Otolaryngology, Ospedale Morgani-Pierantoni, Forlì, Italy; [2] Department of Orthodontics, University of Ferrara, Italy; [3] Unipol Group, Bologna, Italy

SUMMARY

Nowadays, drug-induced sleep endoscopy is widely recognised as a valid tool for diagnosis and treatment planning of obstructive sleep apnoea syndrome (OSAS), as it allows a direct visualisation of sites and patterns of collapse of the upper airways (UA). Various classifications have been proposed in the literature to describe the events observed during DISE, including the NOHL (Nasopharynx cavity and walls, Oropharynx, Hypopharynx, Larynx) classification. This study was aimed at assessing which anatomical structures, according to the NOHL Classification, were most frequently involved in UA collapse in patients with moderate to severe OSAS, and evaluating treatment results with oral appliances (OA), in terms of AHI reduction. The study group consisted of 35 patients (29 M, 6 F, mean age 50.6, average BMI 26) with polysomnographic diagnosis of moderate to severe OSAS, subjected to DISE and classified according to the NOHL classification to identify the anatomical sites and patterns of UA collapse most frequently reported. Patients were subsequently addressed to mandibular advancing device (MAD) therapy and treatment results in terms of AHI reduction were evaluated. In the sample examined, the anatomical structures most frequently involved in the collapse of the UA were the nasopharynx cavity and walls and tongue base, with a correlation index of 0.35 ($p < 0.04$), while no significance was found for the retro-palatal area or larynx. Descriptive analysis revealed multilevel collapse in all patients, involving multiple anatomical structures in obstructive mechanics. In all patients, AHI reduction was observed after treatment with MAD ($p < 0.00$).

KEY WORDS: OSAS, DISE, NOHL classification, MAD therapy, AHI

RIASSUNTO

La drug-induced sleep endoscopy (DISE) è ampiamente riconosciuta come un valido strumento per la diagnosi e la pianificazione del trattamento della sindrome delle apnee ostruttive (OSAS), in quanto consente una visualizzazione diretta dei siti e pattern di collasso delle vie aeree superiori (VAS). In letteratura sono state proposte molteplici classificazioni per descrivere gli eventi osservati duranti la DISE, fra cui la NOHL (Nasopharynx cavity and walls, Oropharynx, Hypopharynx, Larynx) classification (Vicini 2012). Lo studio si prefigge gli obiettivi di identificare quali strutture anatomiche, definite secondo la classificazione NOHL, sono più rappresentate nel collasso delle VAS in pazienti con OSAS da moderato (15 ≤ AHI ≤ 30) a grave (AHI > 30), e valutare il risultato del trattamento con dispositivi orali (OA), in termini di riduzione dell'AHI. Il gruppo studio è composto da 35 pazienti (29 M, 6 F, età media 50,6, BMI medio 26) con diagnosi polisonnografica di OSAS

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Correspondence
Valentina Colabianchi
Department of Orthodontics, University of Ferrara, via Montebello 31, 44100 Ferrara, Italy
E-mail: valentin.colabianchi@gmail.com

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da moderato a severo, sottoposti a DISE e classificati secondo la classificazione NOHL per individuare le sedi anatomiche e i pattern di collasso più frequentemente riportati. I pazienti sono stati successivamente indirizzati a terapia con Mandibular Advancing Devices (MAD), ed è stato valutato il risultato del trattamento in termini di riduzione dell'AHI. Nel campione esaminato, le strutture anatomiche più frequentemente coinvolte nel collasso delle VAS risultano essere il nasofaringe (N) e la base lingua (H), con indice di correlazione 0,35 ($p < 0,04$), mentre non è stata evidenziata significatività per l'area retropalatale (O) e la laringe (L). L'analisi descrittiva ha evidenziato inoltre un collasso multisede in tutti i pazienti, con coinvolgimento di più strutture nella meccanica ostruttiva. In tutti i pazienti è stata osservata una riduzione dell'AHI dopo terapia con MAD ($p < 0,00$), sebbene in alcuni casi non completamente risolutiva della patologia.

PAROLE CHIAVE: *OSAS, DISE, classificazione NOHL, MAD, AHI*

Introduction

Nowadays, oral appliance therapy (OA) is considered to be effective for patients with primary snoring and mild to moderate OSAS, and could be an alternative for severe OSAS patients who refuse positive air pressure (PAP) therapies [1-3]. In the literature, however, there is still controversy about the selection criteria used to discriminate good responders to OA therapy from non-responders. Historically, patient selection has been based on AHI alone, although recent studies have focused on the use of drug-induced sleep endoscopy (DISE) in diagnosis [4].

The technique of DISE, developed by Croft and Pringle in 1991 [5], is aimed at exploring the upper airways during pharmacologically-induced sleep using a flexible fibro-optic endoscope. DISE allows direct visualisation of obstruction sites and patterns of collapse in patients reporting snoring or OSAS, and can be useful in discriminating subjects who would benefit from surgical management from those who would not. During DISE it is also possible to mimic the effects of OA therapy by advancing the mandible with a gentle manoeuvre (pull up), in order to identify any improvements in UA patency or snoring. Patients showing a sufficient increase in UA dimension, as well as a reduction in snoring may be valid candidates for mandibular advancing devices (MAD) as a primary therapy or combined with surgery.

In the literature, many authors have developed different grading systems to describe the anatomical structures involved in UA collapse in OSAS patients [6,7], even though in this study we focused on the NOHL classification published by Vicini in 2012 [8]. According to the NOHL classification, grading and pattern of obstruction can be evaluated at four different anatomic levels: N (Nasopharynx cavity and walls), O (Oropharynx – retro-palatal space), H (Hypopharynx - tongue base) and L (Larynx - epiglottis). Grading of obstruction for nasopharynx cavities and pharyngeal walls can be classified as follows:

- Grade 1: 0-25% collapse;
- Grade 2: 25-50% collapse;
- Grade 3: 50-75 % collapse;
- Grade 4: total collapse during Muller manoeuvre (100%).

The grading system described can be applied for both awake and sleep endoscopy; furthermore, it is possible to define the pattern of pharyngeal collapse (for O and H), as transversal (t), antero-posterior (ap) or concentric (c). The presence of any laryngeal (L) obstruction could be reported as *p* (positive) or *n* (negative), and if a consistent grade of palatine tonsillar hypertrophy is observed, it can be noted in the final report as TS (grade 3 or 4), for an instance N2O4cTS3H3apLn.

The aims of the present study are to define which anatomical structures of UA, defined according to the NOHL classification in DISE, are involved in the obstruction mechanics in moderate to severe OSA patients, and to evaluate treatment outcomes with OA therapy in terms of AHI reduction.

Materials and methods

A retrospective study was conducted on 35 patients (29 males, 6 females, mean age 56.09 ± 9.43 years, mean BMI 26.00 ± 3.52) who underwent polysomnography (PSG) and DISE to assess the presence of OSAS and who were subsequently addressed to MAD therapy.

The study group consisted of patients treated at the Otorhinolaryngology Unit of the 'G.B. Morgagni-Pierantoni Hospital' (Forlì, Italy) from 2007 to 2017. Subjects included in the study met the following criteria:

- age over 18 years;
- diagnosis of moderate ($15 \leq AHI \leq 30$) or severe OSAS ($AHI > 30$);
- poor adherence to C-PAP and eager to find a more comfortable alternative;
- patient suitable health conditions for the execution of DISE in order to clarify the diagnostic question;
- potentially eligible (after an accurate examination performed by a dentist experienced in Dental Sleep Medicine) to receive MAD treatment.

Patients came to the attention of the ENT specialist with a diagnosis of moderate or severe OSAS performed by standard full-night PSG (electron-encephalogram, oculography eye tracking, electromyogram, oronasal flow, pulse oximetry, respiratory effort, position, electrocardiogram, snoring).

The tracks obtained from the recordings were interpreted by a qualified sleep technician using the diagnostic criteria of the 2007 International Classification of Sleep Disorders and the definition of hypopnea was chosen according to the 2007 AASM scoring rules [9] (reduction of the flow ≥ 50% from the baseline, duration at least 10 sec, accompanied by ≥ 3% desaturation or an arousal).
The Epworth Sleepiness Scale Questionnaire (ESS, Johns 1993) was also administered to patients to investigate the degree of daytime sleepiness prior to therapy.
In order to clarify the diagnostic question and select the most suitable therapeutic option, patients underwent DISE with sedation induced by propofol and TCI technique. Heart rate, frequency and saturation were monitored for the duration of the examination. Once adequate sedation was achieved, a flexible fibro-endoscope was introduced through one nostril and it was thus possible to observe sites and patterns of airway obstruction during induced sleep, classifying them according to the NOHL classification. The NOHL classification was used to determine which UA anatomical structure was most frequently responsible for collapse in moderate or severe OSAS patients.
Finally, for all patients a manual mandibular advancement manoeuvre (pull up) was performed, in order to mimic the effect achieved with a MAD-type device. In our sample of 35 patients, 23 showed an increase in UA volume and reduction in snoring, while the remaining 12 reported only a reduction in snoring. Since the pull up manoeuvre resulted in an improvement, in terms of increased UA patency and/or snoring in all the examined cases, all patients were considered suitable candidates for MAD treatment. The OA consists of a customisable device, removable and titled, made with precision silicone impressions (PVS) and a construction bite detected with George Gauge at 70% of the maximum protrusive. The same type of device was not used on all patients: the choice was personalised based on the patient's characteristics.
Patients candidate for MAD therapy showed the following characteristics:

- sufficient number of dental elements to support the device;
- absence of high dental mobility;
- good periodontal health;
- absence of DTMs or functional limitations.

The devices were delivered by dentists experienced in Dental Sleep Medicine and titrated, appointment by appointment, to optimise the therapeutic result based on data from PSG or cardio-respiratory monitoring with MAD in situ during follow-up.
The final PSG was performed at the end of the titration (on average, 6 months from the start of the therapy) with MAD in situ at optimal mandibular advancement with which it was possible to obtain resolution or reduction of symptoms.
For simplification, the AHI emerged from the initial PSG (pre-treatment), was compared with the AHI resulting from the final PSG with MAD in situ, in order to observe any improvements obtained with therapy. Treatment success was expressed as a reduction in AHI below 5 (resolution of OSA) or below 10 (very mild disease), or by a percentage reduction in AHI from baseline, which is considered to be clinically significant (typically 50% AHI reduction).

Statistical analysis

Statistical analysis was conducted with the following objectives:
1. Define the association between the N, O, H, L scores and initial AHI shown by patients
In this regard, the non-parametric correlation (Spearman rank correlation) was used, with the scores (N, O, H and L) expressed as non-continuous values.
In order to define which anatomical site was potentially responsible for collapse described in the NOHL classification and which was more predictive of moderate to severe OSAS, the parameters (N, O, H and L) were analysed individually.
2. Descriptive analysis
Since the sample size may be too small to be clinically appreciable with regards to the obstruction sites detected during DISE, many tables have been provided only for descriptive illustration without any supplementary inferential analysis.
In particular, the relatively small number of the sample (35 subjects) made it necessary to neglect the role of the obstruction patterns (ap, t, c), for which only descriptive analyses were reported.
3. Difference between AHI before and after treatment
The analysis of the difference between AHI pre- and post-treatment value (used to evaluate the response to therapy) was performed with paired sample t-test.
Statistical analysis was conducted with R Statistical software (R Core Team 2018), and the significance was set with a p value < 0.05.

Results

Predictiveness of the scores N, O, H, L with respect to initial AHI

Bivariate analysis showed a Spearman correlation index between score N and the initial AHI of 0.35 (p-value 0.04). For the score O, the correlation index was instead 0.30, (p-

value 0.08), and the score H exhibited a Spearman correlation index of 0.35 (p-value 0.04). The results therefore showed a statistical significance for score N and H, both with a correlation index of 0.35 (p = 0.04), while the score O was weakly significant (p = 0.08). This implies that the nasopharynx cavity and walls (N-Nose) and the tongue base (H - Hypopharynx) were the most represented anatomic areas of collapse in this sample of patients with moderate/severe OSAS.

Descriptive analysis

Tables I-III display the average AHI by score N, O and H respectively as well as the percentages of patients for each obstruction site. No analyses were performed for the score L, because no patient reported obstructions at the level of the corresponding anatomical structure (epiglottis).

Table I. Number of patients and initial average AHI for the score N (0-4).

	Score N				
	0	1	2	3	4
Mean initial AHI	38.5	31.3	44.3	43.9	45.7
Number of patients	4	14	7	8	2
%	11.4%	40.0%	20.0%	22.9%	5.7%

Difference between AHI before and after treatment with MAD

The results of the paired samples t-test showed a reduction of AHI after treatment with MAD compared to AHI pre-treatment (Fig. 1), with a significant difference (p-value = 0.00). In our sample, 40% of patients showed a final AHI < 5, while 31.4% reported a post-treatment AHI between 5 and 10. In the remaining 28.6% of patients, the AHI remained higher than 10, although there was a reduction of the initial value above 50%, indicating a good response to MAD therapy, as shown in Table IV.

Discussion

As widely described in the literature, DISE is an excellent method to define the anatomical sites and patterns of airway obstruction in patients with OSAS, in conditions that are similar to physiological sleep [4-7,10,11].

Among the numerous classifications that can be used in DISE, the NOHL classification proposed by Vicini [8] was chosen for the present study of the anatomical sites involved in the collapse of the UA. In a recent systematic review (Amos 2018) [12], it was found that there is no consensus in the literature regarding the use of a specific classification for the description of obstructive events observed in DISE,

Table II. Number of patients and initial average AHI for score O (1-3).

	Score O					
	1	2			3	
Mean initial AHI	30.0	37.7			46.8	
Number of patients	5	23			7	
%	14.3%	65.7%			20.0%	
	1c	2ap	2c	2t	3ap	3c
Mean initial AHI	30.0	52.5	35.2	29.4	34.7	48.9
Number of patients	5	5	13	5	1	6
%	14.3%	14.3%	37.1%	14.3%	2.9%	17.1%

Table III. Number of patients and initial average AHI for score H (1-4).

	Score H									
	1	2			3				4	
Mean initial AHI	27.5	33.5			39.5				59.5	
Number of patients	2	9			22				2	
%	5.7%	25.7%			62.9%				5.7%	
	1t	2ap	2c	2t	3	3ap	3c	3t	4ap	4t
Mean initial AHI	27.5	35.5	31.8	24.7	77.0	32.4	42.5	38.1	87.0	32.0
Number of patients	2	6	2	1	1	6	6	9	1	1
%	5.7%	17.3%	5.7%	2.9%	2.9%	17.1%	17.1%	25.7%	2.9%	2.9%

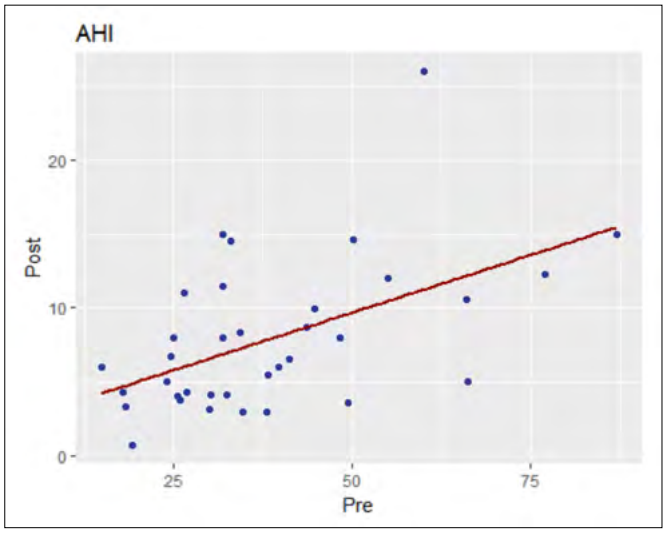

Figure 1. AHI values before and after MAD therapy.

while the grading systems used most are the VOTE classification (38.6%), followed by the classifications of Pringle and Croft (15.9%), NOHL (9.1%) and Bachar (4.5%).

Identification of the anatomical sites responsible for the obstruction and their description turns out to be of fundamental importance to clarify the diagnostic question and select the most appropriate therapeutic option, especially when a surgical solution is required.

The information obtained by DISE is also valuable for selection of patients for MAD treatment [14-16]: in particular, it was observed by Cistulli et al. that MADs showed greater efficacy when tongue base obstruction occurred, while retro-palatal collapse was the main cause of lack of or incomplete response to therapy [16-18].

However, in a study by Friedman et al. it was shown that, contrary to the hypothesis that tongue base obstruction would predict a good response to MAD therapy, OA achieved reasonable response and cure rates in patients with primary retro-palatal, retro-lingual or epiglottis obstruction [19].

This study proposes assessment of sites most responsible for airway collapse in patients with moderate to severe OSAS, to define which structure (between N, O, H and L) described in the classification appears to be more represented and therefore associated with high values of AHI pre-treatment. The results of statistical analysis showed significance for scores N and H (both with correlation index 0.35 and p value 0.04), while score O exhibited a correlation index of 0.30, with p value 0.08 and therefore weakly significant. The L score was not analysed, since all the patients included in the sample scored 0.

N and H scores, emerged as significant from the analysis, refer to the anatomical regions of the nasopharynx cavity and walls and the tongue base, which, according to the results of this study, would be more represented in the dynamics of obstruction in patients with moderate/severe OSAS, while the role of site O (retro-palatal area) is weakly significant.

It has, however, been highlighted in several studies that most obstructions occur at the retro-palatal level. In particular, in the study by Vroegop in 2014 [15], 81% of obstructions occurred at the retro-palatal level, followed by multilevel collapse (68.2%) with involvement of the palate and tongue base (25%). The high prevalence of retro-palatal collapse was motivated, according to the authors, by the high frequency of snoring (due to vibration of soft palate tissues), as a nocturnal symptom commonly reported by OSAS patients.

The results achieved in the present study differ from what has just been described probably due to the retrospective design and the small sample size (35 patients). Furthermore, different classification systems have been used in DISE by previous authors (VOTE classification), which can lead to a different description of the anatomical sites.

However, the descriptive analysis of the sample showed that airway collapse was always multilevel in patients with high AHI values, as observed in other studies [10,13]. The involvement of several sites in the dynamics of obstruction poses the problem of the therapeutic choice, often requiring combined therapies (MAD + CPAP / MAD + surgery).

Regarding the parameter L, no patient reported a collapse at the level of the epiglottis in the sample investigated. Before the advent of DISE, it was estimated that 12% of adult patients with OSAS showed epiglottis collapse [20]. However, Torre et al. asserted in a systematic review that this aspect has long been underestimated and that, thanks to DISE, it will be possible to better clarify the role of the epiglottis in obstructive events of OSAS patients [21].

Unfortunately, it was not possible to define which obstruction pattern was more frequent for O and H, because the small number of subjects included in the sample made it possible to calculate only descriptive statistics.

In the literature, it has been found that high values of AHI and BMI are more frequently associated with complete retro-palatal collapse with concentric pattern, as well as a greater probability of complete collapse at the hypopharynx (including epiglottis), with lateral pattern [13], motivated both by the accumulation of fat at the side of the pharynx.

In subjects treated with MAD, an important reduction of the AHI with respect to the initial value was observed in all patients, underlining the confirmed efficacy of MADs in OSAS treatment. In particular, in the sample of patients examined, obstruction was more frequently observed at

Table IV. Percentages of AHI reduction after MAD therapy compared to initial AHI.

	Initial AHI	Final AHI with MAD	AHI reduction (%)	Percentage of patients
AHI post ≤ 5	19.2	0.7	96.4%	40.0%
	38.0	3.0	92.1%	
	34.7	3.0	91.4%	
	30.0	3.1	89.7%	
	18.3	3.3	82.0%	
	49.5	3.6	92.7%	
	26.0	3.8	85.4%	
	25.6	4.0	84.4%	
	32.4	4.1	87.3%	
	30.2	4.1	86.4%	
	26.9	4.3	84.0%	
	18.0	4.3	76.1%	
	24.2	5.0	79.3%	
	66.1	5.0	92.4%	
5 < AHI post < 10	38.2	5.5	85.6%	31.4%
	39.8	6.0	84.9%	
	15.0	6.0	60.0%	
	41.2	6.5	84.2%	
	24.7	6.7	72.9%	
	25.0	8.0	68.0%	
	32.0	8.0	75.0%	
	48.4	8.0	83.5%	
	34.3	8.3	75.8%	
	43.7	8.7	80.1%	
	44.8	9.9	77.9%	
AHI post ≥ 10	66.0	10.6	83.9%	28.6%
	26.5	11.0	58.5%	
	32.0	11.5	64.1%	
	55.0	12.0	78.2%	
	77.0	12.3	84.0%	
	33.0	14.5	56.1%	
	50.2	14.6	70.9%	
	31.9	15.0	53.0%	
	87.0	15.0	82.8%	
	60.0	26.0	56.7%	

tongue base level (H), which could motivate the success of MAD therapy. Furthermore, it is interesting to observe how, since the study group consists of moderate/severe OSAS patients, MAD therapy often fails to completely resolve the disease (AHI is often maintained > 5). Patients who did not completely respond to MAD therapy, apart from having a very high initial AHI value, reported high scores for the N and/or the O parameters, highlighting once again a multilevel obstruction dynamic that often requires a multidisciplinary approach and evaluation for possible surgery addressed to the sites involved in UA collapse (nasal cavity and walls or palate). It should also be specified that for moderate or severe OSAS patients, the gold standard therapeutic option always remains CPAP. However, the poor adherence to this solution may lead adoption of MAD therapy alone or combined with surgery. Finally, it is noted that patients with moderate or severe OSAS often show comorbidities associated with OSAS, which may affect the final result of the therapy.

The present study has numerous limitations, starting from

its retrospective design and relatively small number of patients involved. It would be interesting, however, to extend the sample and repeat the DISE with MAD in situ to observe the behaviour of the airway in response to mandibular advancement, in order to provide more precise results about the predictability of treatment with OA.

Conclusions

Within the limits of this study, it is possible to draw the following conclusions:

- DISE appears to be the gold standard exam for diagnosis of obstruction sites in patients with OSAS;
- among the structures described in the NOHL classification, the nasopharynx cavity and walls (N) and tongue base (H) were the obstruction sites most frequently reported in this sample of patients with moderate to severe OSAS;
- although MAD therapy is not the gold standard, it is effective in reducing initial AHI in patients with moderate to severe OSAS and contributes to a reduction in symptoms;
- the multilevel nature of the collapse observed in patients with moderate or severe OSAS often requires combined treatments (e.g. MAD + CPAP, MAD + surgery), emphasising the need for a multidisciplinary approach.

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AUDIOLOGY

Verbal task and motor responses (VTMR) in an adult hearing screening programme

L'audiometria con risposte motorie nello screening uditivo di soggetti adulti

Federica Di Berardino[1], Ivan Cortinovis[2], Anna Gasbarre[3], Eliana Filipponi[3], Silvano Milani[2], Diego Zanetti[1]

[1] Audiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy - Department of Clinical Sciences and Community Health, University of Milan, Italy; [2] Medical Statistics, Department of Clinical Sciences and Community Health, University of Milan, Italy; [3] UOC Direzione Professioni Sanitarie, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Italy

SUMMARY

The aim of this study was to test the efficacy of Verbal Tasks and Motor Responses (VTMR) speech audiometry in providing a rapid and true-to-life assessment of hearing-related problems as a single test in adult hearing screening programmes. The VTMR consists in manual execution of 5 verbal commands received by patients at different signal intensity levels and fixed masking noise; it provides a score of speech comprehension in noise. This was a prospective observational study in 916 individuals out of 1,300 volunteers (605 males, 695 females, aged 56 ± 17 years) who completed adult hearing screening. VTMR speech audiometry was performed at signal to noise (S/N) ratios of 0 dB and –10 dB. The difference between normal and hearing impaired subjects in terms of all the considered variables was statistically significant for pure-tone audiometry and VTMR testing. VTMR testing at a S/N ratio of –10 dB with a cut-off of four correctly executed tasks and was a rapid, feasible and efficient means of differentiating between normal and hearing impaired subjects. When used to screen hearing impaired subjects with participation restrictions, the sensitivity and specificity of the VTMR test rose to 90% and 62%, respectively. The VTMR test in noise could be used as a stand-alone tool when screening for impairment and self-perceived participation restriction together.

KEY WORDS: speech audiometry, hearing screening, VTMR

RIASSUNTO

Lo scopo dello studio è di testare l'efficacia di un nuovo test di audiometria vocale a risposte motorie (VTMR) nel rumore da utilizzare per determinare l'handicap uditivo in programmi di screening per soggetti adulti. La VTMR consiste nell'esecuzione manuale di 5 comandi verbali ricevuti dal paziente a diverse intensità di segnale e fornisce un punteggio relativo alla comprensione nel rumore. In questo studio osservazionale prospettico 916 su 1.300 volontari (605 maschi, 695 femmine, età media 56 ± 17 anni), sono stati sottoposti a uno screening uditivo con audiometria tonale liminare e VTMR ad un rapporto segnale/rumore (S/N) di 0 e –10 dB HL. Risultati: la differenza tra soggetti normo- e ipoacusici, in funzione di tutte le variabili considerate, è risultata statisticamente significativa per la combinazione di audiometria tonale e VTMR. Il test VTMR con S/N di –10 dB è risultato essere uno strumento rapido, pratico ed efficiente nel differenziare tra soggetti normo- e ipoacusici con un cut-off di 4 su 5 comandi verbali eseguiti correttamente. Nel sottogruppo dei pazienti con riferita limitazione della partecipazione sociale, la sensibilità e la specificità del test VTMR sono rispettivamente del 90% e del 62%. La VTMR può essere utilizzata singolarmente nello screening di soggetti adulti per testare sia l'impairment uditivo che la limitazione sociale che ne consegue.

PAROLE CHIAVE: *audiometria vocale con risposte motorie, VTMR, screening uditivo*

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Correspondence
Federica Di Berardino
Audiology Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, via Pace 9, 20122 Milan, Italy
Tel. +39 02 5503.3922. Fax +39 02 50320754
E-mail: federica.diberardino@unimi.it

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Introduction

Adult hearing screening programmes are currently increasing worldwide as a result of recent concern regarding the importance of monitoring hearing, increasing awareness of hearing loss and promoting behavioural change by enhancing patient involvement [1,2]. The techniques commonly used in adult hearing screening include anamnesis, visual inspection, pure-tone audiometry and self-assessment of hearing disability [3].

Pure-tone audiometry can be used to screen individuals for hearing impairment, but not for hearing disability, whereas self-assement is used to measure participation restrictions, but may not accurately assess hearing disorders or impairment [4]. Furthermore, there is increasing evidence that the degree of measured peripheral hearing impairment (loss of function) may not completely reflect an individual's real communication performance (speech comprehension) and may provide only a partial picture of the real-life experience of the activity limitations and participation restrictions (handicap) [5].

For this reason, the use of speech audiometry has been introduced in adult hearing screening in order to focus on the actual difficulties experienced by the individual with a hearing problem. These include speech communication difficulties, particularly in challenging listening situations where complications such as background noise, crowds or competing talkers are present [6]. However, pure-tone audiometry and speech audiometry together are not sufficient to measure level of participation and/or participation restriction and describe only partially the social consequences of hearing loss [7].

The Verbal Tasks and Motor Responses (VTMR) speech audiometry test is an original test that was introduced in 2012 as a means of evaluating speech comprehension by soliciting the prompt execution of simple tasks (motor responses) using phonetically balanced verbal commands [8]. As already reported, it allows rapid evaluation of speech comprehension by assessing the ability to simultaneously process auditory and visual information and to perform simple motor tasks with three-dimensional and standardised objects resembling familiar tools. Therefore, the VTMR test differs from other speech tests, and in particular from the vowel-consonant-vowel tests previously proposed for checking speech understanding in adult hearing screening [6]. We chose to use this test because it closely reflects real-life difficulties connected with understanding commands in noise and executing tasks and therefore might provide a measure of participation restriction in hearing impaired subjects.

The aim of this study was to test the efficacy of VTMR speech audiometry in providing rapid and true-to-life assessment of hearing-related problems when used alone to screen simultaneously for both hearing loss and self perceived participation restriction in adult hearing screening programs.

Materials and methods

Subjects

One thousand and three hundred volunteers (605 males, 695 females, 56 ± 17 years) were enrolled by a team of physicians and audiologists stationed in a mobile unit that travelled to 10 different locations in Milan, Italy. The event was promoted by the Public Health Department of the Municipality of Milan. The free programme of the deafness prevention campaign was advertised with flyers, posters and on the Internet. The subjects could make an appointment directly on site or by calling a free phone number. The locations were chosen in order to obtain a realistic sample of the entire urban community (city centre and suburbs, residential and industrial areas, peaceful and noisy neighbourhoods).

In accordance with American Speech-Language-Hearing Association (ASHA) guidelines [3], exclusion criteria consisted of visual identification of physical abnormality of the outer ear, otoscopic identification of ear canal abnormality, cerumen impaction, previous ear surgery or otological disease (such as middle ear pathology e.g. acute otitis media, inactive or active chronic otitis media, congenital ear abnormalities or more than two acute episodes of vertigo or persisting dizziness). Patients with a positive history of psychiatric, neurologic disorders or mild cognitive impairment were excluded.

None of the interviewed subjects had previously taken part in hearing conservation programmes or training courses aimed at managing ear diseases and reducing the risk of hearing loss.

Tests course

After review of clinical history by a physicians, all volunteers were asked to complete an informative questionnaire on audiologic issues that measured their knowledge of managing and preventing ear disease and hearing loss [11]. Clinical otoscopy, consisting of visual inspection of the outer ear using clinical otoscopes, was used for otological evaluation of each subject to identify any individuals requiring medical referral and to determine candidacy for adult hearing screening. The Pass/Refer criteria used were:

- *pass:* normal results in both ears;
- *refer:* visual identification of any physical abnormality of the outer ear, or otoscopic identification of ear canal abnormality, or cerumen impaction, according to the ASHA guidelines [3].

All subjects underwent audiological evaluation with pure-tone audiometry for the frequencies of 500, 1,000, 2,000 and 4,000 Hz using an audiometer (Amplaid A177 plus, Amplifon, Milan, Italy) with TDH-49 headphones. Ambient noise levels inside the sound-treated booth were checked four times a day to verify that they did not exceed American National Standards Institute (ANSI) levels [10]. In order to comply with the ASHA guidelines, 500 Hz values have not been included in the analysis for its higher variability due to their influence on environmental noise [3]. Subjects'hearing was considered normal if responses to pure-tone air-conduction stimuli lower than 25 dB HL at 1,000, 2,000 and 4,000 Hz were obtained in both ears or in the poorer ear, according to the ASHA guidelines [3].

VTMR test

Once the first audiological phase of evaluation had been completed, an external CD player was connected to the audiometer and the VTMR test was played through two loudspeakers placed in front and at the back of the listener (0° and 180° azimuth), at a distance of 1 m from the subject, according to ANSI S3.6-2010 [11]. The VTMR test CD starts with a stereo calibration tone of 1 kHz at 60 dB SPL lasting 30 seconds. The root-mean-squared (RMS) output level of the recorded voice is 60 dB SPL with a peak variation not exceeding ± 3 dB SPL.

The test consists of a set of familiar objects (a base, a hammer and a wooden structure with four sticks and five rings of different colours) and 20 lists of five simple tasks, all with the same level of motor execution difficulty, colour types and spectral frequency pattern (according to the Italian language), that are recorded on the CD with a pause of 8 seconds between each task (Fig. 1). The lists can be used randomly, since the choice of colours and objects was originally determined by a balance in the spectral frequency, and Fast Fourier analysis revealed no significant differences in intensity for each frequency in the 20 lists [8]. Each correctly performed task receives a score of 20, and the results obtained with each list are tallied as a percent-correct value of 100 for each list of five verbal tasks. Hereunder, we report two of the 5-task lists:

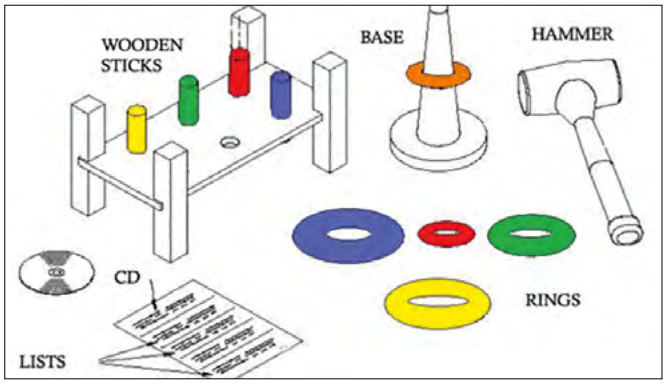

Figure 1. Equipment for VTMR test speech audiometry.

1. with the hammer, hit on the green stick once;
2. take the orange ring off the base;
3. pick up the yellow ring;
4. with the hammer, hit on the blue stick once and on the yellow stick once;
5. put the green ring onto the base.

1. with the hammer, hit on the yellow stick once and on the red stick once;
2. pick up the red ring;
3. take the green ring off the base;
4. put the red ring onto the base;
5. with the hammer, hit on the blue stick once.

After one training list, two lists of VTMR speech audiometry were randomly chosen and proposed to all subjects at two fixed S/N ratios: 0 dB and –10 dB. The choice of –10 dB of S/N ratio was meant to check the speech comprehension behaviour in a worse noisy environment, especially when pure tone hearing was normal.

Participation restriction questionnaires

According to the ASHA guidelines, self-assessment screening of perceived hearing handicap and communication-specific problems was carried out using the Hearing Handicap Inventory for the Elderly questionnaire, short form (HHIEsf) [12]. This inventory is commonly used to investigate the area of participation, in order to assess residual participation restrictions, i.e. the problems or barriers encountered during situations of daily life in which hearing plays a role [13]. It consists of 10 standardised questions including five social or situational items and five emotional response items. A response of "yes" is given 4 points, "sometimes" is given 2 points, and "no" is given 0 points; therefore, the HHIEsf scores range from 0 to 40. According to the HHIEsf raw score handicap range, the post-hoc probability of hearing impairment is reported to be 13% for "no handicap" (0-8), 50% in Mild-to-Moderate Handicap (10-24) and 84% for Severe Handicap (26-40) [14].

The study was approved by the Government Ethical Committee and the Health Department of Milan.

Statistical analysis

The validity of VTMR testing was assessed using the receiver operating characteristics (ROC) curve, the area un-

der the ROC curve (AUC) and Youden's index. Multiple logistic regression analysis was used to identify independent factors that were associated with hearing loss, combining pure-tone audiometry and VTMR testing. All statistical analyses were performed using SAS 9.2 (Cary, NC, USA); a two-sided $p < 0.05$ was considered significant.

Results

Three hundred eighty-four of the 1,300 volunteers interviewed were excluded from VTMR testing since they did not meet inclusion criteria. The following statistical analysis is based on the results obtained from the 916 subjects considered eligible to perform the whole audiological evaluation. Table I shows various characteristics of the subjects tested (age, sex and profession). None had single side deafness. Subjects were divided into two categories: normal and hearing-impaired on the basis of pure-tone audiometry. The results to the HHIEsf questionnaire are reported in Table II.

Figure 2 shows the ROC curves obtained from VTMR testing at a S/N ratio of 0 dB (dotted grey line) and –10 dB (continuous grey line). Since the AUC for a S/N ratio of –10 dB is greater, this S/N ratio is more efficient in differentiating between normal and hearing impaired subjects. As shown in the graph, four correctly executed motor responses represent the cut-off value. This threshold expressed the highest value by the Youden's index (J) (Tab. III).

Table III shows the results of hearing impairment evaluation based on sensitivity, specificity and resulting Youden's index, of each value of VTMR speech audiometry with a S/N ratio of –10 dB. When evaluating the self-perceived participation restrictions (HHIEsf > 24/40), the sensitivity and specificity of VTMR testing increase to 78% and 63%, respectively, at a S/N ratio of –10 dB with a cut-off of at least four correctly executed tasks. If hearing impairment and self-perceived severe participation restrictions are taken into account together, sensitivity and specificity further increased up to 90% and 62%, respectively.

Table IV shows the distribution of normal hearing and hearing-impaired subjects in relation with the number of correct answers to the VTMR test (S/N –10 dB). While all normal hearing subjects answered correctly to the VMTR test by repeating all five motor tasks, only 170 of 405 hearing im-

Table I. Subject characteristics.

Characteristics	Overall (n = 916)	Normal ≤ 25 dB HL (n = 511)	Hearing loss > 25 dB HL (n = 405)
Age [a]	55 (42; 66)	47 (34; 57)	64 (55; 71)
Sex [b]			
M	382 (42.1%)	166 (32.4%)	220 (54.3%)
F	530 (57.9%)	345 (67.6%)	185 (45.7%)
Profession [b]			
Housewife	87 (9.5%)	44 (8.6%)	43 (10.6%)
Retired	278 (30.4%)	80 (15.7%)	198 (48.9%)
Employee	198 (21.6%)	151 (29.6%)	46 (11.4%)
Student	65 (7.1%)	60 (11.7%)	5 (1.2%)
Workman	73 (8.0%)	48 (9.4%)	25 (6.2%)
Unemployed	13 (1.4%)	9 (1.9%)	4 (1.0%)
Teacher	41 (4.5%)	35 (6.9%)	6 (1.5%)
Manager/self employed	108 (11.8%)	54 (10.6%)	54 (13.3%)

[a]: data reported as median (1st quartile; 3rd quartile); [b]: data reported as frequencies (%).

Table II. Results obtained with the HHIEsf questionnaire.

	Overall (n = 916)	Normal ≤ 25 dB HL (n = 511)	Hearing loss > 25 dB HL (n = 405)
HHIEsf [a]	6 (2;12)	4 (0;8)	8 (4;16)
Low [b]	602 (100%)	400 (66.4%)	202 (33.6%)
Mild-to-moderate [b]	260 (100%)	91 (35.0%)	169 (65.0%)
Severe [b]	38 (100)	8 (21.0%)	30 (79.0%)

[a]: data reported as median (1st quartile; 3rd quartile); [b]: data reported as frequencies (%).

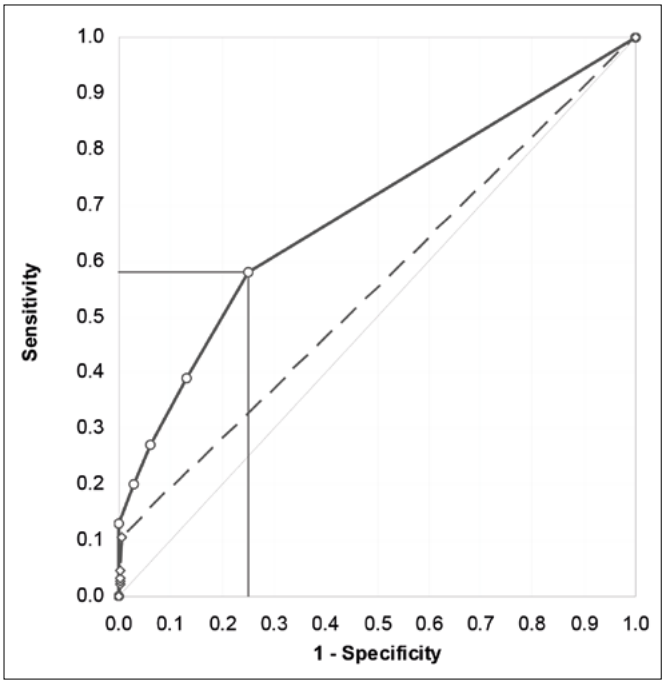

Figure 2. The ROC curves obtained from VTMR testing at a S/N ratio of 0 dB (dotted grey line) and –10 dB (continuous grey line). Since the AUC for an S/N ratio of –10 dB is greater, this ratio is more efficient in differentiating between normal and hearing impaired subjects. As shown in the graph, the cut-off value is four correctly executed tasks since Youden's index is highest for this value.

Table III. Sensitivity, specificity and Youden's index (J) for all possible threshold values of the VTMR test (S/N –10 dB) for hearing impairment and for hearing impairment and participation restriction (HHIEsf > 24/40).

	Hearing impairment			Participations restriction			Hearing impairment and participations restriction		
VTMR	Sensitivity	Specificity	J *	Sensitivity	Specificity	J *	Sensitivity	Specificity	J *
0	0.13	1.00	0.13	0.32	0.95	0.28	0.44	1.00	0.44
1	0.20	0.97	0.17	0.37	0.91	0.29	0.5	1.00	0.5
2	0.27	0.94	0.21	0.5	0.86	0.36	0.64	0.87	0.5
3	0.39	0.87	0.27	0.65	0.77	0.43	0.74	0.69	0.43
4	0.58	0.75	0.33	0.78	0.63	0.40	0.90	0.62	0.53
5	1.00	0.00	0.00	1.00	0.00	0.00	1.00	0.00	0.00

J: sensitivity + specificity –1.*

paired subjects performed it correctly. Furthermore, when considering together the results at pure-tone audiometry and HHIEsf, only 3 subjects gave 5/5 correct answers to the VTMR: two women (44 and 37 years old with a score of 26/40 and 32/40) and one man (71 years old with a score of 28/40) with asymmetrical sensorineural hearing loss. In the normal hearing group, there were only two normally hearing subjects who reported a score of HHIEsf > 24/40 (one 43-year-old man with a score of 30/40 and one 29-year-old woman with a score of 36/40): they returned a score of 5 correctly executed tasks at both S/N ratios at the VTMR testing. In the group of hearing impaired subjects with low or mild-to-moderate participation restrictions, sensitivity was 0.51 and 0.60 and specificity was 0.90 and 0.77, respectively. As reported in Table III, one or more mistakes (< 5/5) at VTMR testing (S/N –10 dB) allowed detection of subjects with hearing impairment and participation restriction (HHIEsf > 24/40) with a good sensitivity and specificity (0.90 and 0.68, respectively). The number of correctly executed motor responses at VTMR testing (S/N –10 dB) were significantly different in relation with sex, age and HHIEsf scores ($p < 0.0001$). Table V compares pure-tone audiometry and VTMR testing using multiple logistic regression analysis with a cut-off of 4 correctly executed motor responses. The difference between normal and hearing impaired subjects was statistically significant for all the considered variables. The results of the VTMR test were homogeneous with pure-tone audiometry, but were slightly more influenced by subjective self-perception (HHIEsf).

Table IV. Distribution of normal hearing and hearing impaired subjects by the VTMR test (S/N –10 dB).

VTMR	Normal ≤ 25 dB HL (n = 511)	Hearing loss > 25 dB HL (n = 405)
0	1 (0.2%)	54 (13.3%)
1	12 (2.3%)	26 (6.4%)
2	20 (3.9%)	32 (7.9%)
3	32 (6.3%)	49 (12.1%)
4	61 (11.9%)	74 (18.3%)
5	385 (75.3%)	170 (42.0%)

Data reported as frequencies (%).

Table V. Multiple logistic regression analysis of factors associated with hearing problems. Comparison between pure-tone audiometry results (pass/fail) and the VTMR test at S/N –10 dB (cut-off of 4 correctly executed motor responses).

Characteristics		Pure-tone audiometry OR (95% CI)	VTMR OR (95% CI)
Age	0-44	1 (ref)	1 (ref)
	45-64	4.9 (3.2-7.6)	2.5 (1.7-3.7)
	65+	26.3 (15.9-43.6)	7.1 (4.9-10.8)
Sex	F	1 (ref)	1 (ref)
	M	2.8 (2.0-3.9)	1.5 (1.1-2.0)
Disability (HHIEsf)	Low	1 (ref)	1 (ref)
	Mild-to-moderate	3.7 (2.6-5.3)	1.5 (1.1-2.1)
	Severe	6.6 (2.5-17.1)	6.0 (1.5-14.0)

OR: odds ratio.

The absence of partecipation restrictions in normally hearing subjects was clearly recognised by VTMR, compared with the severe partecipations restrictions in hearing impaired subjects (> 24/40) (Fig. 3). The AUC for a S/N ratio of –10 dB was 0.835.

Discussion

As stated in ASHA guidelines, the identification of hearing losses exceeding a predetermined screening level (e.g. 25 dB HL) by pure tone audiometry across the frequency range of 1,000 to 4,000 Hz has shown an excellent sensitivity (95-99%) and specificity (78%-99%) [15]. Speech audiometry is a fundamental tool in audiological evaluation, aimed at examining the speech-processing abilities throughout the

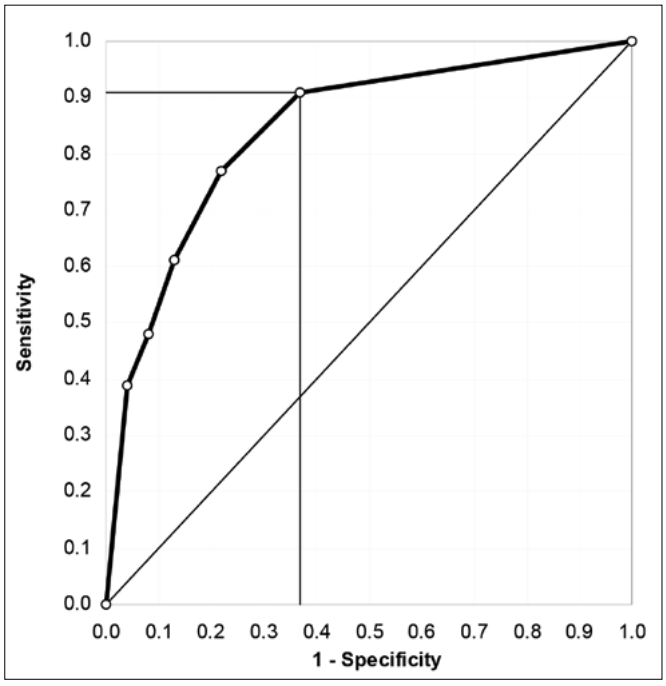

Figure 3. ROC curve obtained from VTMR testing at an S/N ratio of –10 dB (continuous line) of hearing impaired subjects with severe participation restrictions (HHIEsf > 24/40). The AUC for an S/N ratio of –10 dB is 0.835. As shown in the graph, the cut-off value is four correctly executed tasks since Youden's index is highest for this value.

auditory system; it can also be used to crosscheck the validity of pure-tone thresholds [3]. Speech tests have been proposed for adult hearing screening, but have shown widely different results depending on the protocol used; the reported sensitivity and specificity vary between 75% and 84% for the vowel-consonant-vowel [6], and 91-93% for the digit triplet speech test in noise [15,16]. In our study, the sensitivity and specificity of speech comprehension in noise with VTMR test was even lower (58% and 75%) than those of other speech tests when used to screen only peripheral function. In this respect, our findings support the well known advantage of pure tone audiometry for assessment of peripheral hearing impairment [14]. Nevertheless, many studies have shown that the ability to comprehend speech in challenging (e.g. noisy or reverberant) listening situations is influenced either by bottom-up peripheral auditory processes and by top-down cognitive abilities [5,17-22]. However, as reported by Jerger et al., only the synthetic sentence identification (SSI) test and dichotic sentence identification (DSI) are related to cognitive abilities [23].

Difficulty in speech understanding in noisy conditions is one of the most notorious complaints of people with hearing; it is often related to self-perceived hearing disability. In the audiological diagnostic work-up, speech-in-noise tests based on sentences are widely accepted as appropriate tools for assessment of a subject's ability to understand speech in noisy and daily-life situations [24]. However, when proposed as a unique measure of hearing impairment and disability in adult hearing screening programs, the results of speech tests, such as the Synthetic Sentence Identification test, Speech Perception in Noise at an S/N ratio of +8 dB, Dichotic Sentence Identification test and degraded word recognition tasks, were sometimes unsatisfactory or insufficiently reliable, and many authors have concluded that they should have been improved [25-28]. Matthews et al (1990) reported a lack of correlation between Speech Perception in Noise test and total scores on the HHIE [29].

Conversely, when we took into account a measure of severe self-perceived difficulty in comprehension of speech in noisy conditions, the VTMR test in noise at the pre-set cut-off value of 4 of 5 correctly executed tasks correlated well, with the hearing loss identified by pure tone audiometry and the self-report measure of participation restriction: sensitivity and specificity were 0.90 and 0.62, respectively. This finding might be justified by the fact that the VTMR test does not only quantify speech understanding in noise, but combines visual identification, working memory, speech comprehension and motor execution [8]. The VTMR test, in fact, is more redundant than other speech tests, and therefore it might more closely resemble the difficulty and disability experienced by a hearing-impaired individual, especially in the absence of appropriate auxiliary aids and proper support for effective communication.

When attempting to demonstrate a difference in speech comprehension between normal and hearing impaired subjects, a S/N ratio of –10 dB was more effective than a S/N of 0 dB. This finding suggests that a S/N –10 dB better exploits the redundancy of information implied by the selected tasks. Further advantages of the VTMR testing at an S/N ratio of –10 dB with a cut-off of four of five correctly executed tasks are rapidity, low-cost, high specificity and feasibility, which are all useful characteristics in a screening setting.

It has been demonstrated to be a user-friendly test with a high level of redundancy, since it is based on a set of familiar objects whose function is intrinsic, e.g.: the hammer is obviously meant to hit the sticks. The results of the VTMR test are clearly understandable by subjects and may motivate them to seek audiological help. However, a limit of this study is the lack of comparison with other sentences in noise tests; the results cannot be easily transferred to a clinical diagnostic setting: in order to do that, repeatability should be established, by determining consistency over repeated measures and test-rest variability, which is not feasible in a screening setting. In our previous work,

the comparison between VTMR and traditional speech test with bysillabic words was performed in quiet, showing a good correlation between the two tests [8].

Conclusions

Speech in noise tests using the VTMR test instructions were highly sensitive in distinguishing subjects with disabling hearing loss; the risk of false negative results was significantly reduced.

Our findings suggest that this method might be used as a stand-alone tool to simultaneously screen for impairment and participation restrictions, which are complementary and equally important aspects of any adult hearing screening programme.

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AUDIOLOGY

Restoration of auditory network after cochlear implant in prelingual deafness: a P300 study using LORETA

Ripristino del network uditivo dopo impianto cocleare in soggetti affetti da sordità prelinguale: studio del potenziale P300 attraverso l'utilizzo di LORETA

Sara Ghiselli[1*], Flavia Gheller[2*], Patrizia Trevisi[2], Emanuele Favaro[3], Alessandro Martini[2], Mario Ermani[3]

[1] Institute for Maternal and Child Health- IRCSS Burlo Garofolo, Trieste, Italy; [2] ENT Clinic, Department of Neuroscience, Padova University Hospital, Padova, Italy; [3] Neurological Clinic, Department of Neuroscience, Padova University Hospital, Padova, Italy

** S. Ghiselli and F. Gheller contributed equally to this work.*

SUMMARY

The concept of auditory restoration after cochlear implant (CI) in prelingual deafness is well described by a synaptic network model, whose development depends on sensory experience. The aim of this work was to study the associative networks activated by the CI in a population of prelingually deaf patients. In particular, the impact of age at time of first CI fitting and duration of CI use was evaluated. Twenty patients were tested and divided into three groups: early implanted and lengthy CI use (group A); late implanted and lengthy CI use (group B); late implanted and short CI use (group C). Each patient group was compared with a normal hearing age matched control group. All subjects underwent to auditory event-related potentials (ERPs) registration. ERP latencies and their cortical sources were investigated. Cortical source analysis was performed using LORETA (Low Resolution Electromagnetic Tomography) software. P300 latencies were significantly longer in patients than in controls. The amount of cortical activation was found to be significantly directly correlated with duration of implant use and significantly correlated inversely with age at implant. When comparing patients and controls, comparable cortical activation was only found in A patient group, and to a lesser extent in group B, while significantly lower activation was found in patient group C in the frontal and cingulate areas. CI adds a sensory modality in deafness patients, i.e. the auditory one. This involves areas implicated in sensory and cognitive functions, and needs some time to form. The duration of CI use is crucial: our results demonstrate the importance of long term use of the device in addition to an early time of implant.

KEY WORDS: cochlear implant, LORETA, cortical activation, ERPs, hearing loss

RIASSUNTO

La letteratura è concorde su come, in pazienti affetti da ipoacusia perlinguale, il ripristino uditivo secondario ad impianto cocleare (IC) sia paragonabile ad un modello di network sinaptico attivato dall'esperienza uditiva. Scopo di questo studio è la valutazione di quali networks cerebrali si attivino secondariamente ad impianto cocleare in una popolazione di pazienti ipoacusici preverbali. In particolare, verrà valutato come alcuni fattori, quali l'età all'attivazione ed il tempo di utilizzo dell'IC, incidano nel ripristino della percezione uditiva. Sono stati valutati 20 pazienti suddivisi in 3 gruppi: impianto precoce e lungo utilizzo dell'IC (gruppo A); impianto tardivo e lungo utilizzo dell'IC (gruppo B); impianto tardivo e breve utilizzo dell'IC (gruppo C). Tutti i pazienti sono stati comparati con soggetti normoacusici di pari età. La valutazione si è avvalsa dell'utilizzo di potenziali uditivi evento correlati (ERPs); in particolare sono state valutate le latenze dei potenziali (N200 e P300) e le sorgenti corticali tramite utilizzo del software LORETA. Le latenze del potenziale P300 sono risultate aumentate nei pazienti rispetto ai controlli. Dall'analisi delle sorgenti corticali è stato riscontrato che l'attivazione corticale nei pazienti è direttamente correlata con il tempo di utilizzo del dispositivo ed inversamente correlata con l'età d'impianto. Dal confronto dei pazienti suddivisi in gruppi rispetto ai controlli, un'attivazione corticale similare nelle aree frontali e cingolata, è stata riscontrata solo nel gruppo A, in minor misura nel gruppo B e notevolmente ridotta nel gruppo C. In conclusione, l'IC apporta una reale

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Correspondence
Sara Ghiselli
ENT and Audiology Department, Institute for Maternal and Child Health, IRCSS Burlo Garofolo, via dell'Istria65, 34137 Trieste, Italy
Tel. +39 040 3785218
E-mail: sara.ghiselli@burlo.trieste.it

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attivazione delle aree cerebrali implicate nelle funzioni sensoriali e cognitive ma, per ottenere risposte simili ai normoudenti, necessita di un tempo di utilizzo prolungato. I risultati di questo studio evidenziano come la precocità di impianto ed il tempo di utilizzo del dispositivo siano fattori cruciali per l'attivazione dei newtorks cerebrali nei soggetti ipoacusici preverbali.

PAROLE CHIAVE: *impianto cocleare, LORETA, attivazione corticale, ERPs, ipoacusia*

Introduction

Cochlear implant (CI) is a medical device designed to restore hearing perception in patients with severe to profound hearing impairment who fail to benefit adequately from hearing aids [1]. Many studies agree that providing CI early in cases of congenital hearing loss helps patients to develop auditory skills that are comparable with those of their normally-hearing peers [2,3]. Reported outcomes may differ according to the different aetiologies and degrees of hearing loss, prompting changes in neural organisation secondary to auditory deprivation [4,5]. It is well known that there is a sensitive period (before 3.5 years of age) for inserting the CI in order to achieve normal central auditory development and improve language skills [6-8], whereas subjects fitted with CI after this period have worse outcomes [9].

The problem of sensory restoration in early deafness is well explained in a review by Kral et al. [10] on the basis of the connectome concept. The authors said that sensory loss can be seen as a disease involving the connectome, which is a synaptic network whose development depends on sensory experience.

The proper functioning of auditory processing needs integration of many types of information: neuronal activity relies on both bottom-up and top-down integration [11]. Hearing loss causes changes in connectivity "within the auditory system, between sensory systems, and between the auditory system and centres serving higher-order neurocognitive functions" [10]. Auditory input presumably activates a cortical network of higher-order functions, and sensory restoration with CI can improve the connectivity in this network [10]. This system can be studied using neurophysiological and neuroimaging techniques.

Functional MRI (fMRI) is a powerful neuroimaging method for assessing spatial activations, but is only partially feasible in patients with CI due to factors that include a sizable artefact and the risk of the device being displaced due to potential movement within a magnetic field greater than 1.5 Tesla [12,13]. Other approaches have been used to identify cortical auditory activation in patients fitted with CI, such as NIRS or PET. These procedures, however, have good spatial but poor temporal resolution.

Electroencephalography (EEG), on the other hand, allows estimation of cortical areas of activation even at sub-second timescales. Despite poor spatial resolution, EEG has an excellent time resolution. It is completely non-invasive, easy to use, inexpensive and perfectly compatible with cochlear implantation.

In particular, the event-related potential (ERP) P300 may be an excellent measure of attention and memory operations [14]. The P300 wave is one of the late auditory event-related potentials, and is an objective measurement of cognitive processes induced by auditory stimulation. It reflects the cortical processes involved in stimulus evaluation and categorisation, memory operations and decision-making skills. Very few studies have investigated P300 in prelingually deaf CI recipients. Jordan et al. [15] measured P300 in a very small population of three prelingually and two postlingually deaf CI recipients. Henkin et al. [16] enrolled 10 prelingually deaf children fitted with CI (9 to 14 years old) and investigated how an increase of acoustic–phonetic difficulty affected the P300 potential. The interaction between task difficulty and prelingual deafness could not be investigated, however, because there was no control group. Reis et al. [17] studied P300 latency and amplitude in 29 patients with prelingual, severe-to-profound sensorineural hearing loss (without CI), and found significant differences in latency and amplitude that were related to age and severity of hearing loss, respectively. The study had no control group and the ERP was only delivered in Cz electrode. Beynon et al. [18] examined 10 congenitally deaf children fitted with CI when 5 or more years old, who had been using the device for at least 2 years. This study included a control group of normal-hearing subjects with longer P300 latencies (mean 500 msec) than those reported in the literature (mean 300 msec) [19]. A previous study [20] compared N100, N200 and P300 latencies in 15 prelingually deaf CI recipients with those of nine normal-hearing controls. We found all latencies were significantly longer in the patient group than in controls (whose values were consistent with the literature). Henkin et al. [21] studied the P3 component elicited by non-speech and speech oddball discrimination tasks in four prelingual patients with CI. They used LORETA (Low-Resolution Electromagnetic Tomography) [22], a noninvasive functional neuroimaging method based on scalp-recorded EEG, to estimate cortical sources of EEG activity. They found differences between patients and controls, and also between right and left CI recipients.

To date, the age at implant, its period of use and their interaction have not been fully investigated. The aim of our study was to investigate these issues: this was done through

assessment of the cortical sources of P300, using LORETA software, in prelingually deaf CI recipients compared with age-matched normal-hearing controls.

Materials and methods

Inclusion criteria

The inclusion criteria for the study group were: a) congenital non-progressive severe-to-profound bilateral sensorineural hearing loss; b) use of CI; c) no associated disabilities or diseases.

Patients

We enrolled 20 subjects in the control group (3 males and 17 females) and 20 subjects (attending the ENT Clinic at Padua University Hospital) in the study group (11 males and 9 females). The mean age of the control group was 29.05 ± 16.4 (range:10.1-58.4), while for the patient group it was 31.10 ± 18.4 (range:10.5-62.4). The age difference was not statistically significant ($p = 0.3$).

Age at the time of first fitting CI (CI Age) and period of CI use are considered very important parameters. Patients were then divided into groups according to the age at time of CI first fitting, before or after the age of 3 years, (hereinafter referred to as early or late CI age, respectively), and according to the duration of CI use at the time of ERPs recording, less or more than 1 year, (hereinafter named as long or short CI use, respectively).

The three groups are therefore identified as follows: 1) group A, 8 early CI age and long CI use subjects; 2) group B, 5 late CI age and long CI use subjects; 3) group C, 7 late CI age and short CI use subjects. No early CI age and short CI use patients were included in the study because they were too young to perform the task required. The characteristics of the patient groups (sex, age at time of the test, aetiology of hearing loss, age at time of first CI fitting, side of CI, CI brand and study subgroup) are summarised in Table I. Each patient group was compared with a control group matched for mean age and sample size. Controls were normal hearing subjects (thresholds lower than 30 dB at all frequencies). The characteristics of the three groups (age for both control and patient groups, plus age at time of CI and duration of CI use for the patient groups) are summarised in Table II.

The auditory benefit of the CI was assessed in terms of the free-field aided threshold by measuring the pure-tone average (PTA), which is expressed in decibels of hearing level (dB HL) and corresponds to the average air-tonal threshold at the frequencies of 500, 1000 and 2000 Hz. The mean PTA was 32.76 dB HL (range 25-41.2 dB HL) for group A,

Table I. Clinical characteristics of the patient group. CX26 = connexin 26.

Sex	Age at time of test (years)	Etiology	Age at first time of CI fitting (years)	Side of CI	CI Brand	Patient group
F	16.51	Unknown	1.51	L	Cochlear®	A
F	14.82	CX26	1.55	R	Advanced Bionics	A
F	13.29	CX26	2.60	R	Advanced Bionics	A
M	11.30	Unknown	2.53	R	Cochlear®	A
M	12.41	CX26	1.63	R	Advanced Bionics	A
M	10.59	CX26	2.27	L	Cochlear®	A
M	10.50	Unknown	3.02	R	Cochlear®	A
F	20.00	CX26	2.45	L	Medel	A
M	58.70	Unknown	57.36	L	Advanced Bionics	B
F	25.83	Unknown	22.52	L	Cochlear®	B
M	41.99	Rubella	39.86	R	Advanced Bionics	B
M	47.32	Unknown	42.96	BIL	Advanced Bionics	B
F	21.50	CX26	16.77	R	Cochlear®	B
M	39.20	Rubella	38.85	R	Advanced Bionics	C
M	17.92	CX26	17.21	L	Advanced Bionics	C
F	42.38	Unknown	41.31	L	Advanced Bionics	C
M	57.69	Unknown	57.36	L	Advanced Bionics	C
F	62.41	Unknown	61,87	R	Cochlear®	C
M	46.92	Rubella	46.73	L	Medel	C
F	50.80	Familial	50.61	R	Advanced Bionics	C

Table II. Characteristics of the three groups (patients and age-matched controls). Ages (in years) are expressed as mean ± SD and range. CI Age means the age at first time of CI fitting (in years).

Clinical		Patients	Controls	T test (p value)
A	N	8	8	
	Age	13.68 ± 3.30 (10.50-20.00)	13.83 ± 4.77 (10.08-23.41)	0.82
	CI Age	2.20 ± 0.56 (1.51-3.02)		
	CI use	11.48 ± 3.52 (7.48-17.55)		
B	N	5	5	
	Age	39.07 ± 15.38 21.50-58.70	39.08 ± 13.64 (22.48-58.39)	0.98
	CI Age	35.89 ± 16.36 (16.8-42.9)		
	CI use	3.17 ± 1.44 (1.33-4.73)		
C	N	7	7	
	Age	45.33 ± 14.58 (17.92-62.41)	39.27 ± 13.61 (17.69-58.39)	0.47
	CI Age	42.01 ± 13.83 (17.21-57.36)		
	CI use	0.47 ± 0.35 (0.2-1)		

33.75 dB HL (range 22.5-41.25 dB HL) for group B, and 45.17 dB HL (range 31.25-61.25 dB HL) for group C.

P300 recording

EEG recordings were obtained with 19 electrodes positioned according to the International 10–20 System (Fp1, F3, C3, P3, O1, F7, T3, T5, Fz, Cz, Pz, Fp2, F4, C4, P4, O2, F8, T4 and T6) with a linked ears reference. The sampling rate was 2048 Hz. A time window of 700 ms was considered (70 ms pre- and 630 ms post-stimulus). An amplitude window (±70 μV) was used for artifact rejection.

The impedance measured for each electrode was lower than 5 kOhm.

The active oddball paradigm was used. It consisted of a sequence of target and standard stimuli (1/7 proportion, 60 target stimuli), randomly presented to the subjects. The stimuli were audio tones on different frequencies, with a comfortable intensity level for all patients (1000 Hz for the standard, and 2000 Hz for the target; duration 100 msec for both; ISI = 1020-1100; intensity = 90 dB). All subjects were asked to take count of the number of target stimuli administered.

LORETA is a Laplacian-weighted minimum norm algorithm belonging to a family of linear inverse solution procedures [23]. It is used to estimate cortical sources of scalp potentials [21,24]. Estimated electrical sources are obtained considering a brain model based on the Talairach probability brain atlas, digitised at the Brain Imaging Center of the Montreal Neurological Institute [25]. The model includes 6239 voxels (5x5x5 mm resolution). Notably, LORETA is a reference-free method of EEG analysis.

Types of analysis

We performed two analyses: a simple study of N200 and P300 latencies and a LORETA cortical source analysis, including a linear regression analysis with duration of CI use and age of CI surgery as covariates.

Latency analysis

As in the literature and clinical practice, according to which Cz provides the best evoked response, we always considered Cz for this analysis. P300 latencies were identified at the maximum wave amplitude of the third positive peak point. The identification of P300 peak latency was performed through visual assessment of the target stimuli traces [26]. In any case, the maximum positive deflection designated as P300 was calculated automatically by the software for P300 acquisition, thus allowing for validation of the latency values determined by visual analysis of the traces.

Cortical source analysis

First, the difference between the averaged rare response

and the frequent averaged response was calculated for the 19 channels, and for each patient.
This new function ("rare stimuli response minus frequent stimuli response", which may be considered as the pure target stimuli effect) was collapsed into 63 bins, each resulting from the averaged values of 10 msec. LORETA was then applied to this new function considering two time ranges: one from 180 msec to 270 msec (the common range of N200 elicitation for all groups), the other from 270 msec to 460 msec (the common range of P300 elicitation for all groups). The difference in cortical estimated activation were performed comparing the pure target stimuli effect between patients and controls in the three previously-described groups.

Statistical analysis

Normality of data was checked using the Kolmogorov Smirnov test. The t-test for independent groups was used for comparing latencies in the group as a whole (patients and controls).
The statistic used in LORETA analysis was a Student's t-test on log-normalised data. Correction for multiple comparisons was performed using the randomisation approach [27] with 5000 randomisations.
The significance level was set at $p < 0.05$. Latencies analysis were performed using the Statistica 12.0 software package, while source analysis including regression analysis were performed using the LORETA software package.

Ethical issues

The local institutional ethics committee approved the study (n. 3842AO16). All experiments were conducted with the informed and overt consent of each participant or caregiver, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

Results

All subjects (patients and controls) correctly identified all the target stimuli.

Latency analysis

Comparing patients and controls in the study population as a whole, the N100, N200 and P300 latencies were significantly longer in patients than in controls (128.8 ± 19 msec and 97.2 ± 16, respectively, for N100, $p = 0.003$; 239.6 ± 28 msec and 201.5 ± 20, respectively, for N200, $p = 0.0001$; 353.1 ± 47 and 299.5 ± 21, respectively, for P300, $p = 0.0002$).
The N200-N100 interval did not differ significantly in patients and in controls (107.3 ± 31.6 msec and 103.7 ± 19.9, respectively; $p = 0.6$) (Fig 1).

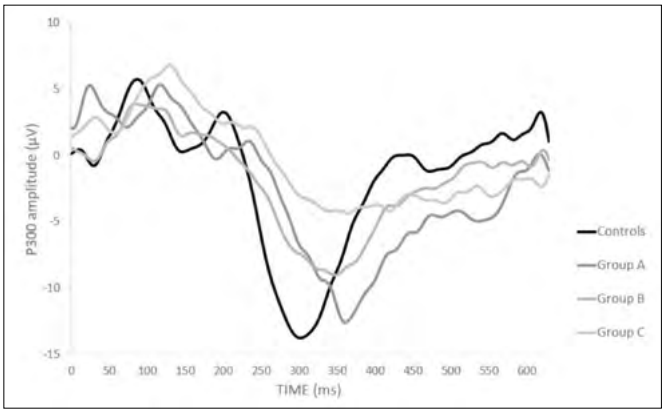

Figure 1. Grand average of target stimuli recorded in Cz in controls (black line) and patients (grey lines, from darker to lighter) in groups A, B and C.

Cortical source analysis

This analysis was performed as explained in the Methods. In group A (Fig. 2), no significant difference was found between patients and controls in the cortical areas, either for N200 (180-270 ms time window) or for P300 (270-460 time window). In group B (Fig. 3), there was greater activation in frontal areas for both N200 and P300 wave in controls, but the difference was not significant, whereas in group C (Fig. 4) this difference reached statistical significance ($p < 0.05$). More precisely, in the N200 time window, controls exhibited a higher activation in frontal areas (BA 8,9 and10) and in the cingulate cortex (BA 24, 32 and 33); and in the P300 time window, we found a significantly

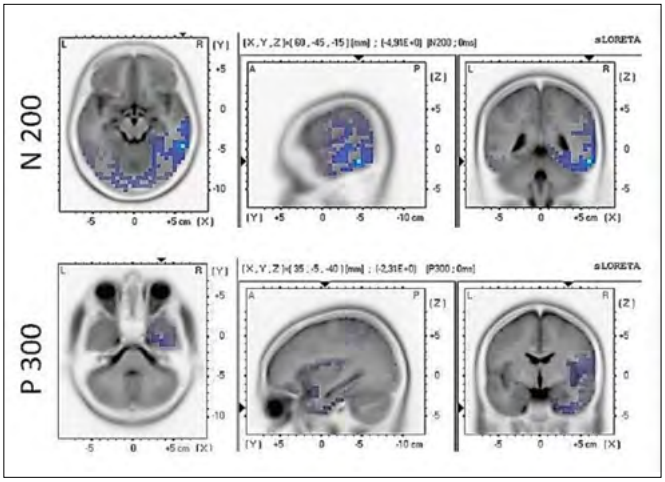

Figure 2. LORETA probabilistic map in cortical difference of activation between patients and controls, in group A. Red colours represent a greater activation in control group, more evident from dark red to yellow. On the contrary, blue colours represent greater activation in the patient group, more evident from dark to light. No significant difference in activation was found in either N200 (above) or in P300 (bottom).

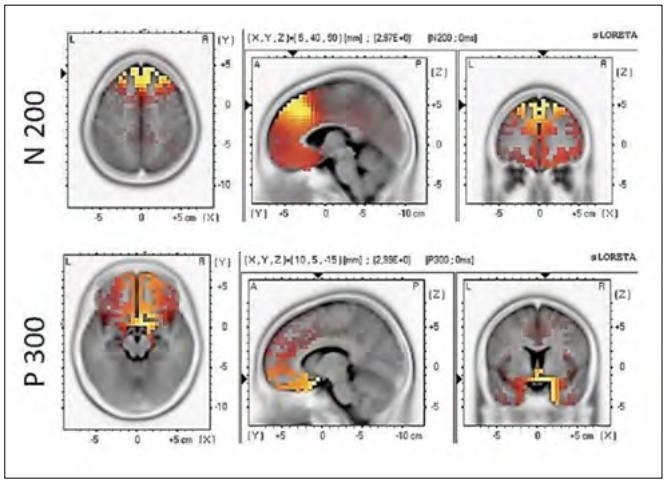

Figure 3. LORETA probabilistic map in cortical difference of activation between patients and controls, in group B. Red colours represent a greater activation in control group, more evident from dark red to yellow. On the contrary, blue colours represent greater activation in the patient group, more evident from dark to light. A greater activation was found in controls, but this difference was not statistically significant in either N200 (above) or in P300 (bottom).

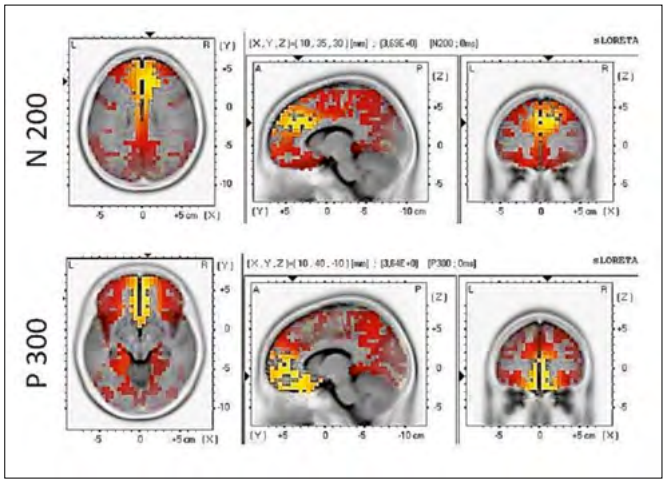

Figure 4. LORETA probabilistic map in cortical difference of activation between patients and controls, in group C. Red colours represent a greater activation in control group, more evident from dark red to yellow. On the contrary, blue colours represent greater activation in the patient group, more evident from dark to light. A greater activation in control group was found (yellow) in the frontal areas and cingulate cortex: this difference was statistically significant in both N200 (above) and P300 (bottom).

higher activation again in frontal areas (BA 10,11, and 25) and in cingulate cortex (BA 32). In the patient group, the amount of cortical activation was found to be significantly directly correlated with duration of implant use and significantly correlated inversely with age at implant, for both N200 and P300 waves, as shown in Table III.

Discussion

The latency analysis showed a significant increase in the N100, N200 and P300 peaks in patients compared to controls (Fig. 1), while the P300-N100 and the N200-N100 inter-peak latencies did not differ significantly between patients and controls. This means that the difference in N200 and P300 latencies found between patients and controls is due mainly to the N100 latency lag (of about 25-30 msec) in the patient group, a finding previously reported by Ghiselli et al. [20]. Using LORETA on magnetoencephalographic data, Larson [28] found that the cortical generators of N100, elicited by the oddball paradigm, were located in the Heschl's gyrus, where previous studies identified the tonotopic map of the human auditory cortex (for an exhaustive review, see Saenz [29]). There can be no this tonotopic cortical map without the auditory sensory modality, and thus a prelingually deaf patient needs to "create" a new cortical network to analyse acoustic input. Furthermore, the absence of auditory experience compromises both the primary field and more extensively the higher-order areas [30]. It may be that such a network cannot achieve the same performance as a perfect tonotopic cortex.

From a point of view of cortical activation, LORETA analysis disclosed a very clear difference when comparing a group of patients (group C) who had only been using CI for a very short period of time (less than one year) and had suffered long-term neural deprivation, with an age-matched control group. A statistically higher amount of activation in the frontal areas and cingulate cortex was apparent in the controls in comparison with patients, for both the N200 and the P300 waves. Conversely, when comparing an early-implanted patient group that had had long-term CI use (group A) with an age-matched control group, no significant differences emerged between patients and controls for

Table III. Linear correlation coefficient (r) and corresponding significance between amount of cortical activation and, respectively, duration of CI use and age at first time of CI fitting.

	N200	P300
Duration of CI use	$r = 0.78$ ($p < 0.01$)	$r = 0.76$ ($p < 0.01$)
Age at first time of CI fitting	$r = -0.71$ ($p < 0.01$)	$r = -0.68$ ($p < 0.01$)

either N200 or P300 (Fig. 2). It is well known that long-term implant use and early CI fitting are associated with good audiological performance [6], but it is noteworthy that these features seem to be associated with a normalisation from neurophysiological standpoint also.

These findings depict two extreme conditions: late implant and short time of CI use, versus early implant and long CI use. An intermediate condition is represented by the patient belonging to group B, which had been using CI for more than one year. In this case a slight, but not statistically significant, tendency for higher activation in controls than in patients was found (Fig. 3).

These results were congruous with the LORETA monovariate regression analysis performed in the patient group, with age of implant and duration of CI use as covariates: the amount of cortical activation was significantly correlated with duration of implant use and significantly correlated inversely with age at implant, for both N200 and P300 waves. It is very important to stress that our results do not imply cognitive impairment due to prelingual deafness: CI provides a new sensory modality in this type of patients, and their neuronal plasticity restores – or rather creates – a functional network which involves the areas implicated in sensory and cognitive modalities. Thus, in other words, CI gives these cortical areas access to a new (for deaf patients) sensory modality. The duration of CI use is clearly crucial: our data suggest that even in case of late-implant, prolonged CI use restores the auditory network. Unfortunately, LORETA software cannot perform multivariate regression analysis, so the pure effect of the duration of CI use and age of implant could not be determined.

The main limitations of the present study are: (i) small sample size; (ii) lack of a group of early-implanted patients with a short period of CI use; (iii) unfeasibility of a cortical source analysis of the N100 wave and limited number of channels. With regards to (i), further patient recruitment is in progress to increase the size of groups A and B to better investigate the relationship between CI age and CI period of use needed for a good performance. The chance to study early-implanted patients with a short use of their CI coincides with the feasibility of administering a P300 paradigm to very young children. The number of EEG channels [20] does not allow for high spatial resolution. However, our results showed strong significance with regards to our specific question. Therefore, various examples of the use of 19 channels in the ERPs cortical source analysis are available in the scientific literature [31-33].

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VESTIBOLOGY

Vestibular pathology and spatial working memory

Patologia vestibolare e memoria operativa spaziale

Giorgio Guidetti, Riccardo Guidetti, Maurizio Manfredi, Marco Manfredi
Vertigo Centre, Poliambulatorio Chirurgico Modenese, Italy

SUMMARY
Thanks to wide central connections the vestibular system is not merely involved in reflexes, but it is also connected to cognitive processes. A growing body of literature suggests that it has a substantial impact on cognitive function. These cognitive interactions include memory, attention, mental imagery, body awareness and social cognition. Spatial working memory (SWM) is a kind of short-term memory that allows to temporarily store and manipulate spatial information. It has a limited capacity and is quite vulnerable to interference. The single most important nonverbal task for assessment of visuo-spatial working memory (VSWM) is the Corsi block tapping task (CBTT), also known as the Corsi Span Test. We evaluated 263 patients suffering from chronic unilateral or bilateral vestibular loss (VL) by eCorsi Block-Tapping test before and after 5 days of instrumental vestibular training (IVT). The data were compared with those of 834 subjects submitted to the same test: 430 healthy people (HP) and 404 patients suffering from chronic VL but not treated by IVT. At all ages, the Corsi block test score was extremely statistically significantly higher ($p < 0.0001$) in HP than in both groups of VL. The score showed a statistically significant difference with age and sex in healthy subjects as younger males obtained the best results. Our study confirms the significant interference of the vestibular input on VSWM and impairment of this cognitive function in patients suffering from chronic UL or BIL. It also shows that IVT is able to improve VSWM even in cases where the deficit is greater.

KEY WORDS: spatial working memory, corsi block-tapping test, vestibular pathology, vestibular rehabilitation training

RIASSUNTO
Grazie ad ampie connessioni centrali il sistema vestibolare non evoca solo riflessi ma è anche collegato a processi cognitivi. Un numero sempre maggiore di studi suggerisce che ha un impatto sostanziale sulle funzioni cognitive. Queste interazioni cognitive comprendono la memoria, l'attenzione, l'immaginario mentale, la consapevolezza del corpo e la cognizione sociale. La memoria operativa spaziale è un tipo di memoria a breve termine che consente di archiviare e manipolare temporaneamente le informazioni spaziali. Ha una capacità limitata ed è piuttosto vulnerabile alle interferenze. Il test non verbale più importante per la valutazione della memoria di lavoro visuo-spaziale (VSWM) è il test a blocchi di Corsi, noto anche come il Test di span di Corsi. A tal fine, abbiamo valutato col test eCorsi Block-Tapping 263 pazienti affetti da deficit vestibolare cronico unilaterale o bilaterale (VL), prima e dopo 5 giorni di training vestibolare strumentale (IVT). I dati sono stati confrontati con quelli di altri 834 soggetti sottoposti allo stesso test: 430 persone sane (HP) e 404 pazienti affetti da VL cronica ma non trattati con IVT. A tutte le età il punteggio del test di Corsi era significativamente più alto ($p < 0,0001$) negli HP rispetto a entrambi i gruppi di VL. Il punteggio era significativamente più alto anche nei giovani rispetto ai vecchi sia nelle HP che nei VL. È significativamente più alto nei maschi che nelle femmine solo negli HP. Il nostro studio conferma l'interferenza significativa dell'input vestibolare sulla VSWM e la compromissione di questa funzione cognitiva in pazienti affetti da VL cronici mono o bilaterali. Esso mostra anche che IVT è in grado di migliorare la VSWM anche nei casi in cui il deficit è maggiore.

PAROLE CHIAVE: *memoria operativa spaziale, test di corsi, patologia vestibolare, training riabilitativo vestibolare*

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Correspondence
Giorgio Guidetti
Vertigo Center - Poliambulatorio Chirurgico Modenese, strada Morane 390, 41125 Modena, Italy
E-mail: giorgio.vertigine@gmail.com

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Conflict of interest
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Introduction

The vestibular system consists of the peripheral vestibular organs in the inner ear and the associated extensive central nervous system projections to the cerebellum, brainstem, lymbic system, thalamus and cortex. The vestibular cortex differs in various ways from other sensory cortices. It consists of a network of several distinct and separate areas. Its core region, the parieto-insular vestibular cortex (PIVC), is located in the posterior insula and retroinsular region, and includes the parietal operculum. A ubiquitous aspect of central vestibular processing is its promiscuity given that vestibular signals are commonly found in combination with other sensory signals [1]. The entire network is multisensory (in particular, vestibular, visual and somatosensory) and bilaterally organised; there are various pontomesencephalic brainstem crossings and at least two transcallosal connections of both hemispheres, between the PIVC and the motion-sensitive visual cortex areas, which also mediate vestibular input. Bilateral organisation is a major key to understanding cortical functions and disorders, for example the visual-vestibular interaction that occurs in spatial orientation. Although the vestibular cortex is represented in both hemispheres, there is only one global percept of body position and motion [2]. This system is important for spatial orientation and balance, both of critical ecological importance, particularly for successful and safe navigation in our environment. However, little is still known regarding central vestibular processing and the brain regions that mediate vestibular motion, and vestibular spatial perception is an area of ongoing research [3].

Thanks to these wide central connections, the vestibular system is not merely involved in reflexes but is also connected to cognitive processes. A growing body of literature suggests that it has a substantial impact on cognitive function. These cognitive interactions include memory, attention, mental imagery, body awareness and social cognition. Cognitive deficits such as poor concentration and short-term memory loss are known by clinicians to occur frequently among patients with vestibular abnormalities of any type [4,5], especially for the elderly [6]. For this reason, emerging research suggests the vestibular system can be considered as a potential window for exploring brain function beyond that of maintenance of balance, and into areas of cognitive, affective and psychiatric symptomology [7].

Furthermore, the links between vestibular dysfunction and cognitive performance can suggest areas of future research and application [7-9]. Damage to the vestibular system specifically leads to cognitive deficits in spatial learning and memory, navigation, mental rotation and mental representation of three-dimensional space, which are not necessarily related to any particular episode of vertigo or dizziness, and therefore may occur even in patients who are otherwise well compensated.

Spatial memory is a cognitive process responsible for recording information about the spatial environment and spatial orientation. It enables a person to remember different locations as well as spatial relations between objects and allows one to remember where an object is in relation to another object. It can be short or long-term. Short-term memory (STM) allows to temporarily store and manage information that is necessary to complete complex cognitive tasks. Spatial working memory (SWM) is a kind of STM that allows to temporarily store and manipulate spatial information. It has a limited capacity and is quite vulnerable to interference. It is well known that the primate dorsolateral prefrontal cortex, especially the area surrounding the principal sulcus, participates in spatial working memory processes. These results indicate that the dorsolateral prefrontal cortex takes part in spatial working memory, especially in the temporary active storage of spatial information.

Recently, it was suggested that a network extending across several cortical areas, including the dorsolateral prefrontal cortex and posterior parietal cortex, takes part in spatial working memory. Human neuroimaging studies showed activation during the spatial working memory tasks in numerous cortical areas, including the dorsolateral prefrontal cortex, frontal eye field, supplementary motor area, premotor cortex, anterior cingulate cortex, posterior parietal cortex and occipital cortex. These results provide supporting evidence that the neuronal links between these cortical areas constitute part of a working memory system. In addition to closely intertwined attentional and oculomotor programming, SWM has also been shown to involve higher-order cognitive processes, such as executive functioning, at the earliest stages of information processing. Thus, depending on the strategies elaborated and task demands, the same spatial information may be represented in SWM by different patterns of activation in the brain. This view is consistent with a model of WM arising from the interaction between higher-order cognitive top down processes governed by the prefrontal cortex and stimulus specific brain regions. Visual attention has a cross-modal influence on activity in the human vestibular cortex: higher attentional loads were associated with decreasing activation in the anterior part of the PIC, whereas no such effect was observed for the posterior PIC. Brain activation was larger for visual attention (VA) tasks than for working memory WM) tasks, but deactivation was larger for WM tasks. VA and WM tasks commonly deactivate a network that includes the frontal, temporal, occipital, and limbic lobes; b) although WM

tasks caused lower overall activation, they produced larger overall deactivation than VA tasks; and c) specific regions in the frontal lobes (PreCG, and PCL) deactivated during WM, but activated during VA tasks [10-13].

Dorsolateral prefrontal cortex (DLPFC) has been shown to be a part of the SWM network, but its specific functional role remains unknown [14].

It has been speculated that stimulating the vestibular system during balance training may induce changes of the hippocampus and parietal cortex possibly via direct pathways between the vestibular system and these brain regions [7-9,15-20] and chronically dizzy patients seem to profit from combining training with medication or brain stimulation.

Neither the side of the vestibular lesion nor the duration of disease seem to influence cognitive performance, but the degree of vestibular dysfunction significantly correlates with cognitive deficit.

The single most important nonverbal task for the assessment of visuo-spatial working memory (VSWM) is the Corsi block tapping task (CBTT), also known as the Corsi Span Test [21]. It also involves spatial attention. The traditional version of Corsi apparatus consists of a set of nine identical blocks (3 x 3 x 3 cm) irregularly positioned on a wooden board (23 x 28 cm). The experimenter points to a series of blocks at a rate of one block per second. Subsequently, the participant is required to point to the same blocks in their order of presentation. The length of the block sequences (starting from 2-block sequences) increases by one item until recall is no longer correct. The procedure ends when the number of wrong reproductions exceeds the proportion of admissible errors per length. A span score is calculated corresponding to the larger sequence the subject can correctly reproduce. The maximum score possible is 9. Some changes have been suggested over time [22]. Several computer-based forms of the test have been developed [23] or by using a mouse to click on the blocks, as well as more peculiar versions of CBTT such as a haptic Corsi and a "walking Corsi".

In Corsi block-tapping task for digital tablets (eCorsi), instead of cubes to be tapped on a board, the setup consists of squares that flash on a computer screen. Participants reproduce the sequences either by tapping blocks on a (touch) screen without substantial differences between the two versions in terms of subjects' performance [24]. On average, most participants achieve a span of five items on the Corsi span test and seven on the digit span task. Differences between traditional CBTT and eCorsi include mostly better control of the inter-stimulus presentation timings in the eCorsi. In fact, with manual tapping the temporal accuracy is particularly difficult to control by the examiner, who can (inadvertently) be slower or faster depending on several factors.

This test is used mainly in neurological diseases (Alzheimer's disease. autism spectrum disorder, depression and affective disorders, Down's syndrome, epilepsy, multiple sclerosis, Parkinson's disease, schizophrenia, stroke and cerebrovascular disease and traumatic brain injury).

Spatial working memory problems are frequently reported following brain damage within both left and right hemispheres, but with the severity often being greater in individuals with right hemisphere lesions. Patients with damage to the right posterior parietal cortex, the dorsolateral prefrontal cortex and hippocampal formation bilaterally made more between-search errors, indicating the importance of these areas in maintaining spatial information in working memory over an extended period of time.

At the Corsi Block Tapping Test, both bilateral and unilateral vestibular patients are significantly impaired in their visuospatial abilities compared with healthy controls [4,24].

SWM declines across the life span even in the absence of disease-related cerebral pathology [25]. One reason for this decline is certainly working memory-related functional cerebral changes, particularly within the prefrontal cortex [26]. Mean span capacity increased incrementally and linearly with age, and no gender difference was observed. The increase in performance with advancing age supports the notion that spatial immediate memory capacity increases with maturation throughout childhood. Comparisons indicated that the span capacity of eighth graders is not statistically different from that of young adults, suggesting an upper developmental plateau for spatial span in early adolescence with an ameliorative effect of education. Task-related functional connectivity appears to be lower in older adults with age-related reductions of prefrontal activation during spatial working memory retrieval. Performance accuracy in older adults is associated with right dorsolateral and anterior prefrontal cortex activation, and with the functional connection between these regions [26]. Sex differences are often reported in spatial abilities. Until a few years ago, it was widely accepted that men outperformed women on almost all spatial tasks. However, some studies show conflicting results, which can be ascribed to the complexity of the variables involved in the visuo-spatial domain and can be better explained by differences in spatial competences. Indeed, these differences could reflect the use of different strategies, rather than different competences, by the two sexes.

Materials and methods

There is moderate to strong evidence that vestibular rehabilitation is a safe, effective management for unilateral peripheral vestibular dysfunction, based on a number of

high-quality randomised controlled trials [27] even in older people [28]. The goal of the present study was to test the hypothesis that a full-immersion vestibular instrumental training is able to improve SWM in patients suffering from chronic vestibular loss, defined by the presence of reduced function of the peripheral vestibular system on one side, which has persisted for 3 or more months. In humans, balance skills have been associated [29] with an increased volume of the hippocampus, basal ganglia and frontal and parietal brain areas. However, data on the effects of balance training on cognitive functions, particularly related to memory and spatial cognition, are rare to date and limited to healthy people [30]. To this end, we evaluated patients suffering from vestibular loss (VL) by eCorsi Block-Tapping test before and after 5 days of instrumental vestibular training (IVT).

We examined 263 subjects with chronic vestibular loss (TVL):

- 154 (58.6%) females (F) and 109 (41.4%) males (M);
- 150 cases (YOUNG) aged 17 to 64 years (mean 48.3 SD 10.7);
- 113 cases (OLD) aged 65 years or more (mean 75.0 SD 5.21).

VL was unilateral right (RL) in 98 cases, unilateral left (LL) in 67 cases and bilateral (BL) in 98 cases.

Subjects on therapy with psychoactive or antiepileptic drugs, suffering from degenerative, neoplastic or severe vascular pathologies of the central nervous system, Meniere's disease, or paroxysmal positional vertigo were not included in the study. Patients with small age-related vascular signs in imaging tests were included.

The vestibular training program consisted of 8 sessions of one hour in 5 consecutive days. Both static and dynamic platforms of various kinds and treadmills were used. Optokinetic stimulations and visual targets of various types were associated with static and dynamic exercises. The degree of stimulation was adapted to the basic performance of each patient and was progressively increased day by day.

Our version of the eCorsi apparatus consisted of a set of nine identical squares of 3 cm irregularly positioned that flash on a touch screen monitor at a rate of one block per second.

Participants must repeat the correct sequence by tapping blocks on the screen in the order of appearance. The length of the block sequences (starting from a 2-block sequence) increases by one item until the subject fails to recall the correct sequence. A span score, that corresponds to the larger sequence the subject is able to correctly reproduce, was calculated. The maximum score was 9.

The data were compared with those of other 834 subjects submitted to the same test:

- 430 healthy people (HP); 224 F (52.1%) and 206 M (47.9%):
  - 300 aged 17 to 64 years (mean 31.57 SD 12.41);
  - 130 aged 65 years or more (mean 72.26 SD 4.79);
- 404 patients suffering from chronic vestibular loss, but not treated by vestibular training (NTVL): 210 F (51.9) and 194 M (48.1%):
  - 234 aged 17 to 64 years (mean 48,94 SD 10.44);
  - 170 aged 65 years or more (mean 75.08 SD 5.25).

Statistical analysis was performed using SPSS (Statistical Package for Social Science). Groups were tested for normality. The difference between the means of normally distributed variables was calculated using Student's t-test. A paired sample t-test was performed to assess the differences in the same subject, while independent samples t-test was used to compare two groups. Differences with a p-value < 0.05 were considered statistically significant.

Results

For all age groups the Corsi block test score reached a high level of statistical significance ($p < 0.0001$) between HP and NTVL and TVL ($p < 0.0001$) (Tabs. I, II).

In the HP group, the span was significantly higher in M than in F (Tab. III). This difference was not significant in the VL and NTVL groups, while it reached significance in TVL (p 0.0068) (Tabs. III, IV).

In both HP and NTVL the score was significantly higher in YOUNG than in OLD (Tabs. III, IV) ($p < 0.0001$ and $p < 0.0001$ respectively).

The difference between UL and BIL remained unclear. In fact, in NTVL was not significant, while it was slightly sig-

Table I. Mean and SD values of the span of eCorsi in HP and NTVL.

	HP			NTVL		
	N	Mean	SD	N	Mean	SD
M	206	6.374	0.922	194	4.804	1.226
F	224	6.004	1.022	210	4.666	3.587
YOUNG	300	6.58	0.778	234	5.184	3.387
OLD	130	5.294	0.774	170	4.112	1.074
YOUNG M	142	6.781	0.685	108	5.25	1.103
OLD M	64	5.468	0.712	85	4.23	1.138
YOUNG F	158	6.399	0.813	126	5.12	4.527
OLD F	66	5.090	0.700	85	4.00	1.000
RL				160	5.237	4.029
LL				118	4.432	1.343
BL				126	4.373	0.986
UL				278	4.896	3.200
Total	430	6.181	0.991	404	4.732	2.720

Table II. Mean and SD values of the span of eCorsi in TVL.

		Before IVT		After IVT	
	N	Mean	SD	Mean	SD
M	109	5.119	1.420	5.598	1.326
F	154	4.664	1.267	4.914	1.266
YOUNG	150	5.267	1.251	5.607	1.236
OLD	113	4.310	1.150	4.646	1,172
YOUNG M	58	5.119	1.421	5.598	1.326
OLD M	51	4.285	1.214	4.735	1.024
YOUNG F	92	5.043	1.176	5.293	1.143
OLD F	62	3.937	1.119	4.187	1.179
RL	98	5.173	1.227	5.418	1.201
LL	67	4.701	1.360	5.149	1.329
BL	98	4.643	1.270	5.0	1.377
UL	165	4.988	1.300	5.309	1.257
Total	263	4.855	1.297	5.193	1.297

Table III. P value in t-test between HP and NTVL groups and between NTVL subgroups by age, gender and kind of VL.

Groups	P value in t-test
HP/NTVL	< 0.0001
M HP/M NTVL	< 0.0001
M/F HP	< 0.0001
M/F NTVL	0.6110 not significant
F HP/F NTVL	< 0.0001
YOUNG/OLD HP	< 0.0001
YOUNG HP/YOUNG NTVL	< 0.0001
OLD HP/OLD NTVL	< 0.0001
YOUNG/OLD NTVL	< 0.0001
UI/BIL NTVL	0.0734 not significant
RL/LL NTVL	0.0379

nificant in TVL (p = 0.0368), with a lower span in BIL (Tabs. III, IV)

Both in NTVL and in TVL the span was significantly higher in RL than in LL (Tab. IV). The difference between HP and TVL remained significant even after IVT.

However, IVT was able to significantly improve the span (Tab. IV). In fact, before IVT there was no statistically significant difference between NTVL and TVL, while there was a marked improvement in TVL after IVT (p = 0.0029) (Tab. IV). On average this improvement was significant in M (p = 0.0107) (Tab. IV). The difference between YOUNG and OLD remained significant, but the improvement of the score was significant in both groups, with a high level of significance in OLD F (p < 0.0001). UL improved significantly more than BIL, without significant differences between RL and LL. However, the difference between UL and BIL was not statistically significant.

Discussion

With a greater number of cases than previously studied, our study confirmed a very significant VSWM deficit in patients suffering from unilateral or bilateral VL at all ages. It is therefore clear that vestibular input is able to interact in a relevant, chronic way even with this cognitive function. The deficit is greater in the OLD, both in HP and in VL, compatibly with the condition of cognitive decay due to age.

The partially worse VSWM deficit in the LL compared to the RL could find explanation in the different ways of projection of the vestibular input on the two sides of the cerebral cortex. Vestibular cortical activations after unilateral caloric ear irrigation was measured depending on both the stimulated ear and the handedness, with a predominant activation of the ipsilateral vestibular cortex following right

Table IV. P value in t-test between HP, NTVL and TVL groups and between TVL subgroups by age, gender and kind of VL before and after IVT.

Groups before IVT	P value in t-test
HP/TVL	< 0.0001
NTVL/TVL	0.4940 not significant
M/F	0.0068
YOUNG/OLD	< 0.0001
UL/BIL	0.0368
RL/LL	0.0215
Groups after IVT	**P value in t-test**
HP/TVL	< 0.0001
NTVL/TVL	0.0105
TVL after/TVL before	0.0029
M/F	< 0.0001
M after/M before	0.0107
F after/F before	0.0843 not significant
YOUNG /OLD	< 0.0001
YOUNG after/YOUNG before	0.0185
OLD after/OLD before	0.0307
YOUNG M after/YOUNG M before	0.0631 not significant
OLD M after/ OLD M before	0.0457
YOUNG F after/YOUNG F before	0.1452 not significant
OLD F after/OLD F before	< 0.0001
UL after/UL before	0.0232
RL after/RL before	0.1594 not significant
LL after/LL before	0.0559 not significant
BIL after/BIL before	0.0607 not significant
UL/BIL	0.0641 not significant

or left caloric ear irrigation. These patterns of vestibular projections in humans, suggesting an importance of the ipsilateral pathways, and thus do not fully correspond with animal data that have stressed bilateral pathways with a contralateral dominance. In general, multiple studies have, however, demonstrated the dominance of the right hemisphere after vestibular stimulation. The activation in the right hemisphere is the same for both right- and left-ear stimulation. At the present time, it seems to us that this hypothesis is not sufficiently demonstrated with regard to VSWM.

The level of high statistical significance of the difference of HP between genders, with lower span in F compared to M, is not as clear in the case of VL. We therefore think that in M the VL involves a greater deficit in the VSWM and therefore reduces the difference between genders. As far as navigation is concerned, various studies have shown that the gender difference or strategies depends on neural substrates. M uses more vestibular inputs than F, which has a strategy more related to environmental visual inputs [27]. Indeed, F typically report navigating on the basis of local landmarks and familiar routes, whereas M report using cardinal directions, environmental geometry and metric distances. Although F do not differ from M in dependence on or ability to use landmarks, they depend less on geometry when reorienting to an environment and are relatively more impaired at finding a target based on directional cues. F also require more environmental cues to remain oriented in an environment and have difficulty following navigation directions based on cardinal directions and metric distances. However, there are no other studies able to demonstrate that this is valid even for VSWM.

The IVT has been shown able to significantly improve VSWM, especially in cases with greater initial deficit, such as OLD F. It may be speculated that the vestibular system during balance training may induce changes of the hippocampus and parietal cortex possibly via direct pathways between the vestibular system and these brain regions [15,16]. It can, therefore, be assumed that the vestibular and visuovestibular stimulations during the 5 days of IVT is able to activate those neuronal circuits that in the case of VL do not guarantee a normal VSWM. It will be necessary to demonstrate in the future if longer training will allow to completely eliminate the difference between VL and HP.

Conclusions

Our study confirms the significant interference of the vestibular input on VSWM and the impairment of this cognitive function in patients suffering from chronic UL or BIL. It also showed that IVT is able to improve VSWM even in cases in which the deficit is greater. This result seems possible even without specific exercises for VSWM. Thus, new frontiers can be opened in the evaluation and treatment of chronic VL and in the study of neuronal circuits related to cortical projections of vestibular inputs.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Endoscopic adenoidectomy: a systematic analysis of outcomes and complications in 1006 patients

Adenoidectomia endoscopica: revisione sistematica di risultati e complicanze in 1006 pazienti

Alberto Maria Saibene[1], Cecilia Rosso[1], Carlotta Pipolo[1], Paolo Lozza[1], Alberto Scotti[1], Filippo Ghelma[2], Fabiana Allevi[3], Alberto Maccari[1], Giovanni Felisati[1]

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

SUMMARY

Adenoid hypertrophy (AH) is an extremely common condition in the paediatric population, relating to different pathological scenarios. Failure in responding to medical therapy often leads to adenoidectomy. While traditional adenoidectomy is indeed a relatively "blind" procedure, endoscopic procedures allow more radical resections, bleeding monitoring and complete Eustachian tube sparing, making adenoidectomy a safer, more manageable and functional procedure. Though the literature widely describes endoscopic adenoidectomy, only small case series are available and the procedure itself has never really taken hold in routine otolaryngology practice. The aim of this article is to report data on endoscopic adenoidectomy in a large single centre patient population. We retrospectively evaluated the medical records of 1006 children who underwent endoscopic adenoidectomy with or without tonsillectomy (respectively 493 and 513 patients). Data on surgical time, blood loss, hospital stay, short and long-term complications, recurrences and post-operative pain were collected. Our analysis showed that the endoscopic approach requires a longer surgical time, but it is associated with less intraoperative blood loss, a lower complication rate and less treatment failures compared to large contemporary case series of either traditional or power-assisted approaches. The overall better outcomes are more noticeable when comparing our data with classic technique case series than with power-assisted case series. Endoscopic adenoidectomy should therefore be regarded as a valid technique, which, in expert hands, lowers the rates of complications and recurrences at the expense of a slightly increased surgical time.

KEY WORDS: endoscopic adenoidectomy, power-assisted adenoidectomy, adenotonsillectomy, adenoidectomy complications

RIASSUNTO

L'ipertrofia adenoidea è una condizione estremamente comune nella popolazione pediatrica, correlata a differenti scenari patologici. Laddove la terapia medica non è sufficiente a gestire la patologia, può essere necessario ricorrere all'approccio chirurgico eseguendo un'adenoidectomia. Mentre la tecnica chirurgica tradizionale è una procedura eseguita relativamente "alla cieca", l'approccio endoscopico permette di eseguire una resezione radicale, con controllo del sanguinamento ed un completo risparmio degli osti tubarici, rendendo l'adenoidectomia video-assistita una scelta più sicura, controllata e funzionale. Nonostante in letteratura venga ampiamente descritta come tecnica, gli studi si sviluppano su piccole casistiche e l'approccio endoscopico non ha mai realmente assunto un posto centrale nella pratica otorinolaringoiatrica. Lo scopo del seguente articolo è di analizzare i risultati dell'adenoidectomia endoscopica eseguita su un'ampia popolazione di pazienti afferenti ad un unico centro. È stata eseguita un'indagine retrospettiva su un database di 1006 bambini sottoposti ad interventi di adenoidectomia endoscopica con o senza tonsillectomia (rispettivamente 513 e 493 pazienti). I dati raccolti si basano su tempo chirurgico, perdite ematiche, tempo di degenza, complicanze a breve e lungo termine, recidive e dolore post-operatorio. L'analisi ha mostrato, in confronto ad ampie casistiche di approcci sia

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Correspondence
Cecilia Rosso
Otolaryngology Department, San Paolo Hospital, University of Milan, via di Rudinì 8, 20142 Milan, Italy
Fax +39 02 81944704
E-mail: rosso.cecilia1@gmail.com

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tradizionali che endoscopici, un tempo chirurgico maggiore, ma allo stesso tempo minori perdite ematiche intraoperatoriamente, così come un inferiore tasso di complicanze e recidive. La differenza nei risultati è maggiormente apprezzabile comparando i nostri dati con quelli della tecnica classica piuttosto che con le casistiche su approcci endoscopici. L'adenoidectomia video-assistita dovrebbe dunque essere considerata una tecnica solida che, in mani esperte, riduce le complicanze e le recidive a spese di un maggior impiego di tempo di lavoro.

PAROLE CHIAVE: *adenoidectomia endoscopica, adenoidectomia power-assisted, adenotonsillectomia, complicanze adenoidectomia*

Introduction

Adenoids are a lymphoid tissue located on the nasopharyngeal posterior wall. Adenoid hypertrophy (AH) is extremely common in the paediatric population, and usually regress spontaneously before reaching an age in the teens. Nevertheless, sometimes AH may induce a pathological condition, due to choanal space obstruction, Eustachian tube compression and/or chronic bacterial colonisation. For example, AH facilitating nasal congestion and recurrent rhinosinusitis, with long-term upper way obstruction can lead to maxillofacial growth alterations and difficulties in physical activity [1]. In other patients, tubaric ostium closure, with or without bacterial colonisation, may cause middle ear effusion with ear fullness or recurrent otitis media [2], with a subsequent risk in language development and communication [3]. Finally, AH has a definite role in snoring and sleep apnoea [4].

Failure in responding to medical therapy in these pathological scenarios might lead to the need for surgical intervention [5,6]. Adenoidectomy is, therefore, one of the most common surgical procedures performed in the daily otolaryngological practice. Nevertheless, the development of medical technologies has also innovated surgical techniques for AH, introducing endoscopic support for better local control and more complete resection. Traditional adenoidectomy (TA) is indeed a relatively "blind" procedure. It doesn't allow to control the surgical field, causing in turn the possibility of leaving partial adenoid tissue that can maintain the closure of Eustachian tubes or choanal obstruction; moreover, it doesn't allow to monitor bleeding points and adequately control them with selective cautery. Finally, besides major general complications related to head and neck general anaesthesia surgical procedures (i.e. airway, respiratory and cardiovascular complications) and bleeding risk, TA may determine neck stiffness, hypernasal voice and velopharyngeal insufficiency, dental trauma and Grisel syndrome [5-8].

In this regard, other techniques have been constantly proposed as an evolution of TA, among which power-assisted endoscopic adenoidectomy (PEA) holds a prominent role. A transoral or transnasal endoscopic approach can improve the assessment of the rhinopharyngeal area, with thorough resections. Furthermore, endoscopy allows a closer inspection of the adenoidectomy procedure, monitoring bleeding and completely sparing the Eustachian tubes. Overall, PEA allows a safer, more manageable and functional procedure. Though PEA is widely described in scientific literature, only relatively small case series are available [9-12] and the procedure itself has never really taken a hold in otolaryngological practice, with the notable exception of endoscopic adenoidectomy for cleft lip and/or palate patients [13].

Many studies have already compared TA and PEA, showing how power-assisted techniques improve management of adenoidectomy in terms of pain, blood loss, recovery and surgical time, and completeness of adenoid removal, albeit in small patient cohorts [14,15]. On the other hand, other authors showed that, although PEA outcomes are superior to TA, subjectively no differences emerged between the two methods [11], and PEA becomes the technique of choice only in specific setting such as cleft lip and palate patients [13].

On this basis, and given the aforementioned literature debate, it seems important to keep developing the technique and sharing scientific evidence, especially if we take into account that adenoidectomy is performed annually in tens of thousands of children.

The aim of our paper is to provide a large single centre case series (the largest available in the literature) in a cohort of 1006 patients who underwent PEA, either with a transnasal or transoral approach. We conducted a retrospective analysis and examined indications to surgery, operative time, recovery time, pain score on a visual analogic scale (VAS) and intra/periprocedural complications such as post-operative bleeding and treatment failures. In order to provide the best reference to our evidence, our results are discussed along with the most recent and complete reviews of adenoidectomy outcomes in literature.

Materials and methods

The study was designed as a retrospective review. Due to its retrospective nature, it was granted exemption from the Internal Review Board of the San Paolo Hospital, Milan.

Inclusion criteria

- Patients aged 3 to 14 years who underwent PEA with or without tonsillectomy at the Otolaryngology Department of the Santi Paolo e Carlo Hospital in Milan, Italy, from 2007 to 2016.
- Indication to PEA following a clinical diagnosis of re-

current upper airways infections, nasal obstruction, recurrent media otitis (AOM), chronic effusive media otitis (OME) and sleep apnoea (OSAS) not responding to adequate medical therapy (see Table I for indications to surgery).
- At least 1 year of follow-up.

Exclusion criteria
- Personal history of cleft lip and/or palate, whether surgically corrected or not.
- Personal history of previous adenotonsillectomy or adenoidectomy procedures.

Study population
From 2007 to 2016, 1132 patients consecutively underwent PEA at our institution. Among these, 1006 children were considered eligible according to our inclusion and exclusion criteria and their medical records were reviewed. 493 children underwent adenoidectomy alone, while 513 underwent adenotonsillectomy. Demographic data are reported in Table I.
Patients who underwent other procedures along with adenoidectomy or adenotonsillectomy (e.g. myringotomy, endoscopic sinus surgery, etc.) were considered eligible for the study (see Tab. I for details on additional procedures). Informed consent for surgery was obtained from both parents of each participant included.

Surgical technique and patient management
All subjects included in the study underwent adenoidectomy or adenotonsillectomy with PEA (see Tabs. I and II for data concerning the surgical procedure). All patients had preoperative complete blood count, PT, and aPTT tested. Among them, 28 showed abnormal results, 15 of whom were diagnosed with coagulation disorders on further testing, and were managed with pre- and/or postoperative medical therapy according to haematological indications. None of these patients was excluded from the case series.
Operation was performed under general anaesthesia, with orotracheal intubation. The surgical field was exposed with a McIvor mouth gag. During PEA, the soft palate was downward retracted with a 10 French intermittent PVC catheter. The procedure started with an adenoid tissue biopsy taken with a small traditional adenotome in order to provide a specimen for surgical pathology, as per our institution requirements which demand a sample of any resected tissue to be sampled and analysed. After biopsy, the PEA procedure took place: adenoidectomy was completed with a 40° curved blade microdebrider introduced through the mouth, under endoscopic vision. Resection usually started along the choanal sill and proceeded downward on the posterior wall of rhinopharynx down to the inferior edge of adenoid tissue. Utmost attention was devoted to preserving the Eustachian tube. After completing the resection, haemostasis was achieved using curved bipolar forceps inserted transorally. The bipolar cautery was also performed endoscopically. PEA endoscopic vision was provided in the transoral technique by transorally introduced 4mm 45° or 70° scope and by a transnasally introduced 3 mm 0° scope in the transnasal technique, according to each surgeon's preference.
All the Otolaryngology Unit surgeons, both senior and junior, took part in the procedures. At least one of the senior surgeons (AMS, CP, LP, AS, AM or GF) took part in each procedure.
Planned postoperative hospital stay was 1 night for adenoidectomy patients and 2 nights for adenotonsillectomy patients.
All patients underwent intraoperative and 5-day post-surgical antibiotic prophylaxis with oral amoxicillin and clavulanic acid (70 mg amoxicillin/10 mg clavulanate/kg in three daily doses) or oral clarithromycin (15 mg/kg in two daily doses, in patients with known beta-lactam or clavulanate allergies). Furthermore, intraoperative steroid prophylaxis with dexamethasone 0.15 mg/kg was given in all children to reduce postoperative nausea and vomiting [16].
Patients and parents were instructed on the same post-surgery behavioural rules (avoid exposition to hot temperatures, eat warm and soft food, restrict physical activity and practice nasal irrigations at least twice a day) for 2 weeks after surgery. Patients were also instructed to promptly report to our otolaryngology department or to our institution emergency department in case of any complication.
Otolaryngological outpatient follow-up was routinely performed 7 days after discharge, then after 3 months in association with flexible endoscopy to evaluate the completeness of the resection, and finally at 1 year after surgery for treatment success evaluation, once again re-evaluating adenoid residues with flexible endoscopy in case of treatment failure.
Clinical indications for surgery, surgical times, additional surgical procedures performed, hospital stay length, postoperative pain, completeness of adenoidectomy, treatment failures, blood loss and perioperative complications were recorded and taken into account.
For surgical time, in order to avoid any bias, we excluded patients who underwent other surgical procedures along with adenoidectomy and adenotonsillectomy. Pain was recorded for all patients using a VAS scale at 12, 24 and 48 hours after surgery. Completeness of adenoidectomy was defined as the presence of an adenoid residue no greater than a grade I according to Cohen and Konak (CK), without tubaric os-

tium obstruction [17]. Intraoperative blood loss was recorded as negligible for amounts lower than 100 ml. Treatment failure was defined as the recurrence of one or more of the initially diagnosed condition at the 1-year follow-up visit.
Data were collected and elaborated in terms of descriptive statistics with Excel (Microsoft corporation, Redmond, WA, US).

Results

We recovered data on 1006 children, 578 males and 430 females, who underwent 493 surgical procedures of power-assisted adenoidectomy, and 513 of adenotonsillectomy in a 9-year period (see Tab. I). Mean age was 6.34 ± 2.22 years (range 3-14 years).
Clinical indications to surgical approach were classified as (see Tab. I):

- recurrent upper airways infections: main cause of adenotonsillectomy procedures (71%) and accounting for 26% of patients requiring adenoidectomy;
- recurrent acute otitis media (OAM) or otitis media with effusion (OME): main indication for adenoidectomy surgery (57.8% of patients), third indication adenotonsillectomy (18.9% of patients);
- nasal obstruction: 36.3% of adenoidectomy indications, 9.9% of adenotonsillectomy patients;
- obstructive sleep apnoea (OSA): 2.2% of children who underwent adenoidectomy procedures were diagnosed with OSA, while 32.9% patients with adenotonsillectomy indication were diagnosed with OSA.

We analysed surgical times, excluding patients where adenoidectomy or adenotonsillectomy were associated to other procedure (e.g. endoscopic sinus surgery, myringocentesis, biopsies, etc.). Mean surgical time for adenoidectomy was 19.24 ± 8.61 min, while mean time for adenotonsillectomy was 34.73 ± 15.23 min (see Tab. II).
We used a VAS as a tool for recording postoperative pain. For adenoidectomy, the median VAS was 3 at 12 hours after surgery, 1 after 24 hours and 0 after 48 hours. For adenotonsillectomy procedures, we observed a median VAS

Table I. Demography, associated surgical techniques, clinical indications, surgical approach and complications in power-assisted adenoidectomy and adenotonsillectomy.

Demography	Adenoidectomy	Adenotonsillectomy	Total
Males	270 (54.8%)	308 (60%)	578
Females	223 (45.2%)	207 (40%)	430
Total	493	513	1006
Associated surgery			
Myringocentesis	105 (21.2%)	27 (5.2%)	132
FESS	8 (1.6%)	1 (0.2%)	9
Other surgery	7 (1.4%)	5 (1%)	12
Clinical indications			
Recurrent upper airways infections	128 (26.0%)	364 (71.0%)	492 (48.9%)
Nasal obstruction	179 (36.3%)	51 (9.9%)	230 (22.8%)
AOM – EOM	285 (57.8%)	97 (18.9%)	382 (37.9%)
OSA	11 (2.2%)	169 (32.9%)	180 (17.8%)
Surgical approach			
Transnasal	112 (22.7%)	72 (14.0%)	184 (18.2%)
Transoral	378 (76.7%)	441 (86.0%)	819 (81.4%)
Transoral approach			
45° transoral optic	47 (9.8%)	0 (0%)	47 (5.7%)
70° transoral optic	341 (90.2%)	441 (100%)	782 (94.3%)
Complications			
Self-limited epistaxis	4	0	
Epistaxis requiring second surgery	2	0	
Epistaxis requiring nasal packing	4	0	
Tonsillar bleeding requiring second surgery	0	4	
Self-limited tonsillar bleeding	0	14	
Allergic reaction requiring ICU	0	1	

Table II. Results after power-assisted adenoidectomy (A) and adenotonsillectomy (AT).

	Intraoperative time (min)	SD	Relevant blood loss (>100 ml)	Complications	Failures	Recovery time	12h VAS score	24h VAS score	48h VAS score	No. patients
A	19.24	8.61	3	10 (2.02%)	4 (0.81%)	1.15	3	1	0	493
AT	34.73	15.23	2	18 (3.5%)	2 (0.4%)	2.06	4	2.7	2.5	513

score of 4, 3 and 2, respectively, at 12, 24 and 48 hours after surgery. 7 patients who underwent adenotonsillectomy showed a 24-hour post-surgery VAS score higher than 6, requiring additional treatment with i.v. tramadol (Tab. II). Usually, patients returned to their baseline quality of life between 4 and 10 days post-operatively.

Only 3 patients showed an intraoperative blood loss higher than 100 ml during an adenoidectomy procedure. These 3 patients reported respectively an estimated 250, 150 and 200 ml blood loss, which did not require blood transfusions. Two patients had an intraoperative blood loss of 250 and 300 ml during adenotonsillectomy, not requiring transfusion. All other surgeries did not result in any significant bleeding.

Mean hospitalisation time after adenoidectomy surgery was 1.15 ± 0.52 days and 2.06 ± 0.45 days after adenotonsillectomy. In both groups discharge was delayed due to uncontrolled pain, insufficient oral fluid and food intake, or complications such as bleeding (see after) or fever. After adenoidectomy, 10 patients had epistaxis (6 the same day as surgery, 3 the following day, 1 after 5 days) (Tab. II). Four of these patients required nasal packing, 4 were self-limited and 2 required revision surgery. Nine of 10 epistaxis events were anterior, and the only posterior epistaxis event was among the two requiring revision surgery. It should be noted that while all these patients underwent only an adenoidectomy procedure, most patients who underwent an associated endoscopic sinus surgery procedure had nasal packs until postoperative day 1, reducing the overall risk of epistaxis. Among adenotonsillectomy procedures, 18 post-surgical tonsillar bleedings were recorded, only 4 of which required surgical revision. A single allergic reaction was managed conservatively in the Intensive Care Unit with corticosteroid therapy and non-invasive ventilation (see Tab. I). Further investigations on this allergic reaction did not clarify whether it could be related to antibiotic prophylaxis or to anaesthesia drugs. The allergic reaction took place after surgery was already started; therefore, the surgical team deemed it safer to complete the procedure since the patient was haemodynamically stable.

For completeness of resection evaluated 3 months after surgery, successful resection was demonstrated in 93.64% of patients. More specifically, 65.31% of patients showed complete excision, while the remaining 28.33% had residual adenoidal tissue no greater than a CK grade I. 62 patients showed a CK grade II residue and 2 children a CK grade III residue. No children with CK grade II or III belonged to the treatment failures group.

For treatment success as evaluated at 1-year postoperative follow-up, after adenoidectomy 4 patients showed persistent nasal obstruction. After adenotonsillectomy, 1 patient reported persistent recurrent pharyngitis, while another reported persistence of sleep apnoea (Tab. II). These 5 patients were further evaluated during the 1-year visit with flexible endoscopy, which documented no residual adenoid hypertrophy.

Overall, short-term complications after power-assisted adenoidectomy were recorded in 2.02% of patients, and in 3.6% of patients after endoscopic adenotonsillectomy. Treatment failures rate were 1.01% for adenoidectomy and 0.38% for adenotonsillectomy. None of these patients belonged to the coagulation disorder group.

Discussion

Adenoidectomy is not only the most common procedure in paediatric otolaryngology, but also, from a general standpoint, one of the most frequently performed surgical procedures worldwide. Even if relatively unchanged over time, the TA technique may result in well-known and widely described side effects and complications. Being a relatively "blind" technique, TA does not allow complete surgical field vision, possibly leading to a tubaric ostia damage, incomplete adenoid removal causing disease recurrence and uncontrolled bleeding [15,18]. On the other hand, TA is an established technique, with an overall low rate of complications, negligible costs and negligible operative times [4].

The introduction of PEA in the early nineties was the only relevant threat posed to the historical predominance of the classic technique. PEA employs transoral or transnasal rigid scopes, providing a complete view of the surgical field with undoubtedly better local control, generally at the expense of a longer procedural time [9].

Many studies have compared TA and PEA in order to shed some light on the advantages of this somewhat innovative procedure, but no study succeeded in providing analytic

data over a considerable case load. For example, many authors reported analytic data on procedural times in TA in wide case series [11,14,15,18-22]. On the other hand, data concerning procedural times in PEA are available only in selected case series, ranging from 10 to 100 patients, reporting conflicting conclusions. For example, according to some authors such as Öztürk [20], Stanislaw [15], Anand [14] and Al-Mazrou [18], PEA shortens operative times, while other studies indicate a longer mean surgical time than TA. Datta [21] and Hussein [22] reported mean operative times of 42.75 and 39.3 min, respectively, both in case series in which PEA was used during adenotonsillectomy procedures.

In order to provide a references in terms of mean intraoperative time, bleeding, short and long-term complications and treatment failures, we summarised the results of 8 solid trials comparing TA and PEA in Table III [11,14,15,18-22]. Regarding procedural times, in our case series PEA performed worse than literature reports on TA. PEA has known longer operative times, although it has to be noted that some authors [11] correctly emphasised that the overall time spent in the operating theatre is more relevant than the procedural time itself. Furthermore, it has to be noted that even literature reports on TA shows highly variable procedural times, which can be explained by analysing other variables in depth, e.g. choice on whether to apply cautery or not [11,22].

Bleeding is another critical point in surgical management. The literature reports that, obviously enough, during PEA, mean blood loss values are significantly lower for isolated adenoidectomy [14,15,18] than in adenotonsillectomy [11,21]. Interestingly, our case series shows slightly different results, with a smaller difference in terms of bleeding between isolated endoscopic adenoidectomy and adenotonsillectomy. Three adenoidectomy procedures registered blood losses

Table III. Results in literatures for traditional (TA) and power-assisted endoscopic adenoidectomy (PEA) in terms of intraoperative time, blood loss, complications, recurrences and overall outcomes.

Mean values	Technique	Intraoperative time (min)	Blood loss (ml)	Complications	Failures	Total	Surgery
Murray [19]							
	TA	8.08	48	0	0	40	A
Songu [11]							
	TA	7.15	22.9	-	3 (3%)	10	A ± T
	PEA	12.02	26.3	-	1 (0.5%)	20	A ± T
Öztürk [20]							
	TA	16.5	-	2 (7.6%)	0	26	A
	PEA	11.8	-	1 (3.7%)	0	27	A
Stanislaw [15]							
	TA	12.5	24	1 (1.1%)	8 (9.1%)	87	A
	PEA	10.1	17.5	1 (1.1%)	1 (1.1%)	90	A
Anand [14]							
	TA	16	40	-	5 (25%)	20	A
	PEA	12	35	-	0	20	A
Al-Mazrou [18]							
	TA	12.3	22.1	4 (28.5%)	7 (50%)	14	A
	PEA	6.2	8.2	3 (11.5%)	1 (3.8%)	26	A
Hussein [22]							
	TA	32.25	-	3 (15%)	4 (20%)	20	A ± T
	PEA	42.75	-	5 (25%)	0	20	A ± T
Datta [21]							
	TA	29.3	21	5 (16.6%)	16 (53.3%)	30	A ± T
	PEA	39.3	31	3 (10%)	0	30	A ± T
Current series							
		19.24	-	10 (2.02%)	4(0.81%)	493	A
		34.73	-	18 (3.6%)	2(0.4%)	513	A + T

A: adenoidectomy; T: tonsillectomy.

over 100 ml (0.6%), compared to only 2 adenotonsillectomy procedures (0.38%). Nevertheless, this difference can be ascribed to a random variation in our patients, considering the overall extremely reduced blood loss in these procedures.

Complications after TA were reported as ranging from 28.5% (Al-Mazrou [18]) to 0 (Murray et al. [19]), while PEA showed a lower complication rates ranging from 25% (Al-Mazrou [18]) to 1.1% (Stanislaw [15]). In our case series, complications were described in 2.0% of patients undergoing adenoidectomy, and in 3.5% of patients undergoing adenotonsillectomy. Though PEA performs better than most literature reports on TA, it is interesting though how selected TA case series with low complication rates [19] did not differ significantly from our case series. When comparing our rate of complications with other PEA literature reports, ours is comparable only to studies including at least 90 patients [15]. This decrease in complications rate in larger case series may be the results of more solid surgical experience in the technique. Nevertheless, in our experience, PEA showed a shallow learning curve, with younger specialists getting a swift hold on the technique, both in terms of surgical times and complication rates.

Recurrences after adenoidectomy surgery are common, as can be seen in the literature with Emerick [24]. In our study, treatment failure rates were 0.81% after adenoidectomy and 0.4% after adenotonsillectomy. It has to be noted though that 6.4% of patients in our study showed a 1-year CK class II-III adenoidal residue, which was not linked to treatment failure. Our results did not significantly differ from literature reports, where treatment failures rate for PEA range from 0 to 3.8%. TA shows higher failure rates, which range from 0 to 53% [14,15,19-22]. Both our data and literature reports therefore suggest that while PEA may be inconvenient in terms of time management, it is associated with greater accuracy and predictability of results.

Since none of the aforementioned randomised controlled trials included relevant data on pain, we chose to compare our data with the VAS score reported by Vons et al. [23] in a cohort of patients treated with TA. Vons et al. [23] recorded pain intensity after day-surgery adenoidectomy and adenotonsillectomy both in hospital and during 1-week follow-up period. Patients were discharged with a median VAS score of 1 after adenoidectomy and 2 after adenotonsillectomy; the score increased at the first measurement at home to 2 for adenoidectomy and 4.5 for adenotonsillectomy procedure. At 48 hours after surgery, a score of 0 points was reported in patients who underwent adenoidectomy surgery, and 3 after adenotonsillectomy. Our data based on the VAS measurement of pain did not significantly differ from that reported in the aforementioned study. It has to be noted that our case series has two major differences in management compared to other studies cited herein, namely patient discharge and antibiotic prophylaxis. For example, many authors proposed PEA as an outpatient procedure [15,20,23,25]. They performed outpatient surgery with day care treatment, followed by 7-day post-operative control or in some cases just by phone call [15]. In our unit, we prefer to maintain at least a 1-day observation after adenoidectomy and 2 days after adenotonsillectomy, to ensure an adequate successful monitoring, which could have positively affected our complication rate, albeit with obviously higher healthcare-related costs. The second major difference is the broad use in our case series of antibiotic prophylaxis, which is not endorsed by any specific guideline. Widespread use of intraoperative and postoperative antibiotic prophylaxis is a matter of debate and, while it may reduce the risk of infection and patient readmission, therefore lowering the complication rate, it can show detrimental effects on inducing antibiotic resistances.

While our work provides interesting insight on a wide single-centre case series, a major drawback when comparing our data with other recent studies is the lack of a control group of patients treated with other techniques. Such lack of comparison is due to our institutional choice to provide PEA to all paediatric patients, which we consider the most reliable technique, but undoubtedly weakens our findings.

Conclusions

Power-assisted adenoidectomy provides safer and more controlled surgical options, in terms of bleeding, short-term and long-term complications and therapeutic failures. In our view, our large case series of 1006 patients definitely confirms those findings, justifying a slightly longer intraoperative time in exchange for overall better outcomes, with an even more significant impact on surgical practice due to the number of patients who will undergo this procedure on a daily basis.

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