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Review

A review of new insights on the association between hearing loss and cognitive decline in ageing

Ipoacusia e declino cognitivo: revisione della letteratura

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SUMMARY

Age-related hearing loss (ARHL) has a multifactorial pathogenesis and it is an inevitable hearing impairment associated with reduction of communicative skills related to ageing. Increasing evidence has linked ARHL to more rapid progression of cognitive decline and incidental dementia. Many aspects of daily living of elderly people have been associated to hearing abilities, showing that hearing loss (HL) affects the quality of life, social relationships, motor skills, psychological aspects and function and morphology in specific brain areas. Epidemiological and clinical studies confirm the assumption of a relationship between these conditions. However, the mechanisms are still unclear and are reviewed herein. Long-term hearing deprivation of auditory inputs can impact cognitive performance by decreasing the quality of communication leading to social isolation and depression and facilitate dementia. On the contrary, the limited cognitive skills may reduce the cognitive resources available for auditory perception, increasing the effects of HL. In addition, hearing loss and cognitive decline may reflect a 'common cause' on the auditory pathway and brain. In fact, some pathogenetic factors are recongised in common microvascular disease factors such as diabetes, atherosclerosis and hypertension. Interdisciplinary efforts to investigate and address HL in the context of brain and cognitive ageing are needed. Surprisingly, few studies have been adressed on the effectiveness of hearing aids in changing the natural history of cognitive decline. Effective interventions with hearing aids or cochlear implant may improve social and emotional function, communication, cognitive function and positively impact quality of life. The aim of this review is to overview new insights on this challenging topic and provide new ideas for future research.

KEY WORDS: Hearing loss • Dementia • Elderly • Cochlear implant • Cognitive impairment

RIASSUNTO

La perdita dell'udito legata all'età o presbiacusia è un deficit correlato al processo irreversibile di invecchiamento che riconosce una patogenesi multifattoriale. Crescenti osservazioni hanno collegato la presbiacusia a una rapida progressione del declino cognitivo e incidentalmente con la demenza. Molti aspetti della vita quotidiana degli anziani sono stati collegati alle loro capacità uditive, mostrando che la perdita uditiva incide sulla qualità della vita, i rapporti sociali, le capacità motorie, gli aspetti psicologici, la funzione e la morfologia di specifiche aree cerebrali. Studi epidemiologici e clinici confermano l'ipotesi di un legame tra queste condizioni e questo lavoro ha lo scopo di fare il punto sui meccanismi patogenetici che sostengono tale associazione. Lo sforzo di un lavoro congiunto tra otorinolaringoiatri, audiologi, neurologi e cognitivisti è quello di chiarire gli aspetti comuni, le possibilità di diagnosi e di intervento precoce al fine di ridurre gli effetti dell'uno sull'altro di questi processi degenerativi. Le osservazioni sperimentali e cliniche si concentrano su differenti aspetti: in primo luogo la deprivazione uditiva per lungo tempo può avere un impatto negativo sulle prestazioni cognitive diminuendo la qualità della comunicazione che porta all'isolamento sociale e la depressione e quindi facilitare la demenza. Al contrario, le capacità cognitive limitate possono ridurre le risorse cognitive disponibili per la percezione uditiva, aumentando così gli effetti della perdita dell'udito. Inoltre, questa associazione può rappresentare la conseguenza di una 'causa comune' nella patogenesi del deficit uditivo e del sistema nervoso centrale. Infatti, molti dei fattori eziopatogenetici sono comuni, quali le cause microvascolari della malattia (es. diabete, aterosclerosi, ipertensione). La sfida di questi anni è quella di aumentare le conoscenze sui rapporti tra invecchiamento cerebrale e cognitivo ed ipoacusia, grazie anche ai progressi del neuroimaging. *Sorprendentemente pochi dati sono stati pubblicati sull'utilità delle protesi acustiche nel cambiare la storia naturale di declino cognitivo. La protesizzazione e gli impianti cocleari possono migliorare le attività sociali e la sfera emotiva, la comunicazione e quindi più in generale la funzione cognitiva, con un globale impatto positivo sulla qualità della vita. Lo scopo di questo lavoro è quello di fornire le informazioni attualmente disponibili in letteratura su rapporto tra declino cognitivo e deficit uditivo nell'anziano, fornendo nuovi spunti di ricerca per il futuro.*

PAROLE CHIAVE: *Ipoacusia • Demenza • Deficit cognitivo • Impianto cocleare • Anziani*

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Introduction

It is well known that both hearing loss (HL) and cognitive impairment are associated with ageing. The first report on the independent relationship between hearing impairment and cognitive dysfunction appeared about 30 years ago [1], suggesting the hypothesis that age-related hearing loss (ARHL) may contribute to dementia. Probably the lack of interaction among ENT specialists, audiologists, neurologists, epidemiologists and cognitive scientists has limited the possibility to better recognise their correlation and impact on elderly people. More recently, growing epidemiological, neurobiological and neuroimaging evidence opened a new interest in this field and an increasing number of reports have focused on the relationship and effects of both HL and cognitive decline on the quality of life and rehabilitative perspectives [2]. ARHL can be defined as a progressive, bilateral, symmetrical HL that reduces an individual's communicative skills due to age and can be considered a multifactorial complex disorder, with both environmental and genetic factors contributing to the aetiology of the disease [3]. Cognitive impairment generically refers to a wide range of conditions ranging from mild cognitive impairment to severe dementia, while different degrees of hearing loss can impact the communicative impairment and quality of life. The increasing prevalence of cognitive decline [4 5] and the devastating impact of dementia on affected individuals and the burden imposed on families and society has made prevention and treatment of dementia a public health priority. Many aspects of daily living of elderly people have been linked to hearing abilities, showing that ARHL affects the quality of life, social relations, motor skills, psychological aspects, function and morphology in specific brain areas. On the basis of clinical evidence, it has been suggested that ARHL is linked with more rapid progression of dementia. The potential public health impact of ARHL in the context of dementia is substantial given the high worldwide prevalence of HL in older adults and the ready availability of existing hearing rehabilitative interventions, which remain risk free and underutilised. Until now, in the literature there are no studies demonstrating the utility of hearing rehabilitation in changing the natural history of dementia. Interdisciplinary efforts to investigate and address ARHL in the context of brain and cognitive impairment in older subjects are challenging. Despite the increasing attention, the relationship between cognitive status and HL is still controversial, and in particular it remains to be investigated whether HL is involved in the causal mechanisms of dementia or whether there is an independent relationship in which ARHL might enhance the effects of dementia. The aim of this paper is to focus on the new insights on epidemiological aspects, prevention, assessment and intervention strategies for older adults with HL who are at risk of developing dementia.

Epidemiology of hearing loss and dementia

Hearing loss affects approximately one-third of adults from 61 to 70 years of age and more than 80 percent of those older than 85 years. After hypertension and arthritis, it is the most common health disorder in older patients. More than 90% of HL in older patients can be classified as ARHL, while few patients are effected by conductive or mixed hearing loss. The impact of ARHL will increase due to the ageing of baby boomers and it is reasonable to assume a further escalation because of the constant growth of average lifespan in industrialised countries. In the US, 26.7 million adults older than 50 years suffer from ARHL and only 3.8 million use hearing aids [6], while, in UK 8.1 million suffer from HL, of whom 1.4 million use hearing aids [4-7]. According to the United Nations, the global population will grow from 6.9 billion in 2010 to 9.3 billion in 2050. The proportion of the population aged 60 or older will nearly double in the same period, reaching 21% of the total population in 2050, or nearly 2 billion of people in 2050. Males demonstrate a higher incidence of presbycusis with earlier onset compared to women. Among European Countries, in Italy, 1 in 6 of people suffer some form of HL, in Finland 1 of 7, while in Sweden and Denmark 1 of 10 people are affected by ARHL. For the WHO, in Europe about 70 million people are affected by ARHL, even if the statistics include also slight hearing levels with threshold greater than 25 dB. Only about 20% of people 65 years or older with moderate to profound ARHL perceive themselves as hearing impaired and about 70% of people with ARHL refuse hearing aids (www.actiononhearingloss.org.uk/your-hearing/aboutdeafness-and-hearing-loss/statistics.aspx). Interestingly, costs for hearing aids are lower than the cost of the untreated HL with an expense cost of € 213 billion per year in Italy and France, about € 22 billion in UK and € 30.2 billion in Germany [5 6]. In developed countries, hearing loss (HL) is very prevalent; although in African and South East Asian regions preventable causes of hearing impairment such as otitis media, sensorineural damage due to nutritional deficiencies, noise-induced hearing loss, ototoxicity and genetic hearing loss from consanguinity are more commonly reported in the literature than ARHL even if they can contribute to this condition [8]. Epidemiological evidence [7-9] supports the association between ARHL and late-life cognitive disorders suggesting that hearing impairment is a modifiable factor that, with appropriate treatment, could facilitate activities of daily living, decrease isolation and loneliness of aged subjects and slow down cognitive decline.

Similar to ARHL, there are gradual and age-related losses in cognitive processing including speed of information processing, memory and attention. Beyond normal age-related cognitive changes, clinically mild cognitive impairment (MCI) increases with age and about one fifth of

people have some degree of cognitive loss by the age of 70 years [10]. The prevalence of dementia increases from 5% in those 71 to 79 years to 37% in those 90 years and older, with an overall prevalence of approximately 14% for those over 70 years of age [9]. Moreover, a continuum between MCI and dementia has been recognised [12 13] and patients with MCI are at an intermediary stage that often, but not always, progresses to Alzheimer's disease (AD), which is the most common form of dementia. It is suggested that the rate of conversion from MCI to AD is about 10% to 15% per year, which increases to 80% after 6 years, and it is higher than the rate of 1-2% per year observed in the general population [14]. Numbers of dementia are impressive: in 2005, 24.3 million people were estimated to have dementia, with 4.6 million new cases of dementia every year (one new case every 7 patient). This number is expected to double every 20 years to 8.1 million people by 2040 [4 5].

Altogether, given the high prevalence of both hearing loss and cognitive decline in older adults that increases in prevalence with age [8-15], it is reasonable to assume that cognitive disorders are common in many of the oldest adults who have ARHL. Therefore, epidemiological evidence supports the hypothesis that there is a link between ARHL and dementia.

The hypotheses on the relationship between age-related hearing loss and cognitive decline

Even if epidemiological, audiological and auditory central testing corroborate the association between HL and incidental dementia [16 17], different relationship are debated. Major evidence supports the hypothesis that cognitive decline can reduce the cognitive resources available for auditory perception manifesting as hearing loss and reduced understanding of speech, also indicated as "cognitive load on perception hypothesis". In contrast, it has been shown that the risk of developing dementia is higher in individuals affected by ARHL [11-13 17] suggesting that hearing loss leads to cognitive decline because of degradation of inputs to brain (Fig. 1). Lin et al. [11] demonstrated that for every 10 dB increase in HL over 25 dB HL there was a 20% increased risk of developing dementia. More recently, Gurcel et al. [18] showed that in adults over 65 years of age the mean time for developing dementia was 10.3 years in those with hearing loss at baseline *versus* 11.9 years for counterparts with normal hearing. Thus, ARHL has been found to be independently associated with poorer cognitive function and incident dementia; in particular, normal hearing individuals, compared to mild, moderate, and severe hearing loss patients had a two, three, and five-fold increased risk of incident all-cause dementia, respectively [13 19]. It has also been demonstrated that ARHL impacts several domains of healthy aging including social engagement, physical mobility and activity, falls, vitality and even dementia, in addition to cognitive dysfunction [1 15 20]. Moreover, it has been demonstrated that scores from several cognitive tests generally declined linearly with increasing levels of HL [12,17]. A strong association has been observed between HL and measures of memory and executive function. Furthermore, a significant association between severe HL and poorer cognitive function has been found administering both verbal and non-verbal cognitive tests to older patients [21-25]. More recently, Dupuis and colleagues [26] confirmed Lin's data, but focused attention on the influence of HL or other sensory deficits on the results of cognitive tests. Nevertheless, this datum is still debated, and previous studies have been prone to exclude this relationship [24 25].

All efforts should be made to establish the relationship between HL and cognition in older patients undergoing to clinical evaluation. In some cases, cognitive losses may be misdiagnosed or conversely over-diagnosed when the sensory abilities of patients are not considered. This matter is especially important when a diagnosis of dementia is based on orally administered evaluation using tests environment in which there may be varying levels of ambient noise. A recent study by Jorgensen et al. [27] indicates that in only 13% of patients in a primary care clinic who were affected by memory loss was hearing status investigated. In summary, the association between ARHL and cognitive impairment is now well established by several cross-sectional and longitudinal studies, and it is unquestionable that hearing loss is more common in patients affected by dementia that in healthy older adults.

Interestingly, it has been postulated that ARHL may act as a ''second hit'' on the brain, thus adversely affecting cognitive performance and increasing the risk of dementia by adding to brain injuries derived from other disorders (e.g., amyloid-beta accumulation, neurofibrillary tangles and microvascular disease). For example, cross-sectional neuroimaging studies have demonstrated that peripheral hearing impairment is associated with reduced cortical volumes in the primary auditory cortex and variation in the integrity of central auditory white matter tracksas described in the following paragraph [28-32 37-40]. Longitudinal data from animal models [33 34] also demonstrated that cochlear impairment may precipitate changes in cortical reorganisation and brain morphometry. Accordingly, confirmation for a link from HL and cognitive impairment is also derived by the evidence that both conditions are sequelae of an underlying pathology such as hypertension, diabetes and/or atherosclerosis (Fig. 1). As previously mentioned, ARHL is a complex multifactorial disorder with both environmental (i.e. noise, ototoxic drugs, atherosclerosis, diabetes, hypertension) and genetic factors (i.e. genetic susceptibility) that contribute to its aetiology. As experimentally shown [3 33 34], the aged cochlea shows degeneration of stria vascularis, sensorineural epithelium and neurons in the spiral ganglion and auditory cortex of the central auditory pathways related to exogenous factors

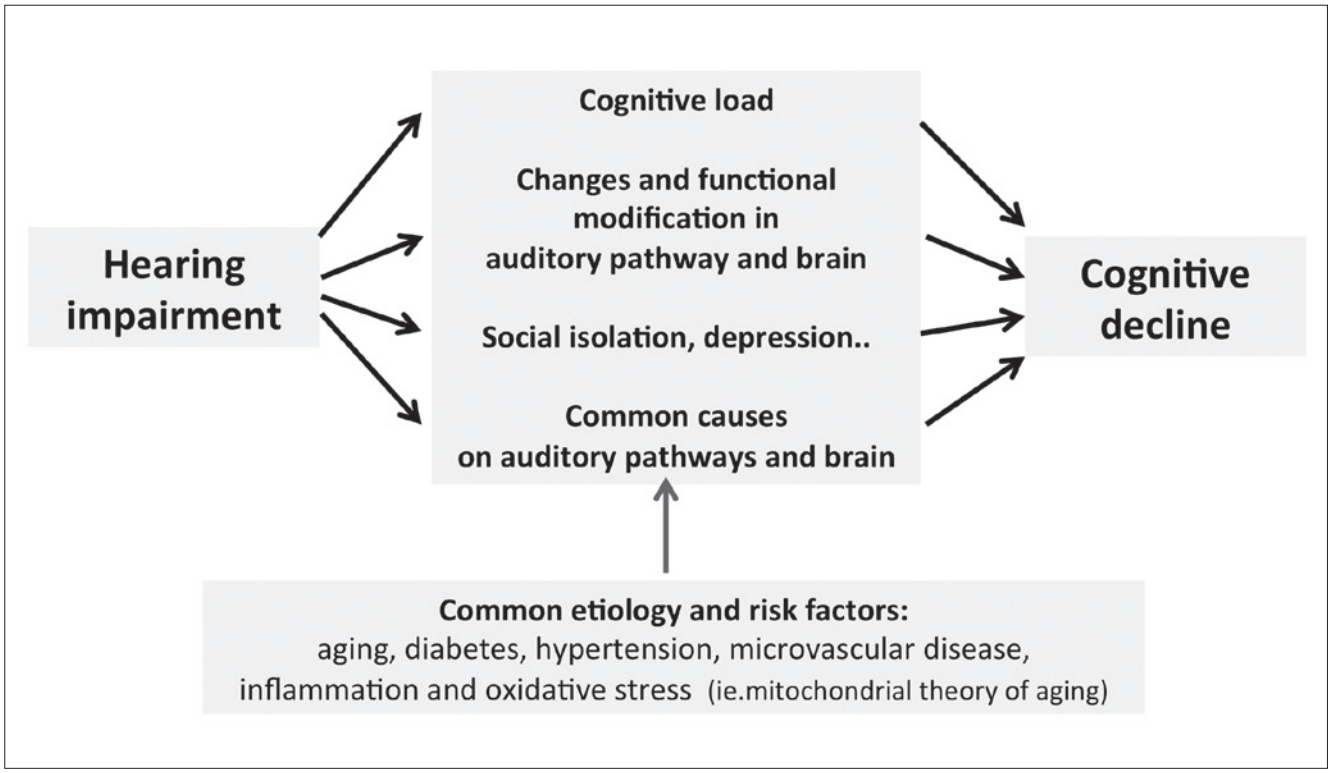

Fig. 1. Conceptual model of the association of hearing loss with cognitive decline (adapted from Lin [2]).

(e.g. noise and ototoxic drugs, vascular risk factors) inducing oxidative stress pathways (including the "mitochondrial theory of ageing") and inflammation; some of these mechanisms are common to neurodegenerative diseases including AD. Experimentally, the role of microvascular damage in the pathogenesis of AHRL has been clearly demonstrated together with the evidence that spiral ganglion deafferentation is associated with altered dendritic architecture of auditory pyramidal neurons [3 33]. Thus, common factors could underlie a simple correlation between hearing and cognition including age, vascular risk factors and social factors (e.g. education) [2 11-13].

Alternatively, mechanistic hypotheses have been proposed that argue for a causal association between ARHL and cognitive decline, including increased social isolation and loneliness, increased cognitive load and changes in brain structure [35]. Further studies will be needed to clarify this association.

All epidemiological and clinical evidence has been organized in the following four hypotheses (Fig. 2): first, cognitive decline may reduce the cognitive resources that are available for auditory perception, increasing the effects of hearing loss, also referred as "cognitive load on perception hypothesis". When the inputs are poor, either through degraded stimuli or impaired perception, additional cognitive resources are required to understand the signal. For the "information degradation hypothesis", an additional effort is required either because the stimoli are degraded, for example in noisy enviromenment, because the perception is decreased, and therefore cognitive resources used for the signal codification are not available for cognitive roles [28]. In contrast, as previouly mentioned, the "sensory-deprivation hypothesis" described by Lin and colleagues [11-13], suggested that hearing loss causes cognitive decline that is permanent or potentially remediable after rehabilitation. According to this hearing impairment increases cognitive effort in patients with cognitive defects and depressive symptoms [35]. A plausible mechanism may be that impaired perception could lead to worsening cognition over time and social isolation which in turn leads to cognitive decline. Finally, a fourth mechanism takes inspiration by the evidence that some common factors cause both declines, also called the "common cause hypothesis", in facts the clinical demonstration is that multiple sensory modalities and cognition appear to decline concurrently in the older patients. As summarised by Lin et al. [2] in a convincing model (Figg. 1, 2), there is a common aetiology for ARHL and cognitive decline, even dementia, that is based firstly, on microvascular and ageing risk factors, and secondly hearing impairment affects different domains such as social isolation, loneliness, increased cognitive load and changes in brain structure that may contribute to the onset of cognitive decline and dementia [2].

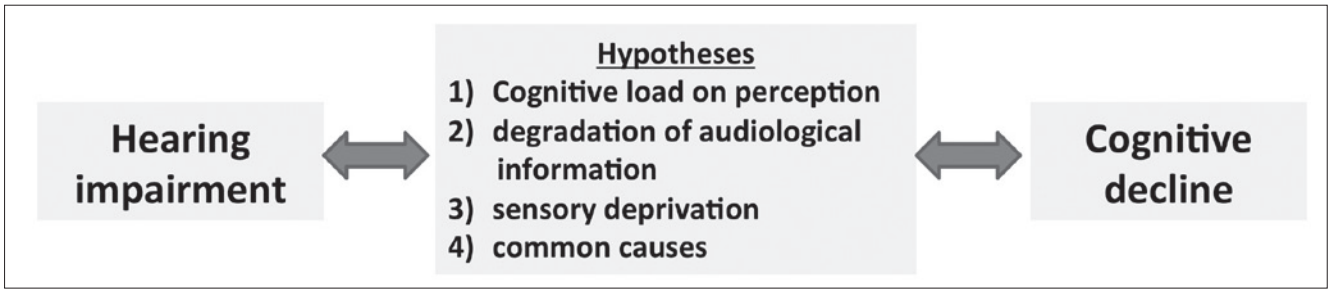

Fig. 2. The epidemiological and clinical evidence is summarised in the following hypotheses on the relationship between HL and cognitive decline.

Peripheral and central origin of ARHL: a link between central auditory processing disorders and cognitive decline

Traditionally, cochlear damage, including hair cell loss and damage of stria vascularis and spiral ganglion neurons, was considered to be the main cause for ARHL according to Schuknecht topology, which correlated the patterns of hearing loss with the location of the hearing defect. Temporal bone studies suggested three main types of presbycusis: *sensory presbycusis* with high frequencies HL caused by hair cell loss and subsequent neural degeneration, *neural presbycusis* characterised by the loss of word discrimination caused by the primary degeneration of cochlear neurons and *metabolic/strial presbycusis* characterised by a flat pure-tone audiometry caused by the atrophy of stria vascularis [36]. Additional types have been described: *mechanical* (cochlear/conductive hypothetical) with changes in the basilar membrane affecting its properties and function, and *mixed and indeterminate* when multiple influences interact [37]. However, sound perception depends not only on normal cochlea but also on the function of the auditory pathway, which may explain the fall of discrimination, in particular in noisy environments, and increasing evidence supports a pivotal role of central auditory processes (CAP) in presbycusis. The role of CAP is well established in several behavioural phenomena such as sound localisation and lateralisation, auditory discrimination, temporal aspects of audition (temporal resolution, masking, integration and ordering), auditory performance with competing acoustic signals and auditory performance with degraded signals. Even if the simplest auditory tasks are influenced by higher-level, non modality-specific factors as attention, learning, motivation, memory and decision processes and higher level contextual information influence the perceptual analysis of the acoustic signal; while various knowledge sources interact and support the auditory processing of spoken language and other complex acoustic signals. Briefly, central auditory process disorders (CAPDs) concern an auditory perceptual dysfunction that cannot be explained on the basis of peripheral hearing loss and refer to impairment in central auditory pathways, such as neural transmission, feature extraction deficit, or information processing problems that lead to impaired speech understanding. CAPD can affect all people at any age (even children or young adults) as a consequence of brain focal injures, or neurological and genetic disorders [38-42].

The existence of ARHL decline in CAPD is well established, but the mechanism and effects are still controversial. While the presence of a pure CAPD seems to be uncommon in older patients, the evaluation of comorbidity between central and peripheral damage using central auditory testing in these patients may be challenging. The prevalence of ARHL and CAPD in a population older than 65 years was 64.1 and 14.3%, respectively [43]. Furthermore, studies on the association between CAP dysfunction and MCI or AD are limited [44]. Many authors identified these disorders in the auditory portions of the central nervous system without clear lesions [39]. The pathophysiology of CAPD is not fully understood, probably involves interhemispheric interaction and *corpus callosum* function. CAPD tests typically require extracting auditory signals in noise or competing signals and the diagnosis of a CAPD can be very tricky in older patients even affected by cognitive decline [39 41]. Gates et al. [16 45] investigated the relationship between CAPD and dementia. In a first study they found that CAPD was evident in subjects with mild AD, whereas peripheral auditory function was not different from control subjects. A link between CAPD and cognitive dysfunction is also explained by the observation that older patients with CAPD seem to be more prone to experience dementia than those without CAPD. Furthermore, in older people with mild, amnestic, single domain cognitive impairment (MCI), severe CAPD is more prevalent than in people with normal cognitive status and the presence of CAD is more likely to be associated with an increased risk of dementia diagnosis in the follow-up period [46 47]. Gates et al. [45] in a 3-year follow-up study showed that severe CAPD was predictive for the risk of subsequent diagnosis of AD. Moreover, as recently reviewed by Panza et al. [44], longitudinal studies also confirmed that the peripheral ARHL is associated with decline of several cognitive domains and accelerated cognitive decline.

As previously mentioned, diagnosis of CAPD is clinically argue and results of auditory central testing controversial.

From 2009 to 2011, the America Academy of Audiology Task Force on Central Presbycusis reviewed 145 papers to understand the evidence on age-related changes in auditory portions of the central nervous system and the impact of such changes on everyday communication and function. Based on this review of the literature, the authors concluded that the evidence for the existence of central presbycusis in the isolated entity is insufficient [48]. On the other hand, recent findings support the existence of central presbycusis as a multifactorial condition that involves age- and/or disease-related changes in the auditory system and brain [44].

Age-related changes in the human central auditory system: morphological and neuroimaging evidence

In the last years, increasing interest has been focused on neuroplasticity of the brain which indicates the changes of its structure and function in response to environment and experience occurring in both synaptic, network and anatomical levels. It is common sense that an "active" life is beneficial for the mind and brain. In fact, it is well known that both physical and intellectual activity have a positive influence on the incidence of neurodegenerative disorders and cognitive decline. Recently, it has been described that enriched environment improves learning, enhances neurogenesis and branching, synapse formation and activity of neurotrophic factors [33 34].

In principle, ageing causes cortical atrophy, which is accompanied by shrinkage of grey and white matter volumes and enlargement of the cerebrospinal fluid space [49]. Post-mortem analyses have shown a decline in the number of dendrites, synapses and neuronal fibres without direct loss of neurons [50]. Thus, as also discussed in the previous paragraph, lifestyle and environment can modulate neuroplasticity even in aged adults, who can be affected by neurobiological and anatomical changes. Major modifications include white matter de-myelination and grey matter shrinkage, altered neurotransmission and neural atrophy that can be enhanced by visual and hearing deprivation involving neural connectivity and brain organisation. In this field, studies are still ongoing. However, growing contributions by neuroimaging and neurobiological findings suggest a cortical and neuronal reorganisation after hearing loss in consequence of adaptive or maladaptive plasticity observed in neurodegenerative diseases and HL induced by exogenous factors or ageing [33 34].

It has been recently demonstrated by MRI that subjects with hearing impairment have accelerated rates of whole brain atrophy as well as specific volume declines in the right superior, middle and inferior temporal gyri over a mean 6.4 years of follow-up [17]. These findings extend the discussion on whether peripheral hearing impairment has broader implications for brain structure and function. Prior cross-sectional neuroimaging studies demonstrated that greater audiometric hearing impairment is associated with reduced volumes in the primary auditory cortex and temporal lobe [28-30]. Other studies, using diffusion-tensor imaging of central auditory pathways, demonstrated decreased fractional anisotropy in the lateral lemniscus and inferior colliculus in individuals with hearing impairment versus those with normal hearing [31 50]. The temporal regions are intriguing because they are important not only for spoken language processing, but also for semantic memory and sensory integration, and are involved in the early stages of mild cognitive impairment or early AD [52]. A shared neuropathological or intrinsic cellular ageing process leading to both cochlear and brain ageing is a mechanistic option. Hearing impairment may also be potentially associated with brain volume changes through reduced neural stimulation of the auditory cortex by impoverished auditory signals [28]. New insights on the biochemical changes in the auditory cortex have been detected by MR spectroscopy, which is an interesting tool for studying cortical mechanisms. In a recent report [53] it was demonstrated that ARHL is accompanied by the reduction of the excitatory activity in the auditory cortex. By using MR spectroscopy, the authors examined metabolite levels in the auditory cortex of subjects older than 65 years either with mild or severe presbycusis, demonstrating significant lower concentrations of glutamate and N-acetylaspartate in aged subjects with increased levels of lactate. Significant differences were not found in other metabolites, including GABA, which is the most important inhibitory neurotransmitter. In summary, the older brain suffers not only from atrophy but also from changes in the content of some metabolites affecting both grey and white matter even if the morphological findings in neuroimaging are still controversial. We expect that in the future robust evidence will be obtained by improvements in neuroimaging techniques. In principle, there is substantial evidence supporting the hypothesis that the modifications observed in the brain in patients affected by ARHL depend more on ageing than on hearing impairment.

Impact of ageing and hearing loss on linguistic abilities

Evidence on the relationship among ageing, hearing loss and linguistic abilities is scarce, however the question of how hearing impairment affects linguistic abilities due to the consequences on the quality of life (i.e. social isolation, depression, etc.) remains an interesting feature. In principle, linguistic abilities do not seem to be affected by age. Although there is little loss of word knowledge, word retrieval during speaking becomes slower and more difficult [54]. This can lead to more frequent occurrences of "tip-of-the-tongue" status, where a desired word or person's name is known, but there is difficulty in its retrieval [55 56].

On the other hand, spoken language comprehension tends to be preserved, despite atrophy in the neural regions involved. Some functional MRI studies identified a two-component model of sentence comprehension: a core sentence-processing area located in the perisylvian region of the left cerebral hemisphere and an associated network of brain regions that support working memory and other resources needed for comprehension of long or syntactically complex sentences [57-59]. In fact, working memory is known to constrain the comprehension of sentences with complex syntactic structures [60] that result in adults in the alteration in producing syntactically complex utterances. The syntactic organisation represents a special burden on working memory [61].

Although, there is a question of whether all aspects of language processing are constrained by a single working memory resource or by a complex of specialised resources [62], there is no doubt that working memory limitations affect cognition in aging adulthood. It might be predicted by two observations: firstly, complex syntax and rapid speech rates operate in a multiplicative fashion in affecting sentence comprehension [63]. Secondly, in spoken language comprehension, it is well known that recognition is superior for words heard within a meaningful sentence than for words heard in isolation. This longstanding observation reflects the general principle that the amount of sensory information needed for correct recognition of any stimulus will be inversely proportional to its probability within a constraining context [64].

This generality, although correct, overlooks the potential importance of the cognitive effort required for comprehension of speech that is syntactically complex [65].

This is important for word recognition because understanding the meaning of a sentence is the force that constrains the probability of a particular word in that context. The comprehension of syntactically complex speech may draw on working memory resources that are already limited in normal ageing [65]; many studies have shown differential effects of syntactic complexity on older adults' comprehension relative to that of younger adults. This latter aspect has been investigated in older adults with hearing loss, because the decreased activation of specialised processing regions of brain, and limited ability to coordinate activity between regions, contribute to older adults' difficulty with sentence comprehension under difficult listening condition [66]. In fact, it would be expected that when older adults with already limited working memory resources are further strained by perceptual effort attendant to even a mild hearing loss, the negative effects on sentence comprehension of age and syntactic complexity can be further multiplied [59].

Stewart and Wingfield [67] confirmed the common findings of better report accuracy for meaningful sentences than for words heard in isolation without a sentence context, but for older adults there was also a significant effect of syntactic complexity of sentence stimuli. This effect was further increased by HL. These results are interpreted in terms of age-limited working memory resources that are impacted both by the resource demands required for comprehension of syntactically complex sentences and by effortful listening attendant to hearing.

An interesting study analysed the role of hearing acuity, age and verbal and cognitive ability in word recognition when words are heard in the absence of a linguistic context, or when heard proceeded by varying degrees of contextual constraint. Results emphasise the importance of cognitive function in auditory performance [57 58], showing in addition, that as the degree of contextual support from a linguistic context increases, the relative contributions of cognitive ability and hearing acuity are reversed. Specifically, in a neutral context there is a large role for hearing acuity on word recognition and a modest role for cognitive ability. By contrast, in the highest context condition, hearing acuity was no longer a significant predictor, but general cognitive ability played a significant role. These findings underscore the need to take into account the relationship of individual differences in cognitive ability and constraints of linguistic context, as well as hearing acuity.

Impact of hearing loss on physical activity and quality of life in the elderly

As previoulsy adduced, maintaining an optimal level of physical functioning is a critical aspect of healthy aging, however, longitudinal studies on the association of hearing impairment with incident functional are not conclusive, with some studies demonstrating a positive association [11-13], and other contributions denying [68]. This heterogeneity on results is likely explained by differences in how hearing (e.g. subjective self-report[3] *vs* objective clinical audiometry) and physical functioning (e.g. activities of daily living, walking difficulty, falls) or other self-reported measures were quantified [68-72].

Chen and colleagues [73] reported that subjects with average greater hearing impairment had poorer short physical performance battery scores and slower gait speeds at two time points 10 years apart, which were also reflected in an increased risk of incident disability and requirement for nursing care in women. Moreover, Gispen et al. [74] showed that moderate or severe hearing impairment in older adults was independently associated with less physical activity as measured subjectively by the self-report and objectively according to accelerometry. Patients with moderate or severe hearing impairment had a 59% greater possibility of having lower levels of self-reported physical activity and 70% greater odds of having lower levels of accelerometer-measured physical activity than those with normal hearing. Interestingly, several studies have demonstrated associations between HL and poor physical functioning [75-80], poor cardiorespiratory fitness, sedentary behaviour and slow

gait speed in older adults [81]. In contrast, other reports have indicated that there is no significant association between HL and physical functioning and activity [82]. Subjective measurement [83] or varying definitions [84] of hearing may explain the reported heterogeneity in study results.
Different mechanisms can explain the observed association between hearing and physical activity. Individuals with moderate or greater hearing impairment may perform less physical activity because they are socially isolated (and thus have less likelihood of exercise in a social setting) than those with normal hearing. Studies have also demonstrated that impaired hearing can contribute to cognitive load and therefore affect attentional and cognitive resources [11 17] that are important for maintaining posture and balance [85]. Impaired hearing can restrict the ability to monitor the auditory environment effectively (e.g., hearing footfalls and other auditory cues that provide orientation to the physical environment), thereby affecting the likelihood of performing physical activities. Alternatively, common pathological processes may underlie impairments in hearing and physical activity. Accordingly with the evidence for a link between presbycusis and cognitive impairment as described above, cardiovascular disease may contribute to HL [83] and poorer health and physical activity. In fact, HL in older patients is often associated with cardiovascular disease (e.g., congestive heart failure, coronary artery disease, angina pectoris, myocardial infarction, hypertension, smoking status, BMI). Alternatively, common neural degeneration affecting not only the cochlea but also the vestibular organ, involved in the balance control, can explain the relationship between HL and poor physical activity.
Growing findings indicate that in older patients *frailty* represents a clinical syndrome characterised by decreased physiologic reserve and weakness that causes an increased vulnerability to stressors [86]. The prevalence of frailty is increased in the institutionalised population. Epidemiologic studies investigating the association of HL with frailty and physical functioning suggest that moderate to severe HL seems to be associated with increased risk of developing frailty, independently of age, demographic characteristics and cardiovascular risk factors [2]. Further studies are needed to determine the pathogenesis of this association.
It is interesting also to take into consideration the effects of *dual sensorial impairment* (i.e. hearing and visual loss, DSI) in older patients and their relationship with cognitive decline. Obviously the effects of late-onset DSI depend by the severity of sensorial impairments in both ears and eyes, however it is demonstrated that DSI affects physical, psychological, and psychosocial well-being [87]. Furthermore, Lin et al. [11] reported that, patients affects by DSI had the greatest odds of cognitive and functional decline, although the risk was not different in patients with visual impairment alone suggesting that the presence of HL does not further decreased the effects on cognition. Nevertheless, more studies are needed to better understand the interaction of visual and hearing impairment in older adults.
Finally, as a consequence of all the aspects interfering with the good health of older patients, Genther et al. [84] found that HL was associated with a 34% increased risk of mortality compared with normal hearing in community-dwelling older adult aged 70-79. After adjustment for other demographic characteristics (sex, education, and study site) and cardiovascular risk factors (diabetes, stroke, and smoking), HL was associated with a 20% increased risk of mortality compared with normal hearing [84]. Two studies examined the association of audiometric HL with mortality. The first paper performed in adults aged 70 and older found an association between HL and mortality after adjusting for demographic characteristics, but this association disappeared after adjusting for various health factors [88]. A second study conducted in adults aged 50 and older used structural equation modeling and found an association between HL and mortality that was mediated through cognitive impairment and walking disability[89]. Finally, in adults aged 67 and older an association between objective HL and increased cardiovascular mortality has been found, but not with all-cause mortality [90]. In contrast with these findings , in others studies this association seems to be inconsistent, so we agree that additional studies are needed in proving the relationship between HL and overall mortality [91-94].

The impact of hearing aids and cochlear implant on eldery deaf patients

On the basis of "a cascade hypothesis" between HL and cognitive decline the natural consequence is that the use of hearing aids (HA) or cochlear implant should be associated with better cognitive performance. It is evident that older adults with untreated moderate to profound hearing loss may develop a cascade of conditions including communication difficulties, social isolation, depression, an association with falls and declines in physical functioning, decreased quality of life and even cognitive decline that could be counteracted by HA (Fig. 3). However, few studies investigated whether auditory amplification can reduce the risk of cognitive decline and dementia. A recent paper addressed the positive association of HA use on cognition that was independent of any positive association of hearing aid use on social isolation and depression. Therefore, the authors suggested that the effects of HA on cognition was not correlated to the reduction of the adverse effects of hearing loss on social isolation or depression and probably related to the direct impact on the hearing amplification on daily life [95]. How HA impact on cognitive performance through a reduction of depression or social isolation or, as a direct consequence, remains controversal. Furthermore, the question how hearing aids might interfere with cognitive decline remains unexplained. Accordingly with the hypothesis suggested by the Dawes et al. [95] untreated hearing loss may increase

the effect of auditory deprivation on the brain resulting in increased cognitive decline. Moreover, cognitive decline can reduce social participation, increase isolation and depression thus reducing the interest for hearing rehabilitation. A randomised clinical trial of HL treatment [96] that examined outcomes beyond measures of speech perception and quality of life, demonstrated improved social and emotional function, communicative abilities and cognitive function in the treatment group. Unfortunately, the reported prevalence of HA users in older adults varies from 21.5% in UK, 11.0% in Australia and approximately 14% in the US with a level of satisfaction that is lower than in young and adult patients [6 97]. Possible explanations for the no-use of HA are the poor quality of amplified sound, the availability of technological solutions and the cost for hearing aids. Further research is needed to determine whether HA independently improves the quality of life of these patients.

An interdisciplinary approach and collaboration between otolaryngologists and neuro-psychologists is mandatory to investigate and address hearing loss in the context of brain and cognitive aging for a correct management of older patients and the decision for hearing aids or cochlear implant (CI).

In the last two decades, the literature has been enriched by several studies based on speech perception outcome, comparing younger and older adult CI recipients. Older adults underwent to CI achieve significant improvement in speech perception performance scores over preoperative performance with conventional amplification [98]. Furthermore, older adults can continue to benefit from cochlear implantation with long-term use although psychosocial changes, hearing deprivation length, age at implantation, and reduced cognitive and learning abilities influence outcomes in elderly patients. A recent paper from Lin's Group [2] addresses the positive impact of both HA and CI on mental health quality of life. Interestingly, the authors found that patients who received CI had twice the gain in the mental component summary score compared to HA recipients at 6 and 12 months after amplification. Di Nardo et al. [98] compared auditory performances and several quality of life outcomes between under 60 years CI users and over 60 years recipients. They found a significant benefit on speech recognition tests compared to preimplantation condition, even if younger CI users scored significantly better in both bisyllabic words and sentences recognition test. No significant difference was found between the study and control group in physical and mental health status, conversation with an outsider, or use of TV and phone. Overall satisfaction derived from CI was higher in the older than in the younger patients. These findings indicate a high level of satisfaction and a dramatic improvement in quality of life and communication abilities after cochlear implantation in elderly people with postlingually bilateral severe-to-profound hearing loss that cannot be explained only by enhancements to auditory perception. More studies that demonstrate a link between CI rehabilitation and cognitive level will be challenging. In 2015, Miller et al. [99] reviewed 5057 articles and concluded that only 3 studies met the full criteria for this topic. The overall results were inconclusive in terms of cognitive benefit provided by cochlear implantation. Mosnier et al. [100] conduced a prospective study on impact of cochlear implant in old people and concluded that hearing rehabilitation using cochlear implantation is associated with an improvement in function in all cognitive domains as early as 6 months after implantation in elderly patients who had abnormal test scores at baseline. More than 80% of patients who had the poorest cognitive scores before implantation improved their cognitive function at the 1-year post implantation interval. In contrast, patients with the best cognitive performance before implantation demonstrated stable results. These preliminary results have never been confirmed in a trial with a larger and more representative cohort. Further research is thus needed to evaluate the long-term influence of hearing restoration on cognitive decline and its effect on public health.

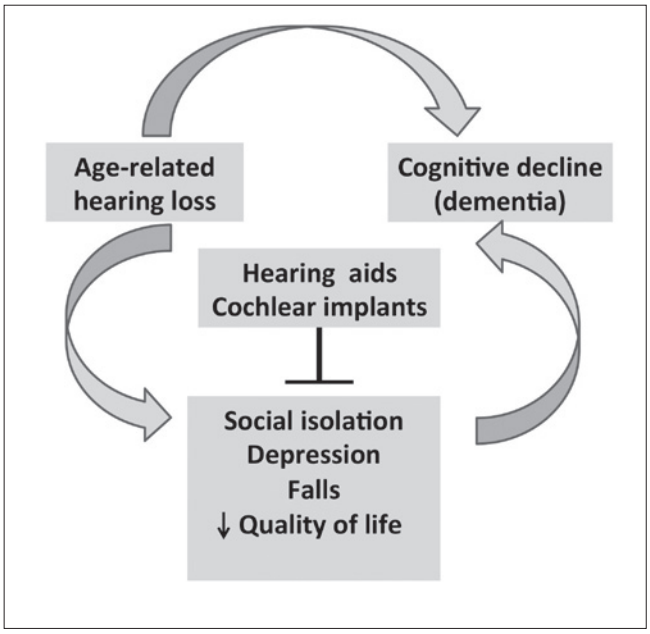

Fig. 3. Untreated moderate to profound hearing loss may develop a cascade of conditions including communication difficulties, social isolation, depression, falls and decreased quality of life that could be counteracted by hearing aids and cochlear implants.

Conclusions

Robust evidence suggests that HL in the elderly is independently associated with development of cognitive decline and dementia. Several hypotheses on the pathogenic relationship between HL and cognitive decline have been

postulated and summarized in a conceptual model in which the hearing impairment impacts cognitive load, changes in brain structure and function, leads to social isolation and depression related with a common aetiology (i.e. genetic and environmental factors).

HL and their putative effects on cognition are highly prevalent in older patients and their effects may be preventable and treatable with rehabilitative devices (i.e. hearing aids and cochlear implants) that remain widely underutilised. Further research is needed to understand if and how hearing aids and cochlear implants can change the natural history of these conditions and improve quality of life in the elderly.

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HEAD AND NECK

Oncological and complication assessment of CO2 laser-assisted endoscopic surgery for T1-T2 glottic tumours: clinical experience

Analisi oncologica e delle complicanze nel trattamento endoscopico mediante laser CO2 dei tumori glottici in classe T1-T2: la nostra esperienza

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SUMMARY

Several therapeutic options are used for treatment of early stage glottic carcinoma (Tis/T1/T2): open partial laryngectomy (OPL), radiotherapy and CO2 laser-assisted endoscopic surgery. Laser surgery has gradually gained approval in the management of laryngeal cancer. We present our experience in endoscopic laser surgery for early stage glottic carcinomas. This was a retrospective analysis of 72 patients with T1-T2 glottic cancer treated with laser cordectomy between 2006 and 2012. All patients had at least a 36-month follow-up period. Percentages for disease-specific survival, disease-free survival (DFS) and laryngeal preservation rates were 98.6%, 84.7% and 97.2% respectively. Considering neoplastic features that could predict long-term oncological outcome, tumoural involvement of anterior commissure and pathological staging (pT) significantly correlate with local recurrence (p = 0.021 and p = 0.035) and with a lowered DFS (p = 0.017 and p = 0.023). Other variables such as clinical staging, type of cordectomy, involvement of other structures and surgical margin status showed no significant impact on oncological endpoints. CO2 laser surgery is a reliable technique for T1-T2 glottic cancer considering oncological outcomes. The recurrence rate seems to be affected by involvement of anterior commissure and pT stage.

KEY WORDS: Larynx • Glottic carcinoma • Laryngeal cancer • CO2 laser-surgery • Early stage • Endoscopic cordectomy

RIASSUNTO

Esistono numerose strategie terapeutiche per il trattamento del carcinoma glottico in stadio iniziale (Tis/T1/T2): la laringectomia parziale a cielo aperto, la radioterapia e la chirurgia endoscopica condotta mediante laser CO2. In particolare quest'ultimo approccio ha gradualmente, ma inesorabilmente, acquisito un ruolo sempre più centrale nel management del cancro laringeo. In questo lavoro presentiamo la nostra esperienza in materia di chirurgia endoscopica laser-assistita delle neoplasie glottiche in stadio iniziale. È stata realizzata un'analisi retrospettiva su un campione di 72 pazienti affetti da carcinoma glottico in classe T1-T2 trattati con cordectomia laser endoscopica nel periodo compreso tra il 2006 e il 2012. Tutti i pazienti avevano almeno 36 mesi di follow-up. La disease-specific survival, la disease-free survival (DFS) e il tasso di preservazione laringea rilevati con il presente studio sono stati rispettivamente del 98,6%, 84,7% e 97,2%. Analizzando l'influenza sull'outcome oncologico a lungo termine di alcune tra le principali caratteristiche della malattia o del trattamento eseguito, abbiamo riscontrato come il coinvolgimento da parte del tumore della commissura anteriore e lo staging patologico della neoplasia (pT) correlino significativamente con un aumentato tasso di recidiva locale (p = 0,021 e p = 0,035) e con una ridotta DFS (p = 0,017 e p = 0,023). Gli altri parametri presi in esame, come staging clinico, tipo di cordectomia, coinvolgimento di altre specifiche sottosedi laringee e stato dei margini di resezione, non si sono dimostrati, invece, correlare significativamente con gli endpoint oncologici stabiliti. La chirurgia endoscopica laser-assistita è quindi una tecnica estremamente affidabile per il trattamento dei tumori glottici in stadio iniziale in termini di outcome oncologico. Il tasso di recidiva risulta significativamente influenzato dal coinvolgimento della commissura anteriore e dal pT.

PAROLE CHIAVE: *Laringe • Carcinoma glottico • Cancro laringeo • Laser CO2, Stadio iniziale • Cordectomia endoscopica*

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Introduction

Larynx carcinoma accounts for 4.5% of malignant neoplasms and glottic cancer makes up approximately 50% of laryngeal tumours [1]. Different options are available for treatment, especially when the tumour is identified at an early stage: transoral laser microsurgery (TLM), open partial laryngectomy (OPL) and radiotherapy (RT) [2 3].

In the last years the use of TLM has greatly expanded. For this reason, it has been debated whether the oncological and functional results of this method are comparable to those of other techniques. OPL allows obtaining larger free margins and better oncological results; it also gives the possibility to treat the neck simultaneously, when required. On the other hand, hospitalisation times are

longer, the rate of complications is higher and functional results are worse [4].
RT is associated with good oncological outcome, but higher costs and longer time of care; the voice is generally good at the end of treatment [5].
TLM can be used to manage Tis, T1, T2 and selected T3 glottic cancers [6 7]. Hospitalisation time is reduced to 1-3 days on average (depending on the type of cordectomy); oncological and functional results are usually good if an experienced surgical team performs the procedure.
In this paper, we analyse our experience in TLM in terms of oncological outcomes. Different prognostic factors were analysed to identify specific tumour features that are related to poor prognosis.

Materials and methods

The study was carried out retrospectively on a series of 72 patients with T1-T2 glottic cancer treated with CO2 laser-assisted endoscopic cordectomy (TLM) between February 2006 and February 2012 at the ENT department of San Raffaele Hospital in Milan, Italy. The original cohort included 120 cases, but we excluded patients who did not reach a minimum 36-month follow-up period (57.4 ± 20.2 months). Forty-eight patients had shorter follow-up period or, alternatively, were missed during the follow-up. The cohort included 66 men (91.7%) and 6 women (8.3%) with a mean age of 65 (range: 35-87) at the time of surgery. No patient had received previous treatment for laryngeal cancer.
All patients underwent pre-operative white light and NBI video-laryngoscopy with flexible endoscope and video-laryngo-stroboscopy. Patients with manifest involvement of anterior commissure, Morgagni's ventricle, subglottis, arytenoids, or with impaired vocal fold mobility underwent contrast-enhanced neck computed tomography (CT) that helped rule out paraglottic space invasion or cartilage infiltration, which would contraindicate TLM. They were also evaluated with angled telescopes (0°, 30°, 70°) immediately before surgery to better explore those critical subsites. According to TNM classification of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) (7th edition) [8], clinical staging of primary laryngeal lesions (cT) was cT1a in 61 cases (84.7%), cT1b in 3 cases (4.2%) and cT2 in 8 cases (11.1%). No regional lymph node metastases (N) were detected at diagnosis, either clinically or with CT.
All surgical procedures were performed under general anaesthesia after oro-tracheal intubation. Tumour excision under microlaryngoscopy was always performed with a Lumenis AcuPulse 30ST CO2 laser (Lumenis Ltd. Yokneam, Israel) with super pulse beam delivery and power tailored on the target structures (4 W for vestibulectomy, 1.5-2 W for cordectomy). Endoscopic resections were graded according to the European Laryngological Society Classification [9] and its more recent revision [10], including 6 types of cordectomy: subepithelial (type I), subligamental (type II), transmuscular (type III), total (type IV), extended (type V) and the latest anterior commissurectomy with bilateral anterior cordectomy (type VI). As far as type III cordectomy was concerned, excision had both diagnostic and therapeutic aim. When deeper resections were indicated, patients achieved pathological diagnosis of lesions with bioptic microlaryngoscopy under general anaesthesia and all available therapeutic options were discussed, focusing on oncological and functional outcomes linked with each procedure.
Endoscopic resections were carried out with an en-bloc or piece-meal technique according to tumour location, extension on glottic surface and ease of laryngeal exposure. No elective neck dissection was performed. In order to evaluate both deep and superficial resection margins, surgical specimens were sent to a dedicated pathologist with a clearly inked margin. A detailed diagram of the surgical procedure was sent together with the specimen in case of piece-meal excision with critical margins specifically indicated.
Resection margins were classified as free, positive (superficial or deep), or unassessable (due to surgical artefacts). In case of a single superficial positive margin, our policy was to assign patients to a careful follow-up since resection margins were approached by photovaporisation. In particular, patients were followed up with monthly endoscopic controls and periodical neck CT evaluation. Patients with deep positive margin underwent revision TLM. Patients with free margins were assigned to 3-month endoscopic follow-up during the first two years, which was increased to 6 months during the third year. No patients underwent RT because of involved resection margins.
Statistical analysis was performed with the SPSS statistical package. The log-rank test and the Kaplan-Meier survival function were applied to assess different disease-free survival (DFS) rates for patients stratified according to variables of interest. Same variables were assessed with regards to recurrence rates with a chi-squared test. A $p < 0.05$ was considered statistically significant.

Results

Nine patients underwent type I cordectomy (12.5%), 14 patients type II (19.4%), 20 patients type III (27.8%), 12 patients type IV (16.7%) and 17 patients type V (23.6%). No type VI cordectomy was performed in our sample since no tumour originating from the anterior commissure was detected. En-bloc resection was preferred in 69 cases (95.8%), while a piece-meal technique was performed in only 3 cases (4.2%).
Median hospitalisation time was 3 days (range: 1-20 days). In particular, patients who underwent type I, II and III cordectomy were discharged on the first postoperative day, while deeper resections generally required hospital-

ization for 3 days. Longer hospital stay was associated with postsurgical complications.

Tumour staging according to pathological examination (pT) was pTis in 8 cases (11.1%), pT1a in 53 cases (73.6%), pT1b in 2 cases (2.8%) and pT2 in 9 cases (12.5%). Anterior commissure was involved in 19 patients (26.4%), vocal muscle in 17 patients (23.6%) and supraglottic structures (Morgagni's ventricle, false vocal cord) in 9 patients (12.5%). Resection margin status showed 38 cases with free margins (52.8%), 13 cases with a single superficial positive margin (18.1%), 7 cases with deep positive margin (9.7%) and 14 cases with unassessable margins due to surgical artefacts (19.4%). No surgical specimens with multiple superficial positive margins were detected.

Major and minor procedure-related complications are common in this kind of surgery. Major complications are defined as those that need extended medical therapies, blood transfusions, early surgical revision, or intensive care unit recovery. Two patients (2.8%) required nasogastric tube insertion to avoid inhalation, while 5 cases (6.9%) underwent prophylactic tracheostomy. All tracheostomies were closed before discharge. No intra-operative complications were reported. Four patients (5.6%) experienced early complications related to the surgical procedure: one case of limited post-operative laryngeal bleeding not requiring surgical haemostasis (1.4%), 2 cases of aspiration pneumonia (2.8%) and one subcutaneous cervical emphysema (1.4%). None required early surgical intervention. Late complications affected 8 patients in our cohort (11.9%): 3 cases of anterior glottic synechia (4.5%) and 5 cases of vocal cord granulomas (7.5%). The latter reported to chronically suffer from reflux-induced laryngitis: at first they were treated with proton-pump inhibitors and logopaedic therapy but later endoscopically excised, since none resolvedwith conservative treatment.

Recurrence is conventionally defined as a biopsy-proven neoplastic lesion in patients treated with TLM less than 60 months prior [11]. Since our study evaluated the first three years after surgical procedure, relapse was defined within the period considered. Recurrence occurred in 11 patients (15.3%) after a mean of 16.8 ± 8.9 months. Ten patients experienced a local recurrence (13.9%): 5 cases underwent salvage TLM (one type II cordectomy, one type III and three type V), 2 patients were treated with RT, 1 with supracricoid OPL and 2 with total laryngectomy followed by adjuvant RT. Two of these patients experienced a second recurrence: both were treated with concomitant chemo-RT. One patient developed cervical lymph node involvement (1.4%) demonstrated by positive fine-needle aspiration cytology (FNAC) and underwent selective ipsilateral neck dissection (Robbins level II-IV [12]. One patient died of disease (1.4%), while 8 patients died for unrelated causes (11.1%).

Table I shows the recurrence rate and DFS stratified according to common variables of interest: cT or pT staging,

Table I. Recurrence rates and disease-free survival (DFS; mean ± standard deviation) stratified according to variables of interest.

Variable		No. of cases	Recurrence rates	p value [a]	DFS in months (mean ± SD)	p value [b]
cT	cT1a	61	8/61 (13.1%)	0.230	33.7 ± 6.8	0.198
	cT1b-cT2	11	3/11 (27.3%)		29.7 ± 11.4	
pT	pTis-pT1a	61	7/61 (11.5%)	0.035	34.0 ± 6.3	0.023
	pT1b-pT2	11	4/11 (36.4%)		27.7 ± 12.1	
Anterior commissure	Free	53	5/53 (9.4%)	0.021	34.3 ± 6.2	0.017
	Involved	19	6/19 (31.6%)		29.7 ± 10.4	
Supraglottis	Free	63	8/63 (12.7%)	0.108	33.6 ± 7.0	0.094
	Involved	9	3/9 (33.3%)		29.0 ± 11.2	
Vocal muscle	Free	55	8/55 (14.5%)	0.756	33.2 ± 7.7	0.760
	Involved	17	3/17 (17.6%)		32.6 ± 8.0	
Cordectomy	Type I	9	2/9 (22.2%)	0.561	34.3 ± 4.3	0.600
	Type II	14	3/14 (21.4%)		31.3 ± 10.2	
	Type III	20	3/20 (15.0%)		32.7 ± 8.3	
	Type IV	12	0/12 (0%)		36.0 ± 0	
	Type V	17	3/17 (17.6%)		32.2 ± 8.8	
	Superficial (type I, II, III)	43	8/43 (18.6%)	0.339	32.6 ± 8.3	0.353
	Deep (type IV, V)	29	3/29 (10.3%)		33.8 ± 6.9	
Resection margin status	Free	38	4/38 (10.5%)	0.250	34.8 ± 3.8	0.193
	Single superficial positive	13	1/13 (7.7%)		33.9 ± 7.5	
	Deep positive	7	2/7 (28.6%)		28.0 ± 13.7	
	Unassessable (surgical artifacts)	14	4/14 (28.6%)		30.0 ± 10.6	

a Chi-squared test; b Log-rank test; cT = clinical staging; pT = pathological staging

involvement of anterior commissure, supraglottis or vocal muscle, type of cordectomy and resection margin status. Statistical analysis highlighted substantial correlation between pT staging or anterior commissure involvement and recurrence ($p = 0.035$ and $p = 0.021$, respectively), as displayed in Figures 1 and 2. Moreover, neoplastic extension to the anterior commissure appears to adversely influence DFS ($p = 0.017$, Fig. 3) as does pT staging ($p = 0.023$, Fig. 4). None of the other parameters reached statistical significance.

Discussion

Early stage glottic cancer can be managed by OPL, RT or TLM. All these methods are associated with good oncological results. For this reason, the choice of treatment should be related to costs, time of hospitalisation, rate of complications and functional results, although the patients' will must be considered first. In fact, there are no prospective randomised clinical trials assessing long-term outcomes associated with these different techniques.

As a general rule, early stage laryngeal tumours should be approached by a single modality of treatment [13 14]. This allows preserving the chance of a second, different treatment in case of relapse and also provides better functional results, since combined approaches (TLM followed by RT) are always associated with worse functional outcome. In our cohort, laryngeal tumour was more common in men than in women (male-female ratio 8:1), as is well known in the ENT literature [15]. This can be largely explained by higher rates of smoking and alcohol assumption in men. Mean age at the time of surgery (65 years) was also similar to those described by other authors [16]. Hospital stay was influenced by type of cordectomy and postoperative complications, as discussed above. Day surgery was generally enough for patients who underwent type I, II and III cordectomy, while deeper resections often required longer stays. Three days was the mean hospitalisation time in type IV and V cordectomy, even though post-surgical complications usually increased hospital stay.

Early postoperative complications generally include subcutaneous emphysema, bleeding, dyspnoea, dysphagia, aspiration pneumonia and laryngo-cutaneous fistula. Subcutaneous emphysema is mainly associated with cricothyroid membrane perforation. This can occur when glottic tumours extend beyond the inferior margin of thyroid cartilage or in commissural lesions in which oncologically-safe resection need to overcome that border [17]. Only 1 patient (1.4%) suffered from subcutaneous emphysema in our cohort; conservative management allowed its resolution before hospital discharge, as stated by Steiner in his assessment of postoperative complications after laser surgery of tumours of the upper aerodigestive tract [18]. In a previous work, Steiner and Ambrosch reported the incidence of post-surgical bleeding to be 7% in supraglottic partial laser-assisted endoscopic resections, 3% in hypopharyngeal ones and 0% in glottic ones [19]. One case in our cohort experienced this postoperative complication, and the haemorrhage stopped without surgical haemostasis. Aspiration pneumonia occurs most frequently in surgical treatment of supraglottic (5.8%) or hypopharyngeal cancers (12.9%) than in glottic tumours (1.7%) [20]. Two patients suffered from this complication within our cohort (2.8%), which is consistent with most of the ENT literature. The rate of postoperative dysphagia is obviously influenced by extension of surgical resection: only 2 patients (2.8%) required nasogastric tube insertion to avoid inhalation.

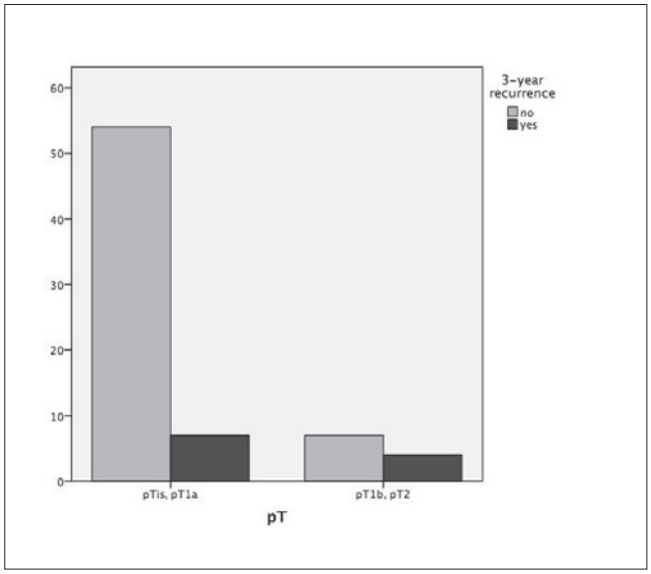

Fig. 1. Bar chart showing 3-year recurrence rates according to pT stage ($p = 0.035$).

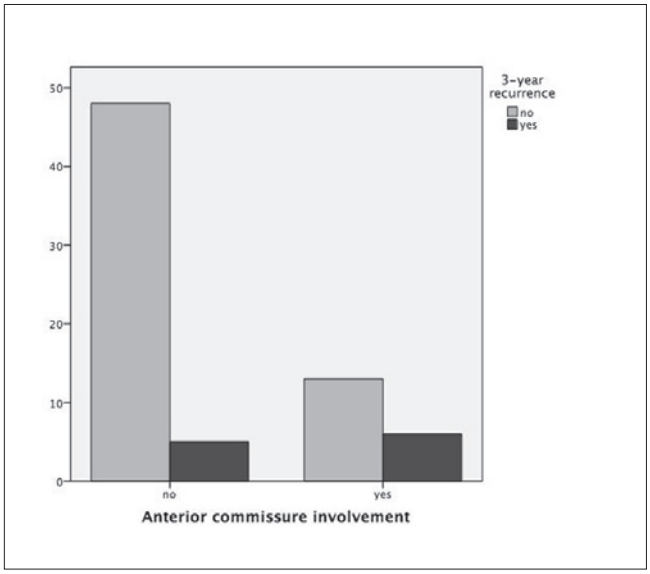

Fig. 2. Bar chart showing 3-year recurrence rates according to anterior commissure involvement ($p = 0.021$).

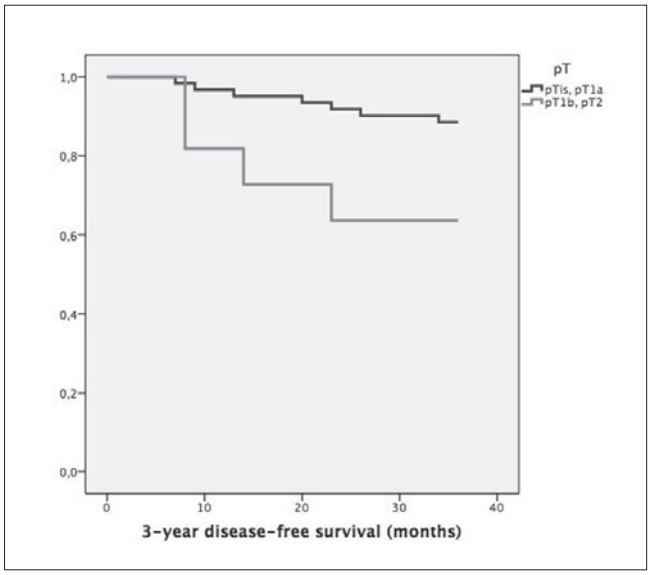

Fig. 3. Kaplan-Meier survival curves stratified according to pT stage (p = 0.023).

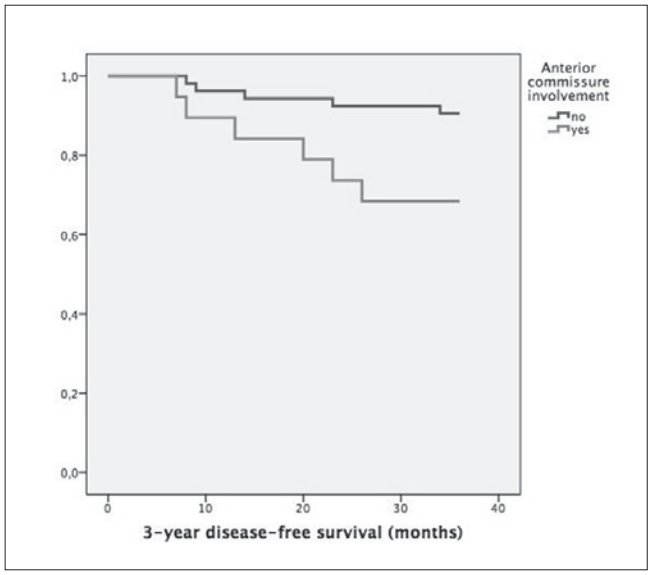

Fig. 4. Kaplan-Meier survival curves stratified according to anterior commissure involvement (p = 0.017).

One of the greatest advantages of TLM compared to OPL is the reduced need for prophylactic tracheostomy [21]. The study by Preuss reported a rate of prophylactic tracheostomy among patients who underwent TLM for laryngeal cancer of 1.9% [22]. As a general rule, our policy is to resort to tracheostomy in patients with a high risk of post-surgical endolaryngeal oedema or bleeding (patients taking anticoagulants or with significant intraoperative haemorrhage). In our cohort, 5 cases (6.9%) underwent prophylactic tracheostomy and all were closed before hospital discharge. However, dividing the temporal range (2006-2012), 4 tracheostomies were performed in the first half (2006-2009), compared to just 1 in the second interval (2009-2012), suggesting a clear decreasing trend. This can be explained with an improved intra- and postoperative management of patients associated with the physiological, surgical learning curve and the low rate of postoperative complications. This is highlighted by Vilaseca: in his investigation the post-surgical complication rate drastically reduced with increasing surgical expertise [23].

Late postoperative complications normally consist of anterior glottic synechia, vocal cord granulomas and arytenoid oedema. Anterior glottic synechiae are clinically relevant since they shrink the laryngeal respiratory space, although they can ease post-surgical glottic adduction and improve vocal outcome. That is why excision is considered only in case of substantial dyspnoea. In our cohort, 3 patients experienced anterior glottic synechia (4.2%) and none underwent surgical intervention. Vocal cord granulomas arise when endoscopic resection reaches inner perichondrium, especially in patients with a history of gastro-oesophageal reflux disease. Five of our patients developed granulomas (6.9%) and all referred to chronically suffer from reflux-induced laryngitis. Proton-pump inhibitor therapy combined with logopaedic rehabilitation did not achieve resolution in any of the affected patients, and they underwent endoscopic excision of granulomas. Arytenoid oedema can cause dyspnoea and dysphagia. In these cases, photovaporisation of the oedematous mucosa by CO2 laser can be useful, and was required by two patients in our cohort (2.8%).

The incidence of laryngeal tumour relapse after TLM was studied for the first time by Steiner and Ambrosch [19]. They reported a relapse rate of 9.5% in stage I and II and 19.5% in stage III and IV. Herein, the recurrence rate was 15.3% (11 cases) and a disease-specific survival rate of 98.6% was seen, with a preservation rate of 97.2%. These results are similar to those described by Lucioni [24].

Accurate preoperative staging allows good correspondence between clinical and postoperative definition of the tumour and can help to predict recurrence. Pre-operative white light and NBI video-laryngoscopy with flexible endoscope, video-laryngo-stroboscopy, imaging assessment (CT, MRI) and intraoperative evaluation with angled telescopes (0°, 30°, 70°) are all tools for such a purpose. Recently, even direct autofluorescence during intraoperative work-up has been shown to be useful [25]. In our study, we found no statistical significance in the association between relapse and clinical staging (p = 0.230), while pathological staging showed a clear correlation with the incidence of recurrence (p =†0.035). The same evidence was noted with regards to DFS shrinkage (p = 0.198 and p = 0.023 for cTNM and pTNM, respectively). This difference can be easily explained by the pathological upstaging that occurred in some cases: Ansarin has already highlighted this possibility [26].

We also found that anterior commissure involvement was related to a higher rate of recurrence (p = 0.021) with a

lower DFS (p = 0.017). Since the recent introduction of type VI cordectomy [10], a pure commissural tumour can be treated in a single session, offering better disease control compared to two-stage bilateral cordectomy. However, this latter technique can be still adopted in case of T1b glottic tumours. Considering T1b tumours, indeed, Roedel found reduced local control with TLM, evidence that was not confirmed in T2 neoplasms with anterior commissure involvement (transcommissural tumours). Moreover, in his experience T1b cancers and anterior commissure involvement in T2 transcommissural tumours did not show a substantial reduction in disease-specific survival [27]. On the other hand, Blanch observed that anterior commissure involvement influenced both relapse rate and disease-specific survival [28].

No significant difference was found between vocal muscle or supraglottic involvement and rate of recurrence (p = 0.756 and p = 0.108, respectively), as these subsites can be easily controlled by TLM.

Although no cases of arytenoid or subglottic region involvement were detected, a higher recurrence rate is associated with tumour extension to those laryngeal subsites [24]; different distribution of submucosal lymphatic drainage within the larynx largely justifies this finding.

A margin of 1 mm is considered oncologically safe in glottic TLM [26]. However, the relationship between resection margin status and relapse rate is still controversial [29-31]. As a general rule, we recommend strict follow-up when a superficial margin is given as involved by pathologists. Instead, when a deep margin is involved we usually perform a revision TLM within a few weeks.

Conclusions

TLM in early stage glottic cancer shows several advantages compared to RT and to OPL, such as reduced intra- and postoperative morbidity and shorter time of care. To date, we consider TLM as the treatment of choice in T1a, T1b and selected T2 and T3 tumours. In fact, it elicits no changes in swallowing and allows preservation of physiological respiration. Early complications are usually manageable without surgery and decrease with increasing surgical experience; on the other hand, late complications frequently need revision procedures, in most cases endoscopically.

TLM shows good results in terms of DFS and OS, comparable to those of RT. The relapse rate is higher (p = 0.021 and p = 0.035) and DFS is lower (p = 0.017 and p = 0.023) when anterior commissure is involved or pT is concerned, respectively. Type of cordectomy, cT, supraglottic or vocal muscle involvement and resection margin status do not significantly impact the recurrence rate.

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Head and neck

How does radiotherapy impact swallowing function in nasopharynx and oropharynx cancer? Short-term results of a prospective study

Qual è l'effetto della radioterapia sulla funzionalità deglutitoria nei pazienti con tumore del rinofaringe e orofaringe? Risultati a breve termine di uno studio prospettico

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SUMMARY

The objective of this study is to report the initial results of a prospective trial assessing instrumental deglutition function in nasopharynx and oropharynx cancers after radio or chemoradiotherapy using intensity-modulated radiotherapy (IMRT). IMRT was delivered aiming to spare the swallowing organ at risk (SWOARs) for Stage II-IV naso- and oropharynx cancer. Objective instrumental assessment included videofluoroscopy (VFS), fiberoptic endoscopic evaluation of swallowing (FEES) and oro-pharyngeal-oesophageal scintigraphy (OPES) at baseline and at 1 month after radiotherapy. Dysphagia parameter scores were calculated at each exam after liquid (L) and semi-liquid (SL) bolus intake: pre-deglutition penetration, aspiration, pharyngeal transit time (PTT) and hypopharyngeal retention index (HPRI). Overall, 20 patients (6 nasophaynx and 14 oropharynx) completed treatment and instrumental assessment after 1 month. Comparison between pre- and post-treatment HPRI score values showed a significant worsening in both FEES-L ($p = 0.021$) and SL ($p = 0.02$) and at VFS-L ($p = 0.008$) and SL ($p = 0.005$). Moreover, a relationship between HPRI worsening at FEES-L and FEES-SL ($p = 0.005$) as well as at VFS-L and VFS-SL ($p < 0.001$) was observed. PTT was not significantly affected by radiotherapy ($p > 0.2$). Only a few patients experienced pre-deglutition penetration (1 patient with base of tongue cancer at FEES-L and SL) and aspiration (1 patient with nasopharynx cancer at OPES-L and FEES-SL) after radiotherapy. Our early results showed that IMRT-SWOARs sparing caused a significant increase in the post-deglutition HPRI score. Longer follow-up will be necessary to evaluate if the increase of HPRI is related to a high risk of developing late aspiration.

KEY WORDS: Intensity and modulated radiotherapy • Deglutition • Fiberoptic endoscopic swallowing evaluation • Videofluoroscopy

RIASSUNTO

In questo lavoro vengono riportati i risultati a breve termine di uno studio prospettico, finalizzato alla valutazione strumentale della funzionalità deglutitoria in pazienti affetti da tumore del rinofaringe e orofaringe sottoposti a trattamento radio o radiochemioterapico con tecnica ad intensità modulata (IMRT). L' IMRT è stata finalizzata, oltre che al miglioramento della conformazione della dose radiante al volume tumorale, alla riduzione della stessa alle strutture responsabili della deglutizione (SWOARs). I criteri dello studio hanno previsto in tutti i pazienti la valutazione strumentale della deglutizione con Videofluoroscopia (VFS), Fibroscopia Endoscopica della deglutizione (FEES) e Scintigrafia Orofaringea (OPES) prima dell'inizio del trattamento e ad 1 mese dal termine dello stesso. Ogni esame è stato eseguito rispettivamente in seguito all'assunzione di un bolo liquido (L) e semiliquido (SL) e per ognuno sono stati calcolati i seguenti valori strumentali: presenza o meno di caduta pre-deglutitoria, presenza o meno di aspirazione, tempo di transito faringeo (PTT) ed indice di ritenzione ipofaringeo (HPRI). Dal Gennaio 2012 al Giugno 2013, un totale di 20 pazienti ha terminato il trattamento ed ha eseguito la valutazione strumentale a 1 mese dal termine della radioterapia. Il confronto tra i valori dell'HPRI prima e dopo il trattamento radiante ha mostrato un peggioramento significativo sia alla FEES-L ($p = 0,021$) e SL ($p = 0,02$) che alla VFS-L ($p = 0,008$) che SL ($p = 0,005$). Inoltre è stata riscontrata una significativa correlazione tra i valori dell'HPRI basale ed a 1 mese alla FEES-L e SL ($p = 0,005$) così come alla VFS-L e SL ($p < 0,001$). Diversamente, il tempo di transito faringeo (PTT) non è risultato essere influenzato dalla radioterapia ($p > 0,2$). Solo in pochi pazienti è stata riscontrata la comparsa di caduta pre-deglutitoria (1 paziente con tumore della base linguale alla FEES-L e SL) e la presenza di aspirazione (1 paziente con tumore del rinofaringe alla OPES-L e FEES-SL). Nel complesso i risultati iniziali del nostro studio mostrano che l' IMRT, finalizzata al risparmio delle SWOARs, determina soltanto un significativo incremento della ritenzione di bolo a livello del distretto ipofaringeo. Un follow-up più lungo sarà necessario per valutare se tale incremento sia associato o meno ad un maggior rischio di sviluppare fenomeni di aspirazione tardivi.

PAROLE CHIAVE: *Radioterapia ad intensità modulata • Deglutizione • Fibroscopia endoscopica della deglutizione (FEES) • Videofluoroscopia*

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Introduction

Nowadays radiotherapy (RT) alone or most frequently combined with chemotherapy (RCT) is considered a valid alternative treatment to surgery for patients affected by head and neck cancer (HNC) in order to preserve the deglutition organ [1 2]. Historically, conventional RT has been burdened by severe and potentially "life threatening" toxicity that limited the delivery of high tumour radiation dose and in most cases affected the final treatment result [3-6]. In this regard radiation-induced dysphagia, as a final multifactorial side effect often requiring enteral nutrition, represents a real "Achille's heel" that occurs in more than 50% of patients and can lead to a malnutritional status and an increased risk of aspiration pneumonia [7-9]. The 1-and 2-year rates of percutaneous endoscopic gastrostomy (PEG) tube dependence is reported, respectively, in 24% and 14%, whereas clinical aspiration pneumonia is reported in 3% of cases [10].

On the contrary, an organ preservation strategy should provide both the highest tumour control probability (TCP) and the minimum function impairment with the subsequent maximum therapeutic index gain.

In fact, reducing deglutition disorders related-symptoms (e.g., oropharyngeal pain, dry mouth, food stuck in the throat and choking) and deglutition disorder related-complications (pulmonary complications) can result both in a significant improvement of patient quality of life (QoL) together with a reduction in hospitalisation costs [11-13].

In the last few decades, the advancement of treatment technologies, such as intensity and modulated radiotherapy (IMRT), has shown promising results in terms of better TCP as well as a reduction of toxicity through the sparing of swallowing organs at risk (SWOARs) [14 15].

Hence, several studies have investigated the impact of RT using IMRT on the deglutition function but are mostly retrospective, addressed to an heterogeneous set of patients and lacking preatreatment swallowing evaluation [16-20].

Moreover, in most cases dysphagia was defined using a surrogate clinical endpoint, such as percutaneous tube dependence (PEG) time, aspiration pneumonia or pharingoesophageal strictures. Differently, the assessment of deglutition function typically includes both clinical and instrumental evaluation [11].

Although several objective patient-reported instruments, such as Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) criteria, the Subjective Objective Management Analytic (SOMA) scale and the Common Terminology Criteria for Adverse Events (CTCAE) are available [20-23], they are variable and have been shown to underestimate deglutition impairment compared with objective instrumental assessment [24]. Indeed, a clear and uniform consensus of objective instrumental deglutition assessment has yet not been clearly defined.

Videofluoroscopy (VFS) and fiberoptic endoscopic evaluation of swallowing (FEES) are considered the gold standards for dysphagia assessment, whereas oropharyngeal-ossophageal scintigraphy (OPES) is considered optional combined with FEES and VFS [25].

Thus, due to the reliability and validity of instrumental assessment tools, the use of all available complementary procedures is suggested by the current literature to properly evaluate swallowing function [25 26].

We therefore initiated a prospective longitudinal study to assess the impact of RT on swallowing function in a homogeneous subset of HNC patients who were candidates for radio or chemoradiotherapy as a radical curative treatment.

The primary endpoint was to evaluate dysphagia parameter changes using pre and post-treatment objective instrumental assessment after IMRT aimed to reduce the radiation dose to the SWOARs.

In this study, we report our preliminary results focusing on acute dysphagia (1 month after treatment), not previously investigated, in order to assess the risk of severe complications during or soon after RT or RCT.

Materials and methods

Patient characteristics

This is an ongoing prospective study carried out by the collaboration of the Department of Radiation Oncology, the Department of Radiology and the Otorhinolaringology and Speech Language Pathologist Unit. The study was approved by the Institutional Review Board of the University of Pisa; all patients signed a study-specific informed consent form.

The eligibility criteria included all patients affected by nasopharynx and oropharynx cancer (Stage II-IVA), with histological proven diagnosis of undifferentiated nasopharyngeal-type carcinoma or squamous cell carcinoma, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2 and age < 80 years old.

Exclusion criteria were the following: a different site from nasopharynx or oropharynx, a different histology from undifferentiated nasopharyngeal type or squamous cell carcinoma, ECOG Status ≥ 3, Stage IVB and C, prior induction chemotherapy or prior HN treatment (surgery and/or RT), diagnosis of concomitant comorbidity which might compromise basic deglutition function (demyelinating or degenerative diseases and connective tissue diseases) and age > 80 years.

Radiotherapy

All patients required bilateral neck irradiation and underwent whole-neck-field IMRT; the anterior low neck field abutting the upper IMRT region was not used in any patient.

The clinical target volumes (CTVs) were directly delineated by the radiation oncologist according to the guidelines of the Italian Association of Radiation Oncology-Head and Neck Working Group [27] and the corresponding planning target volumes (PTVs) were automatically created by uniform expansions of 0.3 cm.
According to our internal image guided radiotherapy (IGRT) protocol, patients underwent weekly cone beam CT (CBCT) set-up control and online correction to reduce systematic set-up errors.
The prescribed doses were 66 Gy at 2.2 Gy per fraction to the high risk gross volume PTV and 60-54 Gy at 2.0-1.8 Gy per fraction to the intermediate (optional) and low risk subclinical PTVs, respectively, delivered concomitantly in 30 daily fractions.
According to the recent computed tomography (CT)-based delineation guidelines by Christianen et al. [28], eight different SWOARs were defined in each CT slice and included in IMRT planning objective functions: superior, middle and inferior constrictor muscle (SPCM, MPCM and IPCM), supraglottic larynx (SL), glottis larynx (GL), cricopharyngeus muscle (CPM) and cervical oesophagus (CE). Thereafter, the mean dose received by each swallowing structures as well as by parotid glands and oral cavity were recorded.
In the IMRT optimisation cost function, target coverage replaced sparing of any SWOARs, parotid glands and oral cavity, but the spinal cord.
The IMRT plans set target prescription goals and spinal cord maximum dose (D_{max}) as the highest priority, whereas SWOAR constraints were set as secondary.

Medical therapy, supportive care and follow-up

Chemotherapy was given weekly using cisplatin 40 mg/m^2 i.v. over 1 h during the 6-week RT course for a maximum of 6 cycles both for patients affected by nasopharynx or oropharynx cancer.
For oropharynx patients with severe comorbidities, cetuximab was administered as an induction dose of 400 mg^2 over 2 h at 1 week before the start of RT and then 250 mg^2 weekly over 1-hour during RT course for a maximum of 6 cycles was administered.
Patients underwent PEG positioning during or after treatment if weight loss was > 10% (grade 2) from pretreatment status.
Acute toxicity was reported according to Common Toxicity Criteria Adverse Effects (CTCAE) version 3 [23], an observer-assessed validated toxicity scale scoring dysphagia between grade 1 (symptomatic but able to eat regular diet) to grade 5 (death).

Evaluation of dysphagia

Oro-pharyngeal-oesophageal scintigraphy (OPES)

OPES investigation entails the acquisition of a rapid sequence of images referring to a single voluntary deglutition which the patient performs on command. It is preferable to carry out this scintigraphic examination after the patient has been without food for at least three hours. Before starting the OPES, the patient should be made to swallow a small amount of non-radioactive water as a test; this helps to train the patients regarding the procedure, ensures patient compliance and assesses the capacity to swallow the amount of liquid foreseen for the examination (5 cc). After about five minutes, the examination begins with the patient in an orthostatic position with his/her face in an 80° oblique projection in front of a single rectangular headed large-field-of–view (LFOV) gamma camera equipped with a low energy-high resolution (LEHR) parallel hole collimator using a 140 KeV (± 10%) energy window. The patient is administered a single bolus of 5 cc of water marked with 37 MBq (1 mCi) of ^{99m}Tc nanocolloid (Nanocoll-Amersham®, UK). Eight images per sec (0.125 sec/frame) are acquired for one min by dynamic acquisitions (with a 64 x 64 matrix and zoom at 1), including the oral region as far as the epigastric area within the imaging field. The pharyngeal region of interest (ROI) is that between the oral cavity and the external reference corresponding to the pharyngo-oesophageal transition [29].
Two seconds after the start, the patient is invited to take the liquid bolus in one deglutition (OPES-L). At the end of the test, a static image lasting 60 sec is acquired, with the patient still in the same position to evaluate any possible tracheo-bronchial aspiration.
After an interval of 30 min, the procedure is repeated, but this time with a semi-solid bolus marked with 37 MBq (1 mCi) of ^{99m}Tc nanocolloid (OPES-SL). The acquisitions are obtained with the same method as with the liquid bolus.

Videofluoroscopy (VFS)

Digital fluoroscopy examinations were performed with a Clinodigit Compact Xframe Italray® device. The digital images were acquired by filming at a frame rate of 30/sec, which was sufficient to record the swallowing act. The acquisition resolution was 30,001 x 3001 x 14 bit.
Digitalised imaging permits the creation of a PACS (Picture Archiving and Communication System), which is a computerised system where images are uploaded, together with the relative supplied by the various diagnostic tools available in the hospital, thus allowing the images to be archived and shared. Furthermore, PACS permits viewing information about any previous investigation the patient was submitted to whenever a new examination was necessary. An image was enlarged on the neck region of the patient in an orthostatic latero-lateral position, and contrast medium was administered. The contrast medium used was Prontobario HD (Bracco®): the packaging supplied contains 98.45 g powder for oral suspension, 340 g barium sulphate.

The powder was diluted in 65 ml of water for the liquid consistency (VFS-L) and in 30 ml of water for the semi-solid bolus (VFS-SL); for each density, the patient was invited to take three 5 cc sips [30-32].

Fibreoptic endoscopic evaluation of swallowing (FEES)

FEES was performed with a flexible fibreoptic rhinopharyngolaryngoscope (Olympus ENF-P3®) connected to a CCD camera and colour monitor and recorded digitally on the Digital Swallowing Workstation (Kay Pentax Ltd®, Montvale, NJ, USA). The examination was carried out by a phoniatrician and a speech therapist and every patient was administered two or more semi-solid (viscous water) or liquid boluses (water marked with blue methylene for easy detection), swallowing 5 cc of each type of bolus [30-32].

Four different dysphagia parameters were calculated and reported at each exam both after liquid (L) and semi-liquid (SL) bolus intake. Pre-deglutition penetration, hypopharyngeal retention index (HPRI) and penetration/aspiration were reported at each exam, whereas pharyngeal transit time (PTT) and white-out phase (WOP) only at VFS/OPES and at FEES, respectively. The evaluation of both pre-deglutition penetration and penetration/aspiration was scored 0 if it was absent and 1 if was present. The latter was defined at FEES and VFS once the bolus entered the upper airways above the vocal cords (penetration) or passed below the vocal cords into the subglottis (aspiration).

The OPES detected only the transit of bolus into the tracheobronchial tree (aspiration), also giving the possibility for semi quantitative measurement of the aspirate.

Thereafter, the penetration/aspiration was classified in 8 different scores according to the worldwide used Penetration-Aspiration Scale at VFS [33].

The PTT was calculated at the end of the test by evaluation of the images recorded (normal < = 1 sec; Score 0), slightly long (≥ 1 to < 1.5 sec; Score 1), long (≥ 1.5 to < 2 sec; Score 2) and very long (≥ 2 sec; Score 3).

The WOP was defined as the total amount of time that the entire view screen was completely white.

The endoscopic examination was reviewed in a frame-by-frame analysis (ATMOS recording system), which allowed marking the examination film at specific points using a running frame-by-frame counter with a capture film rate of 30 frames per sec.

Swallowing initiation was defined as the time from when the bolus reached the horizontal level at the tip of the epiglottis to the start of the complete "white out." The HPRI was calculated as the amount of residue (pooling amount) in the hypopharynx against the Farneti pooling-score scale. Score 0 was considered normal, whereas scores 1, 2 and 3 pathological (mild, moderate and severe, respectively). Dysphagia parameters scores are shown in Table I.

Statistical parameter

We studied three main factors: dysphagia temporal variations, baseline dysphagia and the effect of liquid-semiliquid bolus. Before testing of inferential statistics, a graphical exploration was always performed.

Dysphagia temporal variations

To detect the significant changes in the dysphagia scores, measured at time zero and after 1 month, we used the Wilcoxon test (for continuous variables) and the McNemar test (for dichotomous variables). For continuous variables, worsening score was considered as the transition from a lower to a higher score (e.g. from 0 to 1 or from 1 to 2).

Evaluation baseline dysphagia

To evaluate the association among the primary tumour site (nasopharynx, oropharynx), T stage and N stage with the baseline dysphagia score (low, medium-high) measured by several instrumental analysis, two-tailed chi-square test and Fisher's exact test were used.

Effect of liquid-semiliquid bolus

To evaluate the correlation between deglutition worsening scores (from before to 1 month after treatment) for different bolus consistencies (L and SL) at the same exam

Table I. Videofluoroscopy, fibreoptic endoscopic evaluation of swallowing and oro-pharyngeal-oesophageal scintigraphy dysphagia parameter scores.

	Absent		Present	
Pre-swallowing penetration	0		1	
Penetration/aspiration	0		1	
PTT [a] /WOP [b]	Normal	Mild	Moderate	Severe
HPRI [c]	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)
Videofluoroscopy (Dyer et al. [34])	0 (< 3%)	1 (≥ 3 to < 25%)	2 (≥ 25 to < 55%)	3 (≥ 55%)
Scintigraphy (Fattori et al. [35])	0 (< 5%)	1 (≥ 5 to < 20%)	2 (≥ 20 to < 40%)	3 (≥ 40%)
Fibreoptic evaluation (Farneti et al. [36])	0	1	2	3

Abbreviations

a) PTT = Pharyngeal transit time; b) WOP = White-out phase; c) HPRI = Hypopharyngeal retention index. Values are numbers and (percentage)

(FEES/VFS/OPES), we used a non-parametric correlation analysis.

All statistical analyses, including those on the radiation doses received by the SWOARs (box-plots) and the variations between scores changes (bar graph), were performed using SPSS 21.

Results

Between June 2012 and December 2013, 20 patients with nasopharynx (n = 6) or oropharynx (n = 14) cancer were enrolled. The summaries of baseline patient and tumour characteristics are detailed in Table II. Average ± standard deviation mean doses to the SPCM, MPCM, IPCM, BOT, SL, GL, CPM and CE were 56.7 ± 13.7Gy, 53.4Gy ± 8.2Gy, 44.7 ± 11Gy, 55.7 ± 8.7Gy, 47.5 ± 11.2 Gy, 41.5 ± 11.3Gy, 41.7 ± 12.9Gy and EC 27.8 ± 10.3 Gy, respectively (Fig. 1).

All patients but one, who stopped chemotherapy after two administrations due to a high grade long-term nausea and vomit, received at least five of the planned six cycles of concurrent medical therapy. No patient experienced a significant weight loss (≥ grade 2) requiring PEG positioning during or soon after treatment.

Mucositis G1 was reported in 7 patients (35%) and was G2 in 11 patients (55%) and G3 in 2 patients (10%). Eight patients reported G1 dysphagia (40%), 10 patients G2 (50%) and 2 patients G3 (10%), whereas 10 patients reported G1 xerostomia (50%) and 10 patients G2 xerostomia (50%).

Moreover, 4 patients (20%) referred no pain during the course of treatment, whereas 7 patients referred G1 (35%), 8 patients G2 (40%) and 1 patient G3 (5%).

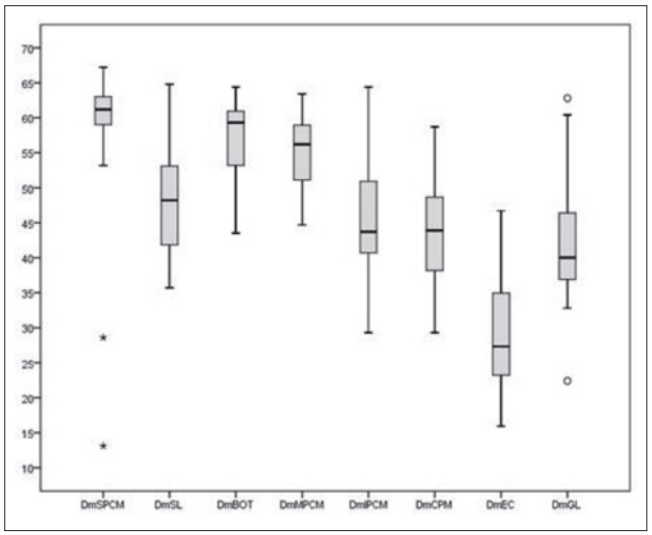

Fig. 1. Dose to the SWOARs.

Abbreviations: SPCM: superior constrictor muscle; MPCM: middle constrictor muscle; IPCM inferior constrictor muscle; SL supraglottic larynx; GL glottic larynx; CMP cricopharyngeal muscle; EC cervical esophagus; Dm = mean dose

Table II. Patient and tumour characteristics.

Characteristic	Patients	
	N	%
Age	43-77	
Mean	62	
Range		
Sex		
Male	16	80
Female	4	20
ECOG Status		
0	16	80
1	4	20
Smoking Status		
No	8	40
< 1 packet	7	35
>1 packet	5	25
Alcohol Intake		
No	9	45
< 1 litre/day	7	35
> 1 litre/day	4	20
HPV Status *		
Negative	7	50
Positive	2	14
Unknown	5	36
Primary Site		
Tonsil	7	35
Base of tongue	5	25
Soft palate	2	10
Nasopharynx	6	30
T Stage		
1	4	20
2	8	40
3	3	15
4	5	25
N Stage		
0	7	35
1	3	15
2	10	50
AJCC Stage **		
II	6	30
III	4	20
IV	10	50
Medical therapy		
None	4	20
Cisplatin	13	65
Cetuximab	3	15

** HPV status was assessed for patients with oropharynx cancer*
***AJCC Stage = American Joint Committee on Cancer*

Variations of swallowing parameters between baseline and 1 month after RT

The examination of the differences between the pre- and post-treatment HPRI score was found to be statistically significant both at FEES-L (p = 0.021) and SL (p = 0.02) and at VFS-L (p = 0.008) and SL (p = 0.005); OPES did not confirm these results (Table III).

HPRI worsening scores from baseline to 1 month after treatment are shown in Tables IV and V.

A total of 11 (55%), 19 (95%) and 12 (60%) patients experienced poorer scores at FEES-L, VFS-L and OPES-L.

Table III. Comparison between pre- and post-treatment HPRI for the three different exams used.

Parameter	Exam	Median (range)		p-value
		Pretherapy	1 month	
HPRI[a] 0-1[b] L[c]	FEES[e]	0 (0-1)	1 (0-2)	0.021
	VFS[f]	1 (0-3)	2 (0-3)	0.008
	OPES[g]	1(0-2)	1 (0-1)	0.480
HPRI 0-1 SL[d]	FEES	0 (0-2)	1 (0-2)	0.020
	VFS	1 (0-3)	3 (1-3)	0.005
	OPES	1 (0-2)	1 (1-2)	0.058

Abbreviations
a) HPRI= Hypopharyngeal Retention Index; b) 0-1= parameter worsening score between baseline and 1 month after treatment; c) L=liquid; d) SL=semiliquid; e) FEES= Fibreoptic endoscopic evaluation of swallowing; f) VFS=Videofluoroscopy; g) OPES=Oropharyngeal oesophageal scintigraphy

All patients showed a poorer HPRI score at VFS-SL and OPES-SL, as well as 14 (70%) at FEES-SL. In this regard, 9 (45%) and 10 (50%) patients showed a severe HPRI score (grade 3) after treatment at VF-L and SL, respectively. Furthermore, the relationship between HPRI worsening at FEES-L and FEES-SL ($p = 0.005$) as well as at VFS-L and VFS-SL ($p < 0.001$), was statistically significant (Figs. 2, 3). On the contrary, PTT and WPO was not significantly affected by RT either after L or SL bolus intake, as shown in Table VI.

Six patients (2 nasopharynx, 1 base of tongue, 1 tonsil and 1 soft palate) showed a worsening of the PTT score resulting in a mild prolongation time (grade 1) at FEES-L and only 1 patient (tonsil) at OPES-L. A mild (grade 1) PTT prolongation was observed in 4 patients (1 tonsil, 1 base of tongue, 1 nasopharynx and 1 soft palate) and 3 patients (1 base of tongue, 1 nasopharynx and 1 soft palate) at FEES-SL and VFS-SL, respectively. Moreover, one patient (tonsil) experienced a moderate (grade 2) PTT prolongation at FEES-SL. No case of PTT prolongation time at 1 month after RT was seen at VFS-L and at OPES-SL.
Finally, analysis of the development of pre-deglutition penetration and aspiration was limited owing to the restricted number of patients with pre-swallowing penetration (only 1 patient at FEES-L and 1 patient at FEES-SL) and aspiration (only 1 patient at OPES-L and 1 patient at FEES-SL) after RT, which did not reach statistical significance.
Specifically, pre-deglutition penetration at 1 month was detected in only 1 patient (base of tongue) at FEES-L and SL and aspiration at 1 month was detected in only 1 patient (nasopharynx) by OPES-L and FEES-SL, respectively.

Baseline dysphagia assessment and tumour characteristics
Association between primary site (nasopharynx vs oropharynx), T stage (T1-2 vs. T3-T4), N stage (N0 vs N1-2) and baseline dysphagia parameters using the three differ-

Table IV. HPRI scores after L bolus by the three different exams used.

				Score									
				0		1		2		3		Score Index	
Time	Parameter	Exam	Total	N	%	N	%	N	%	N	%	Mean	SD
Pretherapy	HPRI	FEES	20	17	85	3	15	0	0	0	0	0.16	0.37
1 month	HPRI		20	9	45	9	45	2	10	0	0	0.65	0.67
Pretherapy	HPRI	VFS	20	6	30	5	25	4	20	5	25	1.47	1.17
1 month	HPRI		20	1	5	4	20	6	30	9	45	2.21	0.92
Pretherapy	HPRI	OPES	20	8	40	11	55	1	5	0	0	0.68	0.58
1 month	HPRI		20	8	40	12	60	0	0	0	0	0.60	0.50

Abbreviations
FEES=Fiberoptic endoscopic swallowing evaluation; VFS=Videofluoroscopy; OPES=Oro-pharyngeal-oesophageal scintigraphy; HPRI=Hypopharyngeal retention Index; SD=Standard deviation

Table V. HPRI scores after SL bolus at the three different exams used.

				Score									
				0		1		2		3		Score Index	
Time	Parameter	Exam	Total	N	%	N	%	N	%	N	%	Mean	SD
Pretherapy	HPRI	FEES	20	16	80	3	15	1	5	0	0	0.28	0.57
1 month	HPRI		20	6	30	14	70	0	0	0	0	0.70	0.47
Pretherapy	HPRI	VFS	20	6	30	5	25	4	20	5	25	1.47	1.17
1 month	HPRI		20	0	0	3	16	6	32	10	52	2.37	0.76
Pretherapy	HPRI	OPES	20	5	25	10	50	5	25	0	0	1.05	0.70
1 month	HPRI		20	0	0	12	60	8	40	0	0	1.40	0.50

Abbreviations
FEES = Fiberoptic endoscopic swallowing evaluation; VFS = Videofluoroscopy; HPRI = Hypopharyngeal retention index; SD = Standard deviation

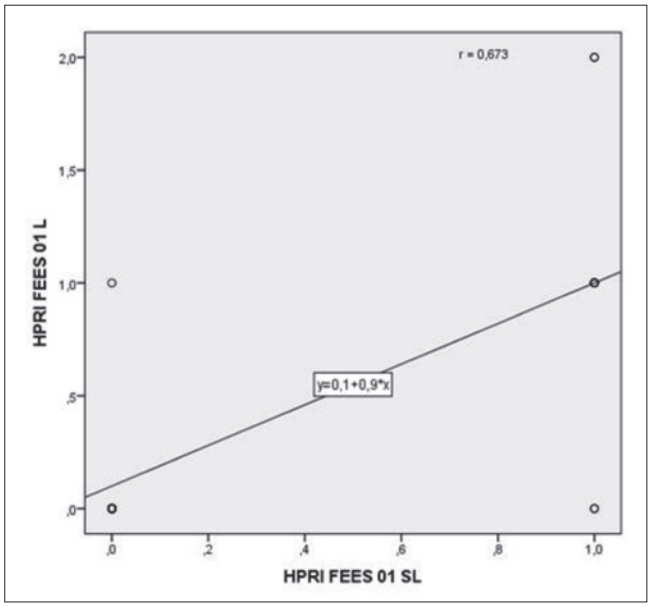

Fig. 2. Relationship between HPRI worsening score at FEES-L and SL.
Abbreviations: 0-1 = parameter worsening score between baseline and 1 month post-treatment. L = Liquid; SL = Semiliquid; HPRI = hypopharyngeal retention index; FEES = Fibreoptic endoscopic evaluation of swallowing.

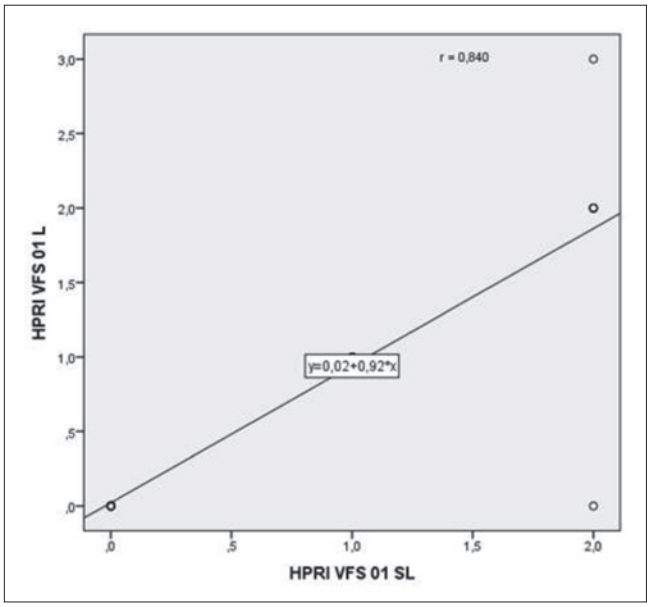

Fig. 3. Relationship between VFS worsening score at VFS-L and SL.
Abbreviations: 0-1 = parameter worsening score between baseline and 1 month post-treatment. L = Liquid; SL = Semiliquid; HPRI = Hypopharyngeal retention index; VFS=Videofluoroscopy.

Table VI. Comparison between pre and post-treatment PTT for the three different exams.

		Median (range)		
Parameter	**Exam**	**Pretherapy**	**1 month**	**p-value**
WOP[a] 0-1 L	FEES[f]	0 (0-1)	0 (0-1)	0.219
PTT[b] 0-1[c] L[d]	VFS[g]	0 (0-3)	0 (0-0)	1.0
PTT 0-1 L	OPES[h]	0 (0-0)	0 (0-1)	1.0
WOP 0-1 SL	FEES	0 (0-1)	0 (0-2)	0.454
PTT 0-1 SL[e]	VFS	0 (0-1)	0 (0-0)	0.756
PTT 0-1 SL	OPES	0 (0-0)	0 (0-0)	1.0

Abbreviations
a) WOP = White-out phase; b) PTT = Pharyngeal transit time; c) 0-1 = parameter worsening score between baseline and 1 month after treatment; d) L = Liquid; e) SL = Semiliquid; f) FEES = Fibreoptic endoscopic evaluation of swallowing; g) Videofluoroscopy; h) OPES = Oro-pharyngeal-oesophageal scintigraphy.

ent exams was assessed after L and SL bolus intake. No significant association was found between primary site, T and N stage with the baseline HPRI ($p > 0.405$) or PTT ($p > 0.314$).
Moreover, analysis of the association with baseline pre-deglutition penetration and aspiration showed a limited number of patients with baseline pre-deglutition penetration and/or aspiration, which did not reach statistical significance.
In more detail, baseline HPRI was altered in 14 patients (70%) at VFS-L and SL and in 13 patients (65%) and 15 patients (75%) at OPES-L and SL, respectively.
These data were not confirmed at FEES-L and SL, as shown in Table VII.
In this regard, 3 patients (1 tonsil, 1 base of tongue and 1 nasopharynx) showed a mild HPRI at FEES-L and SL, and 1 patient (tonsil) showed a moderate HPRI at FEES-SL. In contrast, baseline PTT after L bolus intake was normal in all patients but one (tonsil cancer), in whom mild prolongation (grade 1) was seen at FEES.
Furthermore, moderate PTT prolongation (grade 2) was observed in 3 patients at FEES-SL (2 with tonsil and 1 with base of tongue cancer) and in 2 patients at VFS-SL (tonsil cancer). The PTT was normal in all patients at OPES-SL. Baseline pre-deglutition penetration was detected in only 1 patient (nasopharynx cancer) at FEES-L, VFS-L and OPES-L, in 3 patients at FEES-SL (2 with nasopharynx cancer and 1 with tonsil cancer) and in only 1 patient (nasopharynx cancer) at VFS-SL and OPES-SL. Finally, aspiration was observed in only 2 patients (10%) affected by tonsil and base of tongue cancer, respectively, at OPES-L.

Discussion

The results of our study showed that post-deglutition HPRI was the most sensitive parameter, independently of the exam and consistency of the bolus.
Our data showed a significant number of patients who experienced an increased HPRI score from baseline to 1 month after RT, especially using VFS and FEES rather than OPES. This difference is probably due to the poor anatomical resolution of OPES together with the difficulty for the nuclear physician to correctly create a region of interest (ROI) with the subsequent risk to overestimate the pattern of dysphagia.
Our explanation is supported by the high percentage of

Table VII. Baseline HPRI scores with the three different exams.

HPRI	Grade 0	%	Grade 1	%	Grade 2	%	Grade 3	%
FEES[a] 0[d]L[e]	17	85	3	15	-	-	-	-
VFS[b] 0L	6	30	5	25	4	20	5	25
OPES[c] 0L	7	35	12	60	1	5	-	-
FEES 0SL[f]	16	80	3	15	1	5	-	-
VFS 0SL	6	30	5	25	4	20	5	25
OPES 0SL	5	25	10	50	5	25	-	-

Abbreviations
a) FEES = Fiberoptic endoscopic swallowing evaluation; b) VFS = Videofluoroscopy; c) OPES = Oro-pharyngeal-oesophageal scintigraphy; d) 0 = Baseline evaluation; e) L = Liquid; f) SL = Semiliquid.

patients with baseline increased HPRI score at OPES-L and SL (65% and 75%, respectively), which probably justifies the lack of statistical difference between pre- and post-RT. Hence, we believe that OPES should be considered as a complementary exam in assessment of radiation-induced dysphagia. Indeed, this is supported by a recent systematic review of oropharyngeal dysphagia assessment by Speyer et al. [25].

On the other hand, the significant worsening of HPRI score seen at FEES and VFS was probably related to inflammatory oedema of pharyngeal mucosa, constrictor muscles and base of tongue causing a reduction of tongue strength and motion, pharyngeal contraction and laryngohyoid elevation with a consequent increased number of swallows needed to clear the bolus [37].

Lazaurus et al., Wu et al., and Jensen et al. [38-40] have published similiar results, reporting a significant amount of pharyngeal retention (88-93.5%) and post-deglutition aspiration (59-77.4%) after RT alone for patients affected by different HN cancer sites. Similar results were reported by most studies on patients submitted to concomitant chemo-radiation protocols [41-44].

In our preliminary experience, a linear relationship was observed between HPRI worsening score after L and SL bolus using the same exam. This finding might be explained by a similar muscular effort in the deglutition act for the two different consistencies of bolus. As reported by most literature data, the instrumental assessment of dysphagia is based on deglutition evaluation after L and SL bolus intake [45 46]. Likewise, most patients undergoing radio- or radiochemotherapy for HN cancer favour a soft diet owing to acute radiation-induced mucositis and xerostomia [47].

Thus, dysphagia assessment using solid bolus might have shown a higher percentage of HPRI worsening due to the requirement of a stronger muscular propulsion in this set of patients.

On the contrary, PTT changes from baseline to 1 month after RT were not statistically significant. Among the four deglutition parameters, PTT is the most difficult to disclose regardless of the type of exam. In our experience, no case of severe PTT prolongation was observed either at baseline or 1 month after RT. In addition, only a few patients experienced mild or moderate PTT prolongation after L (30% at FEES and 5% at OPES, respectively) and SL bolus intake (25% at FEES and 15% at VFS, respectively). This result is probably related to the low specificity of the three exams in revealing such a subtle parameter, causing a significant percentage of false negative patients and lack of variations from before to after treatment.

Our clinical study was aimed to prospectively evaluate the impact of RT using IMRT on deglutition function through complementary instrumental assessment.

This issue has been addressed by only few studies [10 16 17 19], mostly reporting retrospective clinical results on patients affected by tumours arising from different HN sites, which limited the validity of the final data.

According to the recent recommendations by the Italian Association of Radiation Oncology, objective instrumental evaluation was performed using FEES, VFS and OPES before and after RT [48]. Selection criteria were defined to properly assess the impact of RT in a homogeneous subset of HN cancer patients to maximally avoid selection bias.

Firstly, we excluded the patients affected by oral, larynx and hypopharynx cancer due to the high prevalence of baseline cancer-related dysphagia [49] as well as those who underwent previous surgery and/or RT in HN region or with deglutition-related comorbidities (i.e. neurological or rheumatological diseases).

Moreover, patients with Stage IVB (T4b or N3) or C (M1) disease were not enrolled mainly due to the poor prognosis that significantly reduces the importance of deglutition evaluation.

Aiming to strictly assess the radiation-induced dysphagia, patients who previously underwent neoadjuvant chemotherapy were excluded due to the significant percentage of chemotherapy-related dysphagia (20-40%) that could worsen deglutition function before the beginning of standard radio- or radiochemotherapy [50].

In fact, the lack of significant correlation between pretreatment dysphagia parameters and tumour characteristics (primary site, T and N Stage) demonstrates the validity of our selection criteria.

Furthermore, our study investigated both acute (1 month)

and late (6 and 12 months) radiation-induced dysphagia.
In this paper, we report the results of acute dysphagia (at 1 month after RT). Our preliminary findings showed that IMRT aimed to SWOARs-sparing caused an increase of post-swallowing HPRI, but did not significantly influence the occurrence of pre-deglutition penetration and aspiration.
In this regard, we believe that the post-treatment increase of HPRI may also be related to mucositis and xerostomia, which occurs during the course of RT, with a consequent increased difficulty to the transit of bolus through the pharyngeal region [51-53].
Therefore, the radiation oncologist must pay attention to maximally reduce the dose delivered to the major salivary glands and pharyngeal uninvolved mucosa rather than to the SWOARs.
In contrast, the use of IMRT aimed to spare SWOARs irradiation, probably contributed to the low incidence (only 1 patient) of post-deglutition penetration and aspiration.
In this regard, Feng et al. [54] initially and Eisbruch et al. [(55)] afterwards, reported the data of the only prospective study by the University of Michigan on 73 oropharyngeal cancer patients undergoing IMRT and evaluated at 3, 12 and 24 months using both clinical (CTCAE scale) and instrumental (videofluoroscopy) assessment criteria. The authors reported a slight worsening of VFS scores (mild to moderate dysphagia) from pre-therapy to soon after therapy (3 months) that did not improve at subsequent follow-up (12 and 24 months).

Conclusions

At present, our early preliminary data seem to confirm the experience reporting no cases of severe side effects (PEG positioning or clinical aspiration) as well as a low percentage of major instrumental dysfunction (pre-deglutition penetration or aspiration). In our opinion, IMRT significantly limits severe acute deglutition sequelae in HN cancer patients compared with historical literature data [(56,57)]. Indeed, longer follow-up and larger sample size are needed to further evaluate if the observed increase of hypopharyngeal retention of food is subsequently related to a high risk of developing late aspiration (6 and 12 months).

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LARYNGOLOGY

Unravelling the risk factors that underlie laryngeal surgery in elderly

Svelare i fattori di rischio che sottendono la chirurgia laringea negli anziani

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SUMMARY

Older patients are not considered good candidates to undergo more challenging therapeutic treatments, e.g. highly invasive surgery and complex chemotherapy. However, their exclusion from standard therapeutic options is not justifiable. Herein, we reviewed 212 patients aged ≥ 70, affected with laryngeal squamous cell carcinoma, and treated with transoral laser microsurgery or open neck (partial / total) laryngectomy with radical intent. The main aim was to compare patient outcomes to identify predictive factors that can be used by surgeons to choose the most appropriate treatment option. In our cohort, patients affected with more advanced tumour and hence treated by invasive open neck surgeries (above all TL) are more prone to develop complications and undergo fatal outcome than those with early disease treated by laser microsurgery, independently of age at surgery. In conclusion, elderly patients affected by laryngeal cancer can be treated similarly to younger patients, keeping in mind that more invasive surgeries are associated with a higher risk of developing complications. The advantages of mini-invasive surgery make it a possible first choice treatment in very old and frail patients suffering from laryngeal cancer, especially considering the recent success in treatment of some advanced stage tumours. Furthermore, comorbidities, by themselves, should not be used as exclusion criteria for subjecting an elderly patient to a different treatment that is from standard therapy.

KEY WORDS: Transoral laser microsurgery • Open partial laryngectomy • Supracricoid partial laryngectomy • Total laryngectomy • Laryngeal cancer • Elderly

RIASSUNTO

I pazienti anziani non sono generalmente considerati buoni candidati per trattamenti terapeutici impegnativi, quali ad esempio la chirurgia molto invasiva e i complessi trattamenti radio-chemioterapici. Ma la loro esclusione dalle opzioni terapeutiche standard non sembrerebbe essere del tutto giustificabile. Nel presente lavoro abbiamo esaminato 212 pazienti di età ≥ 70 anni, affetti da carcinoma squamoso della laringe, trattati chirurgicamente con diverse opzioni terapeutiche: laserchirurgia transorale o chirurgia a cielo aperto (laringectomia parziale e/o totale). L'obiettivo principale era quello di confrontare i risultati, al fine di identificare fattori predittivi utili al chirurgo per scegliere la modalità di trattamento più opportuna. Nella presente coorte, i pazienti affetti da tumore più avanzato e quindi sottoposti a interventi chirurgici a cielo aperto (soprattutto laringectomia totale) risultano maggiormente inclini a sviluppare complicanze, andando incontro a esito fatale, rispetto a quelli con malattia precoce trattati con microchirurgia laser indipendentemente dall' età al tempo dell'intervento chirurgico. In conclusione, i pazienti anziani affetti da cancro della laringe possono essere trattati come i pazienti più giovani, tenendo presente che interventi chirurgici più invasivi determinano un maggior rischio di complicanze. I vantaggi della chirurgia mininvasiva in termini di basso numero di complicanze tendono a renderla interessante come possibile trattamento di prima scelta nei pazienti molto anziani e fragili, anche in casi più avanzati. Infine le comorbidità, di per sé, non rappresentano una giustificazione per sottoporre gli anziani a trattamenti differenti da quelli standard.

PAROLE CHIAVE: *Microchirurgia laser transorale • Laringectomia parziale a cielo aperto • Laringectomia parziale sopracricoidea • Laringectomia totale • Cancro della laringe • Anziani*

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Introduction

The progresses in science, technology and lifestyle are allowing people to live longer and better than those who lived even 50 years ago: as a global average, life expectancy at birth has increased from 46.9 to 70.0 years in the period 1950-2015, and is expected to be 75.9 years in 2050 and 81.8 in 2100 [1]. The "other side of the coin", however, resides in the concomitant increase in diagnosis of diseases that have the age as main aetiological factor (e.g. cardiovascular diseases, dementia, diabetes etc.). Among these, cancer can be considered as an archetype, inasmuch as incidence rates increase with age [2]. As a direct consequence,

in the near future, the number of elderly with cancer will increase substantially [3]. In particular, amongst the different cancer histotypes, epidemiological studies foresee an increase up to 64% in diagnosis of head and neck squamous cell carcinoma (HNSCC) within the next 20 years [4 5]. The guidelines for the treatment of HNSCC, and more specifically laryngeal SCC, require chemoradiotherapy and/or invasive surgery on the basis of tumour stage and the need to preserve organ functionality [6]. In this context, less invasive/function-sparing surgical techniques have arisen in the last decade, although they are often limited to early stage tumours or require careful selection of patients [7-9]. In this scenario, the elderly are not considered good candidates to undergo more challenging therapeutic treatments, especially highly invasive surgery and complex chemoradiotherapy [10-12]. In addition, the management of head and neck cancer in the elderly has been historically heterogeneous, often marred by many prejudices, mainly based on both patient age and general health perceptions. In fact, aging is related to the decline of many physiological and cognitive functions, which may emphasise (and sometimes falsely require) the need to treat the elderly in a different and more limited mode than younger patients, even if no significant comorbidities are present [13].

Nowadays, this common perception is changing: the exclusion of elderly patients from standard therapeutic options is becoming less justifiable, taking advantage potentially of all therapeutic alternatives available after a proper screening. It is therefore essential to better establish the risk to which the patient is subjected for each proposed therapeutic option, be it surgical or non surgical [14].

In this 12-year multicentric retrospective study, we reviewed 212 patients aged at least 70, affected by laryngeal SCC, and treated with radical intent by 3 different types of surgical treatment: transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL) and total laryngectomy (TL). The population was further subgrouped into those 70-79 years old and over-80 based on age at surgery.

The main aims of this study are to evaluate the incidence of complications after laryngeal surgery and identify predictive factors for the occurrence of complications in order to provide surgeons with information to choose the most appropriate treatment option. Due to the excellent oncological results achieved in "young" adult patients with TLM, even for more advanced stage tumours [15], the third purpose was to compare outcomes of TLM in elderly and frail patients, with those undergoing more invasive OPHL or TL surgeries.

Materials and methods

Patients

All patients underwent laryngeal surgery at the Hospital of Modena or at the Martini – San Luigi Gonzaga Hospitals of Turin. As previously described [16], selection was based on routinely performed clinical assessment 3 weeks before surgery to evaluate the superficial and depth extent of the tumour.

Inclusion criteria were: age at surgery ≥ 70 years, histological diagnosis of laryngeal SCC and surgical treatment with a curative purpose as single modality or as part of a multimodality approach. Comorbidities, such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, cardiac disease (i.e. chronic heart failure, arrhythmia, and coronary artery disease), and hepatic, metabolic and cerebrovascular diseases, were not considered as exclusion criteria. OPHL are interventions considered at high risk for complications related to dysfunctional sequelae.

Therefore, more stringent selection criteria were adopted to exclude patients with certain risk factors related to:

- the patient, e.g. inability to climb two flights of stairs, mental status characterised by episodes of disorientation and confusion, clinical and radiological signs of pre-existing presbyphagia and severe osteophytosis at the cervical spine;
- family situation, e.g. absence of caregivers and declared impossibility of adhering to a complete rehabilitation programme;
- tumour, e.g. advanced stage disease needing more extensive resection (classified as OPHL type I + BOT, type IIb + ARY, type III + CAU).

Characteristics of the patient cohort are summarised in Table I.

Surgery and postoperative care

After informed consent was obtained, 212 patients underwent laryngeal surgery between January 1, 2001, and

Table I. Characteristics of the 212 elderly patients undergoing laryngeal surgery according to age, sex, tumour localisation, and pathological status.

Age, y						**No. of patients (%)**
Mean						75.8 ± 4.5
Range						70-91
70-79						171/212 (80.7%)
≥ 80						41/212 (19.3%)
Sex						
Male						199/212 (93.9%)
Female						13/212 (6.1%)
Localisation						
Glottis						173/212 (81.6%)
Supraglottis						39/212 (18.4%)
Pathological Status						
	N0	**N1**	**N2a**	**N2b**	**N2c**	
pTis	12					12/212 (5.7%)
pT1	95					95/212 (44.8%)
pT2	28					28/212 (13.2%)
pT3	28	3				31/212 (14.6%)
pT4	21	14	6	4	1	46/212 (21.7%)

December 31, 2012. The choice of the surgery was based on tumour stage and comorbidities, but not considering chronological age as a discriminatory factor. Surgical procedures were transoral laser microsurgery / cordectomy in 113 patients (53.3%), open partial horizontal laryngectomy in 30 patients (14.2%), and total laryngectomy with or without pharyngectomy in 69 patients (32.5%). One hundred-twenty patients (56.6%) underwent tracheostomy. On the basis of pathological findings (pN+ and/or extracapsular spread, extralaryngeal extent, positive margins), 33 patients (15.6%) were subjected to adjuvant radiotherapy: the primary site and all draining lymph nodes were irradiated with a dose of up to 54 Gy/2 Gy. Regions at higher risk for malignant dissemination received a 12-Gy boost (total 66 Gy/2Gy; range 62-68 Gy). Furthermore, 7 patients (3.3%) received 40 mg/m^2 cisplatin weekly during the course of RT because of a higher risk of local recurrence.

Statistical analysis

The incidence of complications and type of surgery among different groups were evaluated by chi-square tests. The length of time from the date of diagnosis to the date of death (OS) or to the date of death for laryngeal SCC (disease-specific survival) was estimated using Kaplan-Meier curves. At the end of the study, the dates of last consultation for patients still alive were used for type-I censoring. Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare Kaplan-Meier estimates between groups (type of surgery and postoperative complications). The CHAID (chi-square automatic interaction detection) method [17] was used to detect the optimal subdivision in order to maximise the differences in response within the different variables. Logistic regression was used to evaluate independent risk factors for development of perioperative and postoperative complications (within 30 days). These included age at surgery ≥ 80 years, gender, presence of comorbidities, type of surgery and duration of surgery.

Kaplan-Meier curves, log-rank and Gehan-Breslow-Wilcoxon tests were performed using Graphpad Prism version 6.0c (GraphPad Software, San Diego, CA, USA), whereas CHAID analysis and multivariate logistic regression were performed with IBM® SPSS® Statistics version 22 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ as the statistically significant cut-off value.

Results

Patient comorbidities

While 59 of 212 (27.8%) elderly patients who underwent laryngeal surgery did not present concomitant diseases, 86 (40.6%) patients were affected by two or more comorbidities, whereas 67 patients (31.6%) had one comorbidity. The most frequent comorbidities were hypertension (53%), cardiac disease (17%), diabetes mellitus (17%) and chronic obstructive pulmonary disease (COPD) (12%). The severity of each comorbidity was scored and recorded according to the American Society of Anesthesiologists (ASA) physical status classification system [18] (Table II).

Table II. Distribution of patients according to the American Society of Anesthesiologists (ASA) physical status classification system.

ASA	No. of patients (%)
1	14/212 (6.6%)
2	79/212 (37.3%)
3	99/212 (46.7%)
4	20/212 (9.4%)

Surgery and postoperative morbidity

The mean surgical time was 2.17 ± 1.48 h, ranging from 0.5 h to 6.5 h in patients aged 70-79 and from 0.5 h to 4.5 h in patients ≥ 80 years ($p < 0.01$). Amongst treated patients, 25 patients were postoperatively transferred to the intensive care unit (ICU) where they resided for an average time between 4.4 days (70-79 years old patients) and 1.6 days (patients aged ≥ 80; $p = 0.475$). The mean length of hospitalisation was 19.0 days in 70-79 patients and 12.3 in those ≥ 80 ($p < 0.05$).

Perioperative or postoperative complications affected 43 of 212 patients (20.3%) of whom 36 of 171 (21.0%) in the age range 70-79 and 7 of 41 (17.1%) in ≥ 80 years ($p = 0.799$).

Furthermore, stratifying patients for the type of surgery no differences between groups were observed, although open neck techniques showed a significant higher incidence of complications with respect to TLM ($p < 0.001$, Fig. 1).

In 70-79-year-old patients, 19 suffered systemic complications (mainly cardiovascular and pulmonary), 13 patients had local complications (mainly bleedings, fistulas and wound infections) and 4 developed both systemic

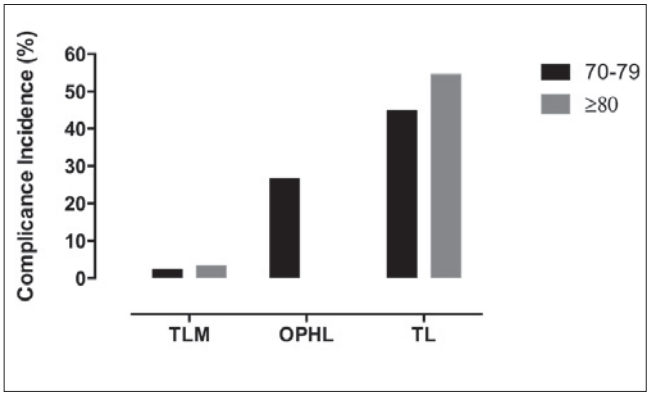

Fig. 1. Incidence of complications on patients treated by transoral laser microsurgery (TLM), open partial horizontal laryngectomy (OPHL), or total laryngectomy (TL).

Table III. Complications in patients.

			Number of events (%)	
			70-79	≥ 80
Complications	**Local**	Fistula	8/36 (22.2%)	0/7 (0.0%)
		Infections	4/36 (11.1%)	0/7 (0.0%)
		Haemorrhage	5/36 (13.9%)	1/7 (14.3%)
		Haematoma	0/36 (0.0%)	0/7 (0.0%)
		Necrosis	0/36 (0.0%)	0/7 (0.0%)
		Dehiscence	0/36 (0.0%)	0/7 (0.0%)
	Systemic	Pneumonia	8/36 (22.2%)	1/7 (14.3%)
		Cardiovascular*	13/36 (36.1%)	2/7 (28.6%)
		Psychiatric#	2/36 (5.6%)	7/7 (100%)
		Death	2/36 (5.6%)	1/7 (14.3%)
		Nephropathy	2/36 (5.6%)	0/7 (0.0%)
		Cerebrovascular event	0/36 (0.0%)	0/7 (0.0%)
		Hyperglycaemia	1/36 (2.8%)	0/7 (0.0%)
		Sepsis	0/36 (0.0%)	0/7 (0.0%)

** Cardiovascular complications included acute myocardial infarction, arrhythmia, and cardiac arrest # p < 0.001 (Fisher's exact test)*

and local complications. Two patients suffered 2 systemic complications, whereas 1 patient had 2 local complications. Two patients (5.6%) died postoperatively. In the ≥ 80 year group, 7 patients developed systemic complications (mainly psychiatric): two patients had more than 1 systemic complication, whereas 1 patient also suffered a local complication (haemorrhage). One patient (14.3%) died postoperatively (Table III). Finally, 48 of 212 patients (22.6%) underwent a second surgical procedure, whereas 11 of 212 patients (5.2%) underwent a third salvage surgery.

Data from the cohort of patients undergoing OPHL are reported in Table IV.

Correlation of age, type of surgery and complications with survival

Patients were followed for a mean period of 3.05 years (range 15 days – 8.61 years). At the last follow-up, 139 of 212 patients (65.55%) were alive without disease, 25 died with disease (11.8%), 39 died for other reason than head and neck cancer (18.4%), whereas 4 were alive with disease (1.9%). The remaining 5 patients were lost to follow-up (2.35%).

At 5-years, overall survival (OS 58.0%) correlated with patient age at surgery. In fact, OS was 64.0% in 70-79 years old patients and 33.9% in those aged ≥ 80 ($p < 0.05$), with 50% mortality at 4.04 years (Fig. 2A). On the contrary, 5-year disease-specific survival (DSS, 79.7%) was not significantly affected by patient age: in fact, DSS was 83.3% and 62.8% in those 70-79 and ≥ 80, respectively (Fig. 2B; $p = 0.062$).

Furthermore, by stratifying the data, the type of surgery or the occurrence of complications greatly affected OS (Fig. 3). In fact, patients treated by total laryngectomy were more prone to fatal a outcome ($p < 0.001$ and $p < 0.05$ with TLM and open partial horizontal laryngectomy, respectively), both as early event and at 5-year OS (37.2%, with 50% mortality at 4.04 years). No sig-

Table IV. Characteristics of patients undergoing open partial horizontal laryngectomy.

Surgery, ELS Classification		**No. of patients (%)**
Type IIa		11/30 (36.7%)
Type IIa + ARY		19/30 (63.3%)
Age, y		
Mean		73.2±2.2
Range		70-78
Comorbidities		**No. of events (%)**
	Arrhythmia	1/19 (5.3%)
	Arteriopathy	1/19 (5.3%)
	Cardiopathy	3/19 (15.8%)
	Hypertension	15/19 (78.9%)
	Ictus	1/19 (5.3%)
	Dyslipidaemia	3/19 (15.8%)
	Hypothyroidism	1/19 (5.3%)
	Diabetes	2/19 (10.5%)
	Epilepsy	1/19 (5.3%)
	HCV infection	1/19 (5.3%)
	Chronic obstructive pulmonary disease	5/19 (26.3%)
Complications		
Local	Infections	2/8 (25.0%)
	Haemorrhage	3/8 (37.5%)
Systemic	Pneumonia	1/8 (12.5%)
	Cardiovascular	5/8 (62.5%)
	Death	1/8 (12.5%)

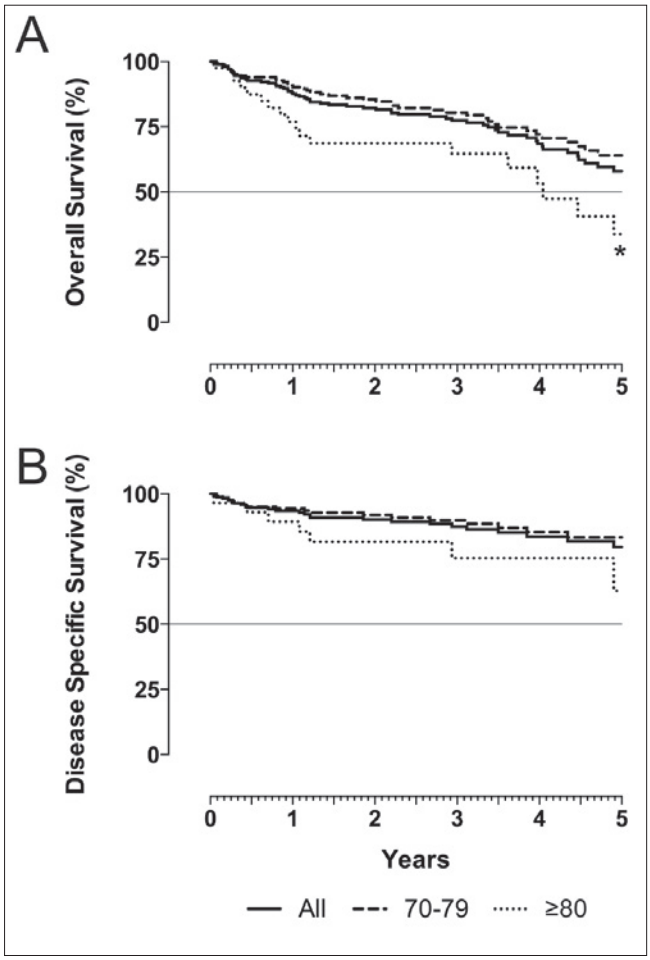

Fig. 2. Overall survival (A) and disease specific survival (B) over a 5-year period in 212 patients with laryngeal cancer. Dotted lines indicate the patient cohort according to the age at surgery. * $p < 0.05$.

nificant differences in 5-year OS were seen between patients undergoing TLM (67.7%) and open partial horizontal laryngectomy (77.9%). Similarly, 5-year OS of patients who experienced perioperative and postoperative complications was 37.5% (50% mortality at 3.50 years), which was significantly lower (as early events, also) than 62.3% (50% mortality at 6.82 years) seen in the other patients.

Age at surgery had a different impact on 5-year OS on the basis of both type of surgery and occurrence of complications (Fig. 4). In fact, patients aged 70-79 and undergoing TLM had a better 5-year OS (74.2%) than those aged ≥ 80 undergoing the same technique (48.3%, 50% mortality at 4.46 years, $p < 0.05$). Likewise, younger patients who did not experience a complication had a 5-year OS of 66.7%, which was significantly high than the older group (42.9%, 50% mortality at 4.46 years, $p < 0.05$). However, more invasive surgery as well as the presence of perioperative and postoperative complications greatly correlated with survival of ≥ 80 patients (0.0% at 5 years), whose 50% mortality was detected at 1.21 years and 0.37 years considering total laryngectomy and occurrence of complications, respectively. Patients aged 70-79 had better prognosis as an early event ($p < 0.01$) as well as 5-year OS ($p < 0.01$) for both total laryngectomy (44.8%, 50% mortality at 4.34 years) and occurrence of complications (49.7%, 50% mortality at 3.50 years).

No comparisons are available for open partial horizontal laryngectomy because all treated patients were aged 70-79 at the time of surgery.

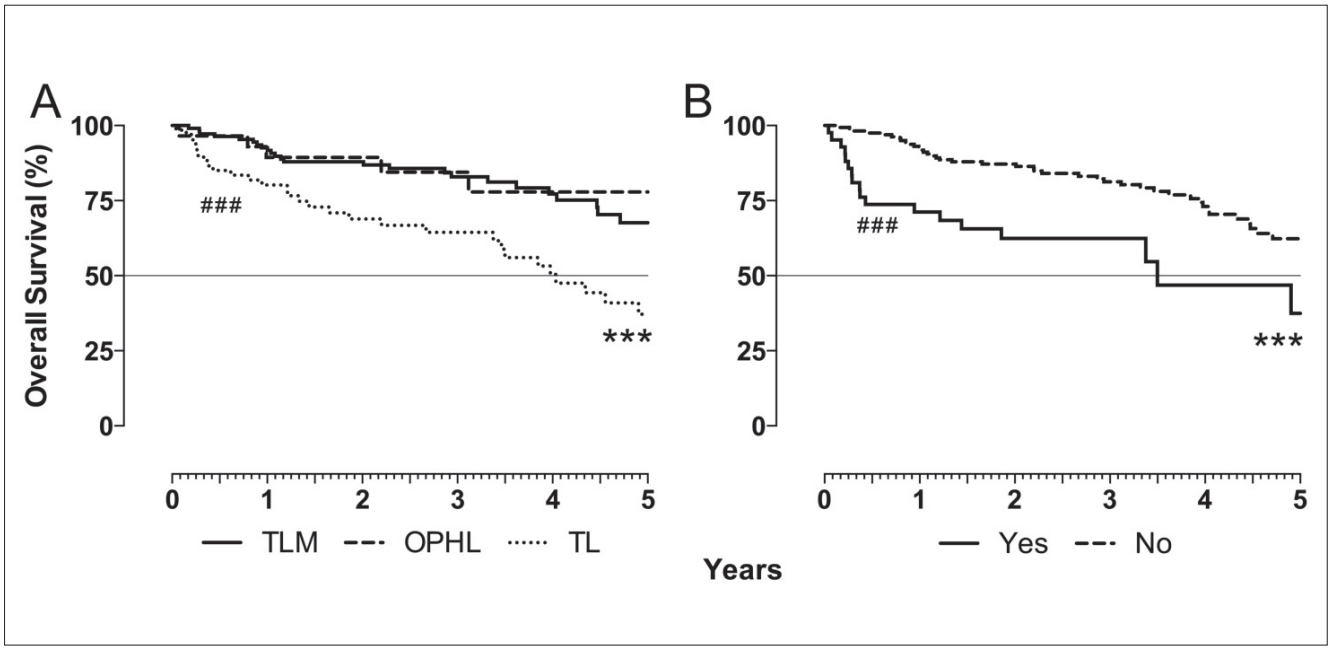

Fig. 3. Overall survival over a 5-year period in patients who underwent different surgical procedures (A) or who experienced peri- and/or post-operative complications (B). *** $p < 0.001$ (Log-Rank test); ### $p < 0.001$ (Gehan-Breslow-Wilcoxon test for early events).

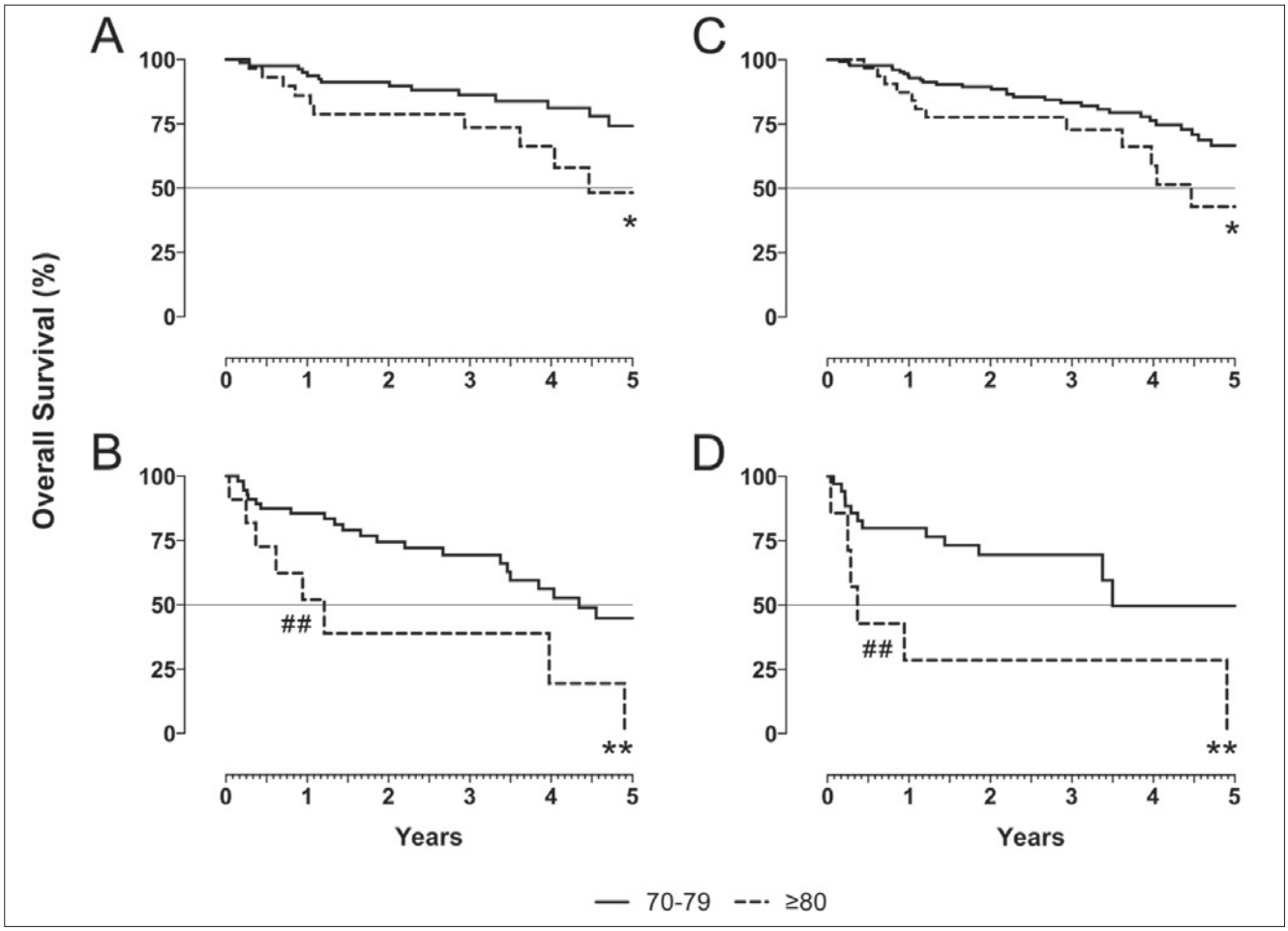

Fig. 4. Overall survival over a 5-year period in patients stratified according to the age at surgery who underwent transoral laser microsurgery (A) or total laryngectomy (B), and who did not experience (C) or otherwise show (D) complications. * $p < 0.05$, ** = $p < 0.01$ (Log-Rank test); ## $p < 0.01$ (Gehan-Breslow-Wilcoxon test for early events).

Risk analysis on the development of complications

Age ≥ 80, sex, comorbidities and ASA physical status classification did not show statistically relevant differences considering the onset of perioperative and postoperative complications, in contrast to the duration and type of surgery. In fact, if surgery length was more than 2 hours, patients had a risk of developing complications of 37.2% compared to 10.4% for patients with surgical time ≤ 2 hours ($p < 0.001$). Likewise, patients undergoing open neck laryngectomy had a higher risk of developing complications (46.4% and 26.7% in patients treated with TL or OPHL, respectively) compared to those treated with an endoscopic technique (TLM – cordectomy, 2.7%, $p < 0.001$).

On the basis of multivariate logistical regression, we calculated the following prediction model:

$$P = \frac{1}{1 + e^{-[0.262 - 0.401(a) - 0.259(b) - 0.021(c) - 0.024(d) - 0.806(e) - 3.423(f) - 0.139(g)]}}$$

where: (a) = patient aged 70-79; (b) = woman; (c) = presence of at least 2 comorbidities; (d) = presence of 1 comorbidity; (e) = treatment by open partial laryngectomy; (f) = treatment by TLM; (g) time of surgery ≤ 2 h.

For total laryngectomy, the formula gave a complication rate of 46.0%-56.5% in ≥ 80 patients and 36.3%-46.5% in those aged 70-79. Similarly, the model foresaw a complication rate of 30.5%-36.7% in patients ≥ 80 treated by OPHL, while it was 22.7%-28.0% in those aged 70-79. TLM-cordectomy had very little impact on the development of complications, regardless of age. In fact, the complication risk was 2.7%-4.1% and 1.8%-2.8% for patients aged ≥80 and 70-79, respectively.

Discussion

Because of the ageing population, clinicians are treating older patients more often than in the past. This, and the introduction of less invasive surgical techniques, has modified the strategies that surgeons apply to treat patients suffering from laryngeal cancer [19]. The elderly are often treated by patient-tailored and less invasive/time-consuming procedures, making the surgeon consider

both survival expectation and quality of life after surgery. Radical surgery on older patients with advanced cancer is, however, not frequent.

The impact of oncological surgery, in particular open surgery, on the delicate equilibrium of the elderly has been the subject of various studies [20-22]. Total laryngectomy separates the airways from the digestive tract, and does not expose the patient to the risk of damage for the ability to swallow, at the expense of a sudden loss of speech (usually irreversible). On the other hand, partial laryngectomy can provide the same oncological radicality while preserving the function of the larynx, even if at a lower quality, and avoiding definitive tracheostomy. The main disadvantages consist in a more restrictive selection of patients, which must be based on parameters related to the tumour, functional and cognitive abilities, absence of serious comorbidities and compliance of the patient and care-giver to an arduous rehabilitative programme, making OPHL an exception and not the rule in the management of laryngeal tumours in old (and mainly in very old) patients. However, the functional results of this surgery are long-lasting [23].

In the elderly, TLM warrants a separate discussion. It is usually employed in treatment of early stage tumour, mainly but not exclusively for glottic neoplasms [24 25]. However, the technique has been recently reported to be an effective surgical option even in the eradication of locally advanced stage laryngeal tumours due to the low rate of cervical node metastases [26]. TLM, in fact, demonstrates a high level of local control, low morbidity, almost total absence of permanent tracheostomy, good compliance of patient to the operation and short hospitalisation times (less than two post-operative days).

Historically, age has been considered as either a negative prognostic factor in advanced laryngeal carcinoma [27] or irrelevant in the early stage for developing local relapses [28] and hence for disease-free survival [29]. Furthermore, age does not have a significant impact on the long-term laryngeal function outcome after open partial laryngectomy, if the patient is selected carefully [30]. In this context, a better understanding of the impact of age and comorbidities on post-operative outcomes in term of survival and complications may help surgeons in suggesting the best therapeutic option to patients [18 22-25].

In the present study, we examined a cohort of old (aged 70-79) and very old (aged ≥ 80) patients (Table I) who underwent three different types of radical surgery. With the exclusion of OPHL that was performed only on 70-79-year-old patients due to the heavy and complex rehabilitation programme needed, the distribution of surgical techniques between groups did not reveal any statistical differences ($p = 0.139$, c2 test). Nonetheless, the lack of OPHL use in ≥ 80 patients did not statistically alter the reliability of comparisons (data not shown). For this reason, OPHL surgery was considered herein.

These are aggressive surgical procedures, initially resulting in severe swallowing dysfunction, most notably aspiration, but normally permitting eventual return to oral nutrition for most patients [31].

Some independent factors influencing post-OPHL aspiration have been well studied: advanced age, extent of supraglottic resection, absence of piriform sinus repositioning and total resection of one arytenoid [32].

Several authors agree that age, in itself, does not constitute an absolute contraindication, but rather a condition of increased risk. Hence, the need to be more restrictive in elderly patient selection and, if recommended, considering in advance a strategy for a simplified management of dysphagia, such as percutaneous gastrostomy [20 23 30 32].

In our experience, it is important to pay attention to: a) the mental status of elderly patients which must be quite normal in order to carry out the complex post-OPHL rehabilitation; b) the presence of motivated caregivers; c) pictures of severe osteophytosis at the cervical spine; and d) clinical and radiological signs of pre-existing presbyphagia.

As resections extended to supraglottic and subglottic sites are often associated with dysphagic sequelae, we prefer to adopt such surgery only in cases requiring resection of the glottis, saving the epiglottic tip, and enlarging to one arytenoid, if necessary [10 33-35]. Adopting this strategy, the complication rate was acceptable (8/30-26.6%), with only one case of fatal cardiac complication, considering a cohort characterised by a mean age of 73.2 +/- 2.2 years.

Despite our analyses, patients ≥ 80, who can be considered to be more frail than those 70-79 due to poorer 5-year overall survival (33.9% *vs* 64.0%, $p < 0.05$), the lack of difference in 5-year disease-specific survival (62.8% *vs* 83.3%, $p = 0.173$) demonstrated that the different mortality rate is not due to causes related to the cancer. In order to ascertain whether it depended merely on the reduced life expectancy of ≥ 80 patients, we analysed the impact of several covariate factors. In particular, the occurrence of perioperative and postoperative complications greatly impaired the overall survival of both 70-79 and ≥ 80 patients. Nevertheless, their occurrence was in relation to the type of surgery employed. The more invasive open neck surgeries provided a statistically higher percentage of patients with complications (up to 46.4%) than TLM (2.6%). However, stratifying the data for age at surgery, the percentage of patients who experienced complications was not statistically different between the two groups ($p = 0.694$, TLM; $p = 0.793$, TL). As a consequence, patients treated by total laryngectomy had the worst overall survival, whereas those undergoing TLM or OPHL had a similar 5-year outcomes. These results are in apparent contrast with the findings of Clayman et al. who compared the actuarial survival curve of the general population for people over 80: the global survival of elderly patients was not negatively influenced by a major operation [36]. Indeed,

TLM was mainly adopted to treat patients affected by early carcinomas, and according to guidelines, open neck surgeries were predominantly performed on those with advanced stage tumours (Fig. 5). Accordingly, patients undergoing major operations were generally affected by more advanced pathology than those treated by less invasive techniques. As a vicious cycle, patients treated by open neck surgeries (above all TL) for a more advanced tumour are understandably more prone to develop complications and undergo fatal outcome, independently from the age at surgery. These findings are consistent with the work of Peters et al. [37], who carried out a large retrospective study on patients in the age range ≤ 40 - ≥ 80 affected by head and neck cancer. They concluded that age itself does not seem to be a contraindication for major head and neck surgery, although the elderly are generally affected by more comorbidities than younger patients. In this regard, it is necessary to underline how, particularly in the elderly, the selection process for curative treatment tends to exclude all patients whose comorbidities are more serious than the average for their given age. This is not a simple process, and is mostly left to the judgment of the clinician rather than an analysis of morbidity indexes. In fact, it is not justifiable to adopt a "protective" therapy for the elderly that differs from the gold standard, apart from cases in which patients present serious comorbidities. The only exception could be when heavy adjuvant therapy is necessary, since elderly patients' compliance to lengthy treatment may be lower. In fact, as already reported, "only surgery-related variables, such as tumour stage and time of intervention, are significantly associated with surgical complications" [37].

Calculating the risk for each patient to undergo perioperative and postoperative complications by multivariate logistic regression, in our cohort the presence of comorbidities was not correlated with the onset of complications. In fact, the only significant covariate factor was the employment of more invasive types of surgery. The divergence with respect to the previous study could due to the operation time evaluated, which did not include the anaesthesiologic time herein.

Conclusions

In conclusion, we infer that elderly patients affected by laryngeal cancer can be treated just as younger patients, keeping in mind that more invasive surgeries are associated with a higher risk of complications. Therefore, while for endoscopic surgery there is no reason to limit or "ponder" whether to perform surgery or not for patients of any age, open surgery on patients ≥ 80 must be thoroughly evaluated due to the higher rate of complications. The advantages of mini-invasive surgery place it as a possible first choice treatment in very old and frail patients suffering from laryngeal cancer, especially considering the recent success in the treatment of some advanced stage tumours [26]. Furthermore, comorbidities, in themselves, cannot justify subjecting the elderly to a treatment other than standard. Rather, the severity of these conditions defines whether the patient should be exposed to major surgical options.

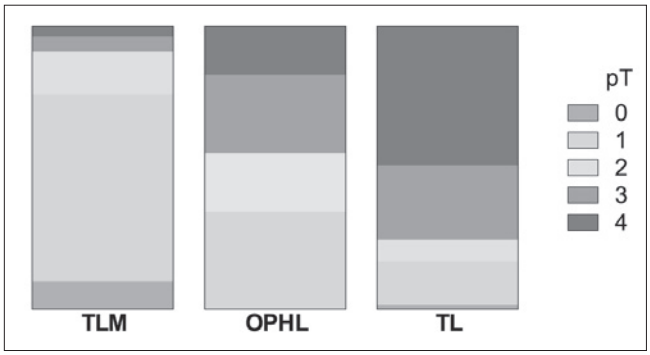

Fig. 5. Surgical procedures in relation to pT classification.

Sharing and improving our knowledge in elderly patients is helpful for all physicians due to the ageing population, with the aim to improve the quality of life and overall survival in the elderly.

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Rhinology

Septal flip flap for anterior skull base reconstruction after endoscopic resection of sinonasal cancers: preliminary outcomes

Septal flip flap per la ricostruzione del basicranio anteriore dopo resezione di tumori nasosinusali: risultati preliminari

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SUMMARY

Over the past decade surgery for sinonasal malignancies encroaching into the anterior skull base (ASB) has evolved from open craniofacial resection to the use of minimally invasive transnasal endoscopic approaches. Using these techniques, ASB reconstruction is most often performed in a multilayer fashion with autologous free grafts (fascia lata or iliotibial tract) which leads to the production of abundant nasal crusting in the postoperative months and discomfort for patients. In carefully selected cases, we propose harvesting a flap from the contralateral nasal septum based on the septal branches of the anterior and posterior ethmoidal arteries (Septal Flip Flap, SFF), which can be rotated to resurface the ASB defect. The exclusion criteria for using the SFF were as follows: cases where the tumour extended to both ethmoid complexes; cases where there was nasal septum or planum spheno-ethmoidalis involvement by the disease; cases of sinonasal malignant tumour with multifocal histology. In our tertiary care referral centre, skull base reconstruction using the SFF was performed in four patients; one was affected by ethmoidal teratocarcinosarcoma, one by persistence of sinonasal undifferentiated carcinoma after radio-chemotherapy, another by olfactory cleft esthesioneuroblastoma and the fourth by ethmoidal squamous cell carcinoma. Successful skull base reconstruction was obtained in all four cases without any intra- or post-operative complications. Post-operatively, nasal crusting was significantly reduced with faster healing of the surgical cavity. No recurrences of disease have been observed after a mean follow-up of 15 months. The SFF can be considered as a safe and effective technique for ASB reconstruction with high success rates similar to those obtained with other pedicled flaps. This flap also ensured a faster healing process with reduction of nasal crusting and improvement in the quality of life of patients in the postoperative period. This technique appears to be a safe and effective option for ASB reconstruction after endonasal resection of sinonasal malignancies in selected cases. Larger case series with a longer follow-up are needed to validate the preliminary results obtained with such an innovative and promising surgical technique.

KEY WORDS: Cerebrospinal fluid leak • Endoscopic endonasal • Nasoseptal flap • Quality of life • Skull base reconstruction • Sinonasal malignancies

RIASSUNTO

Il trattamento chirurgico dei tumori maligni nasosinusali estesi al basicranio anteriore si è evoluto nel corso degli ultimi decenni, passando dalla resezione craniofacciale tradizionale agli approcci endoscopici endonasali. In questi approcci mini-invasivi, il basicranio anteriore viene generalmente ricostruito con tecnica multistrato, utilizzando innesti di materiale autologo (fascia lata o tratto ileo-tibiale), che determinano la produzione di abbondanti crostosità a livello della neocavità chirurgica con conseguente disagio e fastidio per il paziente. In casi selezionati, proponiamo di allestire un lembo di mucopericondrio e mucoperiostio di setto nasale controlateralmente rispetto alla neoplasia, peduncolato sui rami settali delle arterie etmoidali anteriore e posteriore (Septal Flip-Flap, SFF), che può essere ruotato a ricostruire il difetto del basicranio anteriore. Criteri di esclusione per l'allestimento di questo lembo locale sono: tumori con estensione bilaterale ad interessare entrambi i complessi etmoidali; infiltrazione neoplastica del setto nasale e/o del planum sfeno-etmoidale; tumore maligno nasosinusale con istologia potenzialmente multifocale. Nel nostro centro di riferimento di terzo livello, la ricostruzione del basicranio mediante SFF è stata eseguita in 4 pazienti affetti dalle seguenti patologie: teratocarcinosarcoma etmoidale in un caso, persistenza di carcinoma indifferenziato nasosinusale (in esiti di trattamento radio-chemioterapico) in un caso, estesioneuroblastoma della fessura olfattoria in un caso, e carcinoma spinocellulare etmoidale in un caso. Non si sono verificate complicanze intra/post-operatorie, ottenendo il successo della ricostruzione del basicranio nella totalità dei casi. Nel postoperatorio si è osservata una netta riduzione delle crostosità intranasali, con rapida guarigione della neocavità chirurgica. Attualmente, non si sono registrate recidive di malattia, con un follow-up medio di 15 mesi. La ricostruzione del basicranio anteriore mediante SFF si è dimostrata sicura ed efficace, con percentuali di successo elevate, simili a quelle ottenute con altri lembi locali peduncolati. Il SFF garantisce inoltre una maggiore rapidità nel processo di guarigione della plastica del basicranio, con una diminuzione delle crostosità nasali nel postoperatorio e conseguente miglioramento della qualità di vita del paziente. Questa tecnica appare essere valida anche dal punto di vista oncologico per casi estremamente selezionati di tumore maligno nasosinusale. Casistiche più ampie con follow-up a lungo termine sono necessarie per validare i risultati preliminari di questa innovativa e promettente tecnica chirurgica.

PAROLE CHIAVE: *Fistola rinoliquorale • Approcci endoscopici endonasali • Lembo nasosettale • Qualità di vita • Ricostruzione del basicranio • Tumori maligni nasosinusali*

Introduction

Endoscopic endonasal resection, when properly planned and in expert hands, has an accepted role with precise indications in the treatment of sinonasal and skull base malignancies [1]. Reconstruction of anterior skull base (ASB) defects remains the most challenging issue in this field with post-operative CSF (cerebrospinal fluid) leak rates ranging from 3.3% to 4.3% [1].

Various surgical techniques and different materials are employed to repair ASB defects. Free grafts such as nasal mucoperiostium, iliotibial tract, fascia temporalis and fat tissue are mainly used and have acceptable closure outcomes. However, free grafts, especially extra-nasal tissues placed overlay, are usually not completely integrated thus leading to the production in the postoperative months of abundant nasal crusting with subsequent patient discomfort.

Alternatively, regional pedicled flaps, such as pericranial and temporo-parietal, offer the best results in terms of watertight closure, but harvesting them involves external incisions with the subsequent possibility of cosmetic problems and prolonged hospitalisation [2].

In certain cases, when the contralateral nasal fossa and the nasal septum are not involved by the disease, several local pedicled flaps harvested from the nasal cavities can be used. In this regard, the introduction of the Hadad nasoseptal flap (NSF) has dramatically decreased rates of postoperative CSF-leak and improved quality of life of patients, reducing post-operative nasal crusting and hospitalisation [2-4]. However, there are some cases where the NSF has a limited application, particularly in reaching defects involving the most anterior portion of the cribriform plate. Furthermore, in revision cases where large sphenoidotomies and/or posterior septectomies have been performed, the pedicle of the NSF could be damaged, precluding its use. Evidently, surgical alternatives to the NSF are required for ASB reconstruction in such cases. This study describes anatomical details and provides surgical notes for harvesting a pedicled flap based on the septal branches of ethmoidal arteries (septal flip flap, SFF) used in the repair of ASB defects after removal of malignant tumours.

Materials and methods

All patients who underwent endoscopic endonasal resection of sinonasal malignancies were retrospectively reviewed using information retrieved from the database dedicated to skull base procedures of a single Institution. Only patients who underwent skull base reconstruction using the SFF were included.

From an oncological viewpoint, exclusion criteria for SFF utilisation were as follows: cases where the tumour extended on both ethmoid complexes; cases where there was nasal septum or planum spheno-ethmoidalis involvement by the disease; cases of sinonasal malignant tumour with multifocal histology (e.g. intestinal-type adenocarcinoma).

From a technical viewpoint, previous nasal septum surgery (e.g. septoplasty) and cauterisation of ethmoidal artery(ies) for epistaxis or other reasons should be considered as restrictions precluding the use of the SFF. On the other hand, previous radiotherapy and/or chemotherapy do not represent contraindications for the harvesting of such a flap. This study was performed in accordance with policies approved by the local Ethics Committee.

Surgical technique

The endoscopic endonasal resection of malignancies encroaching into the ASB has been described elsewhere [5]. The procedure starts with the endoscopic debulking of the sinonasal tumour in order to assess the extent of disease and its origin and exclude any involvement of the nasal septum (cartilage or bone).

A frontal sinusotomy according to Draf type IIb is performed on the same side as the lesion, exposing the first olfactory fibre which represents the anterior limit of the surgical dissection. A wide sphenoidotomy with removal of the sphenoidal rostrum and intersinus septum is then performed, representing the posterior limit of the resection.

Next, subperiosteal dissection of the naso-ethmoidal-sphenoidal complex, together with the removal of the ipsilateral mucoperiosteum and mucoperichondrium of the nasal septum is performed to radically resect the tumour. The septal cartilage and perpendicular plate of the ethmoid are removed, taking care to preserve the contralateral mucoperiosteum and mucoperichondrium. Intraoperative frozen sections of the contralateral nasal septum mucosa are strongly recommended to exclude tumour involvement.

Once the bony ASB is exposed, the anterior and posterior ethmoidal arteries ipsilateral to the tumour are cauterised and divided. Next, the bony ethmoidal roof is drilled out using a diamond burr and the crista galli carefully detached and removed, exposing the dura of the ASB. The epidural gap is gently detached by inserting cottonoid pledgets between the dural layer and the residual borders of the bony ASB. The dura is then circumferentially incised with angled scissors and resected at a safe distance from the suspected area of tumour invasion.

The resulting skull base defect is reconstructed transnasally in a multilayer fashion using free grafts of iliotibial tract. In detail, the first layer is placed intradurally and the second in the epidural gap. The duraplasty is then resurfaced using the SFF. This pedicled flap is based on the septal branches of the contralateral ethmoidal arteries (Fig. 1) and is harvested using the contralateral mucoperiosteum and mucoperichondrium of the nasal septum as follows: the anterior incision starts superiorly at the level of the posterior wall of the frontal sinus and is carried

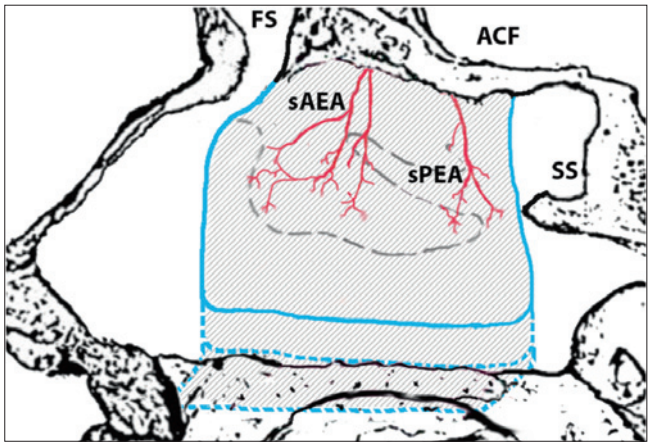
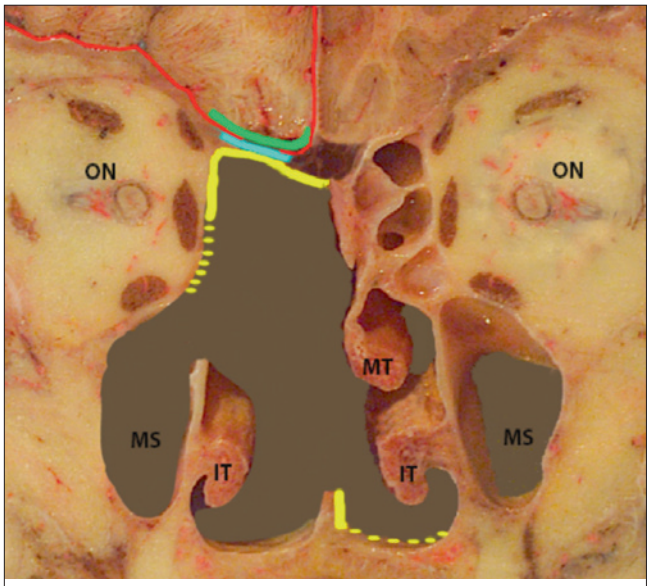


Fig. 1. Anatomical representation of the septal flip flap in sagittal view. The blue lines indicate the incisions on the septal mucoperiosteum/mucoperichondrium for harvesting the flap. The inferior incision (blue dotted line) can be tailored to the size of the skull base defect. Legend: ACF, anterior cranial fossa; FS, frontal sinus; SS, sphenoid sinus; sAEA, septal branches of anterior ethmoidal artery; sPEA, septal branches of posterior ethmoidal artery.



Legend: MT, middle turbinate; IT, inferior turbinate; MS, maxillary sinus; ON, optic nerve.

Fig. 2. Anatomical picture in coronal view representing the multilayer reconstruction of an anterior skull base defect. The red line highlights the dural layer; the green line represents the first layer of iliotibial tract (intradural); the blue lines represent the second layer of iliotibial tract (placed in the epidural gap); the yellow line indicates the septal flip flap resurfacing the defect, also covering the exposed orbital content when needed (yellow dotted line).

on anteriorly, reaching the frontal beak, and downward reaching the nasal floor. Posteriorly, the incision is made vertically from the sphenoidal planum downward to the nasal floor, paying attention not to damage the soft palate. In this phase, the septal branches of the sphenopalatine artery passing over the nasal choana are cauterised and cut. Finally, the two incisions are connected through a horizontal incision back to front at the level of the contralateral nasal floor, including the inferior meatus if necessary. In this way, the SFF is superiorly hinged and freely rotated to cover the ASB defect as a third layer (Fig. 2). The flap is then properly fixed with fibrin glue and Surgicel (Johnson & Johnson Medical, Arlington, TX) and the nasal cavities are packed bilaterally with Merocel 2000 (Medtronic Xomed Surgical Products, Jacksonville, FL) for about 48 hours. No Foley balloon catheter is needed to buttress the flap.

Results

Four male patients with a mean age of 49.8 years (range 16-69 years) underwent a SFF for ASB reconstruction after transnasal resection of sinonasal cancer. Patient data are summarised in Table I. Successful skull base recon-

Table I. Summary of clinicopathological features of the four patients.

	Patient #1	Patient #2	Patient #3	Patient #4
Age/Sex	44/M	69/M	16/M	67/M
Histopathology	Teratocarcinosarcoma	Persistence of sinonasal undifferentiated carcinoma	Olfactory neuroblastoma	Squamous cell carcinoma
Grading	G2	n.a.	Hyams II	G3
Staging	T3 N0 M0	T4b N0 M0	Kadish C	T3 N0 M0
Side/site of origin	Right/olfactory cleft	Left/ethmoid	Left/olfactory cleft	Left/ethmoid
Previous treatment	Induction chemotherapy (CDDP+ADM)	Chemotherapy (Carboplatin+Taxol) + IMRT (62 Gy)	Induction chemotherapy (VCR+ADM+EDX)	None
Extent of surgery	Unilateral ERTC	Unilateral ERTC	Unilateral ERTC	Unilateral ERTC
Adjuvant therapy	IMRT (60Gy)	None	IMRT (70.2 Gy)	IMRT (62 Gy)
Complications	None	None	None	None
Follow-up	12 months	12 months	18 months	18 months
Patient status	NED	NED	NED	NED

Abbreviations: M, male; n.a., not applicable; CDDP, cisplatin (cis-diamminedichloroplatinum-II); VCR, vincristine; ADM, adriamycin; EDX, cyclophosphamide; ERTC, endoscopic resection with transnasal craniectomy; IMRT, intensity modulated radiotherapy; NED, no evidence of disease.

struction was obtained in all four cases without any intra- or post-operative complications (Fig. 3). Post-operatively, patients were followed-up with multiple endoscopic evaluations at given intervals [5] and nasal toilette with removal of nasal crusting as needed. None of the patients developed necrosis of the flap after adjuvant radiotherapy. Regular follow-up was planned with contrast-enhanced MRI scans at given intervals [5]. Currently, there are no recurrences of disease after a mean follow-up of 15 months.

Discussion

Various intranasal pedicled flaps have been described for ASB reconstruction following resection of sinonasal cancers with the aim of reducing CSF leak rates and obtaining better outcomes in terms of nasal morbidity [2-4]. Nowadays, the workhorse for such procedures is represented by the NSF which is extensively used in the management of anterior, middle and posterior skull base defects [2-4].

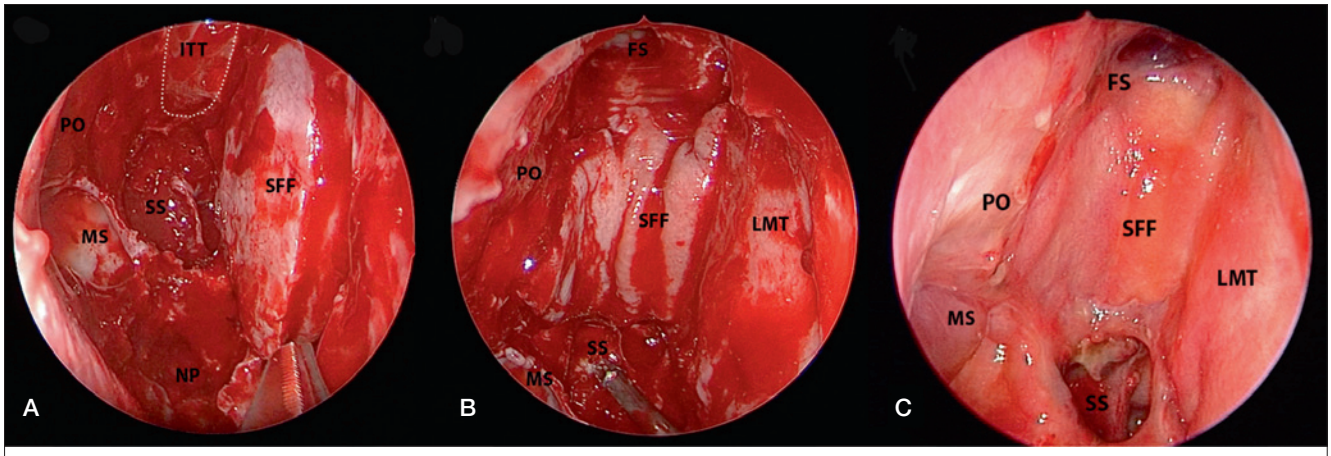
The SFF described here is an easy to harvest flap, based on the septal branches of the ethmoidal arteries and could be an effective option for ASB reconstruction after malignant tumour removal, offering an alternative to the NSF and giving additional value in its greater coverage of the anterior portion of the ASB defect.

We believe that the SFF can be considered as a safe flap because it is supported by a large pedicle with a strong blood supply that makes it very resilient. In this regard, anatomical studies reported the presence of multiple septal branches coming from the anterior and posterior ethmoidal arteries supplying this flap [6]. From a technical point of view, the removal of the crista galli, with its anterior attachment, represents the key point for the ASB reconstruction, not only for inserting the first two layers of iliotibial tract, but also for avoiding hindrances while rotating the SFF. In addition, a surgical trick in harvesting the flap is to bring the anterior incision forward to the frontal beak, allowing the resurfacing of very anteriorly extended skull base defects.

Furthermore, it is advisable to keep the contralateral mucoperiosteum and mucoperichondrium of the nasal septum attached and stretched during tumour removal and to harvest the SFF only at the end of tumour resection in order to better tailor its dimensions to the size and extension of the dural defect and the area to be resurfaced. For example, in cases where the removal of the lamina papyracea and periorbit might be necessary, it is possible to extend the SFF to include the mucoperiosteum of the contralateral nasal floor up to the inferior meatus to increase the length of the flap. In this way, the 'extended' SFF is also able to resurface the exposed orbital content.

Similar to what has been observed with other intranasal flaps [7], we found very encouraging outcomes using the SFF not only in terms of skull base closure, but also in improvement of patients' quality of life. This was especially evident in comparison with extranasal grafts like the iliotibial tract placed overlay. The SFF allows the resurfacing of the surgical cavity with nasal mucosa, preserving the physiological mucociliary clearance and enabling rapid healing with reduction of post-operative crusting.

For these reasons, we believe that in selected cases the SFF might be the most adequate and useful option for ASB reconstruction, even when compared to the Hadad flap, especially in cases of anteriorly extended skull base defects and in conditions where it is necessary to resurface the orbital content. In such situations, the pedicle of



Legend: SFF, septal flip flap; SS, sphenoidal sinus; FS, frontal sinus; PO, periorbit; MS, maxillary sinus; ITT, iliotibial tract; NP, nasopharynx; LMT, left middle turbinate; the white dotted line in A indicates the boundaries of the anterior skull base defect.

Fig. 3. Endoscopic endonasal images of an anterior skull base reconstruction using the septal flip flap (SFF). A) Intraoperative harvesting of the SFF from the septal mucoperiosteum and mucoperichondrium of the left side. There is a visible anterior skull base defect on the right side, extended from the frontal sinus back to the planum sphenoidalis. B) The SFF is rotated to resurface the skull base defect at the end of the surgical procedure. C) Post-operative endoscopic control one month after surgery.

the Hadad flap is too far posterior, limiting the anterior rotation of the flap.

At present, one of the limitations for the use of the SFF may be full-thickness tumour infiltration of the upper part of the nasal septum. In such situations, a conventional NSF, harvested using only the lower portion of the contralateral nasal septum, might possibly be considered a better option.

In every case, multiple intraoperative frozen sections analyses are mandatory to assess the contralateral mucoperiosteum of the nasal septum before its use for ASB reconstruction.

Conclusions

The SFF is a safe and effective technique for ASB reconstruction with high success rates similar to those obtained using other pedicled flaps. This flap also ensures greater speed in the healing process, with a reduction of nasal crusting and corresponding patient discomfort. This technique appears to be a viable option for ASB reconstruction after endonasal resection of sinonasal malignancies in well-selected cases. Larger case series with a longer follow-up are needed to validate these preliminary results.

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Rhinology

Radiofrequency volumetric inferior turbinate reduction: long-term clinical results

Riduzione volumetrica dei turbinati inferiori con radiofrequenze: risultati clinici a lungo termine

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SUMMARY

The aim of our study was to assess long-term results of radiofrequency volumetric tissue reduction of inferior turbinates (RVTR). We performed a prospective long-term longitudinal evaluation of 305 patients affected by rhinitis (114 allergic and 191 non-allergic) who were unresponsive to medical treatment and underwent RVTR (January 2004 - December 2010). Subjects were followed for a mean period of 39.70 ± 19.41 months (range 24-60). Patients completed the NOSE-scale questionnaire pre- and post-operatively after 1 month and yearly for 5-years. Recurrence was assumed if the post-operative total NOSE score increased by at least 75% during follow-up and the patient restarted medical treatments. Estimation of relapse over time was performed by Kaplan-Meyer analyses. We documented overall good satisfaction of patients regarding the procedure, with a good rate of pain control and a low rate of complications. Post-operatively there was a significant improvement in nasal stuffiness, nasal obstruction and mouth breathing ($p < 0.05$). We observed a worsening trend for symptoms after 36 months with progressive increasing rate of recurrences that were significantly higher in allergic than non-allergic patients ($p < 0.05$). We also observed a slight worsening trend of global satisfaction of patients. Our study confirms the minor discomfort and low risk of side effects of RVTR. Our data showed good efficacy of the procedure in the majority of patients for at least 36 months after surgery, and in fact in this time period the cumulative probability to remain relapse-free was up to 0.8. In the following 2 years, we observed a worse temporal trend in term of recurrence rate, and in particular in allergic patients with a significant difference *vs* non-allergic individuals ($p < 0.05$).

KEY WORDS: Non-allergic rhinitis • Allergic rhinitis • Inferior turbinate • Hypertrophy • Radiofrequency • Long-term results • Nasal obstruction • Mouth breathing • Local anaesthesia • Epistaxis • Relapse

RIASSUNTO

Lo scopo del nostro studio è stato quello di valutare i risultati a lungo termine della procedura di riduzione volumetrica dei turbinati inferiori mediante radiofrequenze (RVTR). Abbiamo eseguito una valutazione prospettica longitudinale a lungo termine di 305 pazienti affetti da rinite (114 allergici e 191 non allergici) refrattari alla terapia medica e sottoposti a intervento di RVTR (gennaio 2004 - dicembre 2010). I pazienti sono stati seguiti per un Follow-up medio di 39,70±19,41 mesi (minimo-24, massimo-60 mesi) e sono stati valutati mediante la somministrazione del questionario NOSE-scale prima e dopo l'intervento a distanza di un mese e successivamente ogni anno per 5 anni. I pazienti sono stati considerati affetti da recidiva durante il periodo di follow-up in caso di ricomparsa dei sintomi con un aumento del punteggio totale del NOSE scale di almeno il 75% e necessità di riassumere trattamenti medici. La ricorrenza è stata valutata mediante analisi di sopravvivenza con il metodo di Kaplan-Meyer. Complessivamente abbiamo documentato una buona soddisfazione dei pazienti per quanto riguarda la procedura, con un elevato controllo del dolore e poche complicanze. Nel post-operatorio abbiamo avuto un significativo miglioramento di ostruzione nasale e respirazione orale vicariante ($p < 0,05$). Dopo 36 mesi abbiamo osservato un peggioramento dei sintomi, in particolare, dopo 36 mesi con un progressivo crescente tasso di recidive significativamente più elevato nei pazienti allergici rispetto a quelli non-allergici ($p < 0,05$). Abbiamo anche osservato una leggera diminuizione della soddisfazione generale dei pazienti. Il nostro studio conferma la buona tollerabilità da parte dei pazienti della procedura di decongestione dei turbinati inferiori con radiofrequenze con un basso rischio di complicanze. I nostri dati confermano inoltre una buona efficacia a lungo termine nella maggior parte dei pazienti per almeno 36 mesi dopo l'intervento con una probabilità di rimanere liberi da recidiva in questo periodo sempre superiore a 0,8. Nei mesi successivi si assiste a una progressiva riduzione del beneficio clinico in particolare nei pazienti allergici, con una differenza statisticamente significativa rispetto ai pazienti non allergici ($p < 0,05$).

PAROLE CHIAVE: *Rinite non allergica • Rinite allergica • Ipertrofia turbinati inferiori • Radiofrequenze • Risultati a lungo termine • Ostruzione nasale • Respirazione orale vicariante • Anestesia locale • Epistassi • Recidiva*

Introduction

Turbinate surgery is very common and has been reported as the eighth most common procedure performed by otolaryngologists [1 2]. Bilateral inferior turbinate enlargement occurs in patients suffering from allergic seasonal or perennial rhinitis or vasomotor non-allergic rhinitis with more frequent hyperplasia of the head of the turbinate. Furthermore, chronic inflammatory condition may lead to hyperplasia of the mucosa and sub-mucosa, generally observed on the end of the turbinate, or morphologically presenting as polypoid formation of new tissue [3-5].

At least 13 surgical techniques have been used over the past 130 years [1]. All authors agree that in modern functional nasal surgery there is no place for total or subtotal turbinectomy due to the risk of haemorrhage, postoperative pain and long-term complications, and especially atrophic rhinitis [6]. All reduction techniques are successful, but vary significantly in terms of long-term efficacy and risk of complications. Nevertheless, no ideal standard technique has been developed to date, and in particular there is a lack of prospective and comparable long-term studies, which makes it difficult to recommend evidence-based surgical techniques [7-10].

The aim of our study was to assess the long-term results of radiofrequency volumetric tissue reduction (RFVTR) of the inferior turbinates in patients with nasal obstruction caused by turbinate hypertrophy.

Materials and methods

This single institution longitudinal prospective study was performed at the Department of Head and Neck Surgery Otorhinolaryngology of Catholic University of the Sacred Heart in Rome. The protocol was approved by our institutional board. All subjects gave written informed consent. From January 2004 to December 2010, 337 patients (205 males, 132 females), aged between 18-71 years, underwent RFVTR for treatment of simple bilateral hypertrophy of the turbinates that was not responsive to three-months of conservative therapy (intranasal sprays, antihistamines, systemic decongestants, mast cell stabilisers and allergic desensitisation) [10 11].

A total of 305 (133 female and 172 male) of 337 patients were included for statistical analyses and 32 were excluded because they were lost to follow-up. Of these, 37.37% (114/305) of patients were affected by allergic rhinitis and 62.63% (191/305) by non-allergic rhinitis. Subjects were followed for a mean period of 39.70 ± 19.41 months (range 24-60).

Pre-operative clinical evaluation included complete history and physical head and neck examination with nasal endoscopy, allergy testing through serum total IgE, allergometric skin testing for common inhalant allergens and determination of the levels of specific IgE in serum. In all patients we excluded chronic rhinosinusitis (according to the criteria of EPOS guidelines [8] for chronic rhinosinusitis), previous head and neck cancer, prior radiation therapy, rhinoplasty, active nasal infection, severe septal deformity, septal perforation, facial anomalies, connective tissue disorder and autoimmune disease, or nasal valve region deformity).

Patients were asked to complete a NOSE Scale questionnaire [9] pre-operatively, and then post-operatively at 1 month (Table I) and yearly for a maximum of 5 years. In the first month subjects were followed every week for 4 weeks to complete early evaluation of symptoms such as pain, rhinorrhoea, itching, sneezing, crusting and congestion scored by visual analogue scale (VAS) (range 0-10). The patient was asked to indicate on a VAS the answer to the question: "How troublesome are your symptoms?". Patients were told that 0 indicated 'nasal symptoms not at all bothersome' and that 10 indicated 'nasal symptoms extremely bothersome'. At 4 weeks after surgery patients were asked to formulate a final global evaluation of the procedure using a VAS scale (range 0-10). Successively, patients were followed-up for recurrence at yearly intervals for a maximum of 5 years. At every follow-up patients were asked about the need to restart medical treatment and the NOSE scale questionnaire was repeated. We obtained for every patient a total NOSE scale score from 0 to 20; then scaled to a total NOSE score from 0 to 100 multiplying the scores of the five items by

Table I. NOSE scale questionnaire.

	NOSE scale	Over the past 1 month how much of a problem were the following conditions for you? Please mark the most correct response				
		Not a problem	Very mild problem	Moderate problem	Fairly bad problem	Severe problem
1	Nose obstruction and stuffiness	0	1	2	3	4
2	Nose blockage or obstruction	0	1	2	3	4
3	Trouble breathing through my nose or mouth breathing	0	1	2	3	4
4	Trouble sleeping	0	1	2	3	4
5	Unable to get enough air through my nose during exercise or exertion	0	1	2	3	4

5. Recurrence was assumed if the post-operative total NOSE score increased by at least 75% during follow-up and the patient restarted medical treatments.

All procedures were performed in outpatient facilities with local anaesthesia using cotton strips with a 1:1 mixture of lidocaine and xylometazoline hydrochloride and conscious or deep sedation with midazolam or propofol. No premedication was given. Pain during the procedure was scored as none, mild, moderate and severe.

The surgery was performed using a radiofrequency system Celon Lab Precision (Olympus). Radiofrequency creates ionic agitation in tissue, inducing hypertermic sub-mucosal necrosis. The target temperature can be controlled from 60°C to 75°C to prevent surrounding tissue damage. It allows safe and gentle sub-mucosal volume reduction of hyperplastic nasal turbinate, developing predictably sized lesions in 4-10 sec. The resultant wound contraction and fibrosis of the sub-mucosa causes volume reduction of the inferior turbinate without damage to the overlying mucosa that adheres to the turbinate periosteum. This conservative procedure also damages sub-mucosal nerve fibres and the receptor nerve leading to denervation and hyporeactivity of turbinate mucosa. We never performed turbinate outfracture in combination with RFVTR [10-12].

Technically, the probe is introduced into the turbinate head under direct vision making 3-4 tunnels and maintaining a sufficient distance from the mucosa and bone. The process of ablation is accompanied by an acoustic tone that rises in pitch as the resistance of the tissue increases. No packing or antibiotic therapy was used after the operation.

For statistical analysis, we used Stata IC 12 software for MAC. The results are shown as mean and standard deviation(SD), median and interquartile range(IQR) or frequency relative percentages, as appropriate. With regards to outcome variables, comparisons between time 0 (PRE-intervention) and time 1 (4 weeks POST-intervention) were performed using a paired t-test. Kaplan-Meier analysis was used to estimate recurrence over time; the comparison between two relapse curves was made by the log-rank test. The results were considered statistically significant for p values < 0.05.

Table II. Post-operative mean VAS scores (range 0-10) and standard deviation of symptoms at early evaluation 1 week after surgery.

VAS scale	Mean	SD
Nasal obstruction	0.9	2.0
Rhinorrhoea	2.0	2.8
Itching	1.2	2.1
Sneezing	1.9	2.3
Crusting	2.6	2.8
Intermittent Congestion	4.7	3.1
Persistent Congestion	4.6	3.0

Results

During surgery we obtained a good rate of pain control that was considered absent in 225/305 patients (73.7%), mild in 40/305 (13.3%), moderate in 20/305 (6.5%) and severe in 20/305 (6.5%). A few patients (26/305; 8.5%) required prescription of analgesics after the procedure. The procedures were well tolerated as demonstrated by the early post-operative evaluation (1 week after surgery) using mean VAS values scores of symptoms such as nasal airway obstruction, crusting, sneezing, runny nose and itching (Table II). Results of anesthesiological questionnaires are shown in Table III. In the first months after surgery, the mean global evaluation score was of 7.3 ± 2.1, indicating good satisfaction of patients. No immediate complications such as major bleeding related to the treatment were observed after radiofrequency. Only 4 of 305 patients (1.3%) had postoperatively bleeding and nasal packing was needed. The most common complaints were transient side effects, including minor nasal discharge and post-procedural obstruction for up to 5-7 days. Subjects' estimation of symptoms by the NOSE scale was repeated at every follow-up evaluation. The mean baseline nose scale score and comparison to post-operative values at 1 month after the procedure are showed in Figure 1 and Table IV. We evaluated the temporal trend of the benefit obtained with surgery for the items of the NOSE scale that significantly improved as shown in Figure 2. We observed a worsening trend of the benefit obtained even though some patients experienced no change of benefit for extended periods. We also evaluated the temporal trend of global satisfaction of patients measured by VAS score (range 0-10) as shown in Figure 3.

Table III. Anaesthesiologic questionnaire and results.

Pain control during the procedure	**No pain** 225/305 (73.7%)	**Mild pain** 40/305 (12.9%)	**Moderate pain** 20/305 (6.5%)	**Severe pain** 20/305 (6.5%)
Anxiety during the procedure	**Yes** 76/305 pts (24.91%) **No** 225/305 pts (73.7%)			
Recovery time	**Minutes** 260/305 pts (85.24%)		**Hours** 50/305 pts (16.39%)	
Other problems (nausea, sickness, shiver etc.)	**Yes** 70/305 pts (22.9%) **No** 120 pts (77.4%)			

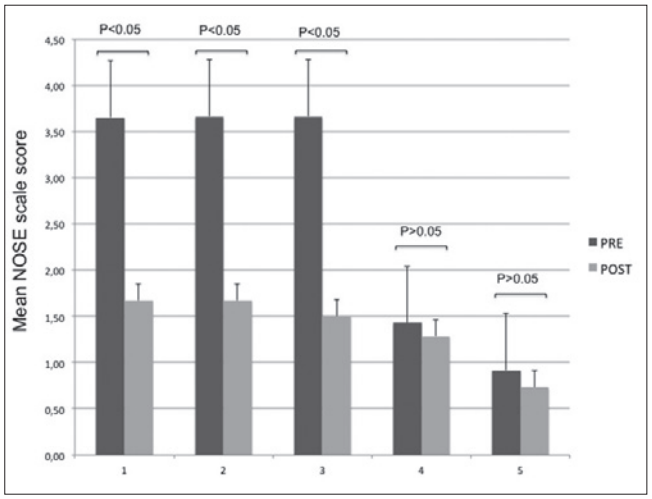

Fig. 1. The figure shows differences respect to baseline of NOSE scale scores items comparing time 0 (PRE intervention) and time 1 values (4 week POST intervention). (1) Nose obstruction and stuffiness. (2) Nose blockage or obstruction. (3) Trouble breathing through my nose or mouth breathing. (4) Trouble sleeping. (5) Unable to get enough air through my nose during exercise or exertion.

Estimation of recurrence was performed in all patients by Kaplan Meyer analysis as shown in Figure 4. The cumulative probability to remain relapse-free was 0.848 at 36 months and 0.531 at 60 months after surgery as shown in Table V. In order to test if allergy could be a discriminating factor in the impact of intervention, the analysis of recurrence was stratified by the presence of allergy (Fig. 5). The analysis showed that allergic patients seemed to be worse in the post-intervention period compared to non-allergic patients, and in particular at long-term follow-up. In fact, cumulative probability to remain relapse-free in allergic and non-allergic patients was respectively 0.839 *vs* 0.807 at 36 months, and 0.616 *vs* 0.357 at 60 months (Table V). The log rank test revealed that the difference between curves was statistically significant ($p < 0.05$).

Discussion

Reduction of the inferior turbinates can be performed using different surgical techniques including total or partial inferior turbinectomy (PIT), lateral outfracture, microdebrider submucosal resection, laser-assisted turbinate reduction, argon plasma surgery, cryosurgery, treatment with infrared light, vidian neurectomy, chemical or electrical coagulation and radiofrequency volume turbinate reduction (RFVTR) [12-14]. The literature [12-15] provides considerable evidence for the efficacy of "hot surgery" in adults with symptomatic, inferior turbinate hypertrophy, with a significant increase in use of these techniques in the past decade. Important adverse effects of these techniques are likely the consequence of the heat generated by the power applied. Atrophic and metaplastic changes of mucosa, crusting and synechia may occur, and the incidence differs for the administered energy with various long-term results [16-21].
Several studies have shown [22-26] that RFVTR can be considered as a safe mini-invasive surgical procedure with only slight nasal mucosa damage, minor discomfort and a low risk of side effects. However, most published studies are observational and have a relatively short follow-up, while reports of long-term assessment of self reported benefits and patient satisfaction of treatment are insufficient. Porter et al. [27] in a small series showed that after

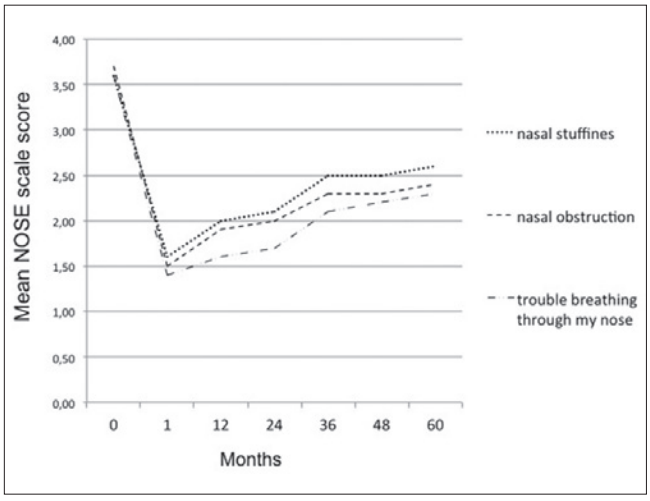

Fig. 2. Temporal trend of the benefit obtained with surgery considering evolution during long-term follow-up of mean NOSE scores for items that significantly improved after surgery.

Table IV. Comparisons between time 0 (PRE intervention) and time 1 (4 week POST intervention) mean and median nose scale scores.

	Nose congestion or stuffiness $p < 0.05$		Nose blockage or obstruction $p < 0.05$		Trouble breathing through my nose or mouth breathing $p < 0.05$		Trouble sleeping $p > 0.05$		Unable to get enough air through my nose during exercise or exertion $p > 0.05$	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Mean	3.6	1.7	3.7	1.8	3.7	1.6	1.5	1.3	1.1	0.7
SD	1.2	1.1	1.2	1.2	1.2	1.2	1.4	1.3	1.2	1.1
Median	4	2	4	2	4	2	1	1	1	0
IQR	1	2	1	2	1	1	3	2	2	1

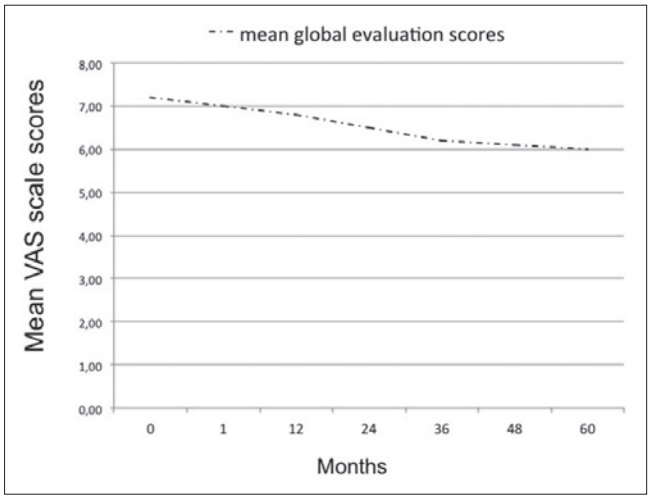

Fig. 3. Temporal trend of global patient satisfaction evaluated during long-term follow-up by the VAS score (range 0-10). The indicator represents the mean VAS scores about global satisfaction at each follow-up visit.

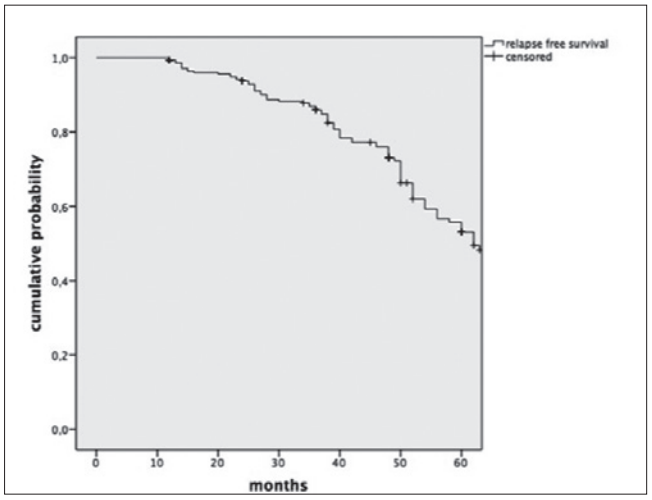

Fig. 4. Estimation of recurrence over time by Kaplan-Meier analysis in all 305 patients enrolled.

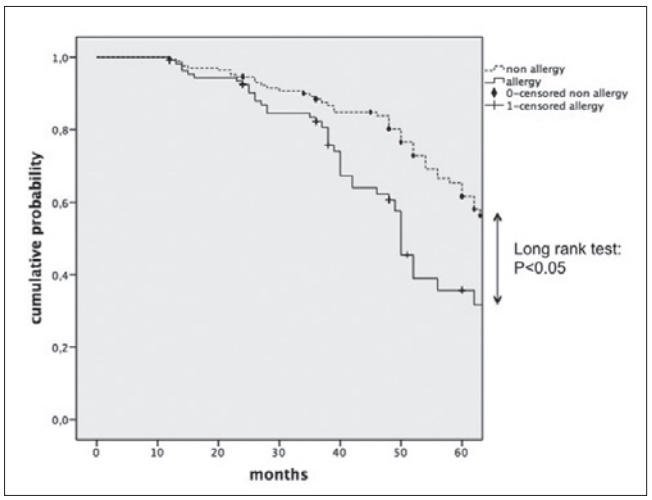

Fig. 5. Estimation of relapse over time by Kaplan-Meier analysis in allergic patients (n = 114) and non-allergic patients (n = 191). The difference between curves was significant by log rank test.

two-years of follow-up there was no significant return of symptoms compared to evaluation at 6 months. Garzaro et al. [12] evaluated patients at 2 months and 2 years after the surgical procedure using the "Sniffin' Sticks" test battery and the NOSE scale. Long-term evaluation showed that radiofrequency treatment for allergic or non-allergic inferior turbinate hypertrophy appeared to provide improvement in olfaction, decrease in nasal resistance and had subjective benefits that were maintained at 2 years after the procedure. Cukurova et al. [10] demonstrated that most patients (82%) showed long-term (60 months) subjective and objective improvement after only one procedure. Safiruddin et al. [28] analysed the self-reported long-term effects of RFVTR treatment using a questionnaire sent to 441 patients who underwent RFA. They included a total of 142 patients. Subjective data retrieved through patient interviews showed a trend of beneficial effect of RFVTR on nasal breathing during daytime, with 60.7% of patients reporting long-term improvement after treatment.

Our data showed overall good satisfaction of patients with the procedure together with a good rate of pain control during surgery and a low rate of complications (1.3% bleeding). Post-operatively we observed (4 weeks after surgery) a significant improvement in nasal stuffiness, nasal obstruction and mouth breathing (Table IV, Fig. 1). We analysed the temporal trend of the benefit obtained with surgery and observed a worsening trend as shown in Figure 2. We also observed a mild worsening trend of global satisfaction of patients as shown in Figure 3. We followed patients over time for recurrence by the Kaplan Meyer method. At the early follow-up for at least 36 months the majority of patients maintained benefits achieved with surgery, and in this time period the cumulative probability to remain relapse free was up to 0.8 as shown in Table V. In the following years, we observed an increasing rate of recurrence with a decrease in cumulative relapse-free probability.

Taking into consideration the increasing prevalence of allergic rhinitis, its impact on individual quality of life and social costs, we investigated if allergy could be a discriminating factor in the impact of the intervention, and in particular on early exacerbations. Limited data are available in the literature on this topic because most published studies on RF turbinate surgery in patients with allergic rhinitis have a relatively short follow-up. Recently, some authors have suggested that urban residence and allergic rhinitis were significantly associated with lower long-term improvement after radiofrequency treatment [29]. Furthermore, Linet al. [11] demonstrated that even though the outcome of RF turbinate reduction for patients with allergic rhinitis responding poorly to medical therapy decreases over time, it was still significant at 5 years after surgery. Herein, it was possible to stratify the analysis of recurrences by the presence of allergy, observing a worse temporal trend in allergic patients compared to non-allergic

Table V. Cumulative probability to remain free of relapse obtained by Kaplan Meyer analyses in all patients and in allergic and non-allergic patients.

	Months of follow-up				
	12	24	36	48	60
All patients	0.993	0.928	0.848	0.722	0.531
Non-allergic patients	0.989	0.930	0.839	0.729	0.616
Allergic patients	0.934	0.902	0.807	0.575	0.357

ones with a statistically significant difference ($p < 0.05$). Our data suggest that allergy affects results of surgery in terms of recurrence at long-term follow-up.

In conclusion, our data confirm that treatment of hyperplastic inferior nasal turbinates due to chronic allergic and non-allergic vasomotor rhinitis by minimally invasive nasal-RFA can be considered a safe procedure that alters nasal mucosa only slightly, while preserving physiologic function with minor discomfort and a low risk of side effects. In fact, the procedure is quick, easy, relatively painless and has the additional benefit of not requiring post-operative nasal packing, with satisfactory results. Furthermore, it appears to be a successful therapeutic option that offers very good results for at least 36 months. In the following 2 years, we observed a worse temporal trend in terms of recurrence rates, especially in allergic patients. Prediction of relapse after this procedure is a challenge for the future, and in particular to improve the success rate. In this regard, the severity and type of inflammation that causes turbinate hypertrophy is one of the factors that should be investigated. Several studies [30-35] have recently demonstrated that inflammation has a very important role in the pathogenesis of the swelling of nasal mucosa, not only in allergic rhinitis, but also in non-allergic rhinitis. Further studies should clarify whether the type and severity of inflammation correlate with the therapeutic success of this procedure.

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AUDIOLOGY

Outcomes of long-term audiological rehabilitation in CHARGE syndrome

Sindrome di CHARGE: risultati a lungo termine della riabilitazione audiologica

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SUMMARY

The aim of this paper is to assess the long-term audiological features and outcomes of hearing rehabilitation in a large group of individuals with CHARGE Syndrome. The study has been conducted retrospectively, on a paediatric patient database, at the Audiology Department of the University Hospitals of Ferrara and Padua. The study sample included 31 children presenting with different degrees of hearing impairment associated with CHARGE syndrome. Hearing was assessed using auditory brainstem responses (ABRs) and/or electrocochleography, or conditioned audiometry (visual reinforcement audiometry [VRA] or play audiometry). Auditory-perceptual outcomes in terms of communication skills and expressive language were also recorded. The effects of hearing rehabilitation (with hearing aids or cochlear implants) in this group of children and language outcomes after rehabilitation were monitored during long-term follow-up. The outcomes of rehabilitation measures differed in relation to the heterogeneous and often severe disabilities associated with CHARGE syndrome, e.g. developmental delay, intellectual delay, visual impairment, thin 8th nerve with retrocochlear auditory dysfunction (as described in cases of auditory neuropathy/dyssynchrony). Oral expressive language was severely impaired in most cases, even after lengthy follow-up, suggesting the need for alternative augmentative communication modes. The early identification of sensorineural hearing loss, and carefully planned rehabilitation treatments, can be of some benefit in children with CHARGE syndrome.

KEY WORDS: CHARGE syndrome • Inner ear • Hearing loss • Cochlear implants • Rehabilitation

RIASSUNTO

Obiettivo del presente lavoro è valutare i risultati della riabilitazione audiologica su un gruppo, numericamente consistente, di bambini affetti da sindrome di CHARGE. Lo studio è stato eseguito retrospettivamente, utilizzando il database dei pazienti pediatrici, presso l'Audiologia dell'Azienda Ospedaliero-Universitaria di Padova e di Ferrara. Sono stati individuati 31 bambini in totale, che hanno presentato diversi gradi di disabilità uditiva associata alla sindrome di CHARGE. La valutazione audiologica è stata eseguita utilizzando i potenziali evocati uditivi (ABR) e/o l'elettrococleografia, oppure le tecniche di audiometria infantile (VRA o play audiometry). Sono stati valutati anche i risultati percettivi, in termini di capacità di comunicazione e linguaggio espressivo. Sono quindi stati studiati gli effetti della riabilitazione uditiva (con apparecchio acustico o impianto cocleare) e in particolare lo sviluppo del linguaggio nel corso di un lungo follow-up. Gli esiti degli interventi riabilitativi sono risultati diversi in relazione alle eterogenee e spesso gravi disabilità associate alla sindrome di CHARGE (ad esempio, ritardo di sviluppo psico-fisico, gravi disturbi visivi concomitanti, disfunzioni uditive retrococleari per neuropatia uditiva/dissincronia associata). Anche dopo lungo follow-up, lo sviluppo del linguaggio è risultato gravemente compromesso nella maggior parte dei casi, suggerendo quindi la necessità di sviluppare modalità di comunicazione alternative in questo gruppo di piccoli Pazienti. L'identificazione precoce della sordità neurosensoriale e l'accurata pianificazione di trattamenti riabilitativi mirati, è in ogni caso fondamentale nei bambini con sindrome di CHARGE.

PAROLE CHIAVE: *Sindrome di CHARGE • Orecchio interno • Ipoacusia neurosensoriale • Impianto cocleare • Riabilitazione*

Acta Otorhinolaryngol Ital 2016;36:206-214

Introduction

The association of conditions was first described by Hall et al., in 1979, in 17 children with multiple congenital anomalies [1]. In the same year, Hittner reported this syndrome in 10 children with ocular colobomas and multiple congenital anomalies [2]. Hence the alternative name of Hall-Hittner syndrome [3]. Pagon et al. first adopted the acronym CHARGE in 1981 [4]. The syndrome comprises a cluster of conditions including: ocular coloboma (C); congenital heart defects (H); atresia of the choanae (A); retarded growth or development and/or central nervous system anomalies (R); genital hypoplasia (G); and ear anomalies, including deafness and vestibular dysfunction (E) [1].

The criteria for diagnosing CHARGE syndrome are listed in Table I. It has been suggested that diagnosis should be considered in any subject presenting with all four of the

Table I. Diagnostic criteria for CHARGE syndrome (from Blake KD et al., 2006 [10], mod.).

Major criteria	Minor criteria
Ocular coloboma	Cardiovascular malformations
Choanal atresia/stenosis	psychomotor retardation
Cranial nerve	Genital hypoplasia
Characteristic ear anomalies	Renal malformations
	Tracheoesophageal disease (i.e. atresia, laryngomalacia)
	Facial clefting
	Developmental delay, and short stature
	Hand dysmorphology
	Hypotonia

major criteria or with three of the major and three of the minor criteria [5 6]. Some of the features of CHARGE syndrome may be difficult to detect in the neonatal period, however, such a diagnosis needs to be kept in mind even for infants meeting one or two of the major and several of the minor criteria [5 6].

Concerning the syndrome's aetiopathogenesis, the majority of CHARGE cases identified so far have been classified as sporadic, but several genes may play a key part in this condition's pathogenesis. In 2005, a team from Radboud University (Nijmegen, Netherlands) using array-based comparative genomic hybridisation identified a small overlapping microdeletion at chromosome 8q12 in two patients with CHARGE syndrome. Therefore, the candidate CHD7 gene within this region was first identified and sequenced in 17 patients [7-9]. Although the CHARGE phenotype may be related to CHD7 gene mutations, there are still doubts concerning any genotype/phenotype correlation between the various features of CHARGE and different mutations in the CHD7 gene [10-12]. The use of genetic analysis as the sole tool for diagnosing this syndrome remains controversial [7 8 13].

External ear malformations have been described in association with CHARGE syndrome, including short and/or hypoplastic pinna with a minimal lobule, a hypoplastic helix or an anomalous concha [6]. Abnormalities have also been reported in the middle and inner ear [5 14 15], and hearing loss in CHARGE subjects may be conductive, sensorineural or mixed, ranging from mild to severe. Vestibular defects/malformations have also been described [16].

So far, only a few reports in the literature have focused on inner ear histopathology in CHARGE based on human autopsy studies. In 1986, Wright et al. [17] analysed the temporal bones of two infants who died soon after birth: the main findings were dysplastic ossicles, absence of the oval and round windows, cochleae that were normal in one case and short in the other, and varying degrees of hypoplasia of the vestibular sensory organs and nerves. In 1987, Guyot et al. [18] reported finding Mondini dysplasia of the pars inferior (cochlea and saccule) and absence of the pars superior (utricle and canals) in the temporal bone of a 7-month-old female with CHARGE syndrome. In 1993, Schuknecht [19] described two cases of CHARGE syndrome. In one, the external auditory canals, tympanic membranes, mallei and incudes were normal, but there was severe dysplasia of the stapes, and no oval windows and mesenchyme obliterating the round window niches. The other case revealed a one-turn cochlea on the right and a half-turn cochlea on the left. Both ears contained a few cochlear neurons in rudimentary modioli; saccules were present but hypoplastic, and the utricles and semicircular canals were lacking [19].

Other evidence come from radiological studies using temporal bone computerised tomography (CT) or magnetic resonance imaging (MRI). Amiel J et al. [20] reported that the main radiological features of CHARGE in their series were hypoplastic incus, Mondini defect and absence of semicircular canals. In 2003, Satar B et al. [21] studied 20 ears in CHARGE subjects and only 3 ears (15%) revealed a completely normal development of the cochlea in both the basal and upper turns; the others showed either mild hypoplasia of the upper turns (13 ears, 65%), or an incomplete partition typical of the classic Mondini deformity (4 ears, 20%). In 2006, Marimoto et al. [22] described 13 CHARGE patients who had cochlear atresia in 20 (77%) of 26 ears. Four of these ears were also assessed using MRI and were found to lack a cochlear nerve. Twenty-one (81%) of the 26 cochleae had some form of dysplasia. Six (23%) of the 26 round windows were aplastic, and 3 (12%) round windows were hypoplastic. Twenty-one (81%) of the 26 oval windows were atretic or aplastic. Fifteen (58%) of the 26 vestibules were hypoplastic or dysplastic. Five (19%) of the 26 vestibular aqueducts were enlarged. The semicircular canals were lacking in all these cases.

Twenty-three (88%) of the 26 facial nerve canals had an anomalous course. Finally, in 2013, Holcomb MA et al. [23] reported that the cochlear nerves were absent or deficient in 13 of 14 ears with sensorineural hearing loss (SNHL) in a series of CHARGE cases.

In conclusion, the prevalence of inner ear anomalies in the CHARGE syndrome has been reported to be higher than 90% [24]; these can include cochlear hypoplasia, in-

complete cochlear partition, Mondini dysplasia, incomplete formation or absence of semicircular canals, utricle and saccule [10 25 26]. Also, the auditory nerve in CHARGE patients can be reduced in diameter or absent, and nerve anomaly can be asymmetric [10 25 26]. It is clear that a correct neuroradiological assessment of these patients is crucial, in particular for the implications regarding the choice of rehabilitative approach that can be provided.

Materials and methods

This retrospective study was conducted on the paediatric patient database, at the Audiology Department of the University Hospitals of Ferrara and Padua.

The study included a total of 31 patients meeting diagnostic criteria for CHARGE syndrome (Table I) and followed regularly from January 1993 to July 2014. Clinical records were examined to ascertain the details of diagnosis and manifestations of CHARGE syndrome, neonatal and subsequent medical history, imaging data, laboratory and clinical findings, auditory perception and communication skills.

The median age of our sample when hearing loss was diagnosed was 21.15 months, and audiological and communication assessment were adapted to each subject's age and stage of development. Auditory brainstem responses (ABRs) were recorded for all patients to ascertain their hearing threshold. An EM 12 Mercury apparatus was used to identify the electrophysiological threshold. Other tests performed in the diagnostic workup and/or during the follow-up included: pure tone testing, behavioural conditioned audiometry (BCA, play audiometry), DPOAE recording, tympanometry and study of stapedial reflexes. Electrocochleography was also performed in some cases. Cortical evoked potentials in hearing-aided and -unaided patients were also used, in accordance with the Australian Hearing Aided Cortical Evoked Potentials Protocols [27], to measure the benefit of any hearing aids, and in the event of suspected auditory neuropathy/dyssynchrony. Based on American Speech-Language-Hearing Association (ASHA) protocols, a loss of 45 dB was defined as mild hearing loss, loss of 46-70 dB as moderate hearing loss, loss of 71-90 dB as severe hearing loss, and loss > 90 dB as profound hearing loss. CT and MRI data were assessed and any malformations were noted.

All subjects were followed up regularly (including phoniatric assessments) except for two patients who were lost to follow-up and three who died. In particular, perceptual and expressive language skills were assessed (and the findings analysed) at presentation and at 6, 12 and more than 36 months after fitting hearing aids (HA) or cochlear implants (CI). The follow-up was longer than 10 years for 8 patients, between 9 and 5 years for another 6 cases and around 3 years in the remaining 10 children. Speech perception was scored with a commonly-used outcome measure, the Speech Perception Category [28] in order to compare subjects across different ages and varying degrees of speech development. Speech perception was stratified on 6 levels: 0 = no detection of speech sounds; 1 = simple detection; 2 = pattern perception; 3 = inconsistent closed-set word recognition; 4 = consistent closed-set word recognition; 5 = open-set word recognition; 6 = open-set word recognition (exceeding performance with previous device).

Expressive language outcomes with rehabilitation (HA or CI) were reported using 6 categories corresponding to the major stages of expressive language development in normally-hearing and normally-developing children, ranging from voice production (category1) to the acquisition of connected discourse conforming to the adult model (category 6), through the stages of single word utterance, first combination of words and first sequences based on syntactic rules (See Legend 4, adapted from Bates E, 1987) [29]. Unconventional assessments were also performed in cases with severe additional disabilities. When standard tests for assessing communication skills were unreliable, interviews with parents and video-recordings were used instead. Parents were asked about behavioural changes observed in their child in response to environmental sounds and communicative interactions. In some cases, the PEACH questionnaire developed by Ching et al. was administered. A modified version of the video-analysis recording proposed by Tait [30] was sometimes used to note eye movements and mimicry in children with severe cognitive impairments, in addition to the information provided by their parents.

Results

The study population of 31 children with CHARGE syndrome included 16 girls and 15 boys (M/F ratio 0.93). All children were Caucasian and came from different Italian regions. The median age when hearing loss was diagnosed was 21.15 months. Table II shows the distribution of the major and minor diagnostic criteria in this sample of patients.

Hearing features and hearing rehabilitation

Fifteen of the 31 subjects had bilateral profound sensorineural hearing loss (SNHL); 10 had moderate to severe SNHL; 5 had moderate- to mild mixed hearing loss; and one had a normal hearing threshold but delayed perceptual development (Table III).

CIs were performed in 7 cases and 2 other patients were candidates for this surgery, while the other 8 children with bilateral profound SNHL were fitted with hearing aids. Air-conduction hearing aids were fitted in the children with moderate to severe SNHL as well as in those with a moderate and/or mixed hearing loss. One child only had

Table II. Prevalence of major and minor malformations in our sample of children with CHARGE syndrome.

MAJOR characteristics					MINOR characteristics				
Patient	Coloboma	Choanal atresia/ stenosis	Cranial nerve involvement	Ear anomalies	Cardiovascular malformations	Psychomotor retardation	Genital hypoplasia	Renal malformations	Tracheo-oesophageal disease
1	+		+	+	+			+	+
2	+		+	+	+		+		+
3		+	+	+	+	+			
4	+		+	+					
5	+		+	+	+	+			+
6	+		+	+	+	+		+	
7		+	+	+	+		+		+
8	+		+	+	+				
9	+		+	+		+			
10		+	+	+	+		+		
11	+		+	+	+				
12	+		+	+	+				
13	+		+	+	+	+			+
14		+	+	+		+			+
15	+		+	+	+	+			
16			+	+	+	+			+
17	+	+		+	+	+			
18	+	+			+	+			
19	+		+	+	+	+	+		
20				+	+		+		+
21	+		+	+		+	+		+
22	+	+	+	+	+	+	+		+
23		+	+	+	+	+			+
24	+	+		+	+	+	+	+	
25	+		+	+	+	+	+		+
26		+	+		+	+			
27		+	+	+				+	+
28	+	+	+	+	+	+			
29	+		+	+	+	+			+
30	+		+	+	+			+	
31	+			+		+			

a large air-bone gap and was successfully rehabilitated by means of a soft band bone conduction hearing aid.

Ear CT and Brain MRI findings

Twenty-one of the 31 subjects underwent high-resolution CT scanning and cerebral MRI under general anaesthesia to study their middle and inner ear, brainstem and brain. MRI alone was performed in another 6 patients. In the remaining 4 cases, the parents refused any neuroradiological investigations due to the risks related to general anaesthesia. Different types of ear malformation were identified, involving the cochlea (n = 19 ears), semicircular canals (n = 30), vestibule (n = 24), the internal auditory canal (n = 12), 8th nerve (n = 17), cochlear nerve (n =3) and facial nerve (n = 7).

There was also evidence of brain anomalies in 18 children, such other nerve hypoplasia and brainstem hypoplasia (the latter in only one case).

Psychomotor profile

Most of the children of the studied group presented some kind of delay in development of cognitive and motor abilities (Table II), mainly represented by a delayed postural control (i.e. difficulties in reaching the vertical position

Table III. CHARGE population: audiological features and rehabilitation (*referred to the better ear).

Patient	Hearing loss (*)	Type of rehabilitation	Communication mode
1	Sensorineural, profound	HA	Verb+sign
2	Sensorineural, profound	HA	(missing)
3	Sensorineural, profound	CI	Italian sign language
4	Sensorineural, moderate	HA	Italian sign language
5	Sensorineural, profound	HA	Very low communication skills
6	Sensorineural, profound	CI	Italian sign language
7	Sensorineural, profound	HA	(missing)
8	Sensorineural, moderate	HA	Verbal
9	Mixed, moderate	HA	Verbal
10	Sensorineural, moderate- severe	HA	(missing)
11	Mixed, mild	HA	Verbal
12	Mixed, mild	HA	(missing)
13	Sensorineural, profound	CI	Very low communication skills
14	Mixed, mild	HA	N/A
15	Mixed, mild	HA	Very low communication skills
16	Sensorineural, profound	CI	Verb+sign
17	Sensorineural, profound	CI	Verb+sign
18	Conductive, moderate	N/A	Verbal
19	Sensorineural, profound	HA	Verb+sign
20	Mixed, severe	HA	Verbal
21	Sensorineural, profound	HA	Very low communication skills
22	Sensorineural, profound	HA	Italian sign language
23	Mixed, moderate	HA	Verb+sign
24	Mixed, severe	HA	Very low communication skills
25	Sensorineural, profound	CI	Italian sign language
26	Mixed severe	HA	Very low communication skills
27	Normal	N/A	Very low communication skills
28	Sensorineural, profound	CI	Very low communication skills
29	Mixed, severe	HA	Italian sign language
30	Sensorineural, profound	HA	Very low communication skills
31	Mixed, moderate	HA	Verbal

or walking) or fine movements (i.e. grabbing or holding), light to moderate cognitive deficits, attention deficit or behavioural disorders. However, none of the children presented a severe cognitive delay, and 11/31 children had a satisfactory intellectual outcome (but always requiring special educational programs adapted to their age, hearing and language impairment, vision loss and to other disabilities).

Speech perception and expressive language development

Our data on speech perception and expressive language outcomes after rehabilitation (with CI and/or HA) were not homogeneous, due mainly to the different associated disabilities, such as developmental delay, intellectual delay and visual impairment (Table IV), and in light of the high mortality rate. Among the 7 children treated with CI, one did not benefit from the device, not even in the detection of loud sounds, probably due to a severe functional impairment of a thin 8th nerve. The other implanted children experienced a slow but consistent improvement in their perceptual abilities, achieving verbal word discrimination after a year or more of using the device. The majority of these patients developed delayed language skills (in comparison to deaf children of the same age treated with CIs). A similar trend was seen among the children with moderate to severe hearing impairments who were fitted with HA, so the results were analysed without distinguishing between the children with CIs and HAs.

Long-term follow-up after rehabilitation (at least 3 years) was available for all cases except the 3 children who died

Table IV. Perception scores and expressive language outcomes in children with CHARGE syndrome.

Patient	Perceptive category				Language development				
	Pre CI/HA	After 6 months	After 1 year	After 3 years or more	Pre CI/HA	After 6 months	After 1 year	After 3 years or more	Italian sign language development
1	1	3	5	5	1	2	3	3	+
2	N/A				N/A				
3	0	1	3	3	1	2	2	3	+
4	3	3	3	3	2	2	2	2	+
5	0	1	1	1	1	1	1	1	
6	0	1	3	3	N/A	1	2	2	+
7	0	1			1	2			
8	0	1	4	3	4	4	4	4	
9	2				2				
10	N/A				N/A				
11	6				6				
12	0	1			1	2			+
13	0	0			2	2			+
14	4	4	4	4	2	2	2	2	
15	N/A				N/A				
16	0	2	3	4	1	2	3	4	+
17	1	2	2		1	2	2		+
18	NO HA 5				6				
19	1	1	2	2	3	3	3	3	+
20	3	4	5	5	3	3	5	6	
21	0	1			1	1			
22	0	0 CAND CI			1	2			+
23	3	4	4		1	2	2		
24	0	0	0		1	1	1		
25	0	1	1		1	2	2		+
26	0	1	1		1	2	2		
27	NO HA 2				1				
28	0	1			1	1	1		
29	0	1	2	4	1	2	3	3	+
30	0	0 CAND CI							
31	4	5	6	6	5	5	5	6	

AUDITORY PERCEPTIVE PERFORMANCE (Geers, Moog, 1987 mod. [28])
0 = no detection of speech sounds
1 = simple detection
2 = pattern perception
3 = inconsistent closed-set word recognition
4 = consistent closed set word recognition
5 = open set word recognition
6 = open set word recognition (exceeding performance with old device)

MAJOR STAGES OF LANGUAGE DEVELOPMENT (Bates, O'Connel, Shore, 1987 mod. [29]).
1 = absent = voicing/babbling
2 = voc =vocalisations/CVC sequences to communicate intentionally
3 = words = first words/single word utterances that have communicative contents
4 = combinations = first words combinations/telegraphic utterances
5 = sentence grammar = combinations based on morphological and syntactic rules
6 = discourse grammar = connected discourse closely conformed to adult model

in early infancy and the 2 lost to follow-up. A slow improvement in auditory skills was recorded in three of the 26 cases followed up at length (who had complex needs and additional disabilities). Auditory-verbal communication as a single mode was only achieved in a few cases, while most patients used both signed and oral languages. One in three children developed some limited intentional communication activities, in addition to intentional vocalising or gestures. Almost all parents of these poorly-performing children nonetheless reported a significant improvement in their child's responsiveness to environmental sounds, and in their perception of their child's

quality of life following hearing rehabilitation, despite their lack of verbal production.

Discussion

It is well known that it is important for a child's development to diagnose and treat any sensory deficits as early as possible. Particularly in subjects with CHARGE syndrome, the combination of visual and auditory impairments with central nervous system anomalies makes audiological/otological intervention essential. Although the anomalies associated with CHARGE are numerous, an increasing number of reports has shown that audiological rehabilitation, and particularly cochlear implantation, may be a feasible rehabilitation method [30-33], and should be considered early because of the children's other communication problems [34], also calculating the risk of unsuccessful stimulation related to a thin 8th nerve and a prognosis of poor cognitive development.

The true incidence of CHARGE syndrome is still not known, but estimates have been in the range of 0.1-1.2/10,000 live births [35]. An epidemiological study of patients with CHARGE syndrome conducted as part of the Canadian Paediatric Surveillance Programme (CPSP) from September 2001-2004 estimated the incidence of this syndrome at 1:8,500 live births [35 36], so the incidence reported internationally may be underestimated [37].

As for the incidence of ear anomalies and hearing loss in CHARGE syndrome subjects, this has been described in 80-100% of reported cases [10], with a prevalence of severe- or profound hearing loss of approximately 50% in series of CHARGE cases [10]. The most frequent inner ear anomalies in patients with CHARGE are cochlear dysplasia, aplasia of the semicircular canals [20 34] (as in our series) and 8th nerve anomalies/dysfunction. High-resolution CT is therefore mandatory, particularly before considering cochlear implantation, to detect anomalies in the middle and/or inner ear and identify any atypical routing of the facial nerve. Obtaining information on the state of the internal auditory canal is also important, as this may provide evidence of aplasia/hypoplasia of the auditory nerve. Patients with CHARGE syndrome should always undergo MRI to assess the 8th nerve [34]. In the series presented here, the cochlear nerve was missing in 3 patients, and many others showed hypoplasia of the vestibulocochlear nerve.

The outcome after hearing rehabilitation (with CIs and HAs) in patients with CHARGE syndrome varies due to the differing extent of other disabilities (e.g. developmental delay and visual impairment). Most of the patients in our series showed some improvement in responsiveness once they were using HAs or had a CI. Open speech comprehension was only seen in one of the four cases. There are few reports in the literature on the outcome of treatment with CIs in CHARGE patients. Lanson BG (2007), Bauer PW (2002) Arndt S (2010), Ahn (2013), Cardoso (2013) and Birman (2015) all demonstrated that CI is a feasible option for such patients, even though variations in temporal bone anatomy can lead to higher surgical risks [34-45]. There is a general consensus that early audiological intervention is important in children with dual/multiple sensory impairments to facilitate their optimal development and enable at least minimal communication [5 34-39 46], but to the best of our knowledge there are still no publications on the long-term results achieved with CIs in children with CHARGE syndrome.

As for any improved communication and perception in our CHARGE patients, prognosis in terms of the effects of rehabilitation should be considered with caution because most of our cases were complicated by cognitive impairments, developmental disorders, or severe physical diseases (respiratory and cardiac insufficiency, severe dysphagia), which compounded the severity of their hearing impairments. Such additional handicaps interfere with the comprehension and production of speech and undermine any benefits achieved thanks to appropriate hearing rehabilitation. Severe physical diseases also mean lengthy hospital stays and other concerns for the child's health and life. Although the auditory-processing and language development in these children is limited by their cognitive and/or physical disorders, careful planning of their hearing rehabilitation (including CI) may offer auditory benefits and some improvements in their communication skills (as seen in our sample). The functional (hearing) prognosis for this particular category of patients should therefore be formulated after carefully weighting patients' auditory and non-auditory factors. A multimodal communication approach (also including sign language) should be planned in advance, tailored to each case and fine-tuned over the course of time.

Conclusions

In conclusion, it is common knowledge that early diagnosis and treatment of sensory deficits is crucial [41]. In the case of CHARGE syndrome, the concomitant presence of characteristic developmental features as well as neuropsychological impairments should be borne in mind in order to plan personalised rehabilitation.

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VESTIBOLOGY

Point prevalence of vertigo and dizziness in a sample of 2672 subjects and correlation with headaches

Prevalenza dei sintomi vertigine e instabilità in un campione di 2672 soggetti e correlazione con il sintomo cefalea

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SUMMARY

Vertigo and dizziness are common symptoms in the general population, with an estimated prevalence between 20% and 56%. The aim of our work was to assess the point prevalence of these symptoms in a population of 2672 subjects. Patients were asked to answer a questionnaire; in the first part they were asked about demographic data and previous vertigo and or dizziness. Mean age of the sample was 48.3 ± 15 years, and 46.7% were males. A total of 1077 (40.3%) subjects referred vertigo/dizziness during their lifetime, and the mean age of the first vertigo attack was 39.2 ± 15.4 years; in the second part they were asked about the characteristics of vertigo (age of first episode, rotational vertigo, relapsing episodes, positional exacerbation, presence of cochlear symptoms) and lifetime presence of moderate to severe headache and its clinical features (hemicranial, pulsatile, associated with phono and photophobia, worse on effort). An age and sex effect was demonstrated, with symptoms 4.4 times more elevated in females and 1.8 times in people over 50 years. In the total sample of 2672 responders, 13.7% referred a sensation of spinning, 26.3% relapsing episodes, 12.9% positional exacerbation and 4.8% cochlear symptoms; 34.8% referred headache during their lifetime. Subjects suffering from headache presented an increased rate of relapsing episodes, positional exacerbation, cochlear symptoms and a lower age of occurrence of the first vertigo/dizziness episode. In the discussion, our data are compared with those of previous studies, and we underline the relationship between vertigo/dizziness from one side and headache with migrainous features on the other.

KEY WORDS: Vertigo • Dizziness • Epidemiology • Migraine

RIASSUNTO

La vertigine e l'instabilità sono sintomi molto comuni nella popolazione la cui prevalenza è stimata tra il 20 e il 56%. L'obiettivo del nostro lavoro è stato quello di determinare la prevalenza di questi sintomi in una popolazione di 2672 soggetti. È stato somministrato loro loro un questionario; nella prima parte sono stati richiesti i dati demografici e se avessero mai sofferto di vertigine o instabilità nella loro vita. L'età media del campione è stata di 48,3 ± 15 anni, il 46,7% erano maschi. Sul totale della popolazione 1077 (40,3%) hanno riferito di aver sofferto di vertigine o instabilità nella loro vita, con un primo episodio occorso all'età di 39,2 ± 15,4 anni. Nella seconda parte del questionario sono state indagate le caratteristiche delle vertigini (età del primo episodio, il tipo di vertigine, presenza di più episodi, esacerbazione posizionale della vertigine, presenza di sintomi cocleari infine la presenza di cefalea da moderata o severa nel corso della vita e le sue caratteristiche cliniche (riferita a un emicrania, pulsante, associata a fono o fotofobia, peggiore con l'attività fisica). È stata osservata una correlazione della vertigine con l'età e con il sesso, essendo la prima 4,4 volte più frequente nelle donne e 1,8 volte nei soggetti con oltre 50 anni. Sul campione complessivo di 2672 soggetti, 13,7% hanno riferito vertigine rotatoria, 26,3% episodi recidivanti, 12,9% esacerbazione correlata alla posizione e il 4,8% presenza sintomi cocleari; il 34,8% ha lamentato cefalea nel corso della loro vita. I soggetti affetti da cefalea presentavano un'incidenza aumentata di vertigini recidivanti, di esacerbazione correlata alla posizione, di sintomi cocleari e un'età più giovane di comparsa del primo episodio di vertigine/instabilità. Nella discussione i nostri dati sono stati confrontati con quelli di precedenti studi. Gli autori sottolineano la correlazione tra vertigine/instabilità da un lato e cefalea con caratteristiche emicraniche dall'altro.

PAROLE CHIAVE: *Vertigine • Instabilità • Epidemiologia • Emicrania*

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Introduction

Vertigo and dizziness are among the most common reasons for medical consultation [1] and they account for 2-3% of total consultations in emergency departments [2]. It has been reported that nearly 26 million people needed a visit in an emergency department for dizziness/vertigo over a period of 10 years (1995-2004) in the US, with a median of 3.6 diagnostic tests per patient [3].

Previous studies focusing on epidemiology of vertigo and dizziness have reported a lifetime prevalence between 20% and 30% [4 5]. In a recent questionnaire-based investigation, the authors calculated in a large cohort of 2987 French subjects that the 1-year prevalence for vertigo was 48.3%, for unsteadiness it was 39.1%, and for dizziness it was 35.6%. The three symptoms were correlated with each other and occurred mostly (69.4%) in various combinations rather than in isolation [6]. In a meta-analysis, a lifetime prevalence of vertigo toward a vestibular disorder was seen in 3% to 10% of the total population [7]. Moreover, dizziness, which is a more undefined condition, is frequently associated with other common diseases and conditions, such as migraine [8], motion sickness [9], orthostatic hypotension, sensation of fainting [10] and anxiety disorders [11].

A recent study confirmed previous findings on the marked female preponderance among individuals with vertigo (one-year male to female prevalence ratio of 1:2.7), and showed that vertigo is almost three times more frequent in the elderly compared to younger individuals [12].

Finally, vertigo and migraine are often comorbid conditions; with the exclusion of vestibular migraine, with prevalence of 0.98% [12], patients with Menière's disease present a higher rate of migraines (around 56%) than the total population [13], and migraineurs more often present benign paroxysmal positional vertigo (BPPV) [14].

The main purpose of our work was to assess the prevalence of vertigo/dizziness in a Caucasian population and establish the relationship of these symptoms with headache and its migrainous features.

Materials and methods

Study design

This was an observational prospective study, based on a self administered questionnaire, carried on in 3 university centres in the period between January and April 2015; subjects were anonymously asked to participate, either connecting to a protected site or on a paper support randomly distributed among outpatients in the withdrawal centres. The first part included only demographic data (sex and age) and the question "Have you ever experienced vertigo and/or dizziness during your lifetime?". Patients were instructed to consider either the feeling that you are dizzily turning around or that your surroundings are dizzily turning about you. Only patients with a positive history for vertigo and/or dizziness were asked to complete the entire questionnaire. Questions to be answered are reported in Table I. Only subjects over 18 years old were included. To characterise the type of headache, four specific questions were included in the questionnaire regarding the feature of symptoms (hemicranial, pulsatile, associated with phono and photophobia and worse during physical efforts); a composite migraine risk score (MRS) was calculated for the patients suffering from headache, giving 2 points for every positive answer, so that MRS could range between 0 and 8.

Population sample

A total of 2672 subjects were included in the study; 1249 (46.7%) were males. Mean age was 48 ± 15.2 years (range 18 to 96). No difference was detected between the group of subjects with and without vertigo for the age at inclusion (48.8 ± 15.3 and 47.6 ± 15.1, respectively). In Table II sex and age distribution (over or below 50 years) are reported. Figure 1 shows the histogram of age distribution of subjects with a positive history for vertigo.

Statistical analysis

Normally distributed continuous variables are reported as mean value ± standard deviation; differences were assessed by a two tailed t test. Categorical variables are reported as rates on total and a chi square test was performed to establish differences between groups. A linear regression model has been performed to quantify the vertigo risk in the 4 classes of subjects (males and females, below and over 50 years); data are reported as odds ratio (OR) (95% confidence interval [CI]). A linear regression test was also performed to correlate MRS with a clinical

Table I. Questionnaire to be completed by subjects with a positive history for vertigo/dizziness.

At which age did you experience your first episode of vertigo/dizziness?	
Do you experience the sensation that surrounding objects are moving or spinning?	
Do you have the sensation of a decrease of hearing level during vertigo?	
Did you experience a single episode or relapsing ones?	
Do you have an onset or increase of symptoms while lying down in bed?	
Have you suffered from moderate to severe headache during your lifetime?	
If yes, did it present with any of the following features?	A. Localised on one side? B. Pulsatile C. Associated with phono- or photophobia D. Going worst during physical effort

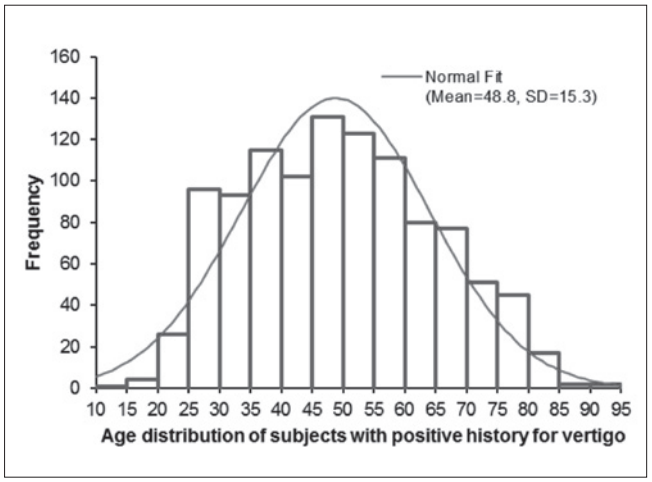

Fig. 1. Age distribution of patients with a positive history for vertigo at inclusion.

history of rotational, positional vertigo and with the age of the first vertigo episode. Analyses were carried out using STATA software v. 13 (Stata Corporation, College Station, 2013, Texas, USA).

Results

No difference were seen between the group of subjects with and without vertigo for age at inclusion (48.8 ± 15.3 and 47.6 ± 15.1, respectively). In Table II sex and age distribution (over or below 50 years) are reported. In Figure 1, the histogram of age distribution of subjects with a positive history for vertigo at inclusion is shown.

In the sample, 1077 of 2672 (40.3%) subjects reported at least one episode of vertigo/dizziness during their lifetime; 768 (71.3%) were females, while 309 (28.7%) were males. Independently from age, females presented a higher rate of vertigo than males (OR = 3.56, 95% CI 3.017225-4.199935; $p \leq 0.001$). Independently of sex, vertigo was more represented in people over 50 years; 479 of 1077(44.5%) with a positive history of vertigo, while 367 of 1595 (23%) without vertigo were over 50 years (OR = 1.37, CI 1.171587-1.60125; $p \leq 0.005$). Considering 1 as the vertigo risk in the sample of males below 50 years, it was 1.8 times higher in males over 50 yo, 4.4 in females below 50 years and 5.2 times higher in females over 50 years ($p \leq 0.001$). In our sample, lifetime risk of vertigo risk was estimated to increase by 1% every 10 years.

Table II. Age and sex distribution of the sample.

Sex	Age		Total
	< 50 years	> 50 years	
Females	820	603	1423
Males	716	533	1249
Total	1536	1136	2672

In the total sample, 367 of 2672 subjects (13.7%) referred a sensation of spinning or movement of surroundings, 702 relapsing episodes (26.3%), 130 (4.8%) the sensation of fluctuating hearing level during vertigo and 347 (12.9%) reported the onset or increase of vertigo while lying down. In the sample of 1077 dizzy subjects, 375 also reported headache episodes (34.8%), 254 with a MRS of at least 4 points, 110 with a score of 2 and only 11 with a score of 0. The prevalence of various features of vertiginous episodes was calculated in the total group and in the subgroup of subjects also referring headache:

- the age of the first vertigo (see Fig. 2) was 39.2 ±15.4 years, while in the subgroup of 375 subjects with headache it was 33.4±15.4 ($p \leq 0.001$). Thirty-four subjects (1.2%) referred vertigo in a paediatric age, 33 reported headaches (all with a MRS of at least 4) and 25 were females. The MRS was 5 ± 2.2 in the sample of headache subjects, while it was 6.1 ±1.7 in the 34 subjects with paediatric vertigo ($p \leq 0.01$);
- a positional component was reported in 351 of 1079 subjects with vertigo (32.5%), in 146 of 375 (38.9%) subjects with headaches ($p = 0.02$) and 130 (51.2%) with a MRS of at least 4 ($p \leq 0.01$);
- a relapsing vertigo was reported in 702 of 1077 subjects (65%), in 280 of 375 (74.6%) headache sufferers ($p \leq 0.01$) and in 242 of 254 (95%) subjects with a MRS of at least 4 ($p \leq 0.001$);
- a sensation of fluctuating hearing level was reported in 130 of 1077 (12%) dizzy subjects, in 63 of 375 (16.8%, $p = 0.02$) headache sufferers and in 52 (20.4%) subjects with at least 4 points on the MRS ($p \leq 0.001$).

Finally, a linear regression test demonstrated an association between the MRS and a positional component of vertigo ($p = 0.001$), rotational vertigo ($p \leq 0.01$), age of first vertigo attack ($p \leq 0.0001$) and relapsing episodes of vertigo ($p \leq 0.0001$).

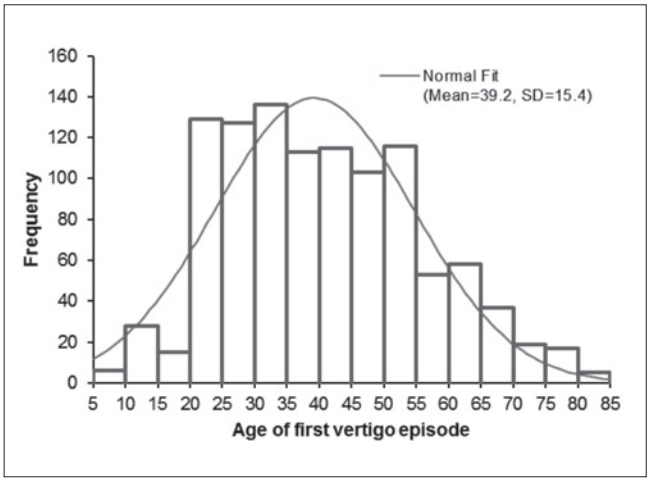

Fig. 2. Age distribution for the first episode of vertigo/dizziness.

Discussion

Our data are consistent with those published in previous reports. In our sample, the point prevalence for vertigo and or dizziness of any kind (i.e. without a definition of severity) was 40.3%. Previously published papers have reported different results, with a lifetime prevalence ranging between 23.2% and 59.2% [4 6], but when patients were asked if they experienced dizziness bad enough to interfere with daily activities, the positive responders decreased to 16.9-29.5% [4 12]. It should be underlined that dizziness is a common and non-specific symptom and may be provoked by various disorders, including neurological, cardiovascular, vestibular and multisensory dysfunctions; moreover, a strict relationship has also been reported with anxiety and panic disorders [5 15]. When asked about vertigo as a symptom (i.e. a sense of rotation or spinning), 13.7% of our sample referred to have experienced it; our data confirm those of previous papers reporting a rate in the range between 7.8% and 21% [4 12]. Other studies, based on general practitioner records, estimated a 12 month incidence of vertigo between 1.78% and 3.4% [16 17]. Commonly accepted clinical practice makes a distinction between vertigo and dizziness, with the first more often associated with a dysfunction of the vestibular system. Nonetheless, it has been underlined in epidemiologic studies that cultural and linguistic factors may play a role in the description of subjective symptoms [18 19].

In our sample, we found an increased prevalence of vertigo in females and in the elderly; in particular, females presented a 4.4-fold increased risk for vertigo, while the age-related risk factor was estimated to be 1.8; these results are consistent with previously published reports [4 6 12 19-23].

More interesting data may be drawn about the correlation between vertigo from one side and headache and migraine to the other. Since not all patients referring moderate to severe headaches in our sample were migraineurs, we decided to assess the migraine probability with a score, the MRS, by evaluating 4 characteristics related to migraine (hemicranial, pulsatile, associated with phono and/or photophobia, worse with physical effort). Patients with higher MRS more frequently presented relapsing episodes of vertigo, referred a sensation of hearing level fluctuation during vertigo/dizziness and presented a lower age of occurrence of the first vertigo attack; moreover, all subjects referring vertigo in a paediatric age presented with a MRS greater than 4.

Far from being exhaustive, it should be noted that the relationship between vertigo and migraine is complex and it has been stated that it goes beyond the diagnostic concept of vestibular migraine [24 25], whose prevalence in total population has been estimated at 0.98% [26]. For example, among patients diagnosed with Meniere's disease, 56% also presented migraine compared to 16% in the normal population [13]; migraine has been found to be three times more common in patients with idiopathic BPPV [27] and two times more common in patients with idiopathic BPPV than in age and sex-matched controls [28]. Vertigo may be a migraine precursor in a paediatric age [29], and motion sickness occurs more frequently in patients with migraine both in paediatric and adult ages, with a reported prevalence between 30% and 50% [30]. Finally, an interrelation between migraine, anxiety and other psychiatric disorders and dizziness has been postulated and a clinical entity including the 3 disorders, the MARD, has been proposed [31]. It should be underlined that vertigo/dizziness with a positional component may be related to BPPV, which is more represented among migraineurs, but it may also be one of the commonest findings in vestibular migraine [32]. Moreover, our data underline that a sensation of decrease of hearing level during vertigo was reported in 12% of total dizzy patients, and above all in 20.4% of dizzy patients with a MRS of at least 4. This percentage includes patients with Meniere's disease, even if not confirmed; nonetheless, a recent paper reported that cochlear symptoms are far from being rare even in subjects with definite vestibular migraine, since 10.7% of patients referred a sensation of a hearing loss often during vertigo and 15.5% sometimes during vertigo [33 34].

As a final consideration, we want to underline the possible risks of bias in our work, above all linked to the representativeness of our sample; even if patients presenting for any ambulatory visit were excluded, and questionnaires were completed for a large part by subjects referring to hospital for a blood exam, it cannot be excluded that responders were above all subjects with previous episodes of vertigo. Nonetheless, our results are in the range of previously published data and confirm the high prevalence of vertigo/dizziness as a symptom in the general population.

Conclusions

Our data, in accordance with previously published reports, confirm the high prevalence of symptoms of vertigo/dizziness in general population. Symptoms present a higher prevalence in females and in the elderly. Finally, an association with migraine was found.

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Otology

Long-term surgical results in microvascular decompression for hemifacial spasm: efficacy, morbidity and quality of life

Risultati chirurgici a lungo termine della decompressione microvascolare nell'emispasmo facciale: efficacia, morbilità e qualità di vita

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SUMMARY

Hemifacial spasm is a condition that may severely reduce patients' quality of life. Microvascular decompression is the neurosurgical treatment of choice. The objective of this work was to describe the efficacy and morbidity of microvascular decompression for hemifacial spasm, evaluate the long-term efficacy on the quality of life and investigate prognostic factors for failure of the procedure. A retrospective study of 446 cases of hemifacial spasm treated by 511 retrosigmoid microvascular decompression over 22 years was conducted. Epidemiological, clinical and imaging findings, treatment modalities and outcomes of patients with pre- and postoperative HSF-8 quality of life questionnaire were studied. Success rate was 82% after first surgery and 91.6% after revision surgery. A low rate of perioperative morbidity was found. Facial palsy was mostly transient (5.5% transient and 0.2% permanent) and cochleovestibular deficit was seen in 4.8% of patients. Revision surgery increased nervous lesions (10.6% to 20.7%). Mean quality of life scores were significantly improved from 18 to 2 over 32, evaluated 7.3 years after surgery. Predictive factors of surgical failure were single conflicts ($p = 0.041$), atypical vasculo-nervous conflicts involving other vessel than postero-inferior cerebellar artery ($p = 0.036$), such as vein ($p = 0.045$), and other compression sites than root exit zone ($p = 0.027$). Retrosigmoid microvascular decompression is a safe and effective treatment of hemifacial spasm. Revision surgery is not to be excluded in case of failure, but does place patients at risk for more complications. Quality of life is improved in the long-term, indicating objective and subjective satisfaction.

KEY WORDS: Hemifacial spasm • HFS-8 score • Microvascular decompression • Neurovascular conflict • Quality of life

RIASSUNTO

L'emispasmo facciale è una condizione clinica che può seriamente compromettere la qualità di vita del paziente. In questi casi la decompressione microvascolare rappresenta il trattamento neurochirurgico di scelta. L'obiettivo del presente lavoro è stato quello di descrivere sia l'efficacia che la morbilità della decompressione microvascolare nel trattamento dell'emispasmo facciale, di valutare l'outcome della procedura in termini di qualità di vita e di individuare eventuale fattori prognostici predittivi dell'eventuale fallimento della procedura. È stata revisionata la nostra casistica di 446 casi di emispasmo facciale trattati complessivamente nell'arco di 22 anni con 511 procedure di decompressione microvascolare con approccio retrosigmoideo. Abbiamo quindi analizzato i reperti epidemiologici, clinici e radiologici, le modalità di trattamento e gli outcome mediante la somministrazione pre e post operatoria del questionario HSF-8. Il rateo di successo è stato dell'82% dopo la prima procedura chirurgica e del 91,6 dopo la seconda procedura. Abbiamo registrato una bassa morbilità perioperatoria. La paralisi del facciale è stato per lo più un fenomeno transitorio (5,5% dei casi, permanente nello 0,2%). Nel 4,8% dei casi si è avuto invece un deficit cocleovestibolare. La chirurgia di revisione è stata invece gravata da un aumentato rateo di lesioni nervose (10.6 -20.7%). La qualità di vita a seguito della chirurgia valutata mediante HSF-8 è risultata migliore con uno score ridotto in media da 18 a 2 su 32. I fattori predittivi di fallimento chirurgico individuate sono stati I conflitti singoli ($p = 0,041$), conflitti atipici non coinvolgenti la PICA ($p = 0,036$), come quelli venosi ($p = 0,045$) e zone di compressione alternative all'emergenza radicolare ($p = 0,027$). In conclusione, la decompressione microvascolare con accesso retrosigmoideo si è rivelata essere una tecnica sicura ed efficace nel trattamento dell'emispasmo facciale. La revisione chirurgica è un opzione percorribile, ma espone a un maggior rischio di complicanze. La qualità di vita è risultata accresciuta a nel lungo termine, dimostrando un elevato grado di soddisfazione e beneficio oggettivo e soggettivo.

PAROLE CHIAVE: *Emispasmo facciale • HSF-8 score • Decompressione microvascolare • Conflitto neurovascolare• Qualità di vita*

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Introduction

Hemifacial spasm (HFS) is characterised by tonic and/or clonic contraction of the facial muscles of one side of the face. The symptoms usually progress in frequency and severity, starting with intermittent twitches in the orbicularis oculi muscle, and spreading downward to the ipsilateral facial muscles.

The most frequent cause of HFS is neurovascular conflict due to a focal compression of the root exit zone (REZ) of the facial nerve by an aberrant vascular structure [1]. In cases identified by magnetic resonance imaging (MRI), retrosigmoid microvascular decompression (MVD) is indicated after unsatisfactory or decreasing effect of botulinum toxin treatment. It consists in a neurosurgical intervention in the cerebellopontine angle, and therefore exposes patients to rare morbidity such as nervous lesion (facial palsy, hearing loss, vestibular dysfunction), neurosurgical (cerebrospinal fluid (CSF) leak, infection, bleeding), scarring and general complications (anesthesia complications) [2]. Therefore, long-term efficacy of MVD must be documented in order to strengthen the benefit-risk ratio.

HFS frequently leads to social anxiety, but can also affect vision, sleep and mental concentration [3]. Such problems have a strong impact on the patient's perception and satisfaction in various aspects of their life [4 5]. Quality of life (QOL) is an important outcome measure in chronic diseases such as HFS, where patients expect to find relief in subjective complains such as social embarrassment. The HemiFacial Spasm 8 Quality of Life Scale (HFS-8) is the reference parameter to investigate efficacy of post-operative results of MVD [6].

This study focused on long-term surgical results in retrosigmoid MVD for HFS. Based on our experience and a review of the literature, our study aimed: (i) to describe the morbidity of this therapeutic approach; (ii) to evaluate the long-term efficacy on QOL; (iii) to investigate prognostic factors for failure of the procedure.

Materials and methods

This work reports on a retrospective study of consecutive cases of HFS treated by MVD in a university tertiary referral centre over 22 years (1990-2012). Patients with non-vascular aetiologies of facial nerve irritation were excluded.

Workup

All HFS patients presented unsatisfactory or decreasing effect of botulinum toxin treatment. HFS onset was reported. All patients were clinically investigated for otological and neurological symptoms. Audiometry for pure tones and speech was performed, and recommendations from the Committee on Hearing and Equilibrium were followed for reporting hearing test results [7]. MRI, focusing on the facial nerve trajectory, was performed to diagnose and localise the neurovascular conflict, and to exclude facial nerve tumour or other differential diagnoses. Failure or recurrence of HFS after MVD was defined by: no change in spasms, worsening of spasms and improvement but persistence of spasms. Preoperative MRI, intraoperative videos, or pictures were reviewed to ensure a missed compression (multiple conflicts). Before revision surgery, a new MRI was performed to identify a missed compression, adhesions around REZ and/or Teflon pledget migration.

Microvascular decompression procedure using a minimal invasive retrosigmoid approach

Surgical strategy was as previously described with microneurosurgical instruments, powered instrumentation and intraoperative facial nerve integrity monitoring system (NIM II®; Medtronic Inc, Fridley, Minnesota) [8 9].

A limited craniotomy behind and close to the sigmoid sinus was performed (2-1.5 cm in diameter). After hyperventilation to diminish CSF pressure, the dura was U-shaped opened. Under binocular microscopy, the cerebellum was depressed spontaneously and progressively helped by CSF aspiration of the cerebellopontine angle cistern. By an endoscopic procedure, the cerebellopontine angle was explored without the use of fixed retraction, allowing clear visualisation of the facial nerve and precise location of the neurovascular conflict. The site of the disorder was exposed safely and non-traumatically with a 30°- or 45° endoscope with a diameter of 4 mm and length of 11 cm. Conflict was treated by interposition of Teflon pledget and/or liberation vessel or nerve from fibrosis or retraction. Multiple offending vessels were searched in multiple possible affected sites in addition to the REZ of the facial nerve.

Post-operative management

A compression bandage was kept for 5 days. No antibiotic prophylaxis was given. Pain was handled with appropriate analgesics. During hospitalisation, computed tomography (CT) was carried out in case of headache or neurological disorder. Audiometry for pure tones was performed at day 7. The patient was discharged after 7 post-operative days.

Facial palsy was treated with high-dose corticosteroids, long-term eye care and facial physical therapy. Vestibular deficit was managed with high-dose corticosteroids and vestibular rehabilitation. Sensorineural hearing loss (SNHL) was initially treated with high-dose corticosteroids. In the event of CSF leak, conservative measures (compression bandage, bed rest, head elevation, stool softeners and acetazolamid) were combined with anti-pneumococcal vaccination. If the leak persisted after 3 days, surgical closure of the breach was indicated.

Follow-up

Resolution of symptoms after MVD was evaluated at a minimum of 2 months post-operatively with otological and neurological assessment. Complete symptoms resolution was considered as immediate or delayed if resolution took less or more than 2 weeks. Audiometry for pure tones and speech was performed at the same time. Follow-up was based on clinical control visits with audiometry at 6 months post-operatively.

HFS-8 quality of life self-questionnaire

This QOL short self-rating scale investigates 8 validated items for severity quotation from 0 (normal) to 4 (severely incapacitated): difficulty driving, reading, watching television/movie, feels depressed, avoids eye contact, feels embarrassed about having the condition, feels worried about other's reaction and sleep disturbance [6]. The HSF-8 score ranged from 0 to 32, the former indicating an excellent QOL and the latter a mediocre QOL. Two HFS-8 questionnaires were submitted to patients by mail or by phone: a retrospective one evaluating preoperative QOL, and a prospective one evaluating presently postoperative QOL (assessment from 2012 to 2014).

Statistical analysis

Continuous data were expressed as mean ± standard deviation or median [25th-75th percentiles]. Symptom prevalence rates were expressed as percentages. The clinical follow-up interval was calculated by year, from the date of surgery to the date of last consultation. Comparison of individual pre- and post-operative QOL scores was carried out by paired Wilcoxon test. The prognostic factors for surgical failure were investigated using independent Student t-tests for continuous factors and chi-square tests for categorical factors. A p value less than 0.05 was considered statistically significant. All analyses were carried out using IBM SPSS Statistics 20.0 (IBM Inc., New York, USA).

Results

Population

Over 22 years, 446 patients underwent retrosigmoid MVD, and 511 procedures were performed. Twelve patients were operated for a failure or a relapse after a first MVD in another institution. Median clinical follow-up was 24 months [3-75].

Among the 446 patients, 160 (35.9%) were male and 286 (64.1%) were female, for a sex ratio of 0.6. Age of HFS onset and at first surgery was, respectively, 49 ± 12 years and 57 ± 12 years. Surgery was single for 384 patients. In 62 cases of failure or relapse after first surgery (including 12 cases with first procedure in another center), revision procedure was performed 25 ± 43 months after first MVD. A total of 77 revision procedures were performed in 62 patients: 52 patients (11.6%) had 2 surgeries, 7 patients (1.6%) had 3 surgeries, 1 patient (0.2%) had 4 surgeries and 2 patients (0.4%) had 5 surgeries.

Imaging and endoscopic findings

Pre-operative MRI was performed in 99.9% of 511 procedures (3 claustrophobics and 1 patient with pacemaker were explored by CT with contrast infusion). Before first surgery, 4 patients (1%) did not exhibit neurovascular conflict on MRI and the nature of vessel was notified in 406 MRI (91%) and 424 procedures (95%) in our data (Table I). The postero-inferior cerebellar artery (PICA) was involved in 77% of per-operative conflicts, vertebral artery (VA) in 38% and antero-inferior cerebellar artery (AICA) in 38%. Among the 74 conflicts classified as "other", 35 (8% of all conflicts) were triple, involving the PICA, VA and AICA. Multiple vessel conflict was 40% in MRI evaluation and 55% in endoscopic evaluation.

Revision surgery for recurrence or failure let to finding incomplete nervous decompression, retraction and fibrosis around REZ and/or Teflon pledget migration.

Surgical efficacy

Resolution of symptoms after first hand MVD was complete and immediate in 54% of cases, complete and delayed in 23.6%, partial in 4.7%, and 4.1% were improved before relapsing. Efficacy was 82% after first surgery and 91.6% after revision surgery.

Complications

At least one complication was seen in 83 patients (19%) after first surgery, and in 23 patients (30%) after revision surgery. Complications are detailed in Table II. No patient died.

Table I. Imaging *vs* endoscopic findings discordance for neurovascular conflicts.

	PICA	VA + PICA	VA	AICA	PICA + AICA	Other	Total
MRI	37% (n = 151)	30% (n =121)	11% (n = 45)	10% (n = 40)	7% (n = 28)	5% (n = 21)	N = 406
Endoscopy	30% (n = 127)	23% (n = 98)	3% (n = 13)	11% (n =46)	16% (n = 66)	17% (n = 74)	N = 424
Discordance	36%	34%	46%	58%	78%	93%	

Discordance was calculated for each surgical conflict as the rate of patients that exhibited a different conflict in MRI.
AICA: Antero-Inferior Cerebellar Artery; MRI: Magnetic Resonance Imaging; PICA: Postero-Inferior Cerebellar Artery; VA: Vertebral Artery

Table II. Complications of retrosigmoid microvascular decompression for hemifacial spasm.

	First surgery (n=434) No. of patients (%)	Revision surgery (n=77) No. of patients (%)
General complications	6 (1.4)	1 (1.3)
Neurosurgical complications		
Infection	7 (1.6)	1 (1.3)
Bleeding	3 (0.7)	0
CSF leak	9 (2)	6 (7.8)
Scarring complications	24 (5.5)	7 (9)
Nervous complications	46 (10.6)	16 (20.7)
Facial nerve		
Transient	24 (5.5)	5 (6.5)
Permanent	1 (0.2)	1 (1.3)
Cochleo-vestibular nerve		
Cochlear nerve		
Transient	9 (2)	5 (6.5)
Permanent	12 (2.7)	3 (3.9)
Vestibular nerve	3 (0.7)	1 (1.3)
Lower cranial nerves (IX, X, XI, XII)		
Transient	4 (0.9)	0

CSF: cerebrospinal fluid

Quality of life

Three hundred and three patients (68%) underwent long-term assessment with the HFS-8 questionnaire; 143 patients were lost to QOL evaluation. Mean (median [25th-75th percentiles]) time between first surgery and evaluation was 7.3 years (6 [3.9-9.7] years). The HSF-8 score dramatically improved after surgery from 18 (18 [13-23]) to 2 (0 [0-0]) over 32 ($p < 0.001$) (Fig. 1).

Prognosis factors

Pre-, peri- and postoperative data were studied as prognostic factors for surgical failure after first MVD (Table III). Failure was significantly associated with single conflict ($p = 0.041$), venous conflict ($p = 0.045$), absence of involvement of PICA in the neurovascular conflict ($p = 0.036$) and absence of involvement of REZ in the neurovascular conflict ($p = 0.027$).

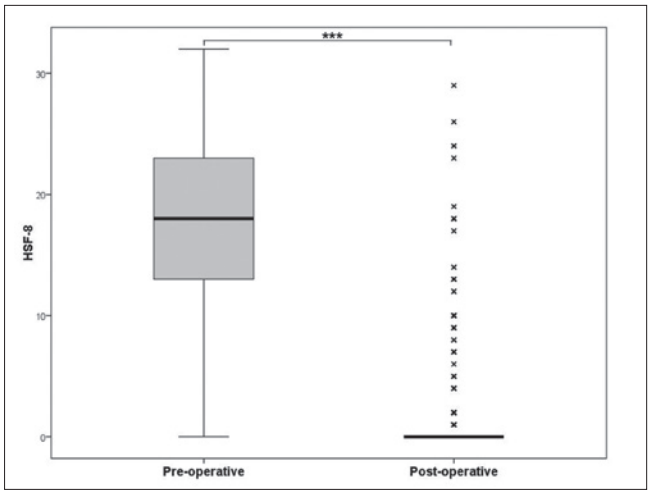

Fig. 1. Pre- and post-operative HFS-8 score. The median is indicated by a thick black line inside the box. The top and bottom of the box are the upper and lower quartile [25th-75th percentiles] and indicate the inter-quartile range (IQR). The whiskers indicate the lowest/highest datum still within 1.5 IQR of the lower/upper quartile. Outliers are marked with a cross. HSF-8 score was significantly improved after surgery (*** $p < 0.001$).

Discussion

HFS is an incapacitating condition whose therapeutic approach warrants due consideration. It is now generally accepted that HFS patients with unsatisfactory or decreasing effects of botulinum toxin treatment should be referred to surgery. We aimed to investigate the results of MVD for HFS, and to evaluate the morbidity of this therapeutic approach and long-term impact on QOL. We retrospectively studied 446 patients who underwent 511 retrosigmoid MVD over 22 years. QOL was quantified by HSF-8 score 7.3 years after MVD. The major findings of this work were a low rate of perioperative morbidity and a significant improvement of QOL after surgery.

MRI is the gold standard for neurovascular conflicts diagnosis

MRI, focusing on the facial nerve trajectory, was performed to diagnose and localise the neurovascular conflict, and to exclude a facial nerve tumour or other differential diagnoses. In our study, only 4 patients (1%) did not exhibit neurovascular conflict on MRI, suggesting a good specificity of imagery. However, the surgeon, helped by endoscopy, must look for any possible conflict since MRI description was discordant from endoscopy qualitatively (vessel involved) and quantitatively (number of vessels and conflicts involved). Therefore, fully trusting imaging risks partial resolution of symptoms. Conflicts involving the PICA and VA were over-described by radiologists, whereas AICA (more difficult to visualise on MRI) conflicts were underestimated. Multiple conflicts were met

Table III. Prognostic factors for surgical failure after first microvascular decompression for hemifacial spasm.

Variable tested	Surgical failure if the variable is present	Surgical failure if the variable is not present	p
Imaging findings			
Multiple conflict	3.5%	6.5%	0.402
PICA	5.4%	4.7%	0.999
VA	3.6%	6.4%	0.311
AICA	6.3%	5%	0.722
REZ conflict	4.8%	5.6%	0.604
Endoscopic findings			
Multiple conflict	2.6%	7.9%	0.041
PICA	3.6%	10.9%	0.036
VA	2.9%	6.3%	0.203
AICA	3.1%	6.5%	0.218
Vein	18.8%	4.5%	0.045
REZ conflict	3.9%	16%	0.027
Post-operative findings			
Nervous complication	7.1%	5.4%	0.230
Mixed nerve palsy	50%	5.3%	0.109

AICA: Antero-Inferior Cerebellar Artery; PICA: Postero-Inferior Cerebellar Artery; REZ: Root Exit Zone; VA: Vertebral Artery

in 55% of interventions versus 40% on MRI. Multiple conflicts must be systematically investigated by MRI. Pre-operative MRI enables to predict vascular pathology [10]. Major changes in MRI protocols or imaging techniques for evaluation of patients were observed between 1990 and 2012. Improvement in imaging modalities since 1990 would result in overestimation of discordance. Recently, for better information, neurovascular conflicts are documented by MRI with three-dimensional constructive interference in steady-state, alone or together with three-dimensional time-of-flight MR angiography [11 12]. In fact, the progress in medical imaging techniques has reduced discordance. However, during an endoscopic surgical procedure, the cerebellopontine angle is explored, allowing clear visualisation of the facial nerve and precise location of the neurovascular conflict, and multiple conflicts must be systematically investigated.

Complications of MVD are mostly few, benign and transient

No death was seen in our study. Extra-nervous complications were few (10%) and always transient. Among cranial nerve injuries, facial palsy was less frequent than literature, either transient (5.5% *versus* 9.5%) or permanent (0.2% versus 0.9%), whereas SNHL, vestibular deficit, or lower cranial nerve palsy (dysphagia, hoarseness, dysphonia) were as rare as in other studies [13]. Revision surgery increased permanent facial palsy and SNHL from 0.2% to 1.3% and from 2.7% to 3.9%, respectively.

Because MVD for HFS is effective in the long-term, nervous complications must be handled with maximum care. Neuromonitoring of the facial nerve and muscles enables, respectively, to minimise the risk of facial lesion and improve the efficacy of MVD (modification of lateral spread responses) [14]. Considering that auditory damage is the first permanent nervous complication, monitoring of brainstem auditory evoked potentials (BAEP) can be helpful in warning the surgeon of auditory damage. Eighth cranial nerve directly compounds the action potential, and auditory brainstem evoked response showed correlation between per-operative electrophysiologic alterations and clinical post-operative hypoacousia. Intraoperative BAEP change and poorer recovery, especially persistent decreases in amplitude greater than 50% in wave V and persistent absolute latency increase of the peak of Wave V, which equals or exceeds 0.5 msec, was a strong indicator for a worse outcome of the hearing capacity. Vigilant intraoperative monitoring of the BAEP and adequate steps for recovery of the BAEP change could prevent hearing loss after MVD for HFS [15-17].

During MVD for HFS, fixed cerebellar retraction has historically been used to expose the cranial nerves. In recent years, some surgeons have attempted to reduce the use of fixed retraction to reduce the incidence of iatrogenic microtrauma and ischaemia within brain parenchyma. Additionally, fixed cerebellar retraction may also lead to operative manipulation and stretching of the cochleovestibular nerve, leading to iatrogenic SNHL and balance issues. Retraction of the cerebellum by a spatula could be the major cause of surgical complications. In our study, the surgical procedure without the use of fixed retraction may greatly reduce the occurrence of SNHL following MVD for HFS [18 19]. Fixed retraction of the cerebellum with self-retaining retractor was never used during any step of the procedure in our institution since the beginning of our use of the minimal invasive retrosigmoid approach [9]. Additionally, endoscopic visualisation by a 30° or 45° en-

doscope decreases cerebellar retraction compared to microscopic visualisation to prevent postoperative SNHL in MVD for HFS [20].

Revision surgery was indicated in case of recurrence or failure of procedure

MVD for HFS is a highly effective treatment, but residual spasms or reappearance of spasms after surgery are not uncommon. Revision surgery for recurrence or failure is associated with incomplete nervous decompression, retraction and fibrosis around REZ and/or Teflon pledget migration. When revision surgery is considered, pre- and postoperative MRI, intraoperative videos, or pictures should be reviewed to ensure a missed compression (multiple conflicts), adhesions around REZ and/or Teflon pledget migration. MRI after MVD contribute to the decision for repeat MVD [21]. We did not find any study incriminating Teflon pledget dysfunction (granuloma or compression) in recurrence or failure of MVD for HFS. However, Haidar et al. showed in a retrospective study a 8-fold decreased rate of recurrence in MVD for trigeminal neuralgia with use of autologous muscle interposition in comparison to Teflon (5.2% *vs* 40%) [22]. We ought to consider the nature of interposition material as a possible cause of failure or recurrence for HFS as it has been suspected for trigeminal neuralgia. Further investigations are needed on this point, and use of autologous muscle interposition should be considered.

Efficacy was increased when revision surgeries were taken into account (from 82% to 91.6%) and comparable to that reported in the literature [13 23 24]. Repeat MVD of the facial nerve may be sufficient to resolve symptoms in selected patients with persistent or recurrent HFS [25]. Hence, the benefit-risk ratio should be explained to the patient: in our study, most patients accepted second surgery (69% versus 13.1-50% in literature) [26]. No consensus has been reached on the timing of re-operation. In 62 cases of failure or relapse after first surgery in our study, revision procedure was performed at 25 ± 43 months after first MVD. Predictive factors of surgical failure were single conflicts, atypical vasculo-nervous conflicts involving other vessels than PICA such as veins and compression sites other than REZ. In these cases, other conflicts of the facial nerve must be systematically investigated and risk of failure must be explained to the patient. Multiple compression sites were met in 55% of patients, but underdescribed by imaging (40%), thus reinforcing the utility of peri-operative extensive endoscopy investigation of the facial nerve. In fact, during endoscopic surgical procedures, the cerebellopontine angle is explored, allowing clear visualisation of the facial nerve and a precise location of the neurovascular conflict, and multiple conflicts must be systematically investigated. Peri-operative neurophysiological data might predict and prevent surgical failure. In fact, residual lateral spread response after seemingly adequate decompression for HFS could be a prognostic factor of outcome of MVD. Adequate decompression in patients with residual lateral spread response improved long-term spasm relief, although the amplitude of residual lateral spread response after adequate decompression does not significantly affect long-term spasm relief [27].

MVD is an effective and durable treatment for HFS

QOL research provides fundamental information about the impact of HFS, its treatment and side effects or complications. HFS patients suffer mainly from emotional distress and fear of social stigmatisation [3]. Therefore, surgical effectiveness cannot be only presumed by partial or total disappearance of spasm. In order to consider patients' subjectivity in various aspects of their life, the HFS-8 questionnaire is the most solid tool for HFS [28].

The HSF-7 scale had been described by Tan et al. as a short, pratical, validated quality of life scale specific to HSF patients [3]. The HSF-7 scale has been found to correlate well with the SF-36 health survey generic quality of life scale. The disease-specific HSF-7 form was extended with the item "sleep disturbance due to spasms". Findings from adding additional items into an existing validated instrument should be interpreted with caution as these items have not undergone the same rigorous validation procedures. Nevertheless, the results from the HFS-8 measurement are consistent with the conclusions from the validated HFS-7 instrument [6 28].

Long-term QOL was significantly increased by MVD in our study. QOL was evaluated in a retrospective way, and introducing a recall bias for pre-operative QOL status: first patients filled in their retrospective questionnaires 15 years after MVD. Subjective perception of previous QOL was inevitably altered. These results should, however, be confirmed in a prospective study.

The retrospective nature over a long period of data collection suffers recording and recollection bias amongst many other limitations of these types of analyses. The accuracy and exact criteria for selection of each patient, uniformity of MR diagnostic technique over 22 years of study and comprehensiveness of recording for complications are some of these issues. The outcome assessment for both treatment and complications are done by the surgeon, and not by an independent neurologist, making the result prone to bias.

Reporting results in a long-time scale highlights that MVD is an effective and durable treatment for HFS. Our mean time of clinical follow-up was 4 ± 4.7 years, but 167 patients (37%) were lost to follow-up less than 1 year after surgery, thus increasing the standard deviation of follow-up. Median time of clinical follow-up was shorter (2 *vs* 2.9 years) than studies in the literature [13]. To our knowledge, the latest follow-up studies performed with HFS-8 questionnaire do not exceed 3 years post-operative (prospective studies) or 4 years post-operative (ret-

rospective studies) [6 28]. In our study, QOL was evaluated 7.3 years after MVD, which seems reasonable to consider its effectiveness. We found no cases of HFS recurrence in either our study or in the literature after a delay of 5 years with no symptoms. In their study, Payner et al. documented an efficacy of 94% after 6 years of follow-up; 86% of recurrences occurred within 2 years post-operative and no patient relapsed after 2 years without having some degree of recurrent spasm [24]. In addition, Miller et al. reported no significant differences in symptom cure rates at 1 year postoperatively compared to a maximum follow-up period of 5 years postoperatively [13]. Therefore, MVD is an effective and durable treatment for HFS, with a significant improvement of long-term postoperative QOL.

Conclusions

This retrospective study included 511 retrosigmoid decompressions for HFS performed over 22 years. MVD is a safe and effective treatment for HFS. Imaging helps the surgeon to find conflicts, but endoscopy prevails in finding and treating any possible source of conflict. Revision surgery is not to be excluded in case of failure or recurrence, but place put patients at risk for more complications. QOL is improved in the long-term, indicating objective and subjective satisfaction of this surgical procedure.

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Letter to the Editor

Considerations on "Endoscopic endonasal approach to the craniocervical junction: the importance of anterior C1 arch preservation or its reconstruction"*

Considerazioni su "Approccio endoscopico endonasale alla cerniera craniocervicale: il ruolo della preservazione dell'arco anteriore di C1 o della sua ricostruzione"

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Acta Otorhinolaryngol Ital 2016;36:228-230

Dear Editor, I should like to make some comments of the paper of Re et al.*. The authors report on 10 patients undergoing endoscopic endonasal decompression for different CCJ pathologies. In 8 patients, the authors were able to preserve the anterior C1 arch, while in 2 cases they reconstructed it with clinical improvement or stabilisation and preservation of spinal stability in all without posterior fixation (mean follow-up of 31 months). Four surgical technical topics deserve particular consideration in this paper.

- The assumed superiority of a transnasal approach compared with a transoral approach to the CCJ.
- The dural opening and tumour removal in case of C1-C2 neoplastic lesions.
- The endoscopic pannus removal and subsequent anterior screw fixation by self-tapping screws for a better fracture healing and spinal realignment (only for inveterate C2 Anderson-D'Alonso type II fractures).
- The anterior arch of C1 reconstruction a) by placing bone chips compressed between the bone under endoscopic control and subsequent fixation with three screws and one plate or b) with autologous bone graft and titanium mash (in a non-union anterior atlas fracture after conservative treatment that developed C1 lateral masses displacement with cranial settling).

Point to point considerations

1) *The assumed superiority of a transnasal approach compared with a transoral approach to the CCJ.*

The authors comment that "the transoral-transpharyngeal technique, is still considered the gold standard anterior approach and still represents the most experienced technique. However, this surgical technique is not properly mininvasive since this approach often involves the splitting of structures such as the soft palate, mandible and maxilla". Otherwise they proudly claim to perform "routinely posterior hard palate outer bone layer drilling in order to make it more flexible to enhance the angle of "nasopalatine line". Such a contradictory statement apparently seems to go against the assumed superiority of a transnasal approach over a transoral approach.

In fact, according to our experience, the 30° endoscope has been proposed for the transoral approach to avoid full soft-palate splitting, hard-palate splitting or extended maxillo/mandibulotomy. Using the endoscope, the operator is able to look in all directions by rotating the instrument. Because the light source is at the level of the abnormality, superior illumination can be obtained. With the aid of an endoscope, abnormalities as high as the mid-clivus can be visualised without extensive soft- or hard-palate manipulation [1-3].

The authors continue as follows: "…the transoral route is not a straightforward approach to the lesion and could present a deep surgical field with a small and asymmetric angle of working related to the mouth opening and upper direction"; "…the endoscopic endonasal approach is a more direct and straightforward approach with a shorter working distance in comparison with the transoral ones, offering a good exposure and working area from the clivus down to C2". According to our experimental and clinical experience, an endoscope assisted transoral approach allows better surgical control of the CCJ. It provides better CCJ exposure in sagittal and transverse planes, providing a larger working channel and an easier manoeuvrability (Fig. 1). The transnasal approach is limited in caudal direction down to the NPL, otherwise the transoral approach is limited in the rostral direction with a maximum to the foramen magnum in normal specimen (Fig. 2). In every individual case, the pros and cons of the appropriate approach have to be taken into account as well as the choice of a combined transnasal and transoral approaches strategy [4].

2) *The dural opening*

To open the CCJ dura is always a challenge.

* M. Re, M. Iacoangeli, L. Di Somma, et al. *Endoscopic endonasal approach to the craniocervical junction: the importance of anterior C1 arch preservation or its reconstruction.* Acta Otorhinolaryngol Ital 2016;36:107-118.

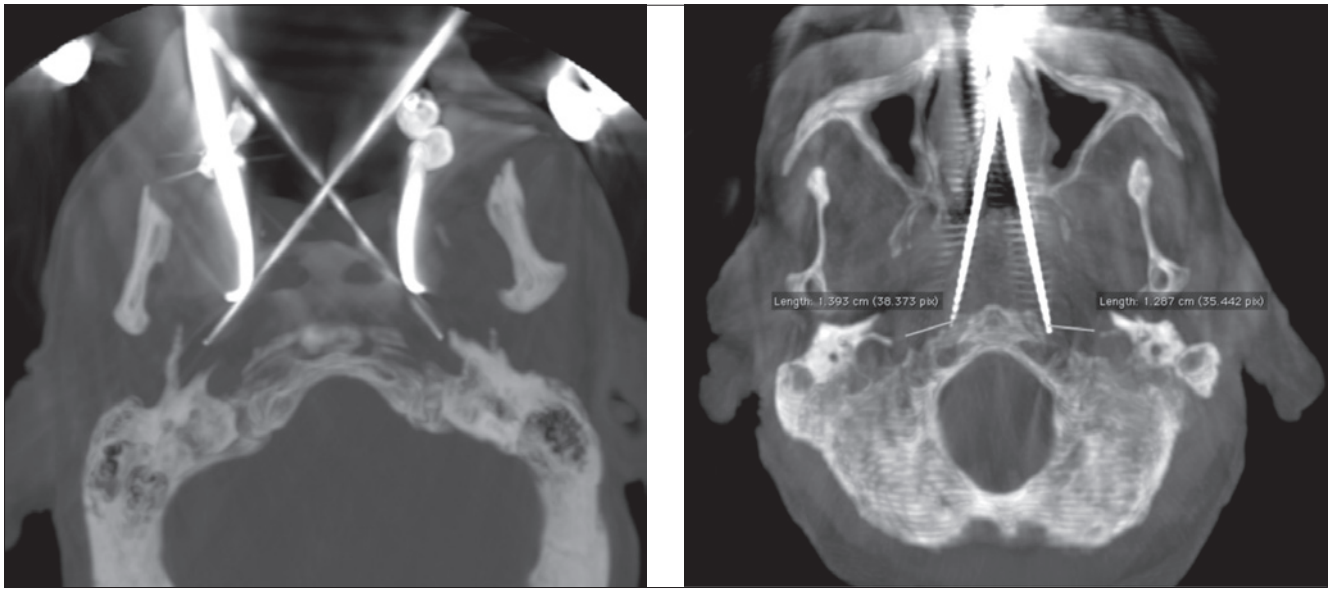

Fig. 1. CT scan axial reconstructions bone window. Lateral coronal surgical domain ina transoral (left) and in transnasal (right) cadaveric specimen using two probes through the oral cavity and nostrils. The transoral surgical span appears wider compared to the transnasal approach.

One of the assumed superiorities of a transnasal approach can be recognised in the authors' statement that "the lower morbidity (of transnasal) can be ascribed to an earlier extubation, prompt oral feeding and lesser risk of bacterial wound contamination, because the mucosal defect created by a transnasal approach is linear, smaller and above the level of the soft palate; on the other hand, the transoral approach ."…also include the risk of bacterial contamination secondary to oral cavity penetration, prolonged postoperative intubation and nasogastric tube feeding, along with potential effects on phonation".

In our personal experience, the only case of fatal postoperative meningitis was related to a pure transnasal approach to the CCJ with inconsistent intraoperative dural repair and subsequent rhinopharyngeal bacterial contamination (unpublished). Thus, it appears inadvisable to open the dura so confidentially in the rhinopharynx since the risk of bacterial contamination is not completely zero as we all should wish for.

3) *The endoscopic pannus removal*

Endoscopic pannus removal and subsequent anterior screw fixation with self-tapping screws appears to be in line with some surgical trends, mainly in the Asiatic literature, which suggests first to release anteriorly and than to stabilise posteriorly in case of "irreducible CCJ compressions"; nevertheless, our experience seems to be innovative [5]. In fact, preoperative irreducibility of the C1C2 dislocations should not be an absolute indication for trans-oral decompression. An attempt to reduce the dislocation under general anaesthesia and

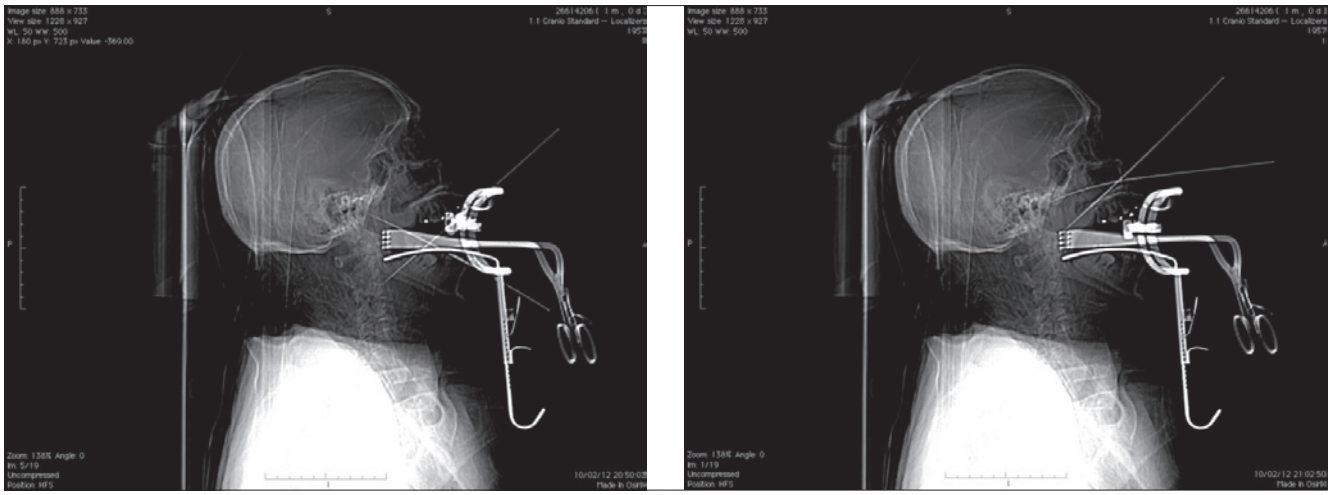

Fig. 2. CT scan sagittal scout view. Sagittal domain in a transoral (left) and in transnasal (right) cadaveric specimen using two probes through the oral cavity and nostrils. The transoral surgical span appears wider compared to the transnasal approach.

during posterior fixation should be made in many conditions. A combination of axial traction with slight extension of the neck on the chest and slight flexion of the head on the neck, although traction only with extension would seem to be more appropriate. In fact, although it may seem to be dangerous, our method helps to reduce C1C2 dislocations better, stretching the ligaments in case of irreducibility and better exposing the local anatomy of the CCJ. Intraoperative neurophysiological monitoring should be considered for these surgical procedures [5].

4) *Anterior arch of C1 reconstruction*

Very interestingly the authors report the observation that atlas ring integrity could prevent the C1–C2 subluxation even in cases of transverse ligament disruption, thanks to the important role of second stabilizers (capsular ligaments, paraspinal muscle, tectorial membrane, anterior longitudinal ligament, and ligamentum flavum) that provide a relevant restraint to C1-C2 segment motion [6 7]. Agraval et al. in a cadaveric study stated that transoral odontoidectomy and resection of the anterior C1 arch destabilise the atlantoaxial joint and risk its stability. After odontoidectomy and arch removal, angular ROM increases significantly in all directions of loading. C1 arch reconstruction with or without odontoidoplasty restores *only partial angular stability* of the atlantoaxial joint but *provides restoration of the ability of the C1 lateral masses to resist splaying,* often observed as postodontoidectomy cranial settling [7]. Atlas reconstruction by itself does not guarantee stability "without inflammatory process of the synovial capsule and joints, the articulation between C0-C1 and C1-C2 already present some grade of fusion that limits the movement and dislocations" as the authors of the present paper correctly clarify along with the observation that "in some cases the transverse ligament with its attachment to the bone, probably, is almost entirely preserved and we noted after few months a sort of fusion between the residual odontoid process and the posterior border of the C1 arch. Keeping this concept in mind, in the last cases we intentionally fused C1 to the residual C2 dens by screws and bone substitutes in order to enhance future spinal stability". More surprisingly, in our experience a complete regeneration of the clivus and odontoid after transoral decompression is possible; in fact, besides the need for accurate complete resection of the periosteum, which apparently was incompletely performed in our case, our experience suggests the need for resection of the odontoid down to the dentocentral synchondrosis, and accurate lateral removal of the bone surrounding the anterior tubercle of the clivus is advised when an anterior CVJ decompression is required in children presenting with evident synchondrosis at neuroradiological investigation [8]. Thus, in conclusion I do not recommend to popularise the non-use of instrumentation systems in such a surgery except in selected cases of spontaneous restorative processes (inflammatory or degenerative) which provide secondary bone fusion [9-11].

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Letter to the Editor

Penetrating injury of the soft palate by a microlaryngeal tracheal tube during GlideScope® intubation

Lesione del palato molle in corso di posizionamento di tubo endotracheale con ausilio di GlideScope®

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Acta Otorhinolaryngol Ital 2016;36:231-232

Dear Editor,

A 57-year-old man presented for suspension microlaryngoscopy and biopsy of a laryngeal lesion that was mildly obstructive. After induction of general anaesthesia, a standard midline approach of GlideScope® laryngoscopy provided good laryngeal exposure. A junior anaesthesiologist made a failed attempt to introduce a 5.0-mm internal diameter cuffed microlaryngeal tracheal (MLT) tube with a malleable stylet curved at 90º in the larynx to facilitate intubation. A slight resistance was encountered while passing the tube into the oropharyngeal cavity and a trace of blood was noted at the tip of the MLT tube upon removing it. Another attempt was made by an experienced anaesthesiologist, during which it was noticed on the screen that the tube was inserted completely behind the pharyngeal mucosa that was lifted up. The tube was withdrawn immediately and with fine manoeuvres reinserted between the vocal cords. The otorhinolaryngologist found severe right sided perforation of the soft palate, which resulted in a lateral pharyngeal wall haematoma with subsequent narrowing of the hypopharyngeal lumen and upper airway. We suspect that the soft palate was perforated during the first pass of the tube which made an entry point to the tube creating a false passage in the pharynx. The false passage was eventually filled with blood after withdrawing the tube and the haematoma was formed. The laceration of the soft palate was sutured and the patient was kept intubated for 24 hours for any unexpected events that might lead to airway obstruction. The next day, the patient was extubated uneventfully and was discharged the day after.

Complications of GlideScope® videolaryngoscopy have been described in the literature [1-5]. With the use of GlideScope®, like any other airway device, there is always a risk of trauma to the pharyngeal mucosa. The risk of trauma to the soft tissue is greatest during passage of the styletted tube through the "blind spot" that exists at the point where the operator loses sight of the endotracheal tube (ETT) tip at the back of the pharynx until it resurfaces within the camera's visual field. In addition, when upward force is applied to the GlideScope®, the tonsils and structures around become stretched and vulnerable to perforation.

All injuries reported in association with the use of GlideScope® videolaryngoscopy were simple laceration and caused by ETT size 7-mm internal diameter or more. In our patient, however, the injury was significant and the tube used was a small size MLT. It is well known that applying the same force to a smaller surface area would result in higher pressure, which means more pressure may be applied using an ETT of narrower diameter. The relatively high pressure may have caused the tip of the tube to cut through oral tissue even though minimal force was applied. Consequently, a styletted sharp-edged small tube with a less surface area, such as the MLT, might be considered as risk factor for causing soft tissue injury. Of note, we used a malleable stylet because the rigid Gli-

Fig. 1. Oropharyngeal view under anaesthesia revealing right soft palate injury.

derite stylet cannot be introduced through the small-size MLT tube.

Many steps have been described in literature to minimise airway trauma while using the GlideScope. First, the ETT should be directly observed before it appears on the monitor to reduce the distance of the blind spot. In addition, the tube should be inserted close to the side of the blade with the bevelled tip facing against that blade. Gentle insertion is highly recommended at all steps on the tube's passage, particularly while inserting it through the blind spot mentioned above, thus mitigating the risk of trauma to the oral cavity structures. Sometimes, however, the described approach cannot be applied. This may be due to the large size of the Glidescope blade, especially in the presence of a small mouth opening, and to the fact that it has to be placed in the midline rather than on the right side pushing the tongue to the left, as it is the case in direct laryngoscopy. It is perhaps time to consider more fundamental ways in which these injuries may be avoided by modifying the device(s), rather than modifying the technique of using it.

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CASES SERIES AND REPORTS

Further characterisation of the recently described *SLC26A4* c.918+2T>C mutation and reporting of a novel variant predicted to be damaging

Caratterizzazione della mutazione SLC26A4 c.918+2T>C e report di una nuova variante potenzialmente a rischio

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SUMMARY

Pendred syndrome (PS) is the second most common type of autosomal recessive syndromic hearing loss (HL). It is characterised by sensorineural HL and goiter with occasional hypothyroidism. These features are generally accompanied by malformations of the inner ear, as enlarged vestibular aqueduct (EVA). In about 50% of probands, mutations in the *SLC26A4* gene are the cause of the disease. Here we report the case of a Portuguese female, aged 47, presenting with severe to profound HL and hypothyroidism. Her mother and sister, both deceased, had suffered from HL and goiter. By MRI and CT, an enlarged vestibular aqueduct and endolymphatic sac were observed. Molecular study of the patient included screening for *GJB2* coding mutations and *GJB6* common deletions followed by screening of all *SLC26A4* exons, as well as intronic regions 8 and 14. Mutation c.918+2T>C was found for the first time in homozygosity in the intronic region 7 of the *SLC26A4* gene. Whilst sequencing the control samples, a novel mutation c.821C>G was found in heterozygosity in the exon 7 of *SLC26A4* gene and was predicted to be damaging. This study thus led to the finding of two novel *SLC26A4* genotypes and provides new insight on the phenotypic features associated with PS.

KEY WORDS: Pendred syndrome (PS) • Hearing loss (HL) • Enlarged vestibular aqueduct (EVA) • Magnetic resonance imaging (MRI) • Computerised tomography (CT) • Videonystagmography (VNG) • Berkeley Drosophila Genome Project (BDGP)

RIASSUNTO

La sindrome di Pendred è, in ordine di frequenza, la seconda causa di ipoacusia su base genetica autosomica recessiva. Si manifesta con un ipoacusia accompagnata dalla presenza di un gozzo tiroideo con eventuale ipotiroidismo. Tali caratteristiche si accompagnano a malformazioni dell'orecchio interno, quali l'acquedotto vestibolare largo. Nel 50% dei casi vi è una mutazione del gene SLC26A4. Riportiamo nel presente lavoro il caso di una paziente portoghese di 47 anni affetta da ipoacusia di grado severo/profondo e ipotiroidismo. La madre e la sorella della paziente, entrambe decedute, erano a loro volta affette da ipoacusia associata a gozzo tiroideo. La risonanza magnetica e la TC hanno entrambe evidenziato un allargamento dell'acquedotto vestibolare e del sacco endolinfatico. La paziente è stata sottoposta a uno studio di GJB2 e GJB6 seguiti da uno screening di tutti gli esoni di SLC26A4 e delle regioni introniche 8 e 14. È stata rilevata, per la prima volta in omozigosi, una mutazione c.918 + 2T>C nella regione intronica 7 del gene SLC26A4. Sequenziando i campioni di controllo è stata rilevata una nuova mutazione c.821C>G presente in eterozigosi nell'estone 7 del gene SLC26A4, per la quale si è ipotizzato un ruolo dannoso. Il presente studio ha condotto alla scoperta di due nuovi genotipi di SLC26A4, e alla miglior definizione degli aspetti fenotipici associati alla sindrome di Pendred.

PAROLE CHIAVE: *Sindrome di Pendred • Ipoacusia • Sindrome dell'acquedotto vestibolare largo • Risonanza magnetica • Tac • Videonistagmografia • Berkeley Drosophila Genome Project*

Acta Otorhinolaryngol Ital 2016;36:233-238

Introduction

Hereditary syndromic hearing loss (HL) includes about 400 syndromes, such as Pendred syndrome (PS). This syndrome is the second most common type of autosomal recessive syndromic HL worldwide [1], with an incidence estimated to be as high as 7.5 to 10 in 100,000 individuals [2 3].

PS is characterised by sensorineural HL, goiter and a partial defect in iodide organification. These features are generally accompanied by malformations of the inner ear, ranging from enlarged vestibular aqueduct (EVA) to Mondini dysplasia [4]. The clinical features observed in PS typically result from biallelic (homozygote/compound heterozygote) mutations in the *SLC26A4* gene. According to the Human Gene Mutation Database more than 260 mutations in the *SLC26A4* gene have been identified to date [5], including splice site aberrations, frame shift and nonsense mutations, as well as large deletions (rare cases) and a relatively common mutation, c.-103 T > C, in a regulatory element of the promoter region of the *SLC26A4* gene [6 7]. The mutation spectrum of *SLC26A4* varies widely among ethnic groups, with certain mutations demonstrating a higher prevalence in specific populations [8-11].

This gene, containing 21 exons, localises to chromosome 7 (7q22.3-q31.1) and encodes the multifunctional anion exchanger pendrin [4 12]. Pendrin is a 73 kDa membrane protein that belongs to the SLC26 anion transporter family. It is comprised of 780 amino acids and is predicted to have 12 putative transmembrane domains, with both the amino- and carboxy-termini located on the cytosol [13 14]. In the C-terminus region a STAS domain (Sulfate Transporter Antagonist of Anti-Sigma Factor) is located,which probably plays an important role in the biosynthesis, function and regulation of this transporter [15 16]. The *SLC26A4* gene is expressed in specific areas of the endolymphatic compartment in the cochlea known to play a role in the endolymph reabsorption [17]. Moreover, in the absence of pendrin, profound prenatal endolymphatic hydrops are observed along with the destruction of many of the epithelial cells surrounding the scala media [17]. Regarding the thyroid organ, pendrin is involved in iodide metabolism as it transports intracellular iodide to the follicular lumen [18] where the normal processes of iodide accumulation, oxidation and organification into thyroglobulin, leading to the production of the thyroid hormone, take place [18]. Patients with PS present a dysfunctional pendrin protein, and the thyroid gland is unable to accumulate and maintain iodide in the follicular lumen, place where thyroglobulin is kept and incorporates iodide to synthesise thyroid hormone [19]. Due to a defect in the synthesis of thyroid hormone, pathologies such as compensatory goiter and hypothyroidism may be present in these patients [19]. Herein, we report the case of a Portuguese female, aged 47, presenting with severe to profound HL and hypothyroidism.

Materials and methods

A Portuguese female presenting with severe to profound HL (Fig. 1) and hypothyroidism was referred for genetic analysis. This patient later reported that her mother and sister, both deceased, had also suffered from HL and goiter.

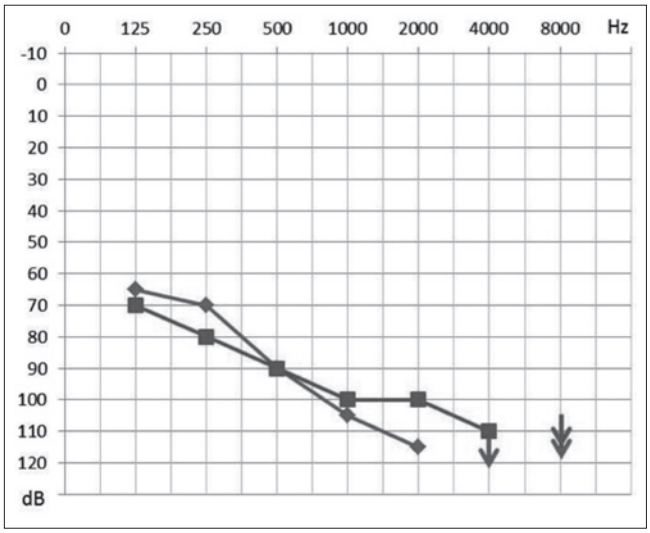

Fig. 1. Audiogram of the patient. Squares in red represent the right ear; diamonds in blue represent the left ear.

Hearing levels were determined by pure-tone audiometry. Imaging study of the ear was performed by magnetic resonance imaging (MRI), computed tomography (CT) and videonystagmography (VNG). A complete clinical history was taken to exclude aetiologies for HL such as infection, acoustic trauma, or ototoxic drugs. The patient reported no familial consanguinity, although this possibility cannot be excluded.

Blood samples were collected after written informed consent was obtained. Total genomic DNA was extracted from peripheral blood using the JetQuick Blood and Cell Culture Kit (Genomed).

Molecular study of the proband included screening of *GJB2*, *GJB6* and *SLC26A4* genes. The most common *GJB6* deletions were screened by multiplex PCR, using the method described by del Castillo [20]. Automated sequencing was performed for the coding exon of the *GJB2* gene [21], and for all exons, as well as intronic regions 7 and 14, of the *SLC26A4* gene (Table I).

Two hundred control chromosomes, from 100 self-reported normal hearing individuals from the Portuguese population, were sequenced for intronic region 7 and exon 7 of the *SLC26A4* gene.

All PCR products were purified using a Jetquick PCR Product Purification Spin Kit (Genomed). The electrophoretograms from bidirectional sequencing were evaluated by visual inspection and pairwise alignment to reference sequences using NCBI's BLAST [22].

The Berkeley Drosophila Genome Project (BDGP) [23] splice site prediction program was used to predict the effect of the splicing mutation found in the patient. The SIFT prediction software [24] was used to predict the effect of a new variant, c.821C > G (p.Ala274Gly), identified in an individual of the control sample.

Table I. *SLC26A4* exons and intronic regions studied.

Primer name	Region	Primer sequence (5'-3')	Amplified region (bp)
SLC26A4 2F	Exon 2	GGCTGCAGCTAACAGGTGATC	432
SLC26A4 2R		GAGGACCGGAGACCGAAAGTC	
SLC26A4 3F	Exon 3	ACAGTTCTTGGCAAAAGCATGG	411
SLC26A4 3R		GAAGGGTAAGCAACCATCTGTCAC	
SLC26A4 4F	Exon 4	TTTGCATCATCATAAAGGCAAAGTC	419
SLC26A4 4R		TGAAATCCCATTTCCCTGACAA	
SLC26A4 5F	Exon 5	CTCAGCTTCTTTCGTGAACAAAC	439
SLC26A4 5R		TTTGGGTTCCAGGAAATTACTTTGT	
SLC26A4 6F	Exon 6	GTGCTATAGGCAGGCTACTAGTGTT	364
SLC26A4 6R		CCTGGCCCAGACTCAGAGAAT	
SLC26A4 7/8F	Exons 7 and 8	TGGGAAGATTCATATGAGAATTGATTG	581
SLC26A4 7/8R		TGGTTGTTTCTTCCAGATCACA	
SLC26A4 IVS8F	Intron 8 (partial)	GTGTGCGTGTAGCAGCAGG	502
SLC26A4 IVS8R		GGACTATTGAAGGAGTATCAGTG	
SLC26A4 9F	Exon 9	CATGTGAAATGGCATGGATGG	583
SLC26A4 9R		GGTCTGGTGAAAGAATCCAACC	
SLC26A4 10F	Exon 10	CGCAGAGTAGGCATGGGAGTTT	314
SLC26A4 10R		TTGTCCTGCTAAGCTCGGTGC	
SLC26A4 11/12F	Exons 11 and 12	AGACAGGGAAGTATGAAGTGTG	555
SLC26A4 11/12R		TTTCTCCTCTGGAGTTCCCAAA	
SLC26A4 13F	Exon 13	AGGTAGTTATCACATGATGGTACCTG	501
SLC26A4 13R		GAGCACAGCAGTAGAGGACAT	
SLC26A4 14F	Exon 14	AAACACCAGAATGATGGGCTC	338
SLC26A4 14R		GTCAGAAGGTGCACTGGATC	
SLC26A4 IVS14F	Intron 14 (partial)	GTTGAGTGCTGCTACCCAGCTCCTC	185
SLC26A4 IVS14R		AGGTAGTAATAACTATGCCAGAC	
SLC26A4 15F	Exon 15	CTACCCAGCTCCTCTGACAA	329
SLC26A4 15R		GCCCTACACAAAGGGAAGAGGG	
SLC26A4 16F	Exon 16	ACCCTTTGAGAAATAGCCTTTCCAG	357
SLC26A4 16R		CCACTCCCGCTTGCCTATAA	
SLC26A4 17F	Exon 17	AGTTTGGGCTGAGGTGAAACC	486
SLC26A4 17R		CAAAGCCCATGTATTTGCCCTG	
SLC26A4 18F	Exon 18	CGCTGGATGTTGCCTCTCT	357
SLC26A4 18R		GGCCTTCAGACATAATGTGCCA	
SLC26A4 19F	Exon 19	TTTCTTAGCTGGGCATGGTAGG	705
SLC26A4 19R		GGAATTTATGTACACAAATCCCAGATCAC	
SLC26A4 20F	Exon 20	AGAAGCACCAGGAAAGCTTCA	283
SLC26A4 20R		GGGAATTATGTTCCCTGACAGTTC	
SLC26A4 21F	Exon 21	CCTAAGATGAGTAGCAGTAAGCA	354
SLC26A4 21R		GCTGCCAAATCGTCTGAATAATTC	

Results

Clinical and audiologic evaluation

The patient had multinodular goiter at the time of diagnosis. Thyroid function was studied and revealed a slight increase in thyroid-stimulating hormone (TSH) levels, while serum thyroxine levels were below normal values. Thyroid microsomal antibodies were negative.

Hearing levels, determined by pure-tone audiometry, revealed severe to profound HL, as referred. After MRI and CT, enlargement of the vestibular aqueduct and the endolymphatic sac were observed (Fig. 2). VNG examination revealed bilateral hyporeflexia.

Molecular analysis

The mutation c.918 + 2T > C (Fig. 3), previously reported

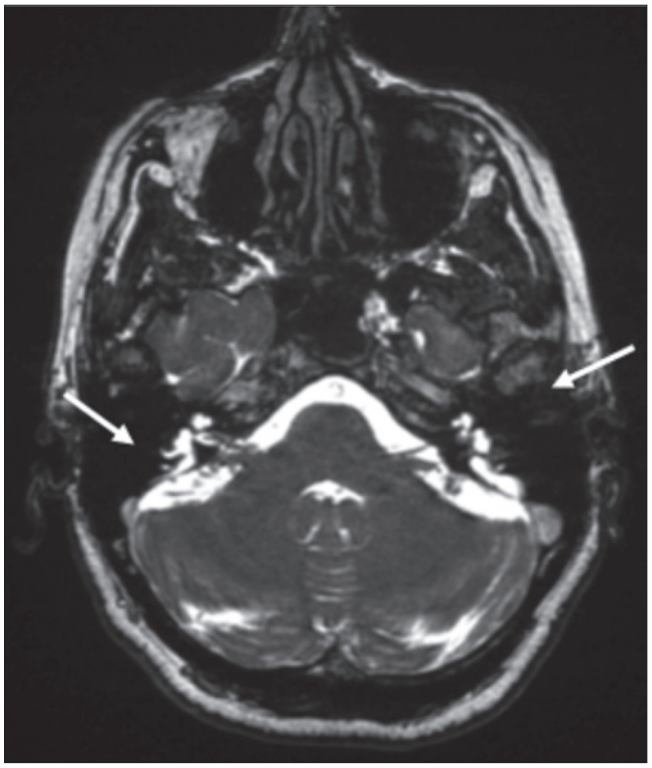

Fig. 2. Axial section MRI (FIESTA). Enlarged vestibular aqueduct (arrows).

by Chai et al. (2013) [25], was found in homozygosity in the intronic region between exons 7 and 8 of the *SLC26A4* gene. We sequenced 200 Portuguese control chromosomes to determine the allelic frequency of this mutation in the Portuguese population. The variant was not found in any of the control samples. No mutations were found in *GJB2* or *GJB6* genes. Regarding its functional effect, c.918 + 2T > C abolishes a donor splicing site, since the first two nucleotides of the intron 7 in the wild-type sequence, a guanine (G) and a thymine (T), respectively, are predicted to be a donor splicing site, with a cut-off of 0.9 and a score of 0.99 (according to the BDGP splice site prediction program). Thus, the presence of the transition T > C leads to the loss of this donor splicing site, thus skipping exon 8 and forming a non-functional protein product.

Whilst checking whether the mutation c.918 + 2T > C found in the PS patient was present in any of the 100 normal hearing control individuals, a new variant, c.821C > G (p.Ala274Gly), was found in heterozygosity in the exon 7 of *SLC26A4* gene (Fig. 4). This mutation changes alanine to glycine at position 274 and is predicted to impair protein function by SIFT software, with a score of 0.04 and a median conservation of 2.24. This variant was not found in any of the other Portuguese controls in the study and is not reported in 1000 Genomes, HGDM, ClinVar, or Pendred/BOR databases from Hereditary Hearing Loss Homepage [26]. Since this individual was a random control from the Portuguese population, no information concerning phenotype was available.

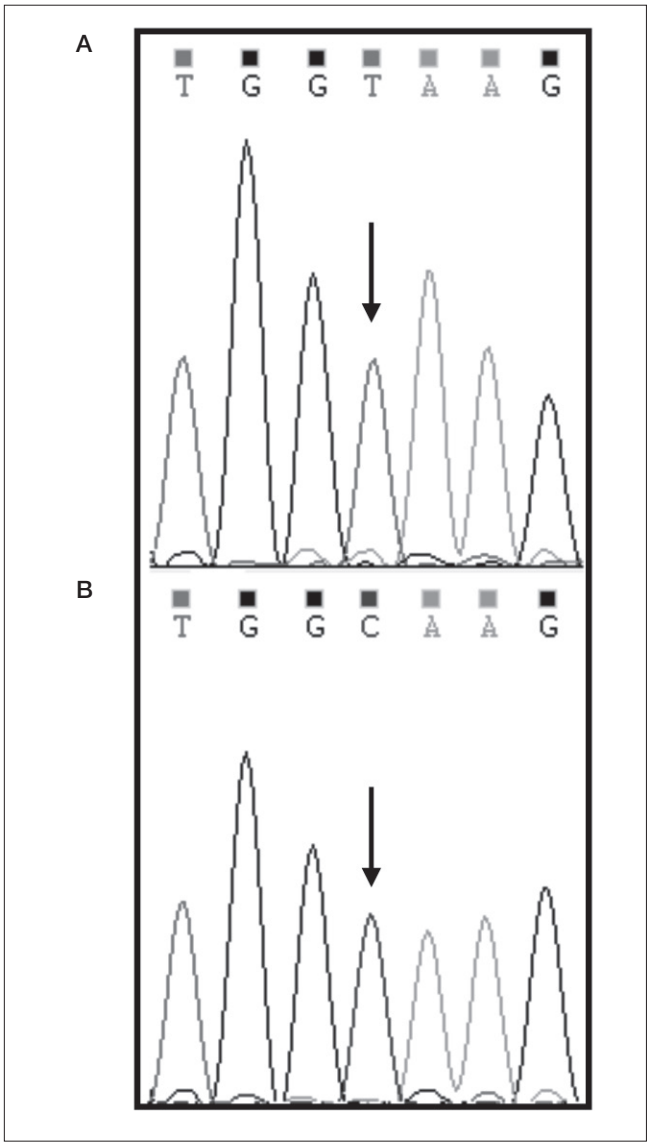

Fig. 3. Electrophoretograms showing: A - wild-type sequence; B - SLC26A4 novel mutation c.918 + 2T > C in homozygosity.

Discussion

Since its discovery, many studies have been performed to better understand the genetics of PS, possible genotype-phenotype correlations and the pathologies associated with this syndromic condition [27-30].

Previously, we found a novel splice site mutation in the *SLC26A4* gene, in a consanguineous Portuguese family [31]. Herein, we report the case of a Portuguese female diagnosed with PS and found to be homozygous for the donor splice site c.918 + 2T > C mutation in the *SLC26A4* gene. This mutation was recently reported by Chai et al. (2013) [25] in a Chinese child. The authors found this mutation in compound heterozygosity with another *SLC26A4* variant, c.919 - 2A >G, and described the patient as a non-syndromic severe to profound HL individual, presenting bilateral enlargement of the vestibular aqueduct [25].

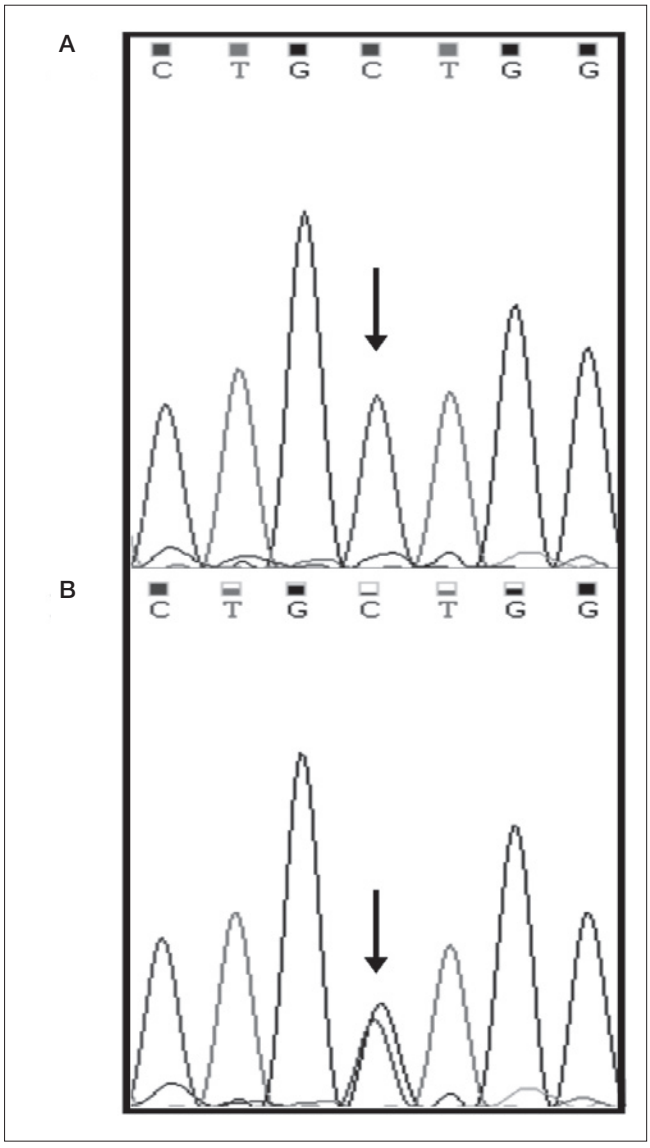

Fig. 3. Electrophoretograms showing: A - wild-type sequence; B - SLC26A4 novel mutation c.918 + 2T > C in homozygosity.

In the present study, we describe for the first time the c.918 + 2T > C mutation in homozygosity in a PS individual and also provide new insight on its phenotypic characterisation. The severe to profound HL phenotype, enlargement of the vestibular aqueduct and endolymphatic sac along with goiter and hyporeflexia are all compatible with features affecting PS patients.

The patient here considered reported that mother and sister, both deceased, had suffered from HL and goiter. This feature does not fit with the recessive pattern of PS inheritance. Due to the lack of additional familial information, the apparently dominant HL and goiter within this family remains to be explained. Since Chai et al. (2013) [25] reported the c.918 + 2T > C mutation in compound heterozygosity with another *SLC26A4* mutation in a child presenting features compatible with PS, we may also consider the hypothesis that the mother could have harboured this mutation in compound heterozygosity, thus giving rise to the HL and goiter phenotype. Although excluded by the patient, we cannot exclude consanguinity in this family, which would better explain the homozygous genotype observed in the patient and the HL and goiter phenotype of her deceased sister. Unfortunately, no information was provided regarding the father.

Conclusions

Having into account that: no alteration was found in all other exons of the *SLC26A4* gene or in the *GJB2* and *GJB6* genes; the c.918 + 2T > C mutation abolishes a donor splicing site and occurs in homozygosity, affecting both alleles; this mutation was not present in any of the 200 Portuguese control chromosomes analysed (allelic frequency < 0.99%), the *SLC26A4* genotype [c.918 + 2T >C + c.918 + 2T > C] could be pointed as the likely cause for the PS phenotype presented by the patient.

Considering the novel variant, c.821C > G (p.Ala274Gly), found in heterozygosity in a control individual, it is predicted to be probably damaging and it was not found in any of the remaining Portuguese control individuals. Further genotyping of Portuguese PS patients might eventually lead to the identification of this allele in a compound heterozygous patient. Moreover, since the mutation spectrum of *SLC26A4* has been shown to vary widely among ethnic groups, future determination of the mutation spectrum of *SLC26A4* gene in the Portuguese population might reveal some interesting specificities.

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CASE SERIES AND REPORTS

Solitary fibrous tumour of the supraglottic larynx

Tumore fibroso solitario della laringe sopraglottica

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SUMMARY

Solitary fibrous tumour (SFT) is a rare, benign, mesenchymal neoplasm that usually arises in the pleura, but rarely involves other sites outside the serosal space (mediastinum, lung, liver, thyroid gland); larynx involvement is very rare with only sporadic cases reported in the literature. We report a case of SFT in a 41-year-old woman with supraglottic laryngeal invovlement; symptoms included dysphonia and mild odynophagia lasting 2 years, and fibre-optic laryngeal evaluation showed a sub-mucosal mass involving the left supraglottis and medial wall of the pyriform sinus. MRI represents the gold standard tool for differential diagnosis (with schwannoma, paraganglioma and haemangioma) and correct staging, while immunohistochemical and cytomorphologic analysis (bcl-2 and CD34 positivity in 90% of cases) is needed for definitive diagnosis. Surgery is the main treatment (endoscopic and open conservative technique), and its goal is a balance between safe oncological resection and good preservation of laryngeal functions; in this particular case an open laryngeal approach was scheduled due to the size of the tumour. Prognosis is good and in only a few cases (especially in pleural SFT) does the biological behaviour take a malignant course.

KEY WORDS: Solitary fibrous tumour • Larynx disease • Benign larynx neoplasm

RIASSUNTO

Il tumore fibroso solitario (SFT) è una neoplasia rara, benigna, di origine mesenchimale che generalmente origina nella pleura ma che raramente può coinvolgere altre sedi al di fuori degli spazi sierosi (mediastino, polmone, fegato, tiroide); il coinvolgimento laringeo è molto raro con solo pochi casi riportati in letteratura. Riportiamo un caso di SFT in una paziente di 41 anni con coinvolgimento della laringe sopraglottica. La sintomatologia è comparsa con disfonia e modesta odinofagia da 2 anni; L'esame fibrolaringoscopico ha evidenziato una massa sottomucosa con coinvolgimento della sovraglottide di sinistra e della parete mediale del seno piriforme. L'RMN rappresenta l'esame principale per escludere altre diagnosi (schwannoma, paragangliome ed emangioma) e per una corretta stadiazione mentre l'immunoistochimica e l'analisi citomorfologica (bcl-2 e CD34 positiva nel 90% dei casi) è la base per una diagnosi definitiva. La chirurgia (endoscopica o cielo aperto) è la prima scelta di trattamento e l'obbiettivo è un bilancio tra la radicalità oncologica e la funzione d'organo; nel caso riportato l'approccio è stato a cielo aperto per il volume della massa tumorale. La prognosi è buona e solo in alcuni casi (specialmente nei SFT pleurici) il comportamento biologico del tumore può essere di tipo maligno.

PAROLE CHIAVE: *Tumore fibroso solitario • Patologia laringea • Tumore benigno laringeo*

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Introduction

Solitary fibrous tumour (SFT), first described in 1931 by Klemperer and Rabin [1], is a benign mesenchymal neoplasm with a predilection for male gender (M/F 6:1) that usually arises in the pleura as a well-defined mass. It rarely involves other sites outside serosal space such as the mediastinum, lung, liver, thyroid gland, orbit and upper aero-digestive tract.

SFT belongs to a tumour category group fraught with diagnostic uncertainty due to the association with haemangiopericytoma [2]. Its diagnosis is not straightforward and is generally based on cytomorphologic, immunohistochemical and radiologic findings. Extra-pleural localization, upper aero-digestive tract and especially the larynx are rarely involved with only a few cases reported in the literature [3-11 19]. Surgery represents the gold standard for treatment and is associated with good prognosis.

Here, we report the rare case of a supraglottic laryngel SFT in a female patient that was treated with a conservative open laryngeal approach.

Case report

A 41-year-old non-drinker and non-smoker woman was referred to our department for progressive dysphonia and mild odynophagia lasting 2 years. She denied any symptoms related to airway obstruction. Her clinical history was negative.

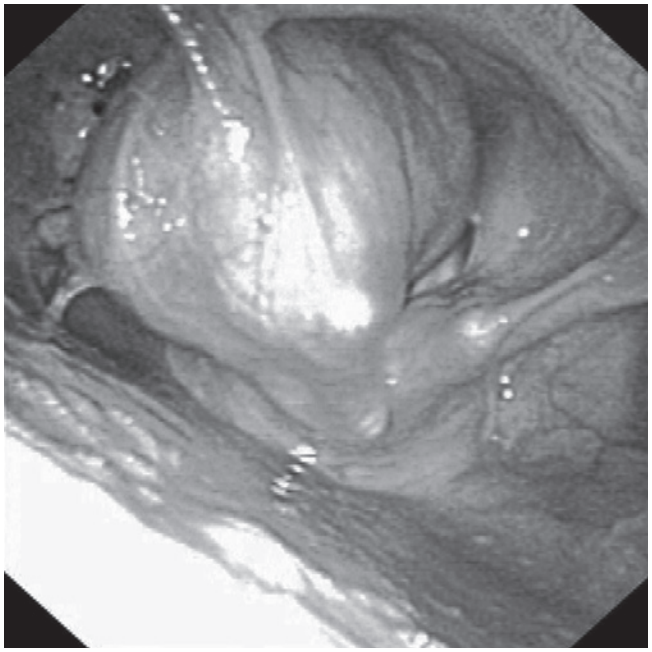

Fig. 1. Fibre-optic hypopharyngeal-laryngeal examination showing a sub-mucosal mass involving the left supraglottis and medial wall of the pyriform sinus.

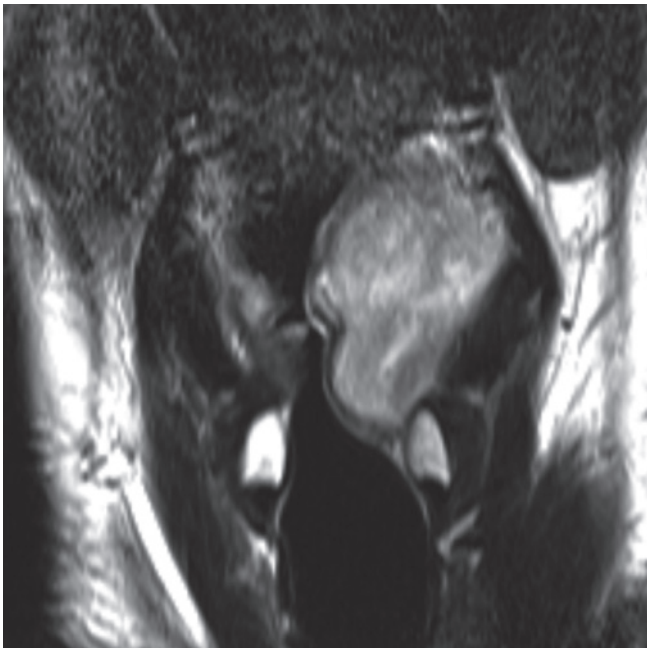

Fig. 2. MRI coronal view showing a solid mass (37x22 mm) arising from the left paraglottic space at the level of the ventricle reaching caudally the conus elasticus; cricoid cartilage is remodelled in its superior and medial aspects.

Physical examination did not reveal any neck masses and nothing relevant was observed in the oral cavity and oropharynx. Flexible fibre-optic hypopharyngeal-laryngeal examination showed a sub-mucosal mass involving the left supraglottis and medial wall of the pyriform sinus, covered by intact mucosa. The left vocal fold was normal in appearance and mobility (Fig. 1).

Magnetic resonance (MR) revealed a solid mass (37x22 mm) arising from the left paraglottic space centred at the level of the ventricle, with caudal spread reaching the conus elasticus. The cricoid cartilage appeared remodelled in its superior and medial aspect. In T2-weighted sequences, the lesion presented non-homogeneous contrast enhancement. No pathologic neck nodes were present (Fig. 2). Axial contrast enhanced computed tomography (CT) revealed low enhancement in both arterial and venous phases. The mass widened the thyroaritenoid space without cartilage infiltration (Fig. 3).

Surgery via an external approach was scheduled. Through a 5-cm transverse cervical neck incision performed along a skin crease at the level of crico-thyroid membrane, the left thyroid lamina was identified and its superior half was removed in order to fully expose the neoplasm occupying the left paraglottic space down to the superior aspect of the cricoid. The tumour shape was rounded and sharp with a tense-elastic consistence, covered by a

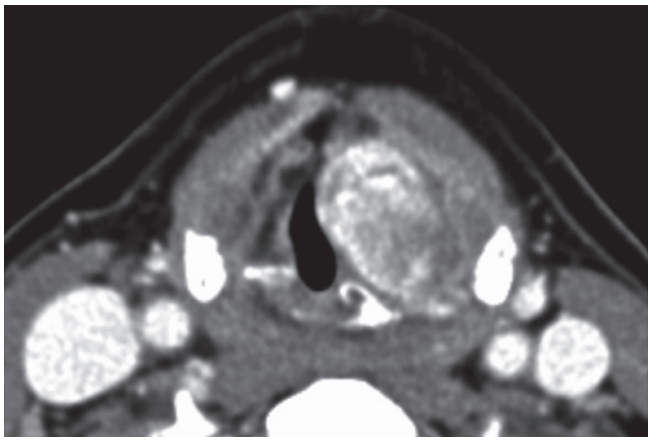

Fig. 3. CT-scan with contrast axial view showing low enhancement in both arterial and venous phases. The mass widens the thyroarytenoid space without cartilage infiltration.

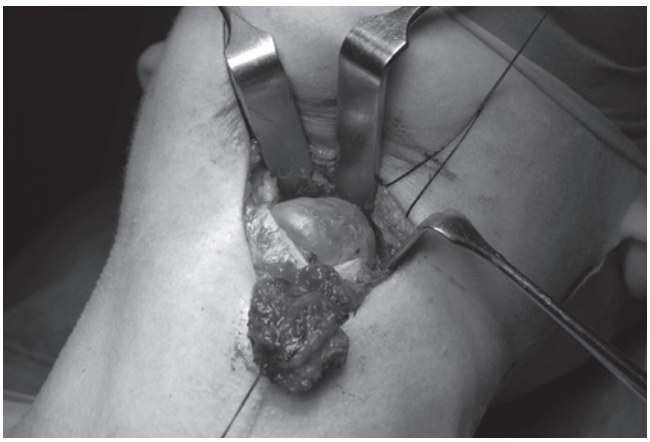

Fig. 4. Intra-operative view showing the surgical approach to the larynx. A 5-cm transverse cervical neck incision at the level of crico-thyroid membrane is performed, and the left thyroid lamina is identified and its superior half is removed in order to expose the neoplasm, occupying the left paraglottic space down to the superior aspect of the cricoid.

homogeneous greyish-coloured avascular capsule. The mass was completely removed with previous identification and preservation of the recurrent laryngeal nerve. The cartilaginous defect was covered by infra-hyoid muscles (Fig. 4). A temporary tracheostomy was performed and removed after 2 days.

Histopathologic examination revealed a solid neoplasm characterised by the presence of spindle cells in a hyalinised stroma; some myxoid spots were also present. Immunohistochemical analysis revealed positivity for CD34 and low positivity for Bcl-2.

Discussion

Solitary fibrous tumour (SFT), also known as benign localised mesothelioma, submesothelioma and subserosal fibroma, is a very uncommon benign neoplasm that arises from pleura and other serosal membranes [12]. Although the mediastinum is the most frequently affected site, other localisation such as lung, urogenital tract, and orbit have been described [13 14]. For these reasons, SFT has been divided in "extrapleural" and "extrathoracic" subgroups [16].

In general, "extrathoracic" SFT has a more indolent course, with a very low rate of malignant transformation and development of distant metastases in 6-10% of cases. In contrast, pleural lesions have a recurrence rate of 9-19% and are associated with a distant metastasis rate of up to 19% [17]. "Extrathoracic" SFT are more commonly symptomatic and when located in the larynx, and they are always associated with long-standing unspecific symptoms like progressive hoarseness, foreign body sensation and phonatory changes. Laryngeal SFT is usually located in the supraglottis, where it appears at endoscopy as a swelling covered by normal mucosa; pure glottic localisations are extremely rare [17] and only sporadic cases of larynx involvement are reported in English literature (Table I).

The lesion is hypothesised to originate from mesenchymal tissue, and in particular from myofibroblastic cells. From a histopathologic standpoint, SFT is characterised by the presence of spindle cells with headlong nuclei arranged in unspecific pattern with a collagenous background, the so-called "patternless-pattern". Immunohistochemical analysis reveals positivity to vimentin, and in about 50% of cases for CD99 and Bcl-2 protein. Staining for cytokeratin, smooth muscle actin, desmin, S-100 protein and CEA is always negative; CD34, which is involved in proliferation of myofibroblastic cells, is positive in 90-95% of cases [18].

SFT is commonly characterised by a slow growth, without invasion of surrounding tissues, associated with mild and vague symptoms, even though cases with malignant transformation, local invasion, recurrence and distant metastases have been reported. This aggressive behaviour is more typically observed in large volume lesions, with a high number of mitoses/field, presence of necrosis or

Table I. Literature review concerning SFT of the larynx (continues).

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Author	**Present case**	**Safneck [3]**	**Benlyazid [4]**	**Alobid [5]**	**Alobid [6]**	**Fan [8]**
Age	41	13	60	29	71	65
Gender	F	M	M	M	F	F
Location	Supraglottic/false VC	Epiglottis	Ventricular fold	False VC	Epiglottis	Supraglottis
Clinical presentation	Dyspnoea/ dysphonia	Foreign body sensation	Laryngeal dyspnea	Hoarseness/foreign body sensation	Foreign body sensation	Hoarseness
Symptoms duration (months)	24	1.5	20	6	6	12
Radiologic findings	Mass	Mass	Mass	Mass	Mass	Polypoid mass
Endoscopic findings	Submucosal avascular sharp mass	Bulky, pedunculated mass	Occupying space mass	Bulky avascular mass	Smooth mass	n/r
Tumour size (cm)	3.7	2.2	2.5	2.5	3.4	3.0
Treatment	Open lateral thyrothomy	Lateral pharyngectomy	Vertical hemilaryngectomy	Laser resection	Lateral pharyngectomy	Partial laryngectomy
Outcome (months)	NED (24) alive	NED (12) alive	NED (14) dead	NED (18) alive	NED(36) alive	NED(6) alive

M: male; F: female; VC: vocal cord; n/r: not reported; NED: not evidence of disease

Table I. Literature review concerning SFT of the larynx (follows).

	Case 7	Case 8	Case 9	Case10	Case 11
Author	**Stomeo [10]**	**Chang [19]**	**Thomson [9]**	**Morvan [11]**	**Dotto [7]**
Age	73	34	49	52	38
Gender	M	M	M	F	M
Location	Supraglottic/ commisure	Supraglottic	Glottic/subglottic	Supraglottic	False VC
Clinical presentation	Foreign body sensation/swallowing disorders	Foreign body sensation	Difficult breathing	Dysphonia/dyspnea	Cough/deepening voice
Symptoms duration (months)	3	6	24	Several months	12
Radiologic findings	Mass	Mass	Mass	Mass	Mass
Endoscopic findings	Submucosal swelling	Smooth submucosal mass	Smooth avascular mass	Bulky avascular mass	Submucosal mass
Tumour size (cm)	1.0	4.0	2.3	5.0	5.1
Treatment	Laser resection	Supraglottic partial laryngectomy	Biopsy	Lateral pharyngectomy	Laser resection
Outcome (months)	NED (24) alive	n/r	NED (12) alive	n/r	n/r

M: male; F: female; VC: vocal cord; n/r: not reported; NED: not evidence of disease

haemorrhages and nuclear atypias, although a benign evolution is seen in 50% of SFTs showing these features [16].

At MR, the lesion typically shows on T1-weighted sequences a signal that is isointense to muscle and variable on T2-weighted, with some areas with a slight enhancement and other areas with iso-hypointensity. These findings are probably due to the different histological arrangement of the tumour, which is rich in collagen and fibroblasts mixed with other areas where these components are less represented [19].

In the present case, CT with contrast revealed a low enhancement during the arterial phase, which became intense and heterogeneous in the interstitial phase, probably in view of the low presence of blood vessels. The axial CT scan showed a well-defined neoplasm occupying the entire left paraglottic space with enlargement of the tyro-arytenoid space, but with no signs of cartilage infiltration.

Based on MR and CT features, differential diagnosis includes other benign lesions such as haemangioma, schwannoma and paraganglioma. In children, haemangioma is typically localised in the subglottic area, whereas in adult patients the supraglottis is more frequently affected; on MRI T1 weighted-images (WI) the lesion shows a signal that is isointense to muscle (with up to 30% of lesions showing high signal foci due to haemorrhage), with a diffuse heterogeneous enhancement, while on T2 WI shows a hyperintense signal compared to muscle tissue and often shows poorly defined margins; phlebitis (small round calcifications of the venous vessels) are typically present. Schwannoma generally arise from the superior laryngeal nerve and tend to dislocate the larynx without involving the laryngeal intrinsic musculature or supraglottic folds. On CT, the disease presents as well defined, hypodense submucosal mass without signs of infiltrative or destructive growth; in MRI, the lesion is isointense to slightly hyperintense in T1WI with strong, inhomogeneous enhancement after gadolinium injection while in T2 WI appear hyperintense. Paraganglioma is a highly vascularised, non-encapsulated lesion that rarely involves the supraglottis, showing on MRI T1WI a typical "salt and pepper" appearance due to signal voids combined with high signal foci secondary to haemorrhages within the tumour, while on T2-weighted sequences the signal of the mass is superior to that of muscle.

Surgery is the mainstay of treatment and can be performed with an endoscopic or open approach in relation to tumour extension. An endoscopic technique is indicated for patients with good laryngeal exposure and for lesions not involving the pharyngeal constrictor muscle or without significant extralaryngeal extension. Otherwise, an open surgical technique is indicated for patients with sub-optimal laryngeal exposure and for bulky lesions invading the paraglottic space, with transglottic or extralaryngeal extension. Tracheotomy can be planned for both types of

techniques and depends on the size and localisation of the mass and anatomical configuration of the upper aerodigestive tract of the patient.

The patient herein underwent an open approach with partial resection of the thyroid lamina and en-bloc resection of the tumour, combined with a temporary tracheotomy and nasal feeding tube (NFT) positioning. The indications for this approach were the considerable volume of the lesion and its cranio-caudal transglottic extension into the paraglottic space reaching the superior border of the cricoid cartilage. In this case, an endoscopic technique was considered unsafe because of potential damage to the inferior laryngeal nerve, since the posterior extension of the tumour was close to the crico-arytenoid joint.

The post-operative course was uneventful, and the tracheotomy and NFT were removed on the 2nd and 4th post-operative days, respectively, and the patient was discharged the day after; endoscopic post-operative evaluation performed at 6 months showed normal motility of the vocal cords and complete healing of the laryngeal mucosa.

At 2-year follow-up, the patient is free of disease and clinically without any signs of recurrence; long-term clinical follow-up is required for possible rare risk of recurrence. In case of a large primary tumour (size > 10 cm), there is a possible association with a more aggressive behaviour of the tumour with metastatic spread within 6 months, although no cases of larynx involvement are described [16].

In conclusion, SFT is a rare benign mesenchymal tumour that very rarely occurs in the larynx. MR represents the first imaging tool, and the main goal of surgery is to ensure complete resection with no impact on upper aerodigestive tract function in terms of phonation and swallowing.

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In ricordo di Maurizio Moratti

7 /10 /1939 - 18 /1/ 2016

Improvvisamente un altro amico ci ha lasciato.
Un grande amico.

Maurizio Moratti era entrato a far parte, nel 1966, del gruppo di giovani specialisti diretto da Giuseppe Borasi nell'Ospedale S. Martino di Genova. Ricordo chiaramente quei suoi primi giorni di servizio e lo rivedo come era allora, magro, esile nella divisa da sottotenente dei Carabinieri, con il viso giovanile illuminato da quel suo sorriso accattivante che ispirava subito una grande simpatia. Nacque ben presto tra Lui e tutti noi del gruppo una fraterna amicizia che, col tempo, si sarebbe radicata sempre più profondamente, anche quando le carriere professionali di ciascuno ci avrebbero separato per lunghi periodi. Maurizio infatti lasciò Genova e si trasferì, per rivestire la carica di Primario ORL, prima a Tortona nel 1975 e poi ad Alessandria nel 1988, ma i nostri rapporti non si interruppero mai. La partecipazione ai congressi della Specialità, i viaggi di studio e di vacanza, la collaborazione alle attività delle nostre Società Scientifiche ci mantennero in continuo contatto per decenni. Per quanto riguarda quest'ultimo aspetto della nostra vita professionale voglio ricordare che dal 1992 al 2002 Maurizio Moratti fece parte del Consiglio Direttivo dell'AOOI e della SIO e nel 2001 organizzò ad Alessandria, con successo, l'annuale Congresso di Aggiornamento AOOI. La partecipazione alla vita e alle iniziative societarie lo fecero conoscere ed apprezzare da tutti i colleghi, ma ancora di più ebbero importanza per renderlo così popolare le sue qualità umane. La sua grande bontà d'animo, innanzitutto, e poi la sua estrema disponibilità, il suo radicato senso dell'amicizia, la sua simpatia. Proprio queste doti gli hanno fatto conquistare la stima e la benevolenza dei colleghi e di quanti hanno potuto conoscerlo. Addio caro amico. Ti ricorderemo sempre con tanto affetto.

Giorgio Sperati

Calendar of events – Italian and International Meetings and Courses

Acta Otorhinolaryngol Ital 2016;36:245-248

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

MAY-DECEMBER 2016

ENDOCHICAGO 7th WORLD CONGRESS FOR ENDOSCOPIC SURGERY OF THE SKULL BASE AND BRAIN • ***May 15-18, 2016 • Chicago (IL) – USA***

Course Directors: Amin B. Kassam, Martin Corsten, Ricardo L. Carrau, Daniel M. Prevedello, Vijay Anand, Theodore H. Schwartz – Website: www.endoworld.org/d-1_7TH_WORLD_CONGRESS

103° CONGRESSO NAZIONALE SIO SOCIETA ITALIANA DI OTORINOLARINGOLOGIA E CHIRURGIA CERVICO-FACCIALE • ***May 25-28, 2016 • Rome – Italy***

President: Roberto Filipo – Website: www.sioechcf.it

STUDIO ENDOSCOPICO DINAMICO DELLA DEGLUTIZIONE – II LIVELLO
May 31 - June 1, 2016 • Rimini – Italy

Scientific Secretariat: Daniele Farneti, Mauro Colombari, Patrizia Consolmagno – E-mail: dfarneti@auslrn.net

HEAL (HEARING ACROSS THE LIFESPAN): "EARLY INTERVENTION: THE KEY TO BETTER HEARING CARE" • ***June 2-4, 2016 • Lake Como – Italy***

Website: www.heal2016.org – E-mail: meet@meetandwork.com – Tel. +39 049 8601818 – Fax +39 0498602389

STUDIO ENDOSCOPICO DINAMICO DELLA DEGLUTIZIONE – I LIVELLO • ***June 3-4, 2016 • Rimini – Italy***

Scientific Secretariat: Daniele Farneti, Elisabetta Genovese, Claudio Vicini – E- mail: dfarneti@auslrn.net

10th INTERNATIONAL CONFERENCE IN CHOLESTEATOMA AND EAR SURGERY
June 5-7, 2016 • Edinburgh – UK

Email: CHOLE2016@tfigroup.com – Website: www.chole2016.org

29th BÁRÁNY SOCIETY MEETING 2016 • ***June 5-8, 2016 • Seoul – Korea***

Website: www.barany2016.org

CORSI PRATICI DI VIDEOCHIRURGIA ENDOSCOPICA NASO-SINUSALE – Corso Senior
June 6-10, 2016 • Milan – Italy

Director: Alberto Dragonetti – Email: a.dragonetti@fastwebnet.it

INCONTRI DI AGGIORNAMENTO IN OTORINOLARINGOIATRIA 2015/2016 - "L'IMMUNOTERAPIA NELLA PATOLOGIA ALLERGICA DEL NASO: PASSATO, PRESENTE E FUTURO"- Prof.ssa Luisa BELLUSSI
June 9, 2016 • Rome – Italy

Director: Gaetano Paludetti – Tel. +39 06 30151

53° INCONTRO DI AGGIORNAMENTO "IPOACUSIA DALLA NASCITA ALLA SENESCENZA"
June 11, 2016 • Roma – Italy

President: Rosaria Turchetta

TORONTO HEAD AND NECK IMAGING COURSE • ***June 11, 2016 • Toronto, Ontario – Canada***

Planning Committee: Kartik S. Jhaveri, Aditya Bharatha, John deAlmeida, Eugene Yu – Website: cpd.utoronto.ca/headandneckimaging

EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY (EAACI) • *June 11-15, 2016 • Austria*

Email: Cornelia.Puhze@eaaci.org – Website: www.eaaci2016.org

SORDITÀ E TECNOLOGIA AUDIOLOGICA TRA ATTUALITÀ E FUTURO • *June 13-14, 2016 • Milan – Italy*

Chairmen: Sandro Brudo, Domenico Cuda

XXXV PANAMERICAN CONGRESS OF OTOLARYNGOLOGY & HEAD AND NECK SURGERY
June 13-16, 2016 - La Habana – Cuba

President: Antonio S. Paz Cordovez – Website: www.orlpanamericanocuba.com

9th INTERNATIONAL SYMPOSIUM ON OBJECTIVE MEASURES IN AUDITORY IMPLANTS
June 15-18, 2016 • Szeged – Hungary

Congress President: József Géza KISS – E-mail: info@congress-service.hu – Website: http://objectivemeasures.org/

13th CONGRESS OF THE EUROPEAN SOCIETY OF PEDIATRIC OTORHINOLARYNGOLOGY
June 18-21, 2016 • Lisbon – Portugal

Email: secretary@espo2016.com – Website: www.espo2016.com

CONGRESSO NAZIONALE DEL CENACOLO ITALIANO DI AUDIOVESTIBOLOGIA
June 23-25, 2016 • Chieti – Italy

President: Adelchi Croce. Scientific Secretariat: Giampiero Neri. E-mail: info@nsmcongressi.it

GIORNATA DI FORMAZIONE AIOOC • *June 20, 2016 • Milan – Italy*

President: Piero Nicolai

50° CONGRESSO NAZIONALE SIFEL • *June, 23-25, 2016 • Catania – Italy*

President: Agostino Serra – Email: eac@eac.it – Website: www.eac.it/

ERS 2016 • *July 3-7, 2016 • Stockholm – Sweden*

E-mail: eberkovitz@kenes.com – Website: http://www.ers-isian2016.com/

26th CONGRESS OF THE EUROPEAN RHINOLOGIC AND THE 35th INTERNATIONAL SYMPOSIUM OF INFECTION AND ALLERGY OF THE NOSE & 17th CONGRESS OF THE INTERNATIONAL RHINOLOGIC SOCIETY (ERS 2016) • *July 3-7, 2016 • Stockholm – Sweden*

President: Pär Stjärne – Website: www.ers-isian2016.com

INTERNATIONAL SUMMER SCHOOL TRANSNASAL ENDOSCOPIC SURGERY: FROM SINUSES TO SKULL BASE - *July 4-8, 2016 • Brescia – Italy*

E-mail: info@servizicec.it – Website: www.summerschool-endoscopicskullbase-brescia.com/

12th OTOLOGICAL MICROSURGERY COURSE • *August 29-31, 2016 • Bern – Switzerland*

E-mail: otology@swiss-meeting.org – Website: http://otology.swiss-meeting.org

4th INTERNATIONAL SYMPOSIUM ON OTOSCLEROSIS, DIAGNOSIS AND TREATMENT
August 31- September 2, 2016 • Utrecht – The Netherlands

E-mail: info@otosclerosis.com – Website: http://www.otosclerosis2016.com/

ENDOSCOPIC COURSE FOR PARANASAL SINUS AND SKULL BASE SURGERY
September 1-3, 2016 • Bern – Switzerland

E-mail: paranasal@swiss-meeting.org – Website: http://paranasal.swiss-meeting.org

INTERNATIONAL MEETING OF RHINOPLASTY SOCIETIES
September, 8-10, 2016 • Versailles (Paris) – France

Chairmen: Wolfgang Gubisch, Bahman Guyuron – E-mail: contact@imrhis2016.com – Website: www.imrhis2016.com/en/

EUROSAS SURGERY • *September 15-17, 2016 • Rimini – Italy*

Organising Secretariat: Filippo Montevecchi, Andrea De Vito – E-mail: filippomontevecchi72@gmail.com; dr.andrea.devito@gmail.com – Website: www.eurosas2016.com/

OTOLOGY 3.0: L'OTOLOGIA NEL TERZO MILLENNIO • *September 22-24, 2016 • Padova – Italy*

Director: Alessandro Martini – E-mail: meet@meetandwork.com

INSTRUCTIONAL WORKSHOP EUROPEAN ACADEMY OF OTOLOGY AND NEURO-OTOLOGY
September 28 - October 1, 2016 • İzmir – Turkey

President: O. Nuri Ozgirgin – Website: www.eaono.org

28th CONGRESS OF UNION OF EUROPEAN PHONIATERS: PHONIATRICS AND COMMUNICATION
September 29 - October 1, 2016 • Bilbao – Spain

Website: http://phoniatrics-bilbaocongress.com

CORSO PRATICO DI ANATOMIA CHIRURGICA E DISSEZIONE SPERIMENTALE OTOLOGICA 2° LIVELLO - XX EDIZIONE • *October 3-7, 2016 • Sanremo (IM) – Italy*

President: S. Nosengo – E-mail: franco.cocchini@studiumorl.com – A cura di: A. Tombolini, F. Baricalla – Co-ordinato da: A. Tombolini – Website: www.studiumorl.com

IFHNOS 2016 • *October 5-7, 2016 • Praha – Czech Republic*

E-mail: ifhnos2016@guarant.cz – Website: www.ifhnosprague2016.org/

5th RHINOLOGY MEETING • *October 13-15, 2016 • Senigallia – Italy*

Directors: Dilyana Vitcheva, Alessandro Varini, Giuseppe Frau, Alessandro Bucci – E-mail: drbucci@libero.it – Website: www.rhinology.eu

SWISS ENDOSCOPIC EAR SURGERY COURSE (SEES) • *October 14-15, 2016 • Bern – Switzerland*

E-mail: anschuetz.lukas@gmail.com – Website: http://sees.swiss-meeting.org

6th INTERNATIONAL COURSE ON FUNCTIONAL AND AESTHETIC SURGERY OF THE NOSE – LIVE SURGERY • *October 16-19, 2016 • Imola (BO) – Italy*

Course Director: Ignazio Tasca – Scientific Secretariat, E.N.T. Department, Imola Hospital, Italy – Tel. +39 0542 662101/293 – Fax +39 0542 662284 – E-mail: i.tasca@ausl.imola.bo.it – Executive Secretariat: A & R Eventi sas di Verlicchi Clara e C., via R. Benassi 28, 40068 San Lazzaro di Savena (BO), Italy – Tel. +39 051 474238 – Fax +39 051 4839525 – E-mail: clara@areventi.it – Website: www.imolarhinoplasty2016.com

ANZHNCS ANNUAL SCIENTIFIC MEETING AND THE IFHNOS 2016 WORLD TOUR
October 25-27, 2016 • The Langham Auckland – New Zealand

E-mail: anzhncs.asm@surgeons.org – Website: www.ifhnosauckland2016.org

15th INTERNATIONAL CONGRESS OF IRANIAN SOCIETY OF OTOLARYNGOLOGY, HEAD AND NECK SURGERY • *November 8-11, 2016 • Tehran – Iran*

E-mail: mahtab_rabbani@yahoo.com – Website: www.iranent.org/congress/

4° CONGRESSO AGGIORNAMENTI IN ORL "ENDORL" • *November 12, 2016 • Montegranaro (Fermo) – Italy*

President: Luigi Fasanella – Scientific Secretariat: Cesare Carlucci – Tel. +39 0733 823030 – E-mail: carlucci7@tin.it

MASTER DI DISSEZIONE E CHIRURGIA ENDOSCOPICA DEI SENI PARANASALI E DEL BASICRANIO
November 14-18, 2016 • Milan – Italy

Director: Alberto Dragonetti – E-mail: a.dragonetti@fastwebnet.it

9th INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN RHINOSINUSITIS AND NASAL POLYPOSIS (ISRNP 2016) • *November 21-23, 2016 • Kuala Lumpur – Malaysia*

E-mail: sympo@isrnp2016.net – Website: http://www.isrnp2016.net/

CORSO MICROSCOPICO E VIDEOENDOSCOPICO DI DISSEZIONE SU CADAVERE PROPEDEUTICO ALLA CHIRURGIA OTOLOGICA • *November 24-25, 2016 • Milano – Italy*

Presidents: Raffaele Pugliese, Alberto Dragonetti – E-mail: corsieconvegni@eurocompany.mi.it

RHINOFORUM 2016 • *December 1-3, 2016 • Warsaw – Poland*

E-mail: info@forumrynologiczne.pl – Website: http://rhinoforum.pl/en

JANUARY-DECEMBER 2017

CORSO DI DISSEZIONE OTOLOGICA, OTONEUROLOGICA E IMPLANTOLOGIA UDITIVA, DISSEZIONE ENDOSCOPICA DELL'ORECCHIO MEDIO E INTERNO • ***January 10-12, 2017 • Paris – France***

Directors: Olivier Sterkers and Daniele Bernardeschi

9th MILANO MASTERCLASS • ***March 24-28, 2017 • Milan – Italy***

Charimen: Paolo Castelnuovo and Pietro Palma – Website: www.milanomasterclass.it

2nd WORLD CONGRESS ON ENDOSCOPIC EAR SURGERY • ***April 27-29, 2017 • Bologna – Italy***

Chairmen: Livio Presutti, Muaaz Tarabichi, Daniele Marchioni

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

Tel. +33 (0)1 44 64 15 15 – E-mail: contact@ifosparis2017.org – Website: www.ifosparis2017.org

4th CONGRESS OF THE EUROPEAN ORL-HNS • ***October 19-22, 2017 • Antalya – Turkey***

E-mail: dburkaya@topkon.com – Website: www.ceorlhns2017.com

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

E-mail: phillip.samual27@gmail.com

JANUARY-DECEMBER 2018

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

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

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

Website: http://ifhnos2018.org/

JANUARY-DECEMBER 2019

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

E-mail: secretariat@14asiaoceania.com – Website: http://14asiaoceania.com/