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Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
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Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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REVIEW

It is 2015: What are the best diagnostic and treatment options for Ménière's disease?

Safeer Shah, Abel Ignatius, Syed Ahsan

Safeer Shah, Abel Ignatius, Wayne State University School of Medicine, Detroit, MI 48201, United States

Syed Ahsan, Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health System, Detroit, MI 48202, United States

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Correspondence to: Syed Ahsan, MD, FACS, Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health System, 2799 W. Grand Blvd. K-8, Detroit, MI 48202, United States. sahsan3@hfhs.org
Telephone: +1-313-9167442

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Abstract

Ménière's disease (MD) is a common cause of recurrent vertigo. Its pathophysiology is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops (EH). However, not all cases of hydrops are associated with MD and it may represent the end point of various etiologies. The diagnostic criteria for MD have undergone changes during the past few decades. A recent collaboration among specialty societies in United States, Europe and Japan has given rise to a new set of guidelines for the diagnosis and classification of MD. The aim is to develop international consensus criteria for MD that would help improve the quality of data collected from patients. The diagnosis of MD can be difficult in some cases as there is no gold standard for testing. Previous use of audiometric data and electrocochleography are poorly sensitive as screening tools. Recently magnetic resonance imaging as a diagnostic tool for identifying EH has gained popularity in Asia and Europe. Vestibular evoked myogenic potentials are also used but lack specificity. Finally, the treatment for MD has improved with the introduction of intratympanic treatments with steroids and gentamicin as well as less invasive treatment with the Meniett device.

Key words: Ménière's disease; Review; Pathophysiology; Diagnosis; Treatment

Core tip: The pathophysiology of Ménière's disease (MD) is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops. This finding is utilized in the newest method of diagnosis

using magnetic resonance imaging with intratympanic or intravenous gadolinium. Changes to the diagnostic criteria have been proposed with collaboration from various international societies. This will help in communication and improve quality of published data. Finally, the use of intratympanic steroids and Meniett pressure treatments offers less invasive and destructive treatments for patients with MD.

Shah S, Ignatius A, Ahsan S. It is 2015: What are the best diagnostic and treatment options for Ménière's disease? *World J Otorhinolaryngol* 2016; 6(1): 1-12 Available from: URL: http://www.wjgnet.com/2218-6247/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5319/wjo.v6.i1.1

INTRODUCTION

Ménière's disease (MD) is an inner ear disorder that is characterized by episodic vertigo, low-pitched tinnitus and fluctuating hearing loss lasting for a minimum of 20 min. In the United States, 190 people per 100000 are affected, with a 2:1 female to male ratio[1]. MD was named after the French physician Prosper Ménière, who in 1861 first argued that MD was an inner ear disorder and not a neurological one[2]. Much time after his death, the most common finding in postmortem human temporal bone studies of MD patients was endolymphatic hydrops (EH), which is the dilation of the membranous labyrinth of the inner ear[3]. It should be noted however that not all cases of EH are associated with MD[4]. The lack of certainty in understanding the pathophysiology of MD makes it difficult to properly diagnose and treat. Most treatments are aimed at reducing endolymphatic size and pressure after which non-responders go on to ablative treatments.

PATHOPHYSIOLOGY

MD is an idiopathic disorder wherein the mechanism underlying its pathophysiology is still unclear and controversial. Affected individuals differ in terms of etiology and thus many studies propose various explanations for the manifestation of symptoms. However, it is generally agreed upon that EH is a consistent histological hallmark of the disease, a phenomenon seen in numerous temporal bone studies[4-7]. EH can be described as a pathologic finding in which the structures bounding the endolymphatic space are distended by an enlargement of endolymphatic volume[8]. The consequent hydropic state leads to various mechanical and chemical perturbations that ultimately give rise to the classic symptoms of MD.

In the cochlea, distension of the scala media causes the endolymphatic space to impinge on the bordering perilymphatic compartments. According to Wit *et al*[9] the degree of distension is related to the mechanical compliance of the membrane involved. This explains why EH is more prevalent in the cochlea and saccule, which are relatively more compliant than other structures such as the utricle or semicircular canals. Long-term distension may eventually lead to rupture of inner ear membranes. For example, rupture of Reissner's membrane has been reported in patients with MD, although Paparella *et al*[10] note the absence of rupture in two thirds of patients. Nonetheless, it has been theorized that membrane rupture leads to an electrolyte imbalance, causing acute vertigo and hearing loss[4,5,8,10,11]. Chemically, the hydropic state also creates a neurotoxic environment that leads to apoptosis of spiral ganglion cells[5]. Excitotoxicity may therefore contribute to the auditory symptoms of MD.

Previous research has shown that almost all patients diagnosed with MD present with EH in the affected ear. However, this consistent finding does not imply that EH is the direct underlying cause of MD. Several studies involving histopathological examinations of human temporal bones have revealed that not every patient with EH presents with symptoms of MD[4,12,13]. This makes it difficult to infer a simple cause-and-effect relationship. Instead, EH may be the result of various etiologies that disrupt normal endolymphatic fluid homeostasis. Semaan *et al*[5] separate these etiopathogenic factors into intrinsic or extrinsic. Intrinsic factors may include hypoplasia of labyrinthine structures, anteriorly and medially displaced sigmoid sinus, genetic factors, and other causes attributable to the inner ear itself. Extrinsic factors include autoimmune disease, allergy, otosclerosis, viral infection and trauma[5].

Genetics

Genetically, MD follows an autosomal dominant pattern with 60% penetrance[14]. Koyama *et al*[15] (1993) found relatively higher levels of histocompatibility antigens in affected patients, with HLA-DR, DQ, DP, A2 and B44 being particularly noteworthy[16]. Furthermore, a missense mutation of the *COCH* gene in the DFNA9 locus has been shown to produce MD-like symptoms such as progressive sensorineural hearing loss and vestibular dysfunction[17]. However, Morrison and Johnson propose that the *COCH* gene is an unlikely candidate for MD[18]. Lastly, an animal model of postnatal EH in mice suggests that genetics may play a role in posttranscriptional modification of the gene product, which also explains phenotypic differences between patients[5]. Overall, investigations into the genetic basis of MD suggest that multiple genes may be involved, and in combination they render certain individuals more susceptible to developing the disease.

Autoimmunity

It is believed that the immunological basis of the pathogenesis of MD may involve reactions between antibodies and tissue antigens, or IgG- and IgM-mediated circulating immune complexes (CICs)[19]. While larger CICs are cleared from circulation, smaller complexes can

Table 1 1995 American Academy of Otolaryngology-Head and Neck Surgery diagnostic criteria for Ménière's disease

Certain	Definite Ménière's + histological confirmation
Definite	⩾ 2 definitive spontaneous vertigo episodes ⩾ 20 min + all criteria in Probable Ménière's disease
Probable	1 definite episode of vertigo audiometric hearing loss on ⩾ 1 occasion Aural fullness or tinnitus in the affected ear Other causes exclude
Possible	Episodic vertigo of Ménière's type with no documented hearing loss or Fluctuating or fixed SNHL with disequilibrium without definitive vertigo episodes Other causes excluded

SNHL: Sensorineural hearing loss.

continue to circulate and accumulate in inner ear tissues, causing a local inflammatory response[19]. Deposition within the stria vascularis and endolymphatic sac may even lead to increased vascular permeability, and the sudden efflux of fluid induces EH and even rupture of Reissner's membrane[20]. Success with steroid-based treatments, which act as an anti-inflammatory agent, also bolsters the argument for an immunologic mechanism in the development of MD[5]. Furthermore, other studies note the presence of intraluminal eosinophilic material within the endolymphatic duct, and conclude that it is evidence of an immunodefensive system in the inner ear as this material contains the macrophages that trap antigen[21,22].

Endolymphatic duct and sac

The longitudinal flow theory states that the unidirectional flow of endolymph begins in the stria vascularis where it is produced, travels through the endolymphatic duct, and is eventually absorbed by the endolymphatic sac[5]. Thus, it follows that narrowing of the endolymphatic duct could impair endolymph absorption at the sac, and consequently result in a hydropic state. In fact, numerous guinea pig models show the development of hydrops following surgical obstruction of the endolymphatic duct[4]. However, Salt and colleagues found that the hydropic state could not be a result of the blockage of longitudinal flow because the rate of endolymph flow was too small. Instead, they believe that endolymphatic homeostasis is not volume-dependent; rather, it is dominated by ion transport and water equilibration *via* osmotic gradients[23,24]. Shinomori *et al*[25] (2001) further this idea by proposing a cytochemical mechanism for the development of hydrops. After blocking the endolymphatic duct in 22 guinea pigs, changes were noted in the cytochemistry of type Ⅰ and Ⅱ fibrocytes as well as nonsensory epithelial cells before the development of hydrops. Blocking the endolymphatic duct changed the composition of perilymph, thus placing osmotic stress on fibrocytes, which are important in maintaining fluid homeostasis. Merchant *et al*[4] hypothesizes that the dysfunction of fibrocytes interferes with K^+ recycling, leading to osmotic imbalance and expansion of the endolymphatic compartment.

CLASSIFICATION

The criteria for diagnosis of MD have undergone various changes within the past few decades. In 1974, the Japanese Society for Equilibrium Research proposed a set of conditions that classified the disorder into either definite or suspicious/uncertain MD. Lopez-Escamez *et al*[26] briefly outlined those conditions as the following: (1) repeated attack of whirling vertigo; (2) fluctuating cochlear symptoms; and (3) exclusion of central nervous system involvement, CN Ⅷ tumor and other cochleovestibular diseases. A diagnosis of definite MD required fulfillment of all three conditions while suspicious/uncertain MD involved two of the conditions with the third being necessarily included[26].

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) also developed a set of guidelines in 1972, which were revised in 1985 and again in 1995. Nearly all studies since then have been based on the 1995 criteria, which classified MD into possible, probable, definite and certain[27] (Table 1). A recent collaboration among the Equilibrium Committee of the AAO-HNS, the Japan Society for Equilibrium Research, the European Academy of Otology and Neuro-Otology, the Korean Balance Society and the Bárány Society gave rise to a new set of guidelines for the diagnosis and classification of MD (Table 2). The aim was to develop international consensus criteria for MD to improve the quality of data collected from patients. Furthermore, clarification was needed with regards to the nature of auditory symptoms[26].

DIAGNOSIS

Audiogram

Traditionally, the most common audiometric configuration for patients with MD involved a "rising" pattern during the early stages, indicating low frequency hearing loss, followed by a flat audiogram in later stages of the disease[28-30]. However, Opheim and Flottorp began to notice a pattern involving a "peak" audiogram in many of their patients with MD[31]. Further investigations have been conducted in order to assess the usefulness of the peak audiogram as a diagnostic tool. In one study, 363 hearing impaired ears with MD were assessed for evidence of a peak audiogram. Paparella *et al*[28] (1982) noted the presence of a peak audiogram "if the air conduction threshold for one test frequency was at least 10 dB better than both hearing thresholds for the two adjacent octave frequencies". The reported sensitivity of the peak audiogram in detecting MD was 41.7%, while the specificity was 93.4%[28]. Therefore, the audiogram appears to be useful in ruling out the possibility of MD in patients without a peak configuration. However, its low sensitivity makes it a poor diagnostic tool on its own. Perhaps the peak audiogram may best be used as an

Table 2 New proposed diagnostic criteria for Ménière's disease

Definite MD
Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h
Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo
Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis
Probable MD
Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h
Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis

MD: Ménière's disease.

adjunctive test to more advanced imaging techniques.

In a separate study by Lee *et al*[29], other audiometric patterns were considered in addition to the peak configuration. These included flat, rising, falling and dip configurations. The results once again supported a relatively higher proportion of the peak audiogram (50.65%), followed by the falling audiogram (26.26%), the dip audiogram (9.24%), and other types accounting for the remaining portion[29]. Again, the low sensitivity of the peak audiogram makes it an unreliable diagnostic test for MD, and this study along with others show the involvement of a wider variety of configurations.

Paparella *et al*[28] also found that those with severe or profound hearing loss were just as likely to have a 2000 Hz peak audiogram as those with mild or moderate hearing loss. This implies that the prevalence of the peak audiogram is unrelated to the degree of hearing loss. Instead, prevalence of the peak audiogram appears to be affected by bilaterality and duration: Bilateral peak configurations are more likely to result in patients with bilateral diseased ears of longer duration[28].

Magnetic resonance imaging

The use of magnetic resonance imaging (MRI) as a diagnostic tool for identifying EH gained popularity in 2007. Nakashima *et al*[32] (2007) used 3-T MRI following transtympanic (TT) gadolinium injection to visualize the endolymphatic space of patients diagnosed with MD, and since then it has been regarded as a possible gold standard test. It is also worth noting that a modified method involves intravenous (*iv*) administration of gadolinium.

The main outcome measure in using MRI as a diagnostic tool is perilymphatic enhancement in various portions of the labyrinth. Perilymphatic enhancement is an indirect measure of EH with progressively lower enhancement representing growing occupation of the perilymphatic space by the hydrops[33]. For example, in the cochlea, decreased visualization of the scala vestibuli indirectly infers increased displacement of Reissner's membrane brought about by EH[34]. Though perilymphatic enhancement is a reliable tool for inferring the presence of hydrops, the possibility of false positive findings cannot be ruled out. This could be due to impaired filtration of gadolinium into the perilymphatic compartment as a result of degenerative changes in the inner ear[33].

Gadolinium injection followed by MRI appears to be a well-tolerated test with good image quality, and relatively few, if any, complications have been reported[35,36]. Furthermore, numerous studies support a high sensitivity of the test for identifying EH in symptomatic ears, whether the contrast is administered intravenously or using the TT method. Recent studies investigating the use of MRI as a diagnostic test report a relatively consistent sensitivity as high as 90%-100%[33,36,37]. These results are comparable with previous investigations and bolster the usefulness of MRI as a diagnostic tool for the presence of EH in symptomatic ears. It is worth noting a recent study that compared MRI with tone burst electrocochleography (ECoG) in the diagnosis of MD. The sensitivity results with MRI differed significantly from previous studies, reporting 47%, 29%, and 8% for definite, probable and possible MD respectively[35].

While gadolinium-enhanced MRI shows promise as a reliable tool for positively identifying hydrops in patients with MD, its specificity requires further investigation. Few studies have been conducted on this measure and the results are variable. For example, Pyykkö *et al*[37] found that MRI visualized EH in 65% of asymptomatic ears (35% specificity). In contrast, other studies yield better results in terms of correctly not identifying hydrops on MRI in asymptomatic ears. Baráth *et al*[34] used Ⅳ Gadolinium injection followed by MRI to look for hydrops in 53 patients with MD, reporting a specificity of 78%. Fiorino *et al*[33] had even better results with TTGad injection, noting no perilymphatic enhancement defects in all unaffected contralateral ears of patients with MD (100% specificity).

Generally, TTGad injection is preferred over the Ⅳ route because it provides a higher perilymphatic signal and thus a better visualization of the compartment[38]. However, the advantages of Ⅳ injection should not be ignored and perhaps could be used in special cases. Of particular importance is its less invasive nature, the ability to simultaneously examine both ears for comparison and the fact that perilymphatic enhancement is independent of the status of the round window membrane[34,39].

ECoG

ECoG is a technique that measures the electric poten-

tials generated in the cochlea in response to an auditory signal. The usual ECoG response consists of a cochlear microphonic (CM), the summating potential (SP) and the cochlear nerve compound action potential (AP). The CM is mainly generated by the outer hair cells closest to the recording electrode. Due to its proximity, the CM closely resembles the waveform of the stimuli and vibrations of the basilar membrane. If the polarity of the stimulus is reversed, the polarity of the CM will also reverse. The alternate polarity stimuli are used to cancel the amplitude of the CM so that SP and AP can be measured. The SP consists of a shift in the baseline of a CM in response to click stimuli and a deflection before the AP in response to tone-burst stimuli. Finally, the AP is the sum of the individual APs from the auditory nerve fibers[40]. Two methods of obtaining ECoG differ by where the electrode is placed: TT has an electrode on the promontory wall of the middle ear and Extratympanic (ET) has one outside of the tympanic membrane. The ET method has a slightly lower sensitivity and specificity because of low signal amplitude, but is still the preferred method due to it being non-invasive and easy to implement. Using tone burst auditory stimuli is more reliable than the commonly used auditory clicks stimuli[41].

The SP/AP ratio is commonly used to identify EH. The thresholds for the ratio vary with some authors suggesting 0.5 for ET with clicks and alternating polarity while others suggest 0.33 for TT. There is no universally agreed SP/AP ratio that we could find[41]. It is thought that altered SP and AP is the result of mechanical asymmetry in the basilar membrane[42].

Electrovestibulography (EVestG) is similar to ECoG except that it measures saccule function instead of cochlear function. Instead of acoustic stimuli, the patient experiences passive whole body tilts in a hydraulically controlled chair located in an electrically and acoustically shielded chamber. The test has shown encouraging results in other neurological diagnostic applications such as Parkinson's disease, depression, and schizophrenia disorder by other studies. It is possible that with more research, EVestG could be used to identify neural firing patterns that are diagnostic in patients with MD[43].

Sensitivity of ECoG ranges from 57% to 71% and specificity ranges from 94% to 96%[41]. A study found 1 kHz tone-burst stimuli to be the most reliable stimuli with a sensitivity of 86% and specificity of 80.5%[44]. ECoG interpretation is complicated by the fluctuating behavior of MD. Sensitivity can go from 60% to 92% when ECOG is used during a symptomatic period[41]. Additionally, sensitivity is found to increase with duration and severity of the disease. A study found 71% sensitivity in stage 1 MD compared to 90% in stage 4, and 43% in MD for less than 1 year duration compared to 100% in 30 years duration[45]. However, ECoG is not a useful tool in differentiating between definite and probable MD[41].

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMPs) are becoming a popular tool to assess inner ear function. Cervical VEMPs utilize the vestibulocolic reflex by measuring the inhibitory potentials of the ipsilateral sternocleidomastoid muscle in response to loud auditory signals. Signals from the acoustically responsive sensory cells and neurons of the saccule are conducted centrally *via* the inferior vestibular nerve[46]. Studies have shown that altered motion mechanics of the distended saccule can lead to an altered VEMP response in MD patients[46]. A cVEMP curve is made by plotting the dB SPL as a function of frequency for tone bursts at 250, 500, 750 and 1000 Hz. Healthy patients are most sensitive at 500 Hz and patients with MD showed a sensitivity shift to 1000 Hz[47]. Thirty percent of unaffected ears in patients with unilateral MD also show a sensitivity shift, but to a lesser degree. This could be because the unaffected ear has a minor form of MD. It was found that normal adults above the age of 60 show a sensitivity shift. In some cases they showed flattening of the threshold response curve. A high proportion of patients with caloric asymmetry $\geqslant$ 25% did not show any VEMP response[47].

Another version of VEMP called ocular VEMP records excitatory potentials from the superior vestibular nerve going to the inferior oblique and inferior rectus muscles of the opposite side[48,49]. It is thought that utricular afferents and some saccular afferents travel through the superior nerve division and most saccular afferents travel through the inferior division. With more research, VEMPs could be used to differentiate dysfunction in the otolith and saccule[50]. VEMP measurement has been found to be a more reliable test for saccule function compared to a calorics[51]. It has been suggested that a negative VEMP test does not rule out MD, however a positive test result suggests that MD is probable[47].

MIGRAINE AND MÉNIÈRE'S

Since the term MD was first coined, the prevalence of migraine among MD patients and MD among migraine patients has suggested a possible link between these two diseases[52]. What was once called Vestibular Ménière's is no longer recognized by the current guidelines for MD[53]. Others suggest that most likely this variant of MD was actually undiagnosed vestibular migraine (VM)[54,55].

Recently, the Migraine Classification Subcommittee of the International Headache Society has proposed diagnostic criteria for VM which have been included in the International Classification of Headache Disorders (ICHD) 3rd beta edition. It should be noted that the term VM could be used interchangeably in other papers with migraine-associated dizziness/vertigo and migrainous vertigo. According to the ICHD, VM is characterized by vestibular symptoms such as vertigo and head motioned-induced dizziness lasting between 5 min and 72 h. Common symptoms in MD such as tinnitus, aural pressure and fluctuating hearing loss other than profound can occur in VM. Likewise, migraine headaches, photophobia and even migraine auras are

common in MD[56]. A pathophysiological relationship between MD and VM remains uncertain however some theories have been proposed. The prevalence of allergy among MD and migraine patients compared to the general population may suggest an immunological link[57]. There is some evidence of increased IgE levels in MD patients that could lead to EH in MD and meningeal vasculature changes in migraines[57,58]. However, more work needs to be done in this area to support this claim.

Early MD can present with early episodic vertigo only and can be difficult to separate from VM. Differentiating MD from VM can be done through the patient's history or by means of vestibular function tests[56]. In VM the spells of vertigo can be anywhere from few minutes to over 24 h. Migraine is more likely the source of vertigo if there are associated features like photophobia, paresthesia, visual disturbances (scintillating lights, visual hallucinations). Meanwhile, patients with MD will eventually develop a progressive hearing loss. In VM while audiometric and vestibular test findings can be found, they are typically mild and do not fluctuate over time[52]. A recent study using VEMP separated MD from VM with a sensitivity of 90% and specificity of 70%[59]. Shepard suggests that if VM is likely, even though MD has not been ruled out, it is better to treat for migraine. Even in cases where both migraine and MD coexist, it is better to treat migraine first[52].

TREATMENTS

Dietary/salt restrictions

The typical first treatment option for an MD patient is a low salt diet consisting of sodium in the range of 1000 mg to 2000 mg per day[60,61]. Some patients with MD report that a salt binge seems to precede an acute episode of MD[61]. The purpose of the diet is to reduce endolymphatic pressure, due to the idea that a high-salt diet can influence the osmotic gradients in the inner ear to develop hydrops[61]. Some however have challenged the idea that a salt diet could affect the plasma sodium level or fluid dynamics in the inner ear. Sodium levels in endolymph have been found to be normal in animals with induced EH and patients from which endolymph were sampled. Thai-Van *et al*[62] suggests the alternative theory that a low sodium intake influences aldosterone secretion that may affect endolymph regulation.

There have been some reports that a low sodium diet associated with diuretics brings positive result[63,64]. However, the evidence in the literature to support low sodium diet as an effective treatment for MD has been lacking. A low salt diet can limit the patient's lifestyle and quality of life. This can often make it difficult to remain on the diet in the long-term[61].

Diuretics

Diuretics are relatively inexpensive and commonly used to treat MD[60]. The purposes of diuretics are to alter ion concentrations in order to reduce endolymphatic volume and pressure. Some have argued against the use of diuretics suggesting that there are too many active mechanisms and buffer systems in the inner ear for diuretics to be useful[65]. As previously noted, smaller studies have found that the use of diuretics with a low salt diet can be beneficial[63,64]. A recent Cochrane review found no evidence in support for or against the use of diuretics because of the lack of articles that meet accepted review standards[66]. Common side effects are weakness, dizziness and headache. Serious side effects are cardiac arrhythmias, hyperkalemia, renal failure and hypersensitivity[67]. Side effects are much more prevalent in the elderly population[68]. It is important to avoid drugs that increase serum potassium concentration and antiarrhythmic drugs because Dyazide can potentiate toxicity. In addition, Dyazide interacts with methotrexate, lithium, cyclophosphamide, pixantrone, and others[67]. Pirodda *et al*[65] suggests diuretics lower blood pressure, which can exaggerate a vasomotor response inducing local ischemia, which can lead to damage.

Betahistine

Betahistine is one of the most widely used drugs to treat MD, with 94% of surgeons prescribing it in the Europe and United Kingdom[60]. In addition to being an H1 agonist and an H3 antagonist, it is thought to promote blood flow into the cochlea through the stria vascularis by its suspected vasodilatory effects[69]. Several clinical trials have shown that Betahistine may in some way improve vertigo, nausea and vomiting[70-74]. However, long term, longitudinal, uncontrolled trials have failed to show a benefit on hearing loss[75,76]. A Cochrane review looking at 243 patients concluded that there is insufficient evidence for the effectiveness of betahistine[77]. Some suggest that it should not be considered the gold standard therapy for MD[78]. However, others suggest that Betahistine is a cheap drug with limited side effects and that if there is no improvement it should be withdrawn[68]. Common side effects are bronchospasms, asthma, drowsiness, lethargy, nausea, headache, eye and skin irritation, peptic ulcers due to its histamine-like activity, mild stomach discomfort[79-81]. However, systematic reviews still tend to underreport the side effects[82].

TT steroid

Steroids have been used to treat an autoimmune response, ischemia and sudden sensorineural hearing loss, all of which have made it a likely candidate for the treatment of MD[61,67,83]. Studies show that steroids can also have mineralocorticoid effects. Dexamethasone increases the principal epithelial sodium transporter of semicircular canals by threefold, possibly influencing the sodium and fluid dynamics in the inner ear[84].

An older study showed promising results, with 82% of patients having improved vertigo when treated with steroids compared to 57% treated with saline injections[85].

One trial showed that 91% of MD patients had adequate control with intratympanic dexamethasone injections and did not require more ablative treatments[86]. A recent review looking at 5 RCT's found that there is enough evidence to support the effectiveness of intratympanic steroid for treating vertigo[87]. There is a small risk of tympanic membrane perforation and middle ear inflammation[67].

TT gentamicin

Gentamicin is an aminoglycoside antibiotic that is used as an ablative treatment for MD. Although both vestibulotoxic and cochleotoxic, the drug has a high affinity for type 1 vestibular hair cells and therefore results in more vestibular damage than hearing loss[88]. Gentamicin is thought to operate by accumulating in hair cells and also interfering with calcium dependent receptors in the plasma membrane by competitive inhibition[89,90]. Aminoglycosides can also interfere with hair cell secondary cell messengers and the integrity of the cell membrane[91]. The drug is titrated to control vertigo symptoms, although some argue to titrate until there are signs of unilateral vestibular weakness. The main goal is to titrate just enough to get the most reduction of vertigo with the smallest reduction of hearing and balance. Titration of gentamicin until there is complete unilateral vestibular ablation is usually unnecessary and can result in worse hearing and balance outcomes[67].

Gentamicin has been shown to be an effective treatment for vertigo with minimal vestibular loss compared to ablative surgeries[87,92]. One RCT comparing intratympanic gentamicin to saline found a reduction of vertigo with an average reduction in hearing thresholds of only 8 dB[93]. Another RCT comparing intratympanic gentamicin to dexamethasone found greater control of vertigo with gentamicin, with minimal hearing damage[94]. Typically 54% of patients only require one injection and 96% do not need further ablative surgeries[95]. Clinical evidence shows that anatomic factors such as adhesions or bone dust can prevent drug uptake by blocking the round window. Middle ear exploration with exposure of the round window membrane and direct application of gentamicin is effective at controlling vertigo in 75% of gentamicin non-responders[96].

Resultant unilateral vestibular hypofunction can cause symptoms of imbalance with rapid ipsilateral head turns[97]. Hearing loss can occur in 17% to 25% of patients[98,99].

Meniett therapy

The Meniett device operates by adding positive pressure to the middle ear, which has shown to influence pressure in the inner ear[100]. This is a noninvasive procedure that involves a short-term ventilation tube and consists of a repeated 0.6-sec. pulse at a range of 0 to 20 cm H_2O at 6 Hz applied to the middle ear. The treatment consists of three to four cycles per day with each cycle lasting for 5 min[101]. It is thought that the pulses vibrate the round window aiding in endolymphatic turnover[67].

A 2014 meta-analysis looking at 12 studies including 2 RCTs found that the device improved short-term vertigo and some hearing[101]. A recent Cochrane review from 2015 looked at 5 RCTs and found that only one showed an improvement in vertigo with positive pressure therapy[102].

The Cochrane review found moderate quality evidence in two studies that hearing is worsened after use of the device[102]. The Meniett device is minimally invasive other than the associated risks of inserting a ventilation tube.

Endolymphatic sac surgery

The endolymphatic sac is an outpouching of the endolymphatic membrane in contact with the dura of the temporal bone[67]. It was originally thought to be involved in the resorption of endolymph but more recently was found to also have an immune function[103]. Endolymphatic sac surgery is aimed at shunting, draining or decompressing the sac, which is thought to prevent hydrops by facilitating outflow of endolymph[67]. Similar results have been noted in decompressing the sac *vs* shunting[104]. The most common shunting technique is the endolymphatic mastoid shunt which involves draining endolymph from the sac into the mastoid cavity[105]. A histological study looked at temporal bones after sac surgery and found that correct placement of the shunt had no relation to vertigo improvement[106]. Ghossaini *et al*[107] noted that in situations when the endolymphatic sac cannot be found, decompressing the surrounding dura gives positive results. Additionally, it is possible that removing the bone surrounding the endolymphatic sac could also lead to decompression[107].

Endolymphatic sac surgery, although invasive, is considered a conservative approach because it leaves the vestibular neuroepithelium and innervation intact. Unilateral MD patients with intractable vertigo and especially bilateral MD patients that do not respond to medical treatments are considered for endolymphatic surgery in order to avoid possible hearing loss with ablative treatments[107]. Some trials have found high rates of long-term improvement in vertigo with low risk of hearing loss[108,109]. Some studies report 55% to 85% hearing stabilization or improvement[110-112]. However, a Cochrane review in 2013 noted that 2 RCTs found no difference between treatment and placebo groups[113]. It should be noted that the low number of patients considered for surgery out of the already low number of patients unresponsive to medical treatment makes it difficult to obtain high-level evidence. Patients who had good primary results from endolymphatic surgery but experience recurrence of symptoms after a period of time can be considered for revision sac surgery. The idea is that iatrogenic osteogenesis and perisaccular fibrosis reestablishes the pathogenic

state by compromising endolymphatic drainage[114-116]. Huang[117] found that perisaccular fibrosis is linked with recurrence of symptoms after surgery. It has been shown that correctional surgery will provide symptom relief[114]. Some reports show that use of intraoperative mitomycin C to the endolymphatic sac area may prevent perisaccular fibrosis[117]. Endolymphatic sac surgery has a small risk to residual hearing, up to 2%[118]. Bleeding from the lateral sigmoid sinus and cerebrospinal fluid leak are other potential complications in endolymphatic sac surgery. Conductive hearing loss after endolymphatic sac surgery has been reported and is thought to be secondary to bone dust making its way to the middle ear[118].

Vestibular nerve section

The purpose of vestibular nerve section (VNS) is to treat vertigo by selectively cutting the vestibular portion of CN Ⅷ while preserving the cochlear portion. This surgery is usually the last option for clinicians when dealing with unilateral MD patients with hearing function that have exhausted all other medical and surgical treatments. Patients without hearing function would be considered for a labyrinthectomy. Patients with bilateral vestibular disease are not considered for a VNS because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss[107]. VNS can be accomplished through either retrosigmoid or retrolabyrinthine approach. The retrosigmoid approach requires a suboccipital craniotomy and the retrolabryinthine approach requires mastoidectomy. Both usually involve decompression of the internal auditory canal in order to identify and section the vestibular nerve. Care must be taken in order to avoid injuring the facial and cochlear nerve[67]. VNS is the most effective treatment for vertigo in MD[107]. Vertigo control rates between 78% and over 90% have been reported in the literature[119-124]. Possible reasons for failure are incomplete sectioning of the vestibular nerve in order to avoid injury to the cochlear nerve and inability to identify the vestibulocochlear cleavage plane[125]. Remaining or recurrent vertigo after surgery can be further treated by intratympanic gentamicin[107]. About 4% of patients experience significant hearing loss[124]. Other complications are facial nerve paralysis, cerebrospinal fluid leak, and headache[107].

Labyrinthectomy

Labyrinthectomy is a destructive treatment involving the removal of the neuroepithelium from the five vestibular organs. The treatment is typically the last resort for unilateral MD patients with severe hearing loss that do not respond to medical and surgical treatments. As was the case for VNS, bilateral MD is a contraindication because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss[107]. Several studies have shown excellent control of vertigo in up to 97% of patients[16,126,127]. There is a 2% risk of facial nerve injury and a 3% risk of CSF leak[128].

CONCLUSION

The pathophysiology of MD is still unclear and controversial, however EH represents the hallmark histological finding in postmortem temporal bone studies of patients. More than likely, it represents the end point of various causes. As we become more experienced with evaluating these patients it is necessary to fine tune the diagnostic criteria for improved communication and improve the reporting of research data across specialties. The new international consensus on diagnostic criteria is an important step towards this.

The diagnosis of MD can be difficult and many commonly used tests are poor screening tools. More specific diagnostic methods are needed to fine-tune the diagnosis and to help differentiate MD from Migraine associated vertigo. Recently MRI for identifying EH has gained popularity.

Finally, new and less invasive and destructive treatments of MD are available with the introduction of intratympanic treatments with steroids and gentamicin as well as the Meniett device.

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MINIREVIEWS

Management of intratemporal facial nerve schwannomas: The evolution of treatment paradigms from 2000-2015

Luv Makadia, Sarah E Mowry

Luv Makadia, Sarah E Mowry, Department of Otolaryngology, Georgia Regents University, Augusta, GA 30907, Untied States

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Correspondence to: Sarah E Mowry, MD, Department of Otolaryngology, Georgia Regents University, 1120 15th Street, Augusta, GA 30907, Untied States. smowry@gru.edu
Telephone: +1-706-7216100
Fax: +1-706-7210112

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Abstract

Intratemporal facial nerve schwannoma (FNS) are rare benign tumors of the skull base. Many of these tumors will be detected during evaluation for symptoms suggestive of vestibular schwannoma. However, there are several signs and symptoms which can suggest the facial nerve as the origin of the tumor. Intratemporal FNS can be multiple, like "beads on a string", or solitary lesions of the internal auditory canal. This variable tumor morphology necessitates multiple treatment options to allow patients the best chance of preservation of facial nerve function. Historically FNS were managed with resection of the nerve with cable grafting. However this leaves the patient with permanent facial weakness and asymmetry. Currently most patients find this outcome unacceptable, especially when they present with good to normal facial nerve function. Facial paralysis has a significantly negative impact on quality life, so treatment regimens that spare facial nerve function have been used in patients who present with moderate to good facial nerve function. Nerve sparing options include tumor debulking, decompression of the bony facial canal, radiosurgery, and observation. The choice of management depends on the degree of facial nerve dysfunction at presentation, hearing status in the affected ear, medical comorbidities and patient preference. Each treatment option will be discussed in detail and suggestions for patient management will be presented.

Key words: Facial nerve schwannoma; Middle cranial fossa; Intratemporal; Translabyrinthine; Stereotactic radiosurgery; Cable graft; Tumor stripping; Facial nerve decompression

Core tip: The management of intratemporal facial nerve schwannoma (FNS) has changed over the past 15 years. Current management strategies involve tumor stripping, bony decompression, radiosurgery, and observation. Each of these treatment options are designed to minimize the risk of injury to a functional facial nerve. Complete surgical excision and cable grafting are reserved for tumors which have already resulted in severe facial weakness. Each management strategy will be discussed in detail with a management algorithm will be presented. Intratemporal FNS are unusual benign tumors affecting the facial nerve as it passes through the bony canal of the temporal bone. Previous management paradigms involved complete resection of

the tumor and nerve with simultaneous cable grafting; however, patients were left with long term facial paresis. Newer treatment strategies resulting in less facial nerve morbidity have become more popular in the last 15 years including: Surgical debulking, stereotactic radiosurgery, bony decompression and observation. Each of these strategies will be discussed with emphasis on facial nerve outcomes and tumor control rates.

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INTRODUCTION

Facial nerve schwannoma (FNS) are rare benign tumors which can affect any part of the facial nerve (FN). Classically these tumors were treated with complete tumor resection and cable grafting of the residual nerve. However within the last 15 years the emphasis on preservation of FN function has become paramount. Various treatment modalities are available to this end: Observation, radiosurgery, debulking/tumor stripping surgery, or decompression of the facial canal. Physicians who manage these patients must understand the risks and benefits of the different treatment approaches and to understand their efficacy in managing FNS patients.

ANATOMY

The FN, cranial nerve Ⅶ, has a complex anatomy and path. The FN can be divided into four segments: The brainstem nucleus and tracts, cisternal segment, intratemporal segment, and peripheral segment. The FN nucleus comprises the motor component whereas the nucleus ambuugus is the first order synapse for the sensory division of the nervus intermedius which runs with the main trunk of the FN. The cisternal segment begins as the nerve exits the brainstem and ends as the nerve enters the internal auditory canal (IAC). This segment has no epineurium. The intratemporal segment begins at the porus acousticus and travels through the bony facial canal to end at the stylomastoid foramen. The intratemporal nerve can be divided into 5 discrete segments: Fundal (IAC), labyrinthine, geniculate ganglion, tympanic and descending (mastoid) segments (Figure 1). The peripheral segment refers to the nerve as it exits the stylomastoid foramen and continues on to the face, where it innervates muscles of facial expression[1].

DIAGNOSIS

Tumors involving the intratemporal FN can be challenging to identify preoperatively. These tumors may have several symptoms in common with the more common vestibular schwannoma (VS) including sensorineural hearing loss, vertigo and imbalance, and tinnitus. While FN dysfunction is relatively uncommon in patients with VS (2%) this symptom is much more common in primary FN tumors. Symptoms suggesting possible FN origin also include lacrimal gland dysfunction and taste disturbance[2,3]. The classic motor symptoms for a FN tumor are recurrent FN weakness (frequently misdiagnosed as bell palsy), hemifacial spasm or slowly progressive facial weakness. These symptoms are not specific to FNS but common to all FN tumors including hemangioma.

However, many FN tumors do not present with FN dysfunction at all. It is common for the diagnosis of FNS to be made intra-operatively; this is particularly true for tumors limited to the CPA/IAC (2) (Figure 2A). As imaging technology has improved over time, it has become much easier to diagnose a FNS before going into surgery. High-resolution computer tomography (HRCT), magnetic resonance imaging (MRI), audiometry and vestibular testing, electroneurography, and electromyography became tools to help make the diagnosis[2,4]. Full discussion of the diagnostic modalities for the FNS is beyond the scope of this article and the reader is referred to other references for more in-depth discussions[5].

FNSs are classically described as a contrast enhancing mass in the course of the FN, on MR. On T1-contrast enhanced MRI, FNSs present as smoothly circumscribed fusiform enhancing mass along the intratemporal FN. Usually, intratemporal FNSs involve multiple segments of the FN and appear as "beads on a string" on MR[6] (Figure 2C).

Other distinct appearances of the FNS are seen along the various segments of the FN. Those limited to the cerebellopontine angle or IAC (CPA-IAC) are very hard to distinguish from VS. Occasionally a labyrinthine "tail", the schwannoma's extension into the labyrinthine segment of the FN canal, can be seen as an indication of a FNS rather than VS. A large CPA-IAC FNS may present with a "dumbbell" imaging appearance, due to the extension of the FNS from the IAC fundus to the labyrinthine segment and to the geniculate fossa[3]. FNSs centered in the geniculate fossa or those that extend along the greater superficial petrosal nerve present with a mass in the middle cranial fossa (MCF)[3] (Figure 2B). These lesions may enhance along the course of the nerve or be discrete, well-defined extradural lesions arising along the floor of the middle fossa. FNSs located in the tympanic segment often lobulate into the middle ear cavity[3]. FNSs arising from the mastoid segment may spread into nearby mastoid air cells, demonstrating unusual, irregular tumor margins as the tumor expands through the air cells along the pathways of least resistance. HRCT images of these lesions reveal a widening or even erosion of the bony canal[3] (Figure 2D).

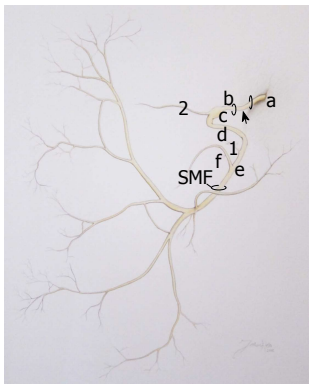

Figure 1 Line drawing of the facial nerve. The nerve takes a very tortuous course through the temporal bone within the Fallopian canal before exiting the skull base at the SMF. Any portion, intra or extratemporal, can be affected by a facial nerve schwannoma. a: Nerve as it exits the brainstem and crosses the cerebellopontine angle; b: Labyrinthine segment; c: Geniculate ganglion; d: Tympanic segment; e: Mastoid segment; f: Chorda tympani nerve; arrow: Intracanilicular segment. [1]Nerve to stapedius; [2]Greater superficial petrosal nerve. (Joshua M Klein, MSM I artist). SMF: Stylomastoid foramen.

HISTORICAL PERSPECTIVES

As the approach to medicine has changed over time, the goals of treatment have evolved. For many benign pathologies, medicine now focuses on maximizing the patients' quality of life (QOL), in addition to treating the disorder. This changing pattern is evident in the treatment patterns for intratemporal FNSs.

Complete surgical resection and grafting were very popular up until the mid-1990s[7]. Many physicians offer tumor resection with cable grafting if the patient presents with facial palsy and facial dysfunction, House-Brackmann (HB) Grade 4 or worse (Table 1)[8]. Grafting provides the possibility that some degree of function will resume, however, full symmetric facial function is never achievable.

Depending on the location of the tumor and the degree of hearing loss at the time of presentation, the surgical approach will vary[6,9]. For tumors involving the geniculate and more medially, the MCF or subtemporal approach is offered to the patients if the tumor does not extend significantly (less than 1.5 cm) into the CPA and the hearing is serviceable (hearing is defined as at least serviceable if it is either Class A or B on the AAO-HNS scale[10]) (Figure 3).

The MCF approach can be combined with a trans-mastoid approach for tumors involving larger portions of the nerve but with serviceable hearing. This combined approach allows for access to multiple segments of the nerve while maintaining the auditory apparatus. When hearing is non-serviceable a translabyrinthine approach is appropriate and can be used for any size or location of tumor[6]. This can be carried out using a nerve graft (greater auricular nerve, sural nerve or cadaveric donor cable graft) or through direct anastomosis[9,11]. Graft length has not been shown to correlate to the degree of facial function, but graft location has been shown to be a factor; the more proximal to the brainstem the first

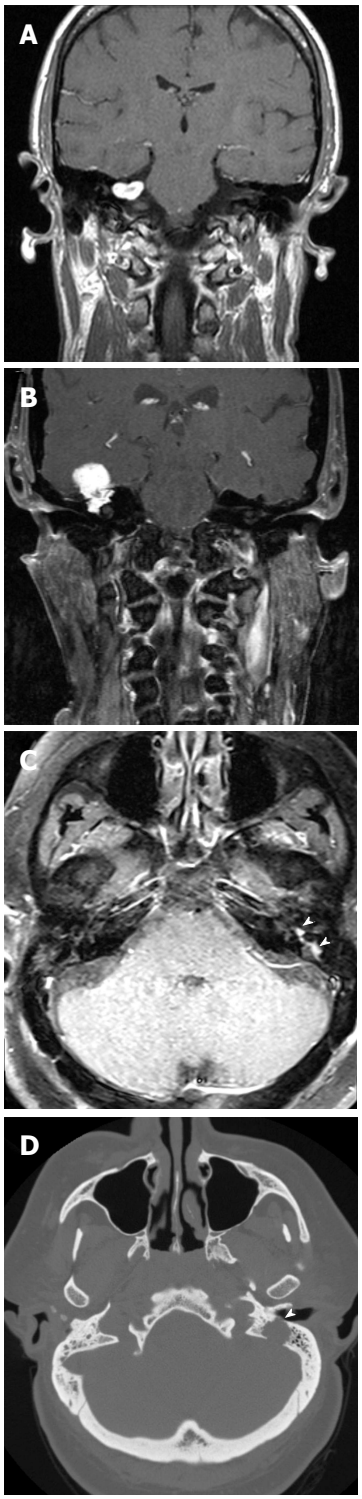

Figure 2 Radiographic images of facial nerve schwannoma. A: Contrasted coronal T1 weighted MRI of right intracanilicular FNS. The patient was presumed to have a vestibular schwannoma but the tumor arose from the FN. The patient underwent tumor debulking with HB grade 1 at follow-up; B: Contrasted T1 weighted coronal MRI of a large FNS arising from the geniculate ganglion with significant extension into the middle fossa and the middle ear. The patient underwent a translabryinthine resection with cable grafting; C: Post contrast axial T1 weighted MRI demonstrating a FNS involving multiple levels of the facial nerve. This is a typical appearance of the "beads on a string" pattern of tumor growth (arrrowheads); D: Axial bone window high resolution computer tomography of the temporal bone demonstrating a large FNS of the mastoid segment causing erosion of both the bony ear canal (arrowhead) and the posterior fossa plate. MRI: Magnetic resonance imaging; FNS: Facial nerve schwannoma; HB: House-Brackmann.

Table 1 The House-Brackmann Scale of facial nerve function (adapted from Ref. [8])

Grade	Description	Gross function	Resting appearance	Dynamic appearance
1	Normal	Normal	Normal	Normal
2	Mild dysfunction	Slight weakness with effort, may have mild synkinesis	Normal	Mild oral and forehead asymmetry; complete eye closure with minimal effort
3	Moderate dysfunction	Obvious asymmetry with movement, noticeable synkinesis or contracture	Normal	Mild oral asymmetry, complete eye closure with effort, slight forehead movement
4	Moderately severe dysfunction	Obvious asymmetry, disfiguring asymmetry	Normal	Asymmetrical mouth, incomplete eye closure, no forehead movement
5	Severe dysfunction	Barely perceptible movement	Asymmetric	Slight oral/nasal movement with effort, incomplete eye closure
6	Flaccid paralysis	None	Asymmetric	No movement

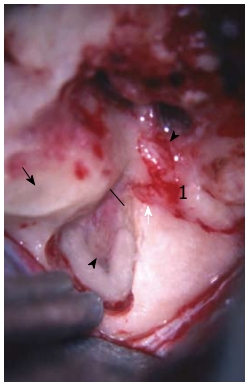

Figure 3 Intraoperative photograph of a left subtemporal/middle cranial fossa approach to the facial nerve. The middle fossa approach to the internal auditory canal is appropriate for decompression of the bony canal surrounding the nerve. Access to the upper tympanic segment (proximal to the cochleariform process) is achievable *via* this approach. [1]Geniculate ganglion. Solid line represents the entrance of the bony facial canal; Solid black arrow: Blue-line of superior semicircular canal; Black arrowhead: Fundus of the internal auditory canal decompressed; White arrow: Labyrinthine segment; White arrowhead: Tympanic segment.

neurorraphy is placed, the worse the FN outcome[6]. Pre-operative FN function is one predictor of ultimate FN function after grafting; those with better pre-operative function do better with grafting than those who present with poorer FN function and have a graft. In patients undergoing total tumor resection, tumor recurrence is not expected[6].

Many studies have shown the negative effects of facial paralysis on psychosocial function and QOL using evaluation tools such as the Glasgow Benefit Inventory, the short-form 36, the Derriford Appearance, the FaCE Scale, and the Facial Disability Index[12,13]. Facial paralysis affects QOL is by limiting the patient's ability to express emotion through facial motor movements, thus affecting their ability to form social relationships and have successful social interactions. This leads to feelings of social isolation[14]. Facial paralysis alters self-perception of facial appearance. People with a disfigured facial appearance are often looked at differently by society and valued less because they do not look "normal", affecting their ability to form relationships and affecting their psychosocial well-being[15]. Because QOL factors are more heavily considered in current treatment algorithms, management techniques that preserve FN function while still successfully managing the tumor may be preferred[7].

ALTERNATIVES TO TUMOR RESECTION

The main alternative management modalities for intratemporal FNSs are tumor debulking, bony decompression, stereotactic radiation, and observation.

Debulking

Debulking or stripping surgery refers to the removal of as much of the tumor as possible while leaving the main trunk of the FN intact[6,16]. The goal of a tumor debulking is to remove as much of the tumor mass as possible while maintaining the anatomic and functional integrity of the nerve. This surgical method can achieve near-total tumor removal. However, by definition, some of the tumor is left on the FN, which can result in tumor regrowth. Debulking surgery is carried out under high magnification microdissection between nerve fibers and the actual tumor. In some cases however, the nerve fibers are scattered in the tumor and thus not suitable for debulking; this cannot be determined until the tumor-nerve interface is assessed intraoperatively[6]. Continuous electromyographic FN monitoring is used during debulking. Short bursts of activity may be present but the microdissection is stopped if fibrillation potentials (trains) are produced[6]. The percentage of tumor removal is then estimated by the end of the operation and can also be assessed *via* volumetric analysis of post-operative MRI scans. As in tumor resection, an MCF or a TL approach can be used, taking into consideration the hearing factors previously mentioned.

Debulking surgery is generally a choice of treatment in patients that do not present with facial dysfunction[16]. This surgical technique can be very useful for tumors of the CPA/IAC, which are generally presumed to be VSs preoperatively. If a FNS is found intra-operatively instead of a VS, the physician may choose to debulk the FNS until fibrillation potentials are encountered, at which point they will leave the rest of the tumor on the nerve. Post-operative FN function is expected to be maintained

(a Grade 1 or 2 HB). In one study, the immediate and long-term postoperative FN function after debulking was evaluated. Out of 11 patients who underwent debulking, only 2 patients had worse than a HB score of 3 upon immediate post-operative evaluation. Results for the long-term follow-up were even better. Only one patient had a score of HB 3; all other patients scored HB 1 or 2[6]. However, patients should be informed of the risk of FN damage and functional decline. There is also a risk of regrowth, because a portion of the tumor is left on the nerve. Therefore, it is imperative to continue following the tumor with serial MRI imaging[6].

Surgical decompression

Bony decompression refers to the removal of the bony facial canal along the course of the FN to relieve the intrafascicular pressure created by the tumor[17-19]. Bony decompression should be considered as a first-line option in patients that are pre-operatively diagnosed with a facial schwannoma and present with normal facial function (HB 1 or 2) and small tumors[6,7,17]. Decompression is beneficial in that it preserves facial function, and may even improve facial function, while also preserving hearing ability[2,6,17-19]. However, because decompression does not treat the underlying tumor, risk of tumor growth does exist[13,17]. Therefore, it is important to continually monitor the tumor post-op using a serial MRI imaging[17]. Wilkinson *et al*[7] reported that in 78.9% of patients undergoing decompression, FN function either remained the same or improved. Furthermore, three patients (15.8%) in the decompression group showed improvement whereas only one patient (11.1%) in the observation group showed improvement. No patients had hearing loss[7].

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a less invasive approach in which external beam radiation is directed at the tumor while minimizing damage to surrounding tissue[20,21]. Ionizing radiation acts at the cellular level to causing DNA damage to the rapidly dividing cells. In rapidly dividing malignant cells, this results in apoptosis and tumor resolution. In benign, slowly growing tumors (such as FNS), SRS does not result in resolution of the tumor; however, tumor growth is controlled and the volume of the tumor may even be reduced over time[21]. Recent evidence suggests that schwannoma cells are relatively radioresistant and tumor control may be more related to radiation induced fibrosis of the tumor vasculature[22].

SRS is typically used for benign tumors less than 3.5 cm in size[20]. A major benefit of SRS is that pre-treatment FN function is preserved and in rare cases, may be improved[23-29]. SRS should only be used in tumors that are demonstrating growth on serial MRI. This may include residual tumors that remain after debulking surgery or partial resection[23,25,27,29].

Large series of FNSs alone are lacking due to the rarity of this lesion[23,27]. Some inferences about effectiveness and long-term effects of SRS for FNS can be taken from the body of literature for VS; however these VS data must be used with caution when counseling FNS patients. Hearing ability in patients undergoing SRS for VS seems to be maintained up to about 5 years post-treatment. However, evidence suggests that beginning 6 years after VS SRS, patients may experience hearing loss, especially in tumors limited to the IAC[23,27,28]. Another risk is potential damage to the FN resulting in worse FN function than pre-treatment levels[23,27,28].

Observation

Observation with serial imaging techniques is now becoming a popular first-line management choice for FNSs. Patients presenting with small FNSs and without facial dysfunction (present with HB 1 or 2) or other neurologic deficit can be followed with MRI, audiograms, and other imaging techniques[2,25,26,30]. This conservative approach may allow the patient to maintain their functional FN for a long period of time, up to 10 years, without having to intervene with a more destructive or invasive approach[25,26,30,31]. It is possible to take a conservative approach because of the slow-growing characteristic of these tumors, allowing the patient to avoid intervention for many years[4,25]. Observation with imaging should be maintained until facial function deteriorates (HB Grade 3 or worse), or the tumor grows significantly in size[2,4,25,26]. At this point, the physician should consider a more aggressive approach[2,4,25,26]. It has been shown that observation for a period of time before doing surgery does not result in worse outcomes, when compared to cases in which surgery was the initial treatment of choice[4]. Observation is especially recommended in elderly patients or those patients who have significant comorbidities[27]. Observation is not an appropriate choice for tumors causing significant brainstem deformation or compression[26].

TREATMENT RECOMMENDATIONS

Poor FN function (HB Ⅳ-Ⅵ) and poor hearing (AAO-HNS class C-D) at presentation a translabyrinthine resection with cable grafting is recommended; Poor FN function (HB Ⅳ-Ⅵ) and serviceable hearing (AAO-HNS class A-B) consider middle fossa ± transmastoid resection; Moderate facial function (HB Ⅲ) and serviceable hearing consider FN decompression *via* MCF and mastoid or consider observation; Good facial function (HB Ⅰ-Ⅱ) and serviceable hearing consider observation or FN decompression *via* MCF and mastoid; Poor surgical candidate or refuses surgery consider radiosurgery if growth demonstrated or observation.

CONCLUSION

In summary, there are currently many options for management of intratemporal facial schwannomas, and the modern practitioner should be familiar with these

various treatment options when counseling patients. A high index of suspicion for FNS will allow appropriate diagnosis and treatment when these patients do present. Non-surgical options are also appropriate management choices for a select group of patients. Good facial function and hearing preservation are possible with a number these surgical techniques.

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CASE REPORT

X-linked deafness: A review of clinical and radiological findings and current management strategies

Sonia Kumar, Thomas Mawby, Vanaja Sivapathasingam, Jane Humphries, James Ramsden

Sonia Kumar, Thomas Mawby, Vanaja Sivapathasingam, Jane Humphries, James Ramsden, ENT Department, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

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Correspondence to: Sonia Kumar, PhD, SpR Otolaryngology, ENT Department, John Radcliffe Hospital, Headley Road, Oxford OX3 9DU, United Kingdom. soniakumar111@googlemail.com
Telephone: +44-1865-741166

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Abstract

X-linked deafness is a rare genetic disorder causing a severe mixed hearing loss. This is due to an abnormal connection between the internal auditory meatus (IAM) and the basal turn of the cochlear leading to a "3rd window effect" and cochlear conductive hearing loss. Patients are traditionally treated with conventional hearing aids however these are often unsatisfactory. Cochlear implantation is a high-risk procedure in such cases due to the risk of inadvertent electrode placement in the IAM. We present three paediatric cases where the hearing loss was managed with a combination of a bone anchored hearing aid in combination with a conventional behind the ear hearing aid. We also present a review of the current literature regarding the management of X-linked deafness.

Key words: X-linked deafness; Bone anchored hearing aid; 3rd window; Cochlear implantation; Paediatric; Conductive hearing loss; Sensori-neural hearing loss

Core tip: X-linked deafness is a rare genetic disorder causing a severe mixed hearing loss. This is due to an abnormal connection between the internal auditory meatus (IAM) and the basal turn of the cochlear leading to a "3rd window effect" and cochlear conductive hearing loss. Patients are traditionally treated with conventional hearing aids however these are often unsatisfactory. Cochlear implantation is a high-risk procedure in such cases due to the risk of inadvertent electrode placement in the IAM.

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INTRODUCTION

X linked deafness (DFXN3) is a rare genetic disorder associated with a mutation on the *POU3F4* gene on the

Xq21 chromosome. Due to its X-linked recessive pattern of inheritance, male patients present with a severe hearing loss whilst female patients may present with normal to mild hearing loss[1]. Patient's present with a mixed progressive hearing loss at a young age, delayed speech and subsequent educational difficulties. They are traditionally treated with conventional hearing aids.

The hearing loss associated with X-linked deafness can be explained by the well-recognised inner ear abnormalities identified. Most notably there is widening of the fundus of the internal auditory meatus (IAM) bilaterally with dilatation of the internal auditory canal. This was first described in the early 1990s across seven pedigrees of patients[2]. In addition there is also an absence of the bony partition between the fundus of the IAM and the basal turn of the cochlear. Abnormalities of the bony modioli, vestibular aqueduct and facial nerve canals have also been described with female patients displaying milder abnormalities compared with the males.

The abnormal connection between the IAM and the basal turn of cochlear acts as a 3rd window and therefore causes both a cochlear conductive loss as well as a progressive profound sensorineural hearing loss. Clinically there is also an association with stapes fixation adding to the conductive component of the hearing loss[1].

The abnormal connection between the CSF filled subararachnoid spaces and the perilymphatic space of the cochlear represents a high risk for surgery such as stapedectomy. This abnormal communication leads to an increased perimlymphatic pressure which in turn leads to perilymph gushing or a "stapes gusher" which is well documented during mobilization of the stapedial footplate[3]. It was suggested therefore that X-linked deafness was an absolute contraindication to stapes surgery due to the risk of gushing[4]. The increased perilymphatic pressure also causes progressive cochlear damage and therefore a progressive sensorineural hearing loss.

Cochlear implantation is a recognized treatment for patients with profound X-linked sensorineural deafness. However there is a risk in such patients of inadvertent electrode placement within the IAM due to the abnormal connection between the basal turn and the IAM. There are several reports of CSF leak during cochleostomy and in some cases minimal auditory benefit[5]. Repeat implantation following wrongful electrode insertion, although possible, is a difficult procedure with many risks including injury to the labarynthine artery[6] and image guided insertion may be useful tool in the future[7].

CASE REPORT

Case 1

An 11-year-old boy from Bulgaria was referred for a cochlear implant assessment when he moved to the United Kingdom. He became deaf as a baby shortly after gentamicin treatment for meningitis at the age of 1. His parents declined a cochlear implant aged 3 and he subsequently learnt to sign, attended mainstream school and wore bilateral behind-the-ear (BTE) hearing aids. As he grew older his communication became more limited and he was only able to repeat 9% of the AB word list when he used both hearing aids. His audiogram is presented below (Figure 1). His air conduction threshold demonstrated a severe to profound loss whilst his bone conduction threshold confirmed a moderate hearing loss. A CT scan showed a wide connection between the IAM and the basal turn of the cochlear and genetic testing confirmed a mutation in the *POU3F4* gene. The patient was fitted with a right bone anchored hearing aid (BAHA), which he wears alongside his BTE hearing aids.

Case 2

TB was referred to the cochlear implant clinic aged 2 years and 10 mo. His hearing loss was identified through the newborn hearing screen and he had been managed with hearing aids. However his thresholds had deteriorated significantly over the last few months. His speech was significantly delayed. There was no family history of hearing loss. His audiogram demonstrated a down-sloping mild to moderate sensorineural loss and an up-sloping conductive loss (Figure 1). The CT scan showed an outpouching in the area of the vestibular aqueduct and a wide connection between the IAM and the basal turn of the cochlear. There was also evidence of fixation of the malleus hear to the anterior attic wall bilaterally. An examination under anaesthetic of the right ear revealed mobile ossicles and therefore TB was fitted with a left BAHA. The BAHA in combination with bilateral BTE hearing aids allowed TB's speech and conversational language to progress.

Case 3

AP is a 7-year-old boy whose hearing loss was identified aged 2 when he lived in India. He was initially treated with conventional hearing aids and a diagnosis of Mondinis malformation of the cochlear was made. Over time he was noted to have a mixed hearing loss and a drop in his low frequency air conduction thresholds (Figure 1). A review of the imaging he underwent in India as a baby has shown the typical appearances of X-linked deafness and he is currently undergoing genetic testing confirmed mutations in *POU3F4* gene alongside his younger brother who also has a hearing loss. He was fitted with a BAHA to use with his conventional hearing aids.

DISCUSSION

In our three cases we have successfully managed the hearing in these patients with a combination of a BAHA alongside a conventional BTE avoiding the complications of implant surgery (Figure 2). Our series of patients all demonstrated a progressive drop in low frequency air conduction thresholds. BAHAs have the advantage of aiding the low frequency thresholds where conventional air conduction aids may fail. In conjunction

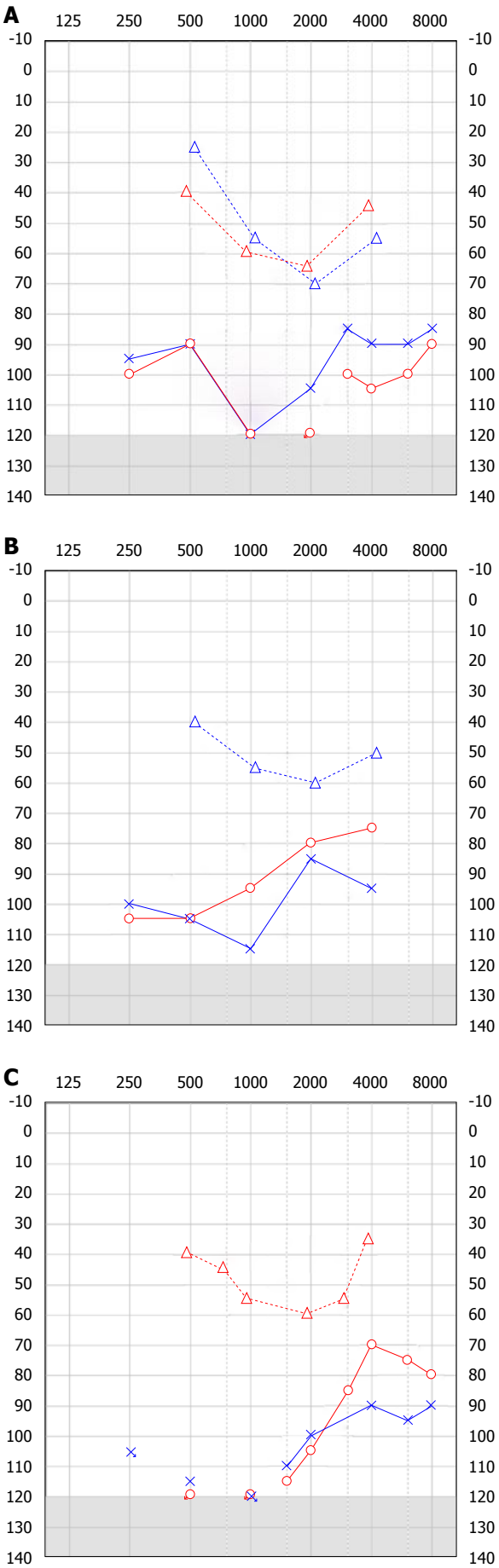

Figure 1 Pure tone audiograms of patients with X-linked deafness pre-operatively.

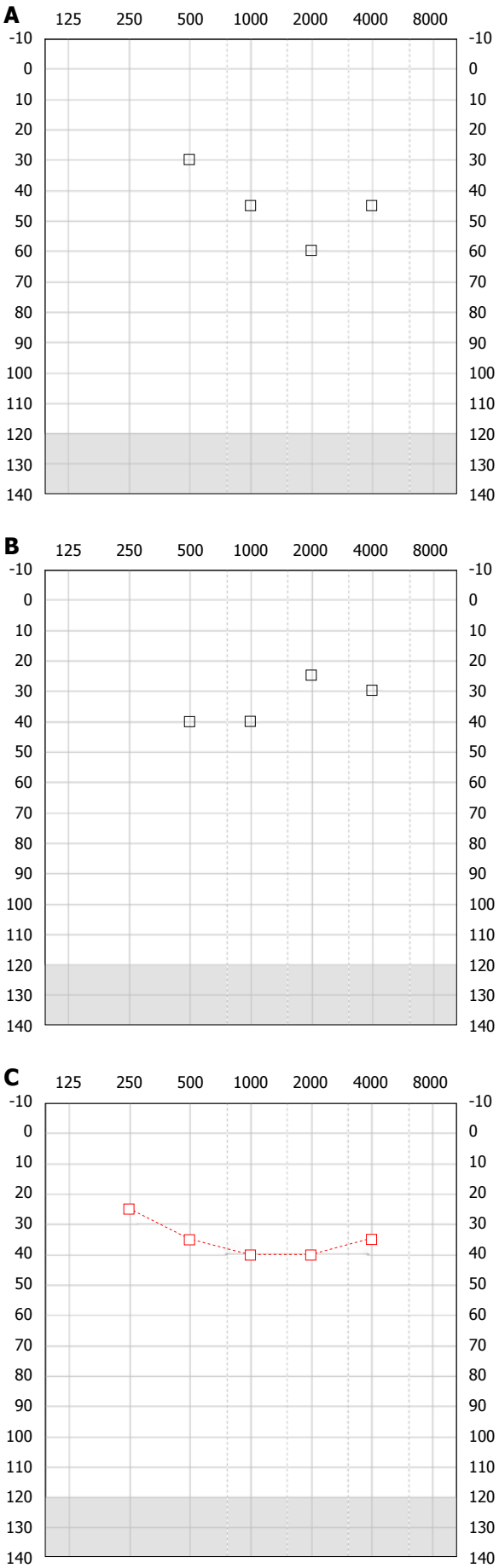

Figure 2 Aided audiograms of patients (bone anchored hearing aid and behind the ear hearing aids in combination).

with a conventional aid for the high frequency loss our patients have reported good outcomes as stated by parents and school. The bone conduction thresholds in our patients were within the limits at which a BAHA is considered beneficial and even our third patients, AP, whose threshold were borderline, had some perceived auditory benefit. BAHA is a safe, quick and well-tolerated procedure and is licensed in the United Kingdom in children aged 5 and over. Those patients that are younger may use the device on a softband.

COMMENTS

Case characteristics

An 11-year-old boy from Bulgaria was referred for a cochlear implant assessment when he moved to the United Kingdom; AP is a 7-year-old boy whose hearing loss was identified aged 2 when he lived in India.

Clinical diagnosis

As he grew older his communication became more limited and he was only able to repeat 9% of the AB word list when he used both hearing aids; over time he was noted to have a mixed hearing loss and a drop in his low frequency air conduction thresholds.

Differential diagnosis

The hearing loss associated with X-linked deafness can be explained by the well-recognised inner ear abnormalities identified.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

The computed tomography scan showed an outpouching in the area of the vestibular aqueduct and a wide connection between the internal auditory meatus and the basal turn of the cochlear.

Pathological diagnosis

Bone anchored hearing aids have the advantage of aiding the low frequency thresholds where conventional air conduction aids may fail. In conjunction with a conventional aid for the high frequency loss the patients have reported good outcomes as stated by parents and school.

Treatment

Cochlear implantation is a recognized treatment for patients with profound X-linked sensorineural deafness.

Related reports

There are several reports of CSF leak during cochleostomy[5] and in some cases minimal auditory benefit[5].

Experiences and lessons

Repeat implantation following wrongful electrode insertion, although possible, is a difficult procedure with many risks including injury to the labarynthine artery[6] and image guided insertion may be useful tool in the future[7].

Peer-review

The paper is well written.

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EDITOR-IN-CHIEF
Steven J Wang, MD, FACS, Associate Professor in Residence, Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, 2233 Post St, 3rd Floor-Box 1225, San Francisco, CA 94115, United States

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World Journal of Otorhinolaryngology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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MINIREVIEWS

Positron-emission tomography/computed tomography imaging in head and neck oncology: An update

Viet D Nguyen, Bundhit Tantiwongkosi, Wyatt J Weinheimer, Frank R Miller

Viet D Nguyen, Department of Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, United States

Bundhit Tantiwongkosi, Division of Neuroradiology, Department of Radiology and Otolaryngology Head Neck Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, United States

Wyatt J Weinheimer, Frank R Miller, Department of Otolaryngology Head Neck Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, United States

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Correspondence to: Viet D Nguyen, MD, Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mail Code 7800, San Antonio, TX 78229, United States. nguyenvd@uthscsa.edu
Telephone: +1-210-5675535

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Abstract

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI, especially in detection of carcinoma of unknown primary, cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management. PET/CT biomarker may further provide an overall assessment of tumor aggressiveness with prognostic implications. As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, the aim of this article is to review the roles of PET/CT in both pre- and post-treatment management of HNSCC and PET-derived parameters as prognostic indicators.

Key words: Positron emission tomography; Staging; Diagnosis; Computed tomography; Head and neck cancer; Management of squamous cell carcinoma; Carcinoma of unknown primary; Second primary malignancy; Surveillance; Recurrence; Prognosis

Core tip: In the pre-treatment phase, positron-emission tomography/computed tomography (PET/CT) is valuable in the evaluation of patients with carcinoma of unknown primary origin, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment

phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

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INTRODUCTION

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). The incidence of head and neck cancer in the United States is approximately 3% of all new cancer cases, accounting for almost 60000 cases each year and 12000 deaths from the disease[1]. Tobacco and alcohol abuse, human papillomavirus (for oropharyngeal cancers), and Esptein-Barr virus infection (for nasopharyngeal cancers) are important risk factors for the development of head and neck cancers. Patient's presentation and clinical findings are occasionally nonspecific and can vary depending on the tumor location in the head and neck. Some of these cancers may escape detection despite detailed physical examination, endoscopy and conventional cross sectional imaging, and pose significant challenges in disease diagnosis and management. Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and ^{18}F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI in select situations, such as detection of carcinoma of unknown primary (CUP), cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management[2-5]. Furthermore, PET/CT as an imaging biomarker may provide an overall assessment of tumor aggressiveness with prognostic implications.

With PET/CT imaging, injected positron-emitting radionuclide ^{18}F-FDG is taken up by metabolically active cells, particularly cancers, in different concentrations depending on their relative metabolic rates. The radionuclide is initially transported into cells through glucose transporters with the same mechanism as for glucose but cannot be further metabolized. PET images are then created by detecting emissions from ^{18}F-FDG and reconstructed into a three-dimensional image. CT images are also generated sequentially and coregistered with PET images using fusion software, enabling functional data obtained on PET to be coupled with anatomical CT images. Quantification of FDG uptake is simplified by measurement of the standardized uptake value (SUV), which represents the activity of ^{18}F-FDG measured over a certain interval after radionuclide injection and normalized to its dose and the patient's body weight[6].

Since the implementation of PET/CT in head and neck oncology over a decade ago with its approval for reimbursement by the Centers for Medicare and Medicaid Services[7], PET/CT has provided high diagnostic accuracy. PET/CT remains especially valuable in detection of regional and distant metastases and evaluation of treatment response. As more patients are cured of their cancers, acute and long-term complications of multimodality approaches including surgery, radiation, and chemotherapy may alter the anatomy and physiology of the head and neck, posing significant challenge in assessing treatment response and detecting residual or recurrent tumor by clinical evaluation and conventional imaging techniques such as CT or MRI. PET/CT may prove helpful with treatment strategy in these patients as well as those with metastatic cervical lymphadenopathy of unknown primary site despite thorough workup.

As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, this article addresses the roles of PET/CT in both pre- and post-treatment management of HNSCC. PET-derived parameters as prognostic indicators are also discussed.

PRE-TREATMENT EVALUATION

Proper staging of the head and neck cancer, regional lymph nodes and detection of distant metastasis is critical for developing optimal treatment and determining prognosis. The tumor node metastasis (TNM) staging system of the American Joint Committee on Cancer, 7th edition is used to stage HNSCC[8]. The extent of the primary tumor (T stage) is site specific, while there is considerable overlap in classifying regional lymph node involvement (N0 to N3 stage) with the exception of thyroid and nasopharyngeal cancers. Metastasis outside head neck regions (*e.g.*, mediastinal and axillary lymph nodes) represents distant metastasis (M stage). Initial evaluation and staging include a combination of physical examination, imaging studies, and direct endoscopy with tissue biopsy or fine needle aspiration.

Imaging exams such as contrast-enhanced CT, MRI and PET/CT are important to assess the extent of local extension, involvement of lymph nodes, and presence of distant metastasis. Multiple studies suggest that PET/CT is superior to conventional imaging (CT or MRI) in initial staging and may alter management, especially when unexpected cervical lymph node or distant metastasis is discovered[2-5]. A multicenter prospective study found that PET/CT improved the TNM staging of the primary cancer

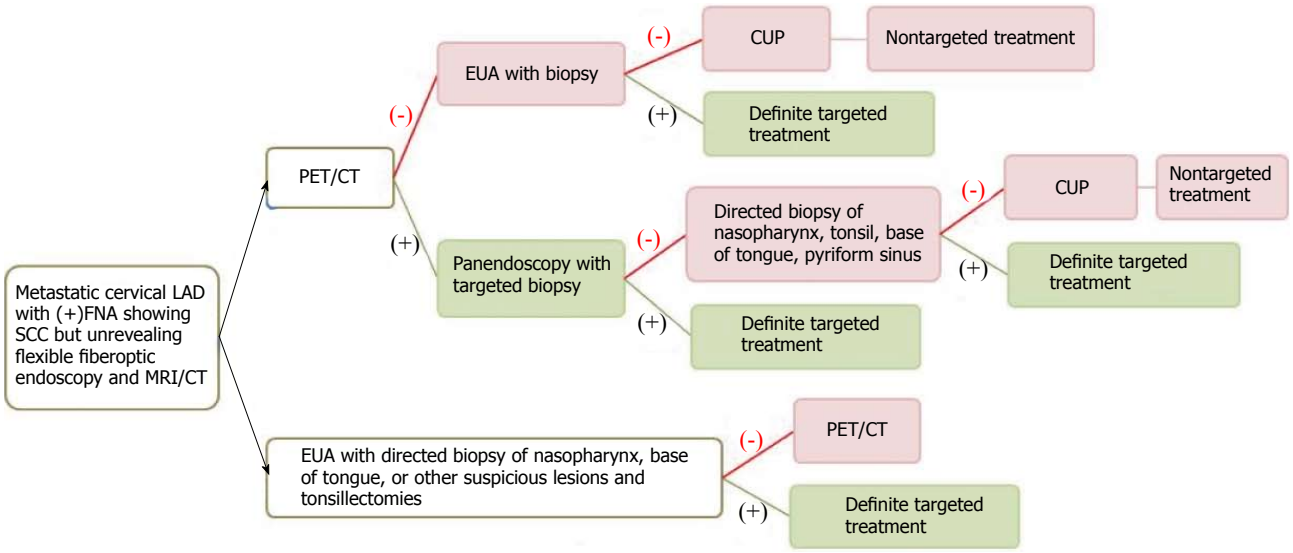

Figure 1 Algorithm in diagnosis and management of carcinoma of unknown primary. LAD: Lymphadenopathy; FNA: Fine-needle aspiration; SCC: Squamous cell carcinoma; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; EUA: Examination under anesthesia; CUP: Carcinoma of unknown primary.

and subsequently altered the management in 13.7% of the patients, mainly due to the ability of PET/CT to detect metastatic or additional disease[9]. Furthermore, PET/CT can provide accurate tumor localization with precise metabolic tumor volumetric measurements, cervical lymph node staging, detection of metastases, and finding of synchronous second primary tumors that may alter radiation fields and doses for patients undergoing radiation therapy. The National Comprehensive Cancer Network issued an update in clinical practice guidelines in head and neck cancer and PET/CT imaging in 2013, recommending the use of PET/CT in initial staging of the oral cavity, oropharyngeal, hypopharyngeal, glottic, and supraglottic cancers for stage Ⅲ-Ⅳ disease as well as mucosal melanoma and nasopharyngeal carcinoma (World Health Organization class 2-3 and N2-3 diseases)[10].

The CT portion of the PET/CT examination provides the superior contrast and spatial resolution to detect malignant tumor using morphology (such as ill-defined, infiltrative, ulcerative features), enhancement, and interval growth. The PET portion demonstrates semiquantitative assessment with SUV of malignant tumor typically greater than 2.5-3.0[11]. Similarly, a maximum SUV greater than 2.5 is 100% sensitive and a maximum SUV greater than 5.5 is 100% specific for malignant lymphadenopathy[12]. However, SUV assessment should be used in conjunction with other clinical data given the overlap between a malignant lesion (high SUV) and a benign inflammatory uptake (low SUV).

Despite the proven efficacy of PET/CT, false negatives of PET/CT may be seen in patients with occult nodal metastases less than 5 mm or metastatic lymph nodes with necrosis[13-15]. Cancers with low metabolic activity or decreased FDG uptake may also limit PET/CT sensitivity. Therefore, PET/CT does not have the sensitivity to replace neck dissection and its usefulness is uncertain in evaluating patients with clinically negative (N0) neck[16]. In addition, the utility of PET/CT in determining the resectability of head and neck cancers has not been fully explored to date; CT or MRI remains the mainstay in these patients[17].

Additional limitations unique to PET/CT include imaging artifacts, lower osseous and soft tissue contrast/resolution (when performed without intravenous contrast) as compared to contrast-enhanced CT and MRI, respectively. PET typically has a resolution of 5 mm[11], while unenhanced CT and MRI have submillimeter resolution[18]. The addition of intravenous contrast to CT and MR enhances visibility of the lesions and enable separation of the lesions from adjacent vessels. In this regard, contrast-enhanced CT and MRI are superior imaging modalities for evaluating T stage of HNSCC. There is currently no clear recommendation for routine use of PET/CT in initial T staging, as several studies demonstrated 5.5%-8.5% of patients had T staging upstaged on PET/CT[2,5].

CUP

Three to five percent of HNSCC patients present with metastatic cervical lymphadenopathy without definite primary site detected[2,19,20] despite a thorough history (often with nonspecific symptoms or no symptoms), combination of physical examination with office flexible fiberoptic endoscopy (for small submucosal lesion), or conventional contrast-enhanced CT/MRI performed. The work up algorithm to search for the primary tumor is shown in Figure 1, adapted from Tantiwongkosi *et al*[21] and Schmalbach *et al*[22].

The choice of treatment depends on staging and histology[23]. With locoregionally advanced cervical lymphadenopathy, the goal of treatment is generally directed at cure; whereas, cervical lymphadenopathy from unknown primary originating below the clavicles may represent incurable disease with distant metastasis. Failure to identify the primary tumor leads to nontargeted treatment (bilateral tonsillectomies, bilateral neck dissection, radiation to cover

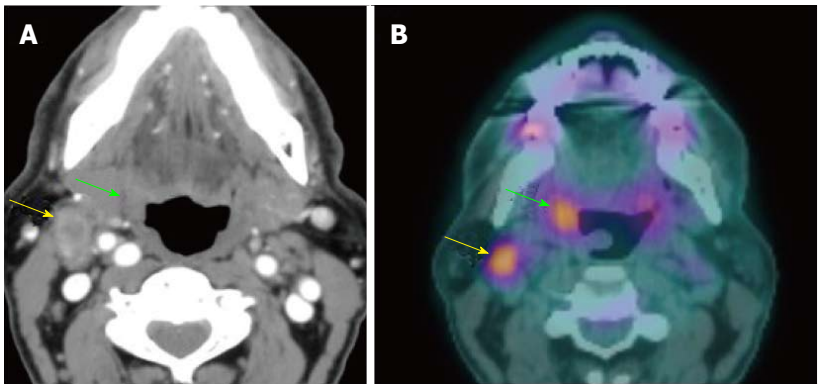

Figure 2 Occult squamous cell carcinoma of the right palatine tonsil. The lesion (green arrow) was not appreciated on physical examination, flexible endoscopy and contrast-enhanced CT (A), but demonstrated hypermetabolic activity on PET/CT with maximal SUV: 3.5 (B). Biopsy directed by PET/CT revealed squamous cell carcinoma of the right palatine tonsil. The right level IIA lymphadenopathy also showed increased FDG uptake (yellow arrow). The patient remained disease free for 5 years after treatment. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value; FDG: 2-fluoro-2-deoxy-D-glucose.

the whole pharyngeal mucosa and neck)[24] resulting in increased complications, morbidity and mortality.

Several studies support the efficacy of PET/CT in detection of primary cancers in patients with CUP (Figure 2). PET/CT is able to identify the primary cancer in approximately 29% to 54% of cases (62%-93% sensitivity, 33%-93% specificity, 56%-89% positive predictive value and 25%-96% negative predictive value)[2,25-31]. A high detection rate of up to 54% can be achieved when the combination of CT, MRI, endoscopy under anesthesia and PET/CT are used. Generally, PET/CT is sensitive and superior for characterizing deep or metastatic cancers, while panendoscopy is more accurate for evaluating smaller or superficial mucosal lesions.

PET/CT is typically performed before panendoscopy to guide the selection of biopsy sites and to avoid erroneous interpretation due to high false positivity (as much as 50%)[29] of FDG uptake at sites manipulated during endoscopy. It is still uncertain when PET/CT should be performed after biopsy; therefore, if carcinoma of unknown primary is suspected, it is best to obtain PET/CT prior to endoscopy and biopsy/tonsillectomy. Over 90% of the unknown primary cancers are squamous cell carcinoma found in Waldeyer's ring (lymphoid tissue of the nasopharynx, palatine tonsils or base of tongue)[22,32]. Due to variable negative predictive value (25%-96%) of PET/CT, panendoscopy with directed biopsies and bilateral tonsillectomies are considered when PET/CT yields negative result[3]. Pattani *et al*[33] suggest careful selection of patients for panendoscopy after a negative PET/CT since primary cancer was only found in 9% of CUP cases (1 out of 11 patients).

Second primary malignancy

HNSCC patients are at increased risk for the development of second primary malignancy (SPM), with synchronous SPM occurring within 6 mo of the index primary cancer or metachronous SPM diagnosed > 6 mo of the index cancer. Approximately 1.4% to 18% of head neck cancer patients have SPMs[34], especially when the index cancers are laryngeal carcinomas. The risk for SPMs remains elevated for at least 10 years[35] and are mostly found in the head and neck, lung and esophagus[36] with the vast majority being squamous cell carcinoma[37]. Since SPM is the second leading cause of non-HNSCC death[38], early detection and treatment of SPM may alter management and improve patient survival[34]. A meta-analysis revealed 87.5% sensitivity and 95% specificity of PET/CT in detection of SPM or distant metastasis, while a negative PET/CT study does not completely exclude the presence of SPM[39]. Given the low incidence of synchronous SPMs at initial evaluation of HNSCC patient, several research studies question the cost-effectiveness of panendoscopy[8]. Therefore, PET/CT may complement or replace panendoscopy in detecting synchronous SPMs. For patients with localized disease (stage Ⅰ or Ⅱ) being treated with either primary surgery or definitive chemoradiation therapy, a thorough physical examination combined with PET/CT may be adequate, obviating the need for panendoscopy unless tissue biopsy under general anesthesia is deemed necessary.

POST-TREATMENT EVALUATION

Therapy response assessment and residual tumor detection

Localized disease (stage Ⅰ or Ⅱ) comprising approximately 30% to 40% of HNSCC is generally treated with either primary surgery or definitive radiation therapy[40]. Locoregionally advanced disease (stage Ⅲ, ⅣA, or ⅣB) associated with high risk of local recurrence and distant metastasis requires a multidisciplinary approach, given the complexity and complications of combined treatment modality that includes surgery, radiation therapy and chemotherapy[41]. In select cases, radical concurrent chemoradiation can be used as a definite therapy in preference to surgery to achieve similar cure rates with preserved functional outcome and less morbidity[42].

For patients with locoregionally advanced disease who have undergone treatment, management of residual abnormalities can pose significant challenge. Both surgery and radiation may cause inflammation, fibrosis and distortion of the head and neck anatomy leading to difficulties of interpretation with conventional imaging, especially differentiating between residual cancer and complete response[43,44]. Inaccurate post-treatment assessment may result in delayed or unnecessary treatment and increased mortality and morbidity. In this regard, multiple studies have shown that PET/CT is superior to conventional anatomic imaging in assessment of tumor response and detection of residual tumor[3,45-47].

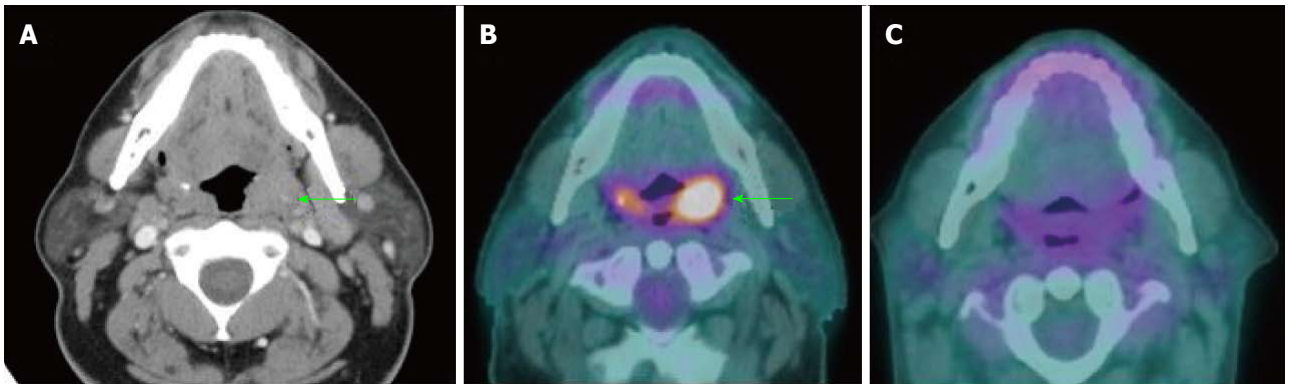

Figure 3 Complete treatment response at primary tumor site. Squamous cell carcinoma of the left palatine tonsil (arrows) was seen on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 11.6. The tumor was no longer hypermetabolic on PET/CT with maximal SUV: 2.8 at 10 wk after treatment (C). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

The sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT for detection of residual primary tumor have been reported as high as 94%, 82%, 75% and 95%, respectively[3]. It is important to note the very high negative predictive value of PET/CT: A negative study highly suggests absence of viable residual disease in both primary site and neck (Figures 3 and 4). The low positive predictive value is due to treatment-related FDG-avid inflammation or infection. A positive PET/CT study in the post-treatment phase needs careful correlation with clinical information and corresponding CT/MRI findings[48]. It is suggested that PET/CT should be performed no sooner than 2 mo after completion of treatment to evaluate for residual tumor while avoiding false positive results and to establish a baseline; however, it may be performed sooner if there is clinically suspected recurrent disease[49]. We generally recommend performing PET/CT around 3 mo after completion of treatment at our institution (Figure 5).

Long-term surveillance and recurrent tumor identification

Patients with complete treatment response, as documented clinically and by structural imaging (CT, MRI, and PET/CT), are generally observed. With advanced chemoradiation therapy, and improving surgical techniques, many patients may have distant metastasis as the first and only sign of treatment failure. PET/CT as a surveillance tool serves the purpose of detecting early recurrent disease, assessing for a metachronous second primary tumor, and excluding interval development of distant metastases. Close interval follow up in the first two to four years following treatment is necessary since 80% to 90% of all recurrences occur within this timeframe[50,51]; while the risk of SPM is higher than recurrence beyond three years[52,53].

PET/CT has 93%-100% sensitivity and 63%-94% specificity in detection of recurrent tumor in both primary site and the neck, respectively[48,54,55] (Figure 6). The negative predictive value of a single PET/CT and double PET/CT (obtained within 6-mo period) are 91% and 98%, respectively. Negative results of two consecutive PET/CT studies could potentially eliminate the need for routine post-treatment imaging if there is no clinical suspicion of tumor recurrence[56]. In addition, there are no differences in survival between PET/CT detected and clinically detected recurrence[57]. Although there is an appreciable radiation dose and lifetime cancer risk associated with PET/CT, the use of this examination is warranted when utilized in the appropriate clinical setting[58].

Metachronous second primary tumor may occur after 6 mo of the index primary tumor with 2.8% annual rate[59]. The incidence of distant metastasis following definitive treatment is 9% with the risk increased in patients with locally advanced stages[59,60] (Figure 7). Overall 17.9% of HNSCC patients develop second primary cancers or distant metastasis, especially in patients with recurrent disease[39,60]. The identification of distant metastatic lesions at the time of restaging recurrent tumors may obviate aggressive surgery while focusing on palliative chemoradiation options[60]. Therefore, PET/CT has strong utility in detecting second primary tumors or distant metastases with high sensitivity and specificity[39].

PROGNOSIS

As an invaluable tool in staging cancers of the head and neck, PET/CT imaging provides metabolic and functional data that may serve as quantifiable prognostic factors. The PET-derived parameters, SUV and its various forms, have been shown correlating well with glucose metabolism rate in various cancers, including HNSCC[61], and are useful in predicting tumor aggressiveness and long-term survival of patients[62]. They have also been used in selecting treatment modality and personalizing treatments. In a study comparing resectable, advanced HNSCC patients treated with surgery followed by chemoradiation therapy *vs* those with chemoradiation and salvage surgery, Roh *et al*[63] found that patients with high FDG uptake and treated with surgery first had better disease-free survival (DFS). In addition, Inokuchi *et al*[64] found that high FDG uptake

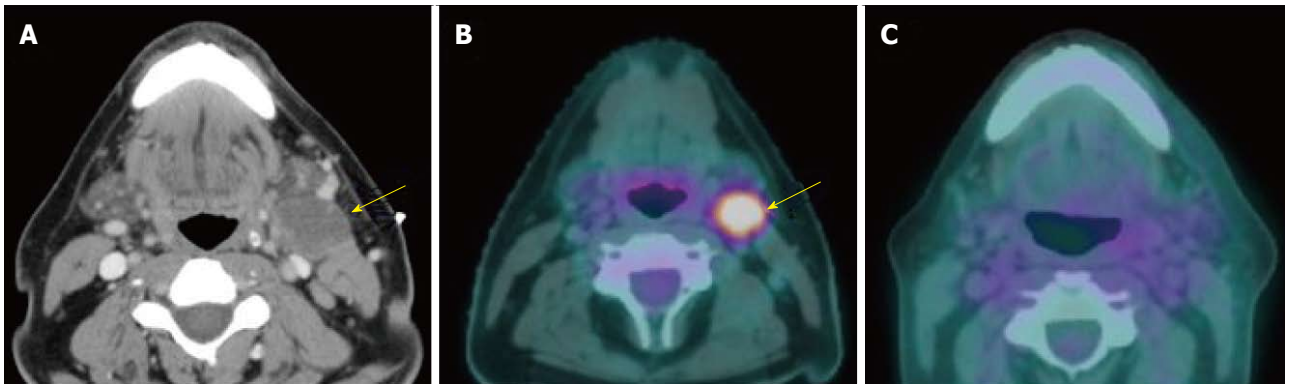

Figure 4 Complete response of metastatic cervical lymph node. Left level IIa metastatic lymphadenopathy (arrows) from the same patient in Figure 3 with squamous cell carcinoma of the left palatine tonsil was identified on both contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 12.1. After treatment, the lymph node was no longer hypermetabolic at 10-wk PET/CT (C) with maximal SUV: 2.5, representing complete response. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

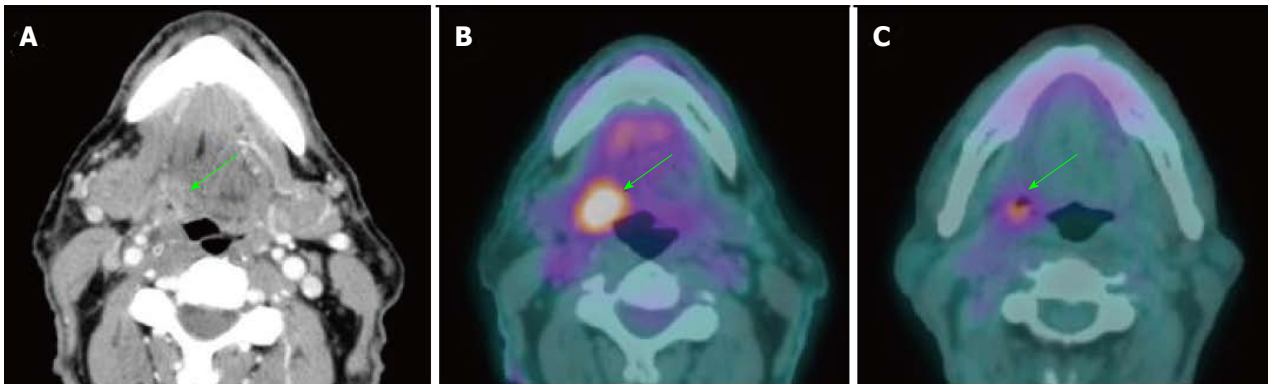

Figure 5 Residual primary tumor. Squamous cell carcinoma of the right base of tongue (arrows) was identified on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 10.2. The tumor remained FDG-avid on PET/CT (C) with maximal SUV: 4.8 at 12 wk after treatment, representing residual disease. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

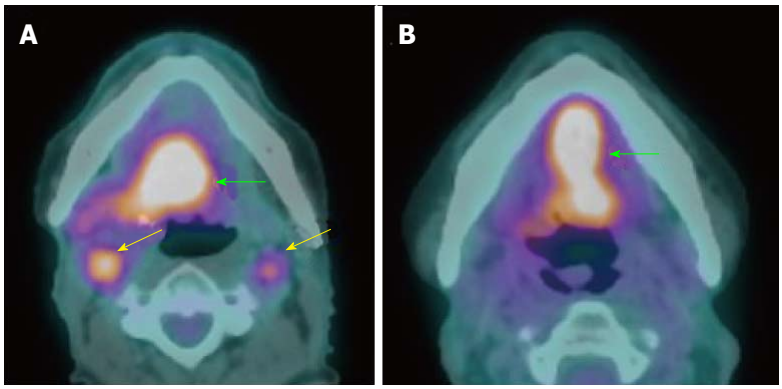

Figure 6 Recurrent primary tumor detected by positron-emission tomography/computed tomography. Squamous cell carcinoma of the base of tongue (green arrows) with bilateral level IIa metastatic lymphadenopathy (yellow arrows) was identified on pre-treatment PET/CT with maximal SUV: 13.2 (A). The tumor remained intensely hypermetabolic on PET/CT with maximal SUV: 6 at 13 mo after treatment (B). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

in HNSCC patients treated with definitive chemoradiation predicted a decrease DFS, nodal progression-free survival, and distant metastasis-free survival. The investigators also suggested using pre-treatment FDG uptake of cervical lymph nodes to select patients for planned neck dissection. They found that patients with high FDG uptake and treated with planned neck dissection had better nodal progression-free survival.

Metabolic tumor volume (MTV), a SUV-based parameter representing the tumor volume that has SUV above a specific threshold, has been suggested in the literature as a robust measure in predicting treatment outcomes. For example, clinical trials are underway to explore if patients with human papillomavirus (HPV)-associated oropharyngeal cancers, which are known to have better prognosis than those not associated with HPV, would have similar cancer control with less intensified and therefore less toxic treatment options[65]. It has been suggested that this patient population could be stratified further based on MTV. Patients with more aggressive HPV-related HNSCC, as suggested

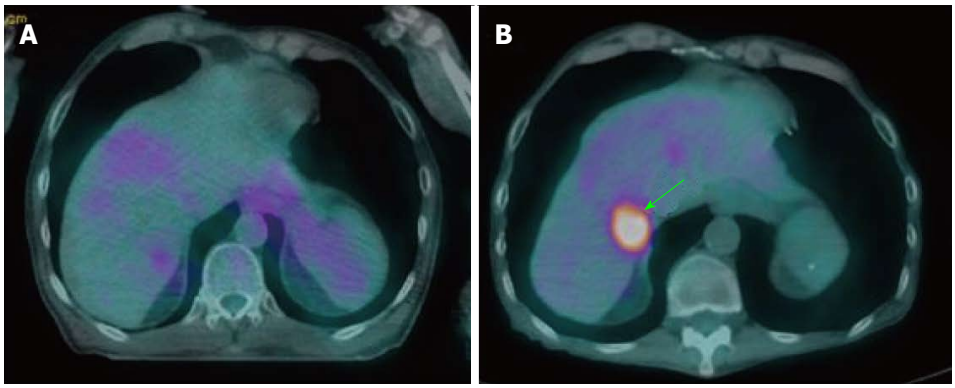

Figure 7 Failure of treatment due to distant metastasis. A: Pre-treatment PET/CT of the patient with squamous cell carcinoma of the base of tongue in Figure 6 did not reveal any increased FDG uptake in the liver; B: PET/CT performed at 13 mo after treatment showed new hepatic metastasis (arrow), representing treatment failure. PET/CT: Positron-emission tomography/computed tomography; FDG: 2-fluoro-2-deoxy-D-glucose.

by the increased MTV, had significantly poorer outcomes in one study conducted by Tang *et al*[66]. In addition to MTV, total lesion glycolysis (TLG) was first introduced by Larson *et al*[67]. It is the product of mean SUV and MTV, combining the volumetric and metabolic information of PET/CT to evaluate treatment response. Recent studies demonstrate the usefulness of TLG for evaluating head and neck cancers, with high TLG correlating to increased risk of adverse events or death[62,68,69].

The PET-derived parameters are also currently used in combination with other prognostic factors. N-stage, T-stage, and pre-treatment SUV of lymph node when used in combination have been shown better at predicting distant metastasis-free survival than individual factors[70]. Recently, there has been increased interest in identifying prognostic molecular biomarkers. Moeller *et al*[71] incorporated HPV status in addition to post-treatment FDG uptake in their mortality risk assessment. In addition conventional parameters (SUV, MTV, TLG, tumor volume, and diameter) in PET/CT, textural parameters to assess tumor heterogeneity such as coefficient of variation, skewness, and kurtosis may also provide prognostic information but are not fully explored in head and neck oncology.

CONCLUSION

With wide-spread availability and use, PET/CT imaging maintains an important role in head and neck oncology. In the pre-treatment phase, PET/CT is valuable in the evaluation of patients with carcinoma of unknown primary origin before panendoscopy and biopsy, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

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MINIREVIEWS

Embryology of the nose: The evo-devo concept

Roger Jankowski, Samuel Márquez

Roger Jankowski, Service ORL et Chirurgie Cervico-Faciale, Centre Hospitalier Régional Universitaire, 54500 Vandoeuvre les Nancy, France

Roger Jankowski, Faculté de Médecine, Université de Lorraine, 54500 Vandoeuvre les Nancy, France

Samuel Márquez, Departments of Cell Biology and Otolaryngology, SUNY Downstate Medical Center, Brooklyn, NY 11203, United States

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Correspondence to: Roger Jankowski, MD, PhD, Professor, Service ORL et Chirurgie Cervico-Faciale, Centre Hospitalier Régional Universitaire, Bâtiment Louis Mathieu, Allée du Morvan, 54500 Vandoeuvre les Nancy,
France. r.jankowski@chu-nancy.fr
Telephone: +33-3-83155402

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Abstract

Aim was to gather relevant knowledge in evolution and development to find a rational explanation for the intricate and elaborate anatomy of the nose. According to classic embryology, the philtrum of the upper lip, nasal dorsum, septum and primary palate develop from the intermaxillary process, and the lateral walls of the nasal pyramid from the lateral nasal processes. The palatal shelves, which are outgrowths of the maxillary processes, form the secondary palate. The median nasal septum develops inferiorly from the roof of the nasal cavity. These valuable embryologic data do not explain the complex intricacy of the many anatomical structures comprising the nose. The evo-devo theory offers a rational explanation to this complex anatomy. Phylogenically, the nose develops as an olfactory organ in fish before becoming respiratory in tetrapods. During development, infolding of the olfactory placodes occurs, bringing the medial olfactory processes to form the septolateral cartilage while the lateral olfactory processes form the alar cartilages. The olfactory fascia units these cartilages to the olfactory mucosa, that stays separated from brain by the cartilaginous olfactory capsule (the ethmoid bone forerunner). Phylogenically, the respiratory nose develops between mouth and olfactory nose by rearrangement of the dermal bones of the secondary palate, which appears in early tetrapods. During development, the palatal shelves develop into the palatine processes of the maxillary bones, and with the vomer, palatine, pterygoid and inferior turbinate bones form the walls of the nasal cavity after regression of the transverse lamina. Applying the evolutionary developmental biology (evo-devo) discipline on our present knowledge of development, anatomy and physiology of the nose, significantly expands and places this knowledge in proper perspective. The clinicopathologies of nasal polyposis, for example, occurs specifically in the ethmoid labyrinth or, woodworker's adenocarcinomas, occurring only in the olfactory cleft can now be explained by employing the evo-devo approach. A full understanding of the evo-devo discipline, as it pertains to head and neck anatomy, has profound implications to the otolaryngologist empowering his skills and abilities, and ultimately translating in improving surgical outcomes and maximizing patient care.

Key words: Nose; Evo-devo; Embryology; Development; Anatomy

Core tip: The intricate and elaborate anatomy of the human nose can be best understood by gathering knowledge in evolution and development. Phylogenically and ontogenically, the nose results from two distinct entities: The olfactory and respiratory organ. In vertebrates, the olfactory placodes give rise to the fibrocartilaginous nose made of alar and septolateral cartilages, olfactory mucosa and the olfactory fascia; the respiratory nose develops by evolutionary remodeling of the palatal bones under the olfactory nose. In humans, the mammalian olfactory chambers are transformed into olfactory clefts and lateral masses of the ethmoid, and the transverse lamina separating the olfactory and respiratory noses has disappeared.

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INTRODUCTION

Embryology of the nose is poorly described in classical textbooks, in which full of gaps and controversies are found about the different embryologic origins of the nasal bones, cartilages and soft tissue envelopes.

Embryology of the face is, in fact, a very difficult topic, which becomes more understandable in the evo-devo concept[1]. The evo-devo theory links the evolution from simple species to complex human development[2,3].

CLASSIC EMBRYOLOGY

In classic embryology textbooks[4,5], the first 28 day of gestational life the face develops from five swellings: The paired maxillary and mandibular processes and the unpaired frontonasal process.

During the fifth week, the nasal placodes (*i.e.*, nasal discs and nasal plates) develop as a result of ectodermal thickenings and can be observed on the frontonasal process.

In the sixth week, infolding of the ectoderm at the epicenter of these nasal placodes initiates the formation of an oval pit (see below description of nasal pits) resulting in the division of the raised edge of each placode into medial and lateral nasal processes (Figure 1A).

During the sixth week, the medial nasal processes fuse to form the intermaxillary process (Figure 1B), which is the primordia of the septum and bridge of the nose (Figure 1C).

By the end of the seventh week, there is a lateral and inferior expansion of the medial nasal processes at their inferior tips before fusing to form the anterior roof of the oral cavity (Figure 1B). As the poles of the maxillary swellings continue to develop they come into contact with the intermaxillary process where they fuse with each other. On the superior labial region, the intermaxillary process develops into the philtrum (Figure 1C). Formation of the nasal passages result as the nasal pits deepen penetrating its underlying mesenchyme during week 6 of development. Mesenchyme is loosely organized cells derived from mesodermal embryonic tissue that develops into connective and skeletal tissues. An ectodermally enlarged nasal sac is formed during the last days of the sixth week by the fusion of the deep endings of the nasal pits, which are topographically located superoposterior to the intermaxillary process. During the last days of the sixth week and the first few days of the seventh week, a proliferation of cells occurs at the posterior wall and floor of the nasal sac forming a thickened plate-like fin of ectoderm origin essentially isolating the oral cavity from the nasal sac but still maintaining an epithelial continuity between the regions. This "keel" structure is now referred to as the nasal fin. The nasal sac enlarges as a result of vacuoles developing within the nasal fin and then it fuses with the sac. The nasal fin begins to attenuate to a thin membrane named the oronasal membrane, which demarcates the oral cavity from the nasal sac. Towards the end of the seventh week, the oronasal membrane obliterates creating the opening of the primitive choana. Formation of the nasal cavity floor, or primary palate, occurs by the backward growing of the intermaxillary process.

Throughout the eighth and ninth week, the development of the definitive and secondary palate occurs. The main portion of the definitive palate develops by two shelve-like outgrowths from the maxillary processes. These two thin medial extension outgrowths are called the palatine shelves, which appear during the sixth week of development. While these shelves are directed in a downward manner on either side of the tongue, it is during the ninth week where these shelves rotate and ascend rapidly attaining a horizontal position above the tongue. Fusion of the primary palate and the palatine shelves (along the midline) assists in the formation of the secondary palate (Figure 1D). The order of fusion first begins at the ventral region of the palatine shelves before proceeding dorsally.

Mesenchymal condensations occurs when previously dispersed mesenchymal cells come together to differentiate into a single tissue type and is considered the critical transitional stage that precedes cartilage formation during embryonic development[6]. When these mesenchymal cell condensations occur in the ventral region of the secondary palate endochondral ossification ensues to achieve the formation the hard palate. At the dorsal region of the secondary palate, myogenic mesenchymal cells come together to form the muscular layer of the soft palate.

During the formation of the secondary palate, there is a proliferation of cells from the mesoderm and ectoderm region of the medial nasal and frontonasal processes that help form the nasal septum along its midline. As a result,

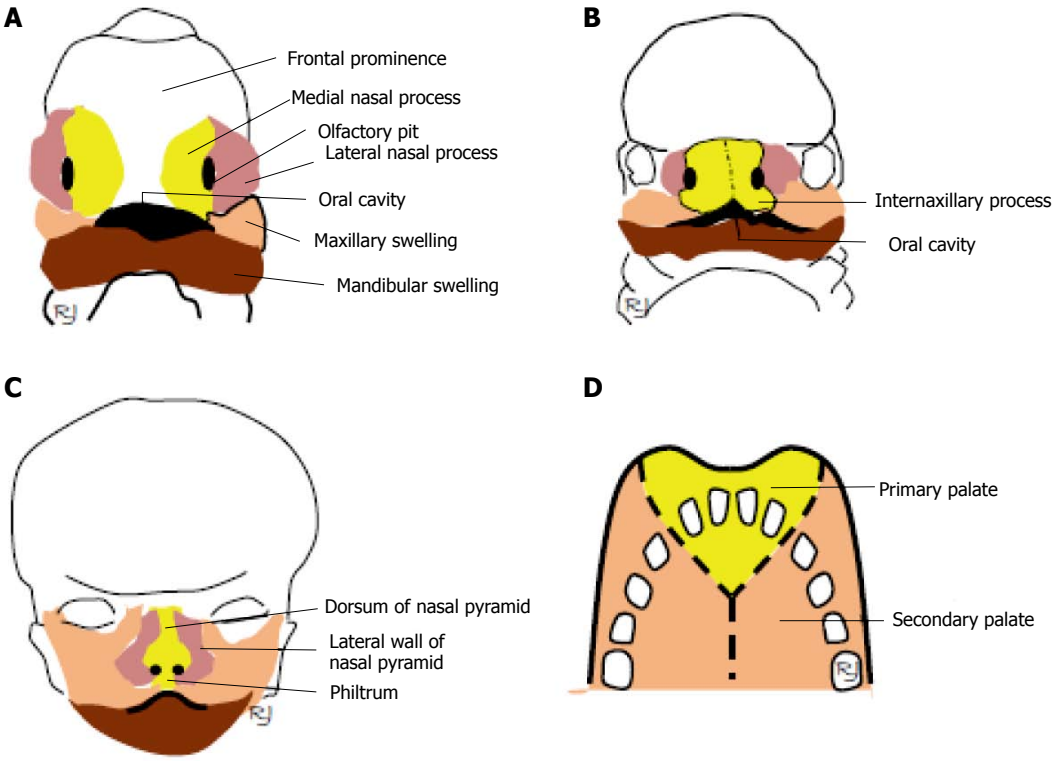

Figure 1 Classic embryology of the nose. A: Formation of the medial and lateral processes of the nose on the raised rim of the olfactory placodes; B: Formation of the intermaxillary process by fusion of the medial nasal processes; C: The intermaxillary process is seen as the primordium of the bridge and septum of the nose and the lateral nasal processes as the primordia of the lateral walls of the nasal pyramid; D: The intermaxillary process is seen as the primordium of the primary palate.

the two nasal passages of the nasal cavity have now been established, communicating with the pharynx located posterior to the secondary palate. This communicating portal is now termed the definitive choana.

According to classical concept, the philtrum of upper lip, the nasal dorsum, septum, and primary palate originate from the development of the intermaxillary process, whereas the lateral walls of the nasal pyramid develop from the lateral nasal processes (Figure 1A-C).

Two major questions which can be addressed to this classic description are why the nose is formed by such a complex intricacy of different anatomical structures, and why the origin and formation of these are not found in the classic embryological description. Examining the formation of the nose in the evolution of species may, actually, give clues to the answers[1].

THE NOSE IN EVOLUTION

The first vertebrates were jawless fish named agnathans who are classified in the phylum Chordata and sub-phylum Vertebrata and whose fossil ancestors can be traced back to the Cambrian period around 500 million years ago.

Living agnathans display a primitive or rudimentary olfactory organ. This organ consists of a median blind duct that communicates with the environment by means of an external nostril, but there is no posterior opening into the pharynx. The olfactory mucosa lies at the blind end in a chamber of the anterior braincase and is connected to the brain through olfactory filaments.

Lungfish played a critical role when organisms shifted from an aquatic mode of life to a terrestrial setting representing one of the most dynamic major adaptive shifts during the course of evolution. It was von Bischoff who first described the presence of choanae in lungfishes in 1840 as he considered these organisms excellent models for examining respiratory morphology of early tetrapods (*i.e.*, a four-footed organism) as they appeared intermediate in morphology between amphibians and fishes[7].

The anatomy of lungfish shows that the olfactory passages open posteriorly in the oral region and into the respiratory portion of the organism. These posterior communicating pathways, however, were in all likelihood not used for the purposes of respiration but rather to increase the power of olfaction. The buccopharyngeal pump passes forceful currents of water between the nasal and oral regions as these fishes perform suction feeding and may perhaps serve as the mechanism by which they increase their olfactory sense.

When the first tetrapods arrived, which includes all vertebrates higher than fishes (*e.g.*, amphibians, reptiles, *etc.*) one can appreciate the remarkable morphological diversity seen in body form of later tetrapods allowing them to utilized an equally broad array of terrestrial ecological niches.

In amphibians, their ability to smell is derived from the superficial oscillatory movements of their buccal floor in order to establish intimate contact to their immediate

surroundings be it a terrestrial or aquatic medium. The nasal respiratory function, however, is secondary as skin respiration is predominant. Amphibians, as a result, recruited the olfactory organ, as an intermittent tool for its respiratory apparatus.

Thus, with the amphibians the primary olfactory nose has evolved towards a nose devoted to olfaction and respiration. The amphibian nose communicates externally *via* the external naris and connects with the oral cavity posteriorly to the primary palate by the internal naris. The nasal cavity of amphibians is lined by olfactory epithelium with the exception of its ventro-lateral wall region.

Rocek and Vesely[8] reported on the larval development of the South American toad (*i.e.*, *Pipa pipa*) showing that the anterior skeletal portion of the amphibian snout is already formed by the following cartilaginous structures. First, a cartilaginous septolateral unit whose outgrowths occurs laterally from a "cartilago oblica" emanating from the "planum internasale"; and two, the distinct formation of a pair of "cartilago alaris". The latter two assemblies appear to be persistent and continuous with the posterior end of the cartilaginous skeleton thereby essentially protecting its olfactory chambers.

In the early fully terrestrial tetrapods, a transverse sheet of dermal bones has developed inferior to the braincase specifically in the roof of the mouth posterior to the internal naris and primary palate (Figure 2A). This dermal portion of the secondary palate consists of four paired bones: The vomer, palatine, ectopterygoid and pterygoid bones, which lie as a flat sheet between the two maxillary bones. Each internal nostril is bounded by the premaxilla of the primary palate anteriorly, the maxilla laterally, the vomer medially, and the palatine bone posteriorly[9]. This secondary hard palate configuration was probably the precursor in allowing permanent breathing to travel through the primary nose as inspiratory air would travel through a non-collapsible oral cavity before going to the trachea.

The reptilian vertebrate representative, the crocodilians, exhibit many of the above characteristics as does the mammalian condition, which also shares this bauplan suggesting convergent evolution taking place. Tracking the phylogenic history of the crocodilian, which spans over two-hundred million years, one can observe its akinetic skull features including the formation of its secondary nose.

Crocodilian evolution has been characterized by the gradual constitution of an akinetic skull and the formation of a secondary nose. Simultaneously with many modifications and reconfigurations of its palatal bones a secondary bony nasal passageway progressively develops, permitting inspiratory airflow to enter through its external naris and exit posteriorly through the internal naris or choana, which gradually shifted posteriorly until they were completely contained by the pterygoid bones.

Current hypotheses state that the evolution of feeding behaviors may have been the driver for the structural modifications of the crocodilian rostrum: The displacement and remodeling of the bones configuring the crocodilian secondary palate, which may initially have occurred reinforce the snout and skull instead of providing a physical bony partition between the oral and nasal cavities. As a result, the secondary nose could be regarded as an incidental byproduct of the masticatory mechanical forces between the dermal bones of the secondary palate and the skull base. The vacuities that were then occupied with air from the primary nose, were finally recruited to provide for the physiological function of breathing.

The fundamental configuration of the nasal fossa is a highly conserved region. As one tracks the evolution from crocodilian to the mammalian skull, very little change can be observed in this region with its persistent and constant morphology seen in a great majority of mammalian groups.

In mammalian groups, the palate separates the nasal and oral cavities: Primary, secondary, and soft palate. The primary internal naris remains as a vestigial opening, *i.e.*, the anterior palatine canal, which is topographically positioned between primary and secondary palate.

The primary nose fully opens behind a virtual, coronal plane through the anterior palatine canal, into both the respiratory and olfactory noses. Respiratory and olfactory noses are separated from each other by the transverse lamina, a thin, bony axial structure. Thus, the respiratory nose appears as two paramedian, long axial channels walled in on the inferior, lateral and medial sides by the reconfiguration of the primary palatal bones (vomer, palatine, pterygoid, and inferior turbinate bones) between the two maxillary bones and their palatine processes, and partitioned from the olfactory nose through the transverse lamina. The olfactory nose is completely embedded in the anterior cranial base, that is, the ethmoid bone[10].

The living primates (which include humans) are taxonomically classified in two suborders: *Strepsirrhini* and *Haplorhini*, the latter group includes our human ancestors[11]. Through the course of primate evolution, profound changes in the nasal fossa allow one to differentiate the haplorhines from strepsirrhines and all other mammals.

The word haplorhine means "dry nose" whereas strepsirrhine means "wet nose". As a result, strepsirrhine primates exhibit wet noses similarly to dogs and cats. Haplorhine primates have a fused frontal bone suture as well as a fused mandibular symphysis. While both haplorhine and strepsirrhine primates have a complete orbital ring of bone, only the haplorhine exhibit a complete bony enclosure posteriorly separating the periorbital contents from the temporalis muscle as it traverses through the infratemporal fossa on its way to attaching the coronoid process of the mandible[12]. The superior portion of the haplorhine nasal fossa is constricted by the orbital cones, which come about from the combined effect of orbital convergence and orbital frontation. Orbital convergence refers to the extent to which the orbital opening faces anteriorly improving stereoscopic vision that include the element of depth perception[13].

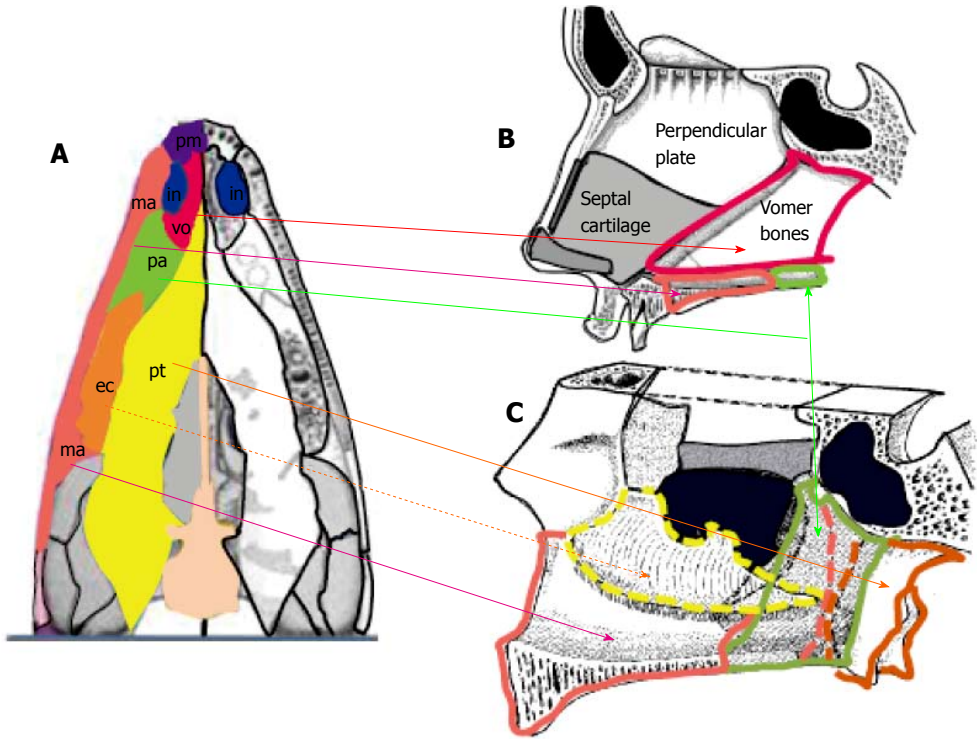

Figure 2 Evo-devo origin of the respiratory nose. A: The palatal bones in the tetrapods (in: Internal naris; pm: Premaxilla; ma: Maxilla; vo: Vomer; pa: Palatine; pt: Pterygoid; ec: Ectopterygoid); B: Anatomy of the nasal septum in human (perpendicular plate of ethmoid and septal cartilage form the septum of the olfactory nose); C: Anatomy of the nasal lateral wall in human (ethmoid bone removed).

Orbital frontation refers to what extent the superior and inferior margins are to the plane of the orbital opening so that more "frontated" organisms tend to view from the orbital socket more horizontally rather than superiorly[13]. In most haplorhines, there is a considerable reduction of their snout length when compared to strepsirrhines. There is one more important anatomical distinction between these two subOrders of primates that resides within the nasal fossa and that is an absence of a transverse lamina in haplorhines, which translates in them not having a bony partition separating the respiratory and olfactory region within the nasal cavity proper.

Strepsirrhines, on the other hand, exhibit a partitioned respiratory and olfactory region within the nasal cavity by possessing a transverse lamina coupled by their complex ethmoturbinate system. But while the order of *Primates* is classified within the microsmatic group of mammals (this group shifted from an olfactory mode of existence to a visual reliance of subsistence), carnivores (classified as macrosmatic meaning their whole existence is based on smell) have the most complex and elaborate turbinate system in all of mammalia. Possession of four or more ethmoturbinates is found in strepsirrhines in contrast to the reported range of one to three pairs found in haplorhines. In addition, the haplorhine ethmoturbinates appear more reduced in size and are less intricately scrolled. Moreover, it appears that the tendency is toward a decrease and reconstitution of ethmoturbinate structural reorganization across the different haplorhine primate taxa.

While traditionally primates have been classified as microsmatic as mentioned above, other authors describe primates undergoing a reduction in their olfactory prowess. In 1970, Cartmill[14] proposed the visual predation hypothesis of primate origins, which may help to explain this reduction. The visual predation hypothesis explains the adaptive significance of a variety of skeletal features that characterize modern primates as they transitioned to an arboreal mode of life[14]. The change in orbital orientation enhanced stereoscopic vision, which was essential in the manually effective capture of food in a three dimensional setting of arboreal life but it may have initiated a cascade of morphological events to occur elsewhere in the craniofacial region particularly in the nasal area. As bony orbital modification and re-orientation occurred in these primates there was a concurrent reduction and re-arrangement of ethmoturbinate complexity to a more simple inferior-to-superior re-organization and, finally, a partial but not complete loss of olfactory mucosal area.

In humans, the evolutionary pattern of the nasal region as seen in the haplorhine non-human primates is continued in our species. The human nose appears as one organ with no morphological evidence distinguishing between the respiratory and olfactory noses. Studies of inspiratory airflow patterns in the nasal cavity, however, show the path of air flowing along the nasal floor and lower medial portion of the cavity (comparable to the inferior and middle meatus region) mimicking the respiratory pathway of an organism that possesses a transverse lamina[15].

The olfactory mucosa has been mapped to a small surface immediately inferior to the cribriform plate and to

the upper portions of the nasal septum[16]. The reduction of the olfactory mucosa seen in humans is strongly associated with the adaptive shift of a quadropedal locomotion gait to bipedality. *Homo erectus* is considered the first committed biped in our evolutionary history, which required the repositioning of the foramen magnum (a more anterior inferior placement) in order to balance the skull over the vertebral column and accommodate erect posture. These morphological changes had the effect of changing the orientation of the cribifrom plate from a vertical to a more horizontal manner. This resulted in a conversion of the mammalian olfactory nose into the human ethmoid complex, partitioned on each side in two clinically relevant compartments: The olfactory cleft medially and the ethmoid labyrinth laterally (in which the olfactory mucosa has disappeared).

Despite the evolutionary trend towards regression in the sense of smell, the embryologic development of the human nose is best understood when considering its olfactory origin, the subsequent respiratory reorganization, and the constriction of the ethmoid bone imposed by the orbital cones.

THE EVOLUTION DEVELOPMENT BIOLOGY (EVO-DEVO) OF THE HUMAN NOSE

The evo-devo approach, in comparison to the classical concept, explains why the nose is formed by a complex intricacy of different anatomical structures, and offers a rational explanation to this question[1] (the development of the paranasal sinuses, which occurs after birth, is not mentioned in this paper).

Phylogenically, the nose is exclusively an olfactory organ in fish, and the respiratory nose develops in crocodilians. Ontogenically, the growth and development of the olfactory nose precedes the development of the respiratory nose.

Development of the olfactory nose

Development of the olfactory capsule: The first embryologic evidences of the nose appear during the fourth week under the mask of two olfactory placodes on the frontal process of the embryo. Simultaneously, the corresponding wall of the brain undergoes rapid mitotic activity with a small bulge becoming visible and demarcating the olfactory region. Histologically, the future olfactory bulb and structures called the amygdaloid body and hippocampal formation are found in the forebrain[17].

Approximately, at five weeks Carnegie stage (CS) 15, (Carnegie staging is a method for dating embryos), the appearance of an olfactory pit is observed. This occurs with the invagination of the central portion of the placode. The invagination is in the direction of the adjacent brain where an olfactory elevation appears. Crest cells begin to gather together forming cords or filaments that travel within the mesenchyme.

At CS 16, the future olfactory bulb and the olfactory tubercle appear as elevations along the olfactory area of the cerebral hemispheres, or telencephalon. Between these two telencephalic elevated regions and the olfactory pit there is a significant and concentrated area of mesenchyme through which crest cells and olfactory epithelium must penetrate as they migrate to their destinations.

At CS 17 (approximately six weeks), the olfactory pit gives rise to the olfactory sac along with the development of the olfactory fin. The olfactory fin is an important structure as it separates the primitive nasal and oral cavities.

At CS 18 (6 ½ wk), the formation of the superficial fiber layer of the olfactory bulb originates from the fiber contribution of the olfactory nerve. There is an increase in the separation between the floor of the nasal (olfactory) sac and the oral cavity along with the appearance of a primitive olfactory septum between the olfactory sacs. The primordia of the olfactory centers, which represent the highly complex group of neurons, will be located near the juncture of the temporal and parietal lobes where they will continue to develop in the brain.

At CS 19, as vacuoles cultivate within the nasal fin they fuse with the nasal sac resulting in the sac's enlargement. The nasal sac's enlargement thins the nasal fin to a slender membrane before rupturing and forming the primitive choanae.

At CS 20 and 21, the various olfactory centers maintain their development within the brain while the olfactory epithelial fibers penetrate the sea of mesenchyme to establish connections.

At CS 22, the lateral walls of the olfactory sacs begin to fold over to form furrows and ridges, that increase the surface of olfactory epithelium.

At CS 23 (around the eighth week), the mesenchymal olfactory septum between the olfactory sacs has become cartilaginous and is now part of the olfactory capsule, which in itself is cartilaginous based. The olfactory capsule presents with its typical "M" shape morphology enveloping and separating both olfactory conduits from the brain.

During human foetus development from the ninth to tenth weeks, six major furrows develop along with their corresponding ridges or folds called ethmoturbinals (*i.e.*, turbinates arising from the ethmoid) arising from the lateral aspect of the cartilaginous olfactory capsule. This cartilaginous precursor will undergo mineralization forming the ethmoid bone.

Development of the olfactory conduits: The olfactory placodes are ectodermal thickenings. Infolding occurs at the epicenter of each olfactory placode and, as the placodes deepen, a raised rim on each placode results dividing the medial and lateral olfactory processes. The intermaxillary process is formed when the medial olfactory processes fuse at the midline.

In the images of the Wistar rat fetus[18,19], the primary

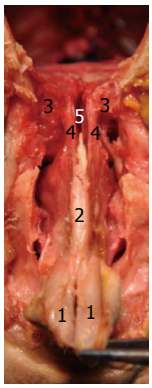

Figure 3 Anatomy of the olfactory nose. The alar (1) and septolateral (2) cartilages are united to each other and to the ethmoidal skull base (3) by the olfactory fascia (4) (the perpendicular plate of the ethmoid (5) has been partially removed).

nose becomes evident through the gap between the vertical palatal processes, after removal of the tongue. The histologic coronal sections of the snout of these rats clearly show that, the septum of the primary nose is already present and complete, before the flip up and development of the respiratory nose and secondary palate.

Additionally, from a phylogenic perspective, the cartilaginous skeleton of the amphibian snout is already comprised of a cartilaginous septolateral unit and an independent pair of "cartilago alaris", and precedes the appearance of the secondary palate and respiratory nose in crocodilians.

From these observations, it seems logical to hypothesize the following: The invagination movement of the center of the olfactory placodes could also pull in the raised rim of each placodes resulting in bringing the medial olfactory processes to fuse at the midline. Formation of the septolateral cartilage ensues before bringing the lateral olfactory processes in front of the septolateral cartilage, giving origin to the alar cartilages. The quadrangular plate of the septolateral cartilage connects to the perpendicular plate arising from the cartilaginous nasal capsule (*i.e.*, the forerunner of the ethmoid bone) to form the septum of the olfactory nose, which is visible in the Wistar rat fetus study[18,19].

Thus, the olfactory placodes and their derivative pits give rise by differentiation to the following: (1) The olfactory mucosa; (2) The septolateral and alar cartilages; and (3) The connecting tissues lying in between these structures, *i.e.*, the olfactory fascia[20].

The different fibrous portion of the olfactory fascia may be described as ligaments that unit the nasal cartilages to each other and to the olfactory mucosa, and the fibrocartilaginous nose to the facial and skull base skeleton.

These elements form the olfactory nose (Figure 3), which in humans stay separated from the braincase by the ethmoid bone, and largely communicates with the respiratory nose at the expense of the disappearance of the transverse lamina, a bony plate phylogenically separating the olfactory and respiratory nose until the stage of early primates.

Development of the respiratory nose

Phylogenically, the respiratory nose first appears in crocodilians. Based on paleontological data, the vomer bones are two plates of bone staying horizontal between the internal naris of early tetrapods which fused as a distinct plate located in the sagittal plane dividing the air passages of crocodilians[21].

Some evidence of a similar rearrangement in mammals has been published in a study of the Wistar rat secondary palate development[18,19]. The flip up of the palatal processes leads to their fusion behind the primary palate, leaving a gap between the upper surface of the secondary palate and the inferior border of the septum of the olfactory nose, which is progressively closed by a structure growing from the fused palatal shelves towards the septum of the olfactory nose. This growing structure, in the evo-devo concept, is believed to be the fused vomer bones[1].

The principle influence in palatal formation within crocodilians and other mammals appears to be in the significant development of the so-called palatine processes of the maxillae, the bones that give rise to the dentition, which push back the dermal palatal bones and is at the origin of their morphological changes and anatomical rearrangement. Applying the evo-devo perspective, the human respiratory nose appears as two paramedian, long axial conduits walled in on their inferior, lateral and medial sides by the rearranging of the dermal palatal bones (vomer, palatine, pterygoid, and inferior turbinate bones) between the two maxillary bones and their palatine processes (Figure 2). The transverse lamina, a bony structure which phylogenically was the floor of the ethmoidal chambers and the roof of the respiratory nose probably disappeared in the haplorhine ancestor of humans secondary to the constriction of the nasal fossae by the frontation and convergence of the orbital cones and the retraction of the snout.

The soft palate has evolved from the crocodilian basihyal valve, a significant gular fold that archers across the pterygoids immediately in front of the internal choana allowing crocodilians to have efficient respiratory function during submerged aquatic conditions. The basihyal valve consists of the following two flaps: The upper flap descends from the palate and gives rise to the mammalian soft palate, and the lower flap, located at the back of the tongue, is stringently reinforced by the hyoid cartilage (or the hyoid-epiglotic complex).

CONCLUSION AND FINAL THOUGHTS

The development of the nose can be seen as the invagination of the olfactory organ between the two maxillae towards the anterior cranial base, with its floor being secondarily disturbed by the onset of nasal respiratory development at the expense of the oral cavity. Application of the evo-devo perspective provides new insight not only to the development of the nose,

its complex nasal physiology and anatomy but more importantly, may explain the predisposition, direction and spread of various diseases in otorlaryngology. Armed with this knowledge, the otolaryngologist will better understand the clinical issues permitting modification of standard diagnostic, surgical and therapeutic management of the different diseases afflicting the craniofacial and neck regions. As a result, employing the evo-devo concept to our already pool of knowledge on Ear, Nose and Throat institutes will generate favorable surgical outcomes and, in effect, maximize patient care.

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ORIGINAL ARTICLE

Retrospective Study

Use of Holmium:Yag laser in early stage oropharyngeal squamous cell cancer

Jagdeep S Virk, Mike Dilkes

Jagdeep S Virk, Mike Dilkes, Department of Head and Neck ENT, Barts and Royal London Hospitals, London E1 1BB, United Kingdom

Author contributions: Virk JS drafted the manuscript and performed literature searches; Dilkes M performed, collated and analysed all data.

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Correspondence to: Jagdeep S Virk, MA, MRCS, DOHNS, E, Department of Head and Neck ENT, Barts and Royal London Hospitals, Whitechapel Road, Whitechapel, London E1 1BB, United Kingdom. j_v1rk@hotmail.com
Fax: +44-203-8452964

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Abstract

AIM: To evaluate the efficacy of Holmium:Yag laser resection for oropharyngeal squamous cell cancer.

METHODS: A prospectively collected case series of all patients with oropharyngeal squamous cell carcinoma undergoing laser resection using the Holmium:Yag laser technique only over a 15 year period at a tertiary referral centre. All patients underwent long term follow up with regular clinical and radiological surveillance, when indicated. All patients were operated on under general anaesthetic with a laser-safe endotracheal tube. Typically laser resection was performed first using an operating microscope, followed by neck dissection. The tumour was held with a Luc's forceps or Allis clamp. The Holmium: Yag laser was implemented *via* a fibre delivery system. The Holmium:Yag laser fibre, of 550 micron diameter, was inserted through a Zoellner sucker and attached *via* steri-strips to a second Zoellner suction to provide smoke evacuation. The settings were 1J/pulse, 15 Hz, 15 W in a continuous delivery modality *via* a foot pedal control. The procedure is simple, bloodless, effective and quick. All surgeries were performed as day cases.

RESULTS: Twenty-seven oropharyngeal squamous cell cancer patients were identified, at the following subsites: 23 lateral pharyngeal wall/tonsil, 2 anterior faucal and 2 tongue base. Of the 23 tonsil tumours, 19 required no further treatment (83% therefore had negative histopathological margins) and 4 required chemoradiotherapy (17% were incompletely excised or had aggressive histopathological features such as discohesive, perineural spread, vascular invasion). The 2 patients with anterior faucal pillar neoplasia needed no further treatment. Both tongue base cancer cases required further treatment in the form of chemoradiotherapy (due to positive histopathological margins). Postoperatively, patients complained of pain locally, which resolved with regular analgesia. There were no postoperative haemorrhages. Swallowing and speech were normal

after healing (10-14 d). There was one case of fistula when neck dissection was carried out simultaneously; this resolved with conservative management. All patients were followed up with serial imaging and clinical examination for a minimum of five years. Median follow up was 84 mo.

CONCLUSION: Holmium:Yag lasers are a safe and effective treatment for Stage 1 and 2 squamous cell carcinoma of the oropharynx, excluding the tongue base.

Key words: Holmium:Yag; Laser; Human papillomavirus; Oropharyngeal; Squamous cell carcinoma; Cancer; Squamous cell cancer

Core tip: Oropharyngeal squamous cell carcinoma is increasing in incidence. Management is controversial due to the large human papillomavirus cohort. The gold standard remains single modality therapy for early stage disease, either primary surgery or radiotherapy. Laser resection is one of the viable surgical options. We present a series of patients treated with Holmium:Yag laser resection. Holmium:Yag lasers are a safe and effective treatment for Stage 1 and 2 squamous cell carcinoma of the oropharynx, excluding the tongue base. Its uses could be extended within the speciality and elsewhere, particularly with a robotic arm.

Virk JS, Dilkes M. Use of Holmium:Yag laser in early stage oropharyngeal squamous cell cancer. *World J Otorhinolaryngol* 2016; 6(2): 41-44 Available from: URL: http://www.wjgnet.com/2218-6247/full/v6/i2/41.htm DOI: http://dx.doi.org/10.5319/wjo.v6.i2.41

INTRODUCTION

Oropharyngeal squamous cell carcinoma (SCC) is increasing in incidence. This has been confirmed in large epidemiological studies both in the United States and the United Kingdom recently[1]. This is principally due to the human papilloma virus (HPV) infected cohort of patients, particularly subtype HPV-16. HPV-associated oropharyngeal SCC comprises the vast majority of oropharyngeal SCC[1].

All patients undergo cross-sectional imaging and biopsy for pathological and radiological staging (Table 1)[2]. The gold standard of management remains single modality therapy for early stage disease (T1-2 NO-2a MO)[3], either primary surgery or radiotherapy, with both reported to be equally successful[4]. Decisions are based upon patient choice and co-morbidities (*i.e.*, ability to undergo general anaesthetic), size and position of the tumour (less than 4 cm and preservation of superior pharyngeal constrictor) and the functional deficit[5].

Early stage disease incorporates N1 and N2a neck disease. Hence, neck dissection should also be considered if there are positive nodes (with no radiological evidence of extra capsular spread). Ipsilateral selective level II-IV neck dissection may be warranted even with negative imaging.

Laser resection is one of the viable surgical options. Many modalities have been described but fall into two broad groups of trans-oral carbon dioxide laser surgery or trans-oral robotic surgery. Other options, apart from radiotherapy, include photodynamic therapy, diathermy excision or through open approaches with reconstruction (such as transmandibular with free flap reconstruction)[2,5].

In contrast to the commonly used carbon dioxide laser resections, we present a series of patients treated with Holmium:Yag laser resection in the oropharynx for these squamous cell carcinomas. We believe that the properties of the Holmium:Yag laser system is well suited to implementation in the oropharynx in view of its unique ability to vaporize, ablate (due to its longer wavelength of 2100 nm), coagulate soft tissues, a relatively low depth of thermal penetration (0.4 mm), excellent haemostasis and a wide range of tissue effects.

MATERIALS AND METHODS

A prospectively collected case series of all patients with oropharyngeal squamous cell carcinoma undergoing laser resection using the Holmium:Yag laser technique only over a 15 year period at a tertiary referral centre. The hospital ethics committee approved this study as it did not affect the standard of care offered to the patients.

Surgical technique

All patients were operated on under general anaesthetic with a laser-safe endotracheal tube. Typically laser resection was performed first using an operating microscope, followed by neck dissection. The tumour was held with a Luc's forceps or Allis clamp. The Holmium:Yag laser was implemented *via* a fibre delivery system. The Holmium:Yag laser fibre, of 550 micron diameter, was inserted through a Zoellner sucker and attached *via* steri-strips to a second Zoellner suction to provide smoke evacuation. The settings were 1J/pulse, 15 Hz, 15 W in a continuous delivery modality *via* a foot pedal control. The procedure is simple, bloodless, effective and quick. All surgeries were performed as day cases.

RESULTS

Twenty-seven oropharyngeal squamous cell cancer patients were identified, at the following subsites: Twenty-three lateral pharyngeal wall/tonsil, 2 anterior faucal and 2 tongue base. Of the 23 tonsil tumours, 19 required no further treatment (83% therefore had negative histopathological margins) and 4 required chemoradiotherapy (17% were incompletely excised or had aggressive histopathological features such as discohesive, perineural spread, vascular invasion). The

Table 1 Oropharyngeal squamous cell carcinoma staging

Tx	Primary tumour could not be assessed; information unknown
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour less than 2 cm
T2	Tumour between 2 and 4 cm
T3	Tumour larger than 4 cm (or affecting epiglottis)
T4	(1) Moderately advanced local disease growing into local structures (larynx, tongue, palate, medial pterygoid) (2) Advanced local disease, affecting internal carotid, lateral pterygoid, nasopharynx
Nx	Lymph nodes cannot be assed or information unknown
N0	No lymph nodes affected
N1	One ipsilateral lymph node, less than 3 cm
N2	(1) One ipsilateral lymph node between 3 and 6 cm (2) Two or more ipsilateral lymph nodes, less than 6 cm (3) Contralateral lymph nodes, less than 6 cm
N3	Any lymph node greater than 6 cm
M0	No distant spread
M1	Distant site affected

2 patients with anterior faucal pillar neoplasia needed no further treatment. Both tongue base cancer cases required further treatment in the form of chemoradiotherapy (due to positive histopathological margins).

Postoperatively, patients complained of pain locally, which resolved with regular analgesia. There were no postoperative haemorrhages. Swallowing and speech were normal after healing (10-14 d). There was one case of fistula when neck dissection was carried out simultaneously; this resolved with conservative management.

All patients were followed up with serial imaging and clinical examination. Median follow up was 84 mo. At this longer term follow up, there were no recurrences in the 19 patients who received laser resection alone. Of the remaining 6 patients who had multimodality therapy in the form of surgery and chemoradiotherapy, there was nodal recurrence in one of the tongue base cancers.

DISCUSSION

Over the last 20 years, the applications of lasers in otolaryngology have increased exponentially. Holmium:Yag lasers have the unique ability to vaporize, ablate (due to its longer wavelength of 2100 nm) and coagulate soft tissues alongside extremely hard materials, such as calculi, making it the laser of choice for a range of interventions for not only otolaryngologists but also in the fields of urology, orthopaedics, gastroenterological and general surgeons[6,7]. Holmium:Yag has a relatively low depth of thermal penetration (0.4 mm), excellent haemostasis and a wide range of tissue effects, allowing use for urological stone surgery, urethral strictures, benign prostatic hypertrophy, biliary stones, nephrectomy, laryngeal lesions, nasal polyposis, turbinoplasty and orthopaedic procedures[6]. We present a novel role for the Holmium:Yag laser.

The Holmium:Yag system, in its role for oropharyngeal SCC, is particularly useful as it allows a bloodless field, a lateral thermal necrosis of 2 mm (thus generating an extended clearance margin from tumour) and, when used in conjunction with an operating microscope, permits magnification and closer inspection of these margins. The latter precision inspection is particularly important with regard to the superior pharyngeal constrictor, as tumours are often adjacent or partially involving this muscle and, magnification can allow at least partial preservation, which is important to prevent exposure of parapharyngeal fat and the vital structures within. A further advantage of the Holmium:Yag system is that, as a result of the pulsed effects, no laser tip cooling is necessary[7,8]. In addition, these operative procedures are quick, with each taking around 20 min, and can be performed as day cases with the associated lower costs. These features make this type of laser system preferable to the standard carbon dioxide laser.

Disadvantages reported include post-operative oedema in comparison with standard techniques and pain. To avoid the potential for fistula formation, some centres recommend staged procedures, with the neck dissection performed a few weeks after the initial laser resection[6].

Overall the Holmium:Yag laser was safe and effective for lateral pharyngeal wall, tonsil and faucal pillar tumours. Only a small proportion required any further treatment at long term follow up. The main group of failures were tongue base tumours as they were too difficult to access and identify. This is confirmed in recent literature and so, radiotherapy remains an important treatment regime[9]. However, trans-oral robotic surgery or lateral pharyngotomy are better surgical options at this subsite and have shown comparable outcomes to radiotherapy in experienced centres[10-12]. In addition, minimally invasive surgical techniques are associated with superior quality of life, as compared to the historically extensive open procedures and are cost-effective due to the short stays[11-13]. Further research (ECOG-3311, NTC01898494) is currently underway to ascertain the best options for these patients, particularly in the context of HPV-16 associated outcomes[14].

We recommend the addition of the Holmium:Yag laser into the armamentarium of the otolaryngologist, particularly in cases of oropharyngeal SCC, where it has been shown to be safe, cost-effective with comparable outcomes to standard therapies.

COMMENTS

Background

Oropharyngeal squamous cell carcinoma is increasing in incidence. Management is controversial due to the large human papilloma virus (HPV) cohort. The gold standard remains single modality therapy for early stage disease, either primary surgery or radiotherapy.

Research frontiers

Laser resection is one of the viable surgical options. Currently carbon dioxide laser is favoured but further research is warranted in different modalities.

Innovations and breakthroughs

In this study, the authors demonstrated through a series of patients that, Holmium:Yag laser is safe, cost-effective with comparable outcomes to standard therapies in the treatment of oropharyngeal squamous cell carcinoma (SCC).

Applications

Hol:Yag laser should be added to the head and neck surgeon's armamentarium for consideration for use on oropharyngeal SCC, excluding the tongue base.

Peer-review

All relevant current literature was studied and referenced.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Word perception in noise at different channels in simulated cochlear implant listeners

Prawin Kumar, Himanshu Kumar Sanju, Sudhir Kumar, Varun Singh

Prawin Kumar, Himanshu Kumar Sanju, Sudhir Kumar, Varun Singh, Department of Audiology, All India Institute of Speech and Hearing, Karnataka 570006, India

Author contributions: Kumar P conceived the study; Kumar P and Sanju HK designed the study; Sanju HK and Kumar S analyze the data; Sanju HK, Kumar S and Singh V performed the data collection; Kumar P, Sanju HK and Singh V wrote the manuscript; all authors critically reviewed the manuscript and reviewed it.

Institutional review board statement: The study was reviewed and approved by All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India.

Clinical trial registration statement: This study is registered at All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India.

Informed consent statement: Written consent taken from all participants.

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Data sharing statement: We are ready to share data.

Correspondence to: Himanshu Kumar Sanju, Research Officer, Post Graduate in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru-6, Karnataka 570006, India. himanshusanjuaiish@gmail.com
Telephone: +91-740-6093279

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Abstract

AIM: To find out effect of different signal-to-noise ratios (SNRs) on word perception at different number of channels.

METHODS: Thirty participants with normal hearing in the age range of 18-25 years (mean age 23.6 years) were involved in the study. For word perception test, there were 28 key-words embedded in sentences comprises of four lists processed for different channels (4, 8 and 32 channel) using AngelSim program at -5, 0 and +5 SNRs. The recorded stimuli were routed through audiometer connected with computer with CD player and presented in free field condition with speakers kept at 0° azimuth in a sound treated room.

RESULTS: Repeated measure ANOVA showed significant main effect across different SNRs at 4 channel, 8 channel and at 32 channel. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR.

CONCLUSION: Present study highlights the importance of more number of channels and higher signal to noise ratio for better perception of words in noise in simulated cochlear implantees.

Key words: Cochlear implants; Perception; Signal-to-noise ratio; Speech; Noise

Core tip: Present study highlights the effect of different signal-to-noise ratios (SNRs) on word perception at different number of channels. Thirty young adults with normal hearing were involved in the study. Word perception test were carried out at different channels with multiple SNRs. Result showed significant main effect across different SNRs at 4, 8 and 32 channel. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5, 0 and -5 dB SNR. The present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees.

Kumar P, Sanju HK, Kumar S, Singh V. Word perception in noise at different channels in simulated cochlear implant listeners. *World J Otorhinolaryngol* 2016; 6(2): 45-49 Available from: URL: http://www.wjgnet.com/2218-6247/full/v6/i2/45.htm DOI: http://dx.doi.org/10.5319/wjo.v6.i2.45

INTRODUCTION

Earlier studies in cochlear implant has revealed that performance in speech recognition enhanced with increase in number of channels[1-5]. Previous studies have shown that speech perception improves with increase in number of channels in quite listening condition up to 4 to 7 channels[6,7]. Fishman *et al*[2], in 1997 assessed speech recognition in subjects using Nucleus-22 speech processing strategy with increase in number of electrodes. Result showed that speech perception score was poor for all subjects with single electrode cochlear implant listeners and they also observed improvement in speech perception with increase in number of electrodes from 1 to 4 with all test materials. They also found no significant difference in speech perception when number of electrodes increases to 7, 10 and 20. In a similar way, Friesen *et al*[8] in 2001 assessed speech perception with vowel, consonant, word and sentence in listener with Nucleus-22 and Advanced Bionics Clarion cochlear implant and compared scores with normal hearing individual. In that study, speech perception was measured as a function of number of electrodes and signal to noise ratios (+15, +10, +5, 0 dB). Outcomes of the study showed that speech perception improves with increase in number of channels (up to 7 or 8) at all signal to noise ratios. It was also observed that with SPEAK speech processor there was no improvement in speech perception for vowel and consonant recognition with greater than seven electrodes at all noise levels. However, for individuals with normal hearing, performance continued to increase up to at least twenty electrodes. For difficult speech materials like word and sentences, marginal significant increase in speech perception with increase in number of electrodes, *i.e.*, 7 to 10 in Nucleus-22 listeners. In a similar line, Verschuur[4] in 2009 compared patterns of consonants features recognition as a function of channel number in users of Nucleus 24 device with normal hearing subjects listening to acoustic model which mimics similar to that device. They reported that the large changes to channel number had no substantial changes in performance. Similarly, Friesen *et al*[5] in 2009 done speech perception test with CVC stimuli at 2, 4, 8, 12, and 16 spectral channels on 10 normal hearing subjects. They observed that performance with CVC stimuli enhanced with increase in number of spectral channels. Perreau *et al*[9], in 2010 also investigated speech perception test in spatially separated noise with different number of channels. They reported that the performance was affected for all subjects as the number of electrodes was reduced. A study done by Zeitler *et al*[10], in 2009 examined speech recognition outcome with reduction in the number of functional channel after post-implantation. The result showed that even though reduction in number of channels does not have a direct influence on performance of speech recognition, the reduction of five or more number of channels can suggest impending device failure. From the above literature it can be observed that most of these studies done in quite listening situation, whereas everyday listening situation contains background noise in our day-to-day life. So, there is a need to study the effect of different signal-to-noise ratio (SNR) on word perception at different number of channels of cochlear implant in simulated conditions. The aim of the study is to find out effect of different SNRs on word perception at different number of channels.

MATERIALS AND METHODS

Participants

Thirty participants with normal hearing in the age range of 18-25 years (mean age 23.6 years) were involved in the study. All the subjects were having hearing threshold within normal limits revealed by pure tone thresholds of $\leqslant$ 15 dBHL at 250 to 8000 Hz. Further, ipsilateral and contralateral reflexes were checked at 500, 1000, 2000 and 4000 Hz for all subjects and tympanometry with 226 Hz probe tone with middle ear analyzer was used to confirm normal middle ear functioning for all subjects. Those participants who were having any other otological, neuromuscular and neurological problem were excluded from the study.

Testing environment

All the behavioural tests were carried out in a sound treated room. The permissible noise level was as per the guidelines in ANSI S3.1 (1999). Laboratory room were well illuminated and air conditioned for the comfort of the researcher as well as subjects.

Instrumentation

For pure tone audiometry and word perception test, calibrated dual channel clinical audiometer (PIANO Inventis) was used for all participants. For tympanometry

Table 1 Mean and standard deviation of correct raw score (words) with different number of channels at various signal-to-noise ratios

	-5 dB SNR		0 dB SNR		+5 dB SNR	
	Mean	SD	Mean	SD	Mean	SD
4 channels	4.00	3.25	5.26	3.27	8.63	5.14
8 channels	15.10	5.84	18.00	4.84	19.86	4.04
32 channels	23.90	5.17	25.63	3.71	26.93	1.70

SNR: Signal-to-noise ratio.

and reflexometry, calibrated GSI-Tympstar Immittance meter was used for all participants.

Procedure

Modified version of Hughson and Westlake procedure was used for pure-tone audiometry (Carhart and Jerger[11], 1959) across octave frequencies from 250 to 8000 Hz for air conduction and frequencies from 500, 1000, 2000 and 4000 Hz for bone conduction. To carry out tympanometry and reflexometry middle ear analyzer was used using a probe tone frequency of 226 and 500 Hz, 1000, 2000, and 4000 Hz stimuli were used for ipsilateral and contralateral reflex. For word perception test, there were 28 key-words embedded in sentences comprises of four lists processed for different channels (4, 8 and 32 channel) using AngelSim program at -5, 0 and +5 SNRs. The subjects were instructed to write the sentences. They were encouraged and motivated to predict the sentence. No repeat presentation and feedback were provided. All the subjects were asked to sit comfortably without excessive head movement. Testing was done from most adverse listening condition (4 channels, -5 dB SNR) to least adverse listening condition (32 channels, +5 dB SNR). Rest period was provided after completion of each channels condition. The recorded stimuli were routed through audiometer connected with computer with CD player and presented in free field condition with speakers kept at 0° azimuth in a sound treated room. During testing the listener was seated at 1 meter distance in front of loudspeaker (Grason-stadler audio monitors) in a sound treated room. The stimuli presented at three different SNRs (-5 dB, 0 dB and +5 dB) by varying the level of speech noise (generated by PIANO Inventis double channel audiometer), keeping signal constant at 40 dB SL at different number of simulated channels, *i.e.*, 4, 8 and 32 channels. The subjects were supposed to write the sentence heard from loudspeaker. Raw scores were calculated for keywords (number of correct keywords in each sentence).

Statistical analysis

The statistical analysis of the study was performed by a biomedical statistician. Data of the study was analyzed using SPSS 17.

RESULTS

Descriptive statistics, repeated measure ANOVA and bonferroni multiple pairwise comparisons were done using SPSS 17 to analyze the data collected from all subjects. Descriptive statistics was done to find out mean and standard deviation of score at different channels with different SNRs. Repeated measure ANOVA was done to find out any significant main effect across different SNRs at 4, 8 and 32 channels. Further, Bonferroni multiple pairwise comparisons was done to find out any significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR.

Descriptive statistics showed that mean score increased (better) with increase in number of channels for words (Table 1). Similarly, descriptive statistics also revealed that mean score increases (better) with increase in SNR, *i.e.*, -5, 0 to +5 dB for words (Table 1). Repeated measure ANOVA showed significant main effect across different SNRs at 4 channel [$F(2, 87) = 125.05$; $P < 0.05$; $\chi^2 = 0.742$]; 8 channel [$F(2, 87) = 198.09$; $P < 0.05$; $\chi^2 = 0.820$]; and at 32 channel [$F(2, 87) = 167.85$; $P < 0.05$; $\chi^2 = 0.794$]. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR (Table 2 and Figure 1).

DISCUSSION

The aim of the present study was to find out effect of different number of channels on word perception at different SNRs. The result showed significant improvement in word perception with increase in number of channels. This study also revealed significant improvement in word perception with increase in signal to noise ratio at different number of channels. Present study also quantified the deteriorating effect on word perception with decrease in SNR at different channels. Finding of present study is in consonance with previous literature[1,3,5,8-10]. However, there are few studies not in agreement with present findings[2,4]. In general, performance increases with increase in number of channels (4 channels < 8 channels < 32 channels) and of favorable SNR (+5 dB SNR > 0 dB SNR > -5 dB SNR). However, minimum 8 channels are required to achieve at least more than 50% performance irrespective of adverse listening condition (-5 dB SNR). Probably at lesser numbers of channels, information is spectrally sparse and hence poorer performance which further deteriorates in adverse listening condition (-5 dB SNR). The outcome of present study also showed that deteriorating effect of noise persists even at 32 channels condition. Similarly, the outcome of present study revealed that effect of number of channels on word perception in noise and showed that most individuals with CI are unable to fully utilize the spectral information given by the more number of channels in noisy condition. Friesen *et al*[8], in 2001 measured speech perception with various number of electrodes at different signal to noise ratios of +15, +10, +5, 0 dB, and in quiet. The outcome of the study showed speech recognition score

Table 2 Bonferroni multiple pairwise comparisons at all the possible combinations for words (4, 8 and 32 channel) at +5 dB signal-to-noise ratio, 0 dB signal-to-noise ratio and -5 dB signal-to-noise ratio ($^bP < 0.001$)

SNR	Channels	8 channels (mean difference)	32 channels (mean difference)
+5 dB SNR	4 channels	-11.23[b]	-18.3[b]
	8 channels		-7.06[b]
0 dB SNR	4 channels	-12.73[b]	-20.36[b]
	8 channels		-7.63[b]
-5 dB SNR	4 channels	-11.1[b]	-19.9[b]
	8 channels		-8.8[b]

SNR: Signal-to-noise ratio.

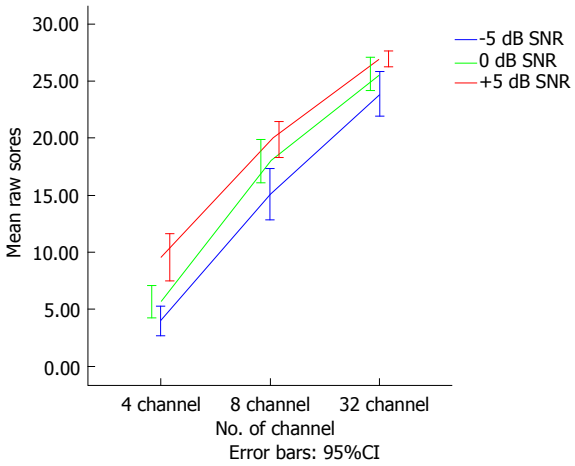

Figure 1 Error bar graph of mean score for words with 4, 8 and 32 channels at +5 dB, 0 dB and -5 dB signal-to-noise ratio.

improved with increase in number of electrodes (up to seven or eight). They also found that on administration of difficult speech material like words and sentences, performance was increased (marginally significant) with increase in number of electrodes, *i.e.*, 7 to 10 in nucleus-22 cochlear implant listeners. Liu *et al*[12], in 2004 assessed effects of number of electrodes on Mandarin tone perception in children using Nucleus CI 24 cochlear implant. They reported significant decrease in Mandarin tone perception score with decrease in number of electrodes in children using CI 24 implants. Similarly, Perreau *et al*[9], in 2010 also investigated speech-in-noise test at different numbers of electrodes in individuals with bilateral cochlear implant. The result revealed that 3 to 4 electrodes is sufficient to get maximal performance on speech-in-noise tests in individuals with bilateral cochlear implant. However, few individuals with cochlear implant shows gradual decrement in speech recognition in noise with decrease in number of functional electrodes. Zeitler *et al*[10], in 2009 showed that although deactivation does not have direct impact on speech perception score, the reduction of 5 or more electrodes can suggest impending device failure. The finding of the current study is in contrast with the study done by Fishman *et al*[2], in 1997 reported no differences in speech perception score on any test in the 7-, 10-, and 20-electrode conditions. They also showed no difference in speech perception score with 4 and 20 electrodes processor on sentence and consonant test. The outcome of present study is in contrast with the study done by Verschuur[4] in 2009 also showed that large changes in number of channels in the Advanced Combination Encoder signal processing strategy revealed no significant changes in speech perception score. However, the present study was done on simulated cochlear implantees, audiologist or clinical specialist needs to be cautious before implementing present finding on individuals with cochlear implant.

The outcome of the present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees. Present study also quantified the deteriorating effect on word perception with decrease in SNR at different channels. Current study also showed that minimum 8 channels are required to achieve at least more than 50% performance irrespective of adverse listening condition (-5 dB SNR).

COMMENTS

Background

Earlier studies in cochlear implant have revealed that performance in speech recognition enhanced with increase in number of channels. Previous studies have shown that speech perception improves with increase in number of channels in quite listening condition up to 4 to 7 channels.

Research frontiers

From the above literature it can be observed that most of these studies done in quite listening situation, whereas everyday listening situation contains background noise in the authors day-to-day life. So, there is a need to study the effect of different signal-to-noise ratio (SNR) on word perception at different number of channels of cochlear implant in simulated conditions. The aim of the study is to find out effect of different SNRs on word perception at different number of channels.

Innovation and breakthroughs

The authors compares word perception score at three different SNRs (-5 dB, 0 dB and +5 dB) by varying the level of speech noise (generated by PIANO Inventis double channel audiometer), keeping signal constant at 40 dB SL at different number of simulated channels, *i.e.*, 4, 8 and 32 channels. The result showed significant improvement in word perception with increase in number of channels. This study also revealed significant improvement in word perception with increase in signal to noise ratio at different number of channels.

Applications

The outcome of the present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees.

Terminology

Signal to noise ratio is signal-to-noise ratio (abbreviated SNR or S/N) is a measure used in science and engineering that compares the level of a desired signal to the level of background noise. It is defined as the ratio of signal power to the noise power, often expressed in decibels.

Peer-review

Well written paper with good language and grammar.

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Meatoplasty: A novel technique and minireview

Todd Kanzara, Jagdeep S Virk, Anthony O Owa

Todd Kanzara, Jagdeep S Virk, Anthony O Owa, ENT Department, Queen's Hospital, Barking, Havering and Redbridge University Hospitals NHS Trust, Romford, Essex RM7 0AZ, United Kingdom

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Correspondence to: Todd Kanzara, LLB (Hons) MRCS (ENT), ENT Department, Queen's Hospital, Barking, Havering and Redbridge University Hospitals NHS Trust, Rom Valley Way, Romford, Essex RM7 0AZ,
United Kingdom. todd.kanzara@nhs.net
Telephone: +44-790-8960034
Fax: +44-208-8692964

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Abstract

We describe a modified aural meatoplasty technique. The technique has been mainly used for mastoid surgery but it may also be used to address other causes of meatal stenosis. It involves removing most of the cartilage in the conchal bowl and soft tissue in the external auditory meatus. Cartilage from the helical root may also be sacrificed as part of this procedure. Our technique produces an excellent cosmetic result and an adequate meatoplasty which is easy to monitor in the outpatient setting.

Key words: Meatoplasty; Cartilage; Reconstruction; Mastoid; Conchal bowl

Core tip: A successful meatoplasty addresses the bony, soft tissue and cartilaginous portions of the external auditory meatus. At least one, if not all these factors, can contribute to external auditory canal stenosis. Cartilage from the helical root can be resected in order to create an adequate meatoplasty.

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INTRODUCTION

Creating an adequate meatoplasty is a critical step in allowing access and ventilation of the ear canal. Meatoplasty is often performed in conjunction with mastoid surgery. To create a successful meatoplasty, the surgeon considers the 3 main factors that contribute to meatal stenosis: (1) excess skin and soft tissue; (2) aberrations in the anatomy of the cartilage; or (3) the bony tympanic ring[1]. A range of techniques and variations have been reported in the literature since the original descriptions in 1893 by Stacke and Shwartze[2].

We present a technique developed at our centre by the senior author to ensure suitable meatoplasty size

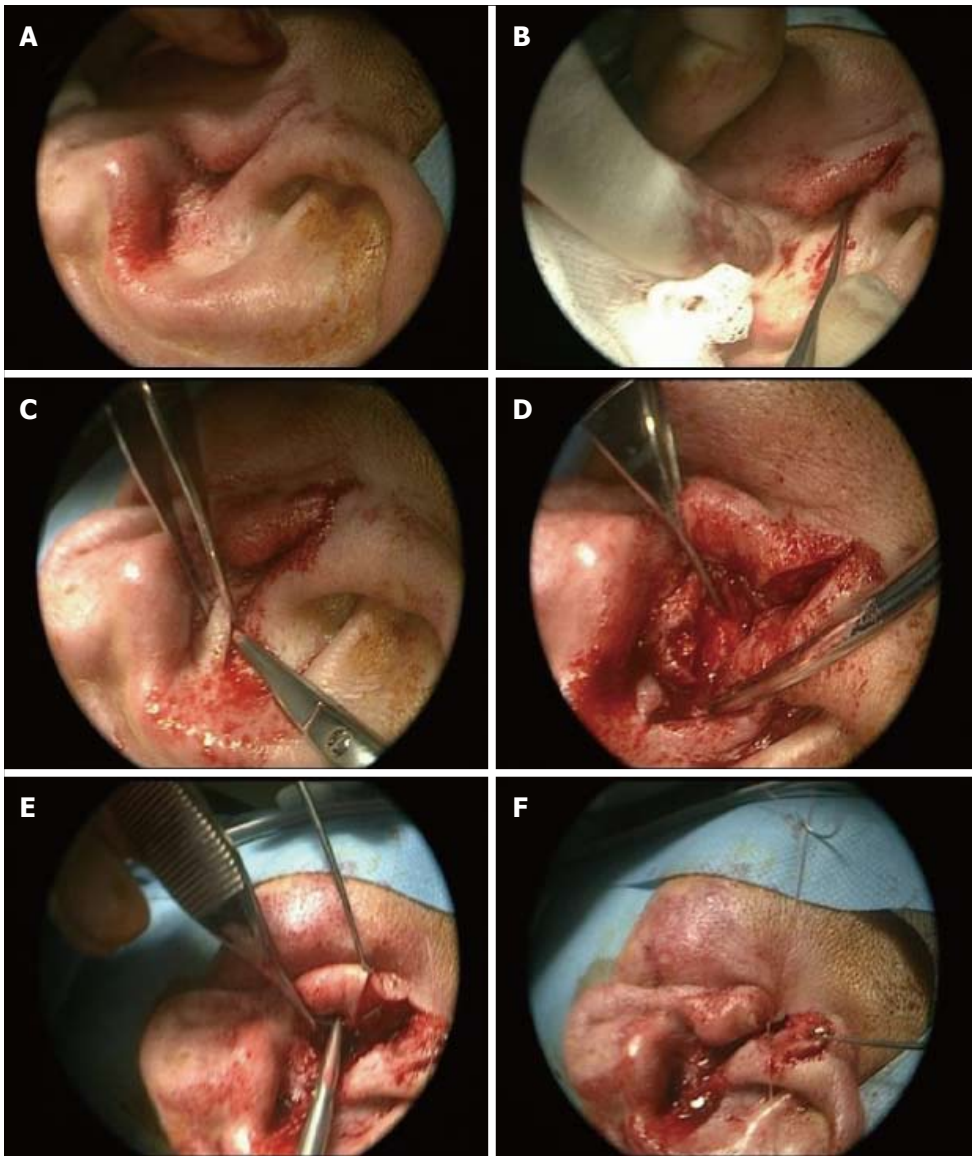

Figure 1 Meatoplasty technique. A: Endaural incision; B: Superiorly based conchal bowl incision; C: Conchal cartilage harvested; D: Excess skin and soft tissue resected; E: Closure of anterior endaural incision to prevent cartilage exposure; F: Closure of endaural incision, 154 mm × 183 mm (120 × 120 DPI).

whilst maintaining cosmesis, principally in conjunction with mastoid surgery.

OPERATIVE TECHNIQUE

The steps include performing an endaural incision to bone (Figure 1A), followed by a skin incision over the superior aspect of the conchal bowl/cartilage (Figure 1B). A large portion of conchal cartilage is then removed, which can be used as part of the reconstruction in tympanomastoid surgery (Figure 1C). To facilitate the meatoplasty redundant mucosa and soft tissue is excised medial to the skin incision. An important factor is removal of prominent cartilage, for example at the root of the helix. The resultant skin flap is rotated into the cavity such that the meatoplasty is widened. Following this, absorbable sutures are used to ensure the tragus remains anterosuperior, by suturing the anterior edge of the endaural incision (Figure 1D). The free edge of conchal skin is opposed with absorbable suture (Figure 1E and F). An adequately sized meatoplasty should not require splinting by packing such as with bismuth iodoform paraffin paste (BIPP).

This technique for meatoplasty over the preceding two years has resulted in very good functional and cosmetic outcomes in all 54 patients (Figure 2). We have managed to achieve a dry, auto cleaning ear with very good cosmetic results in all cases. We have not had any cases of stenosis or troublesome granulation. Therefore, we propose our technique as a useful adaptation in performing meatoplasty.

DISCUSSION

There is an abundance of meatoplasty techniques in the literature reportedly producing very good results in

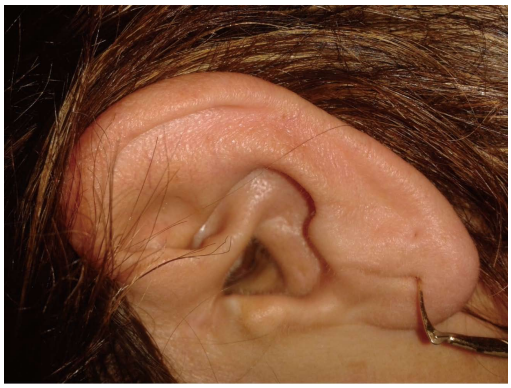

Figure 2 Post-operative result.

the respective author's hands. These techniques rely on creating a meatoplasty using a fibrocartilaginous posterior meatal flap in a post-auricular approach mastoidectomy, or partially resecting conchal bowl cartilage for the endaural approach[3]. Traditional thinking with regards to meatoplasty surgery has tended to focus on creating a large meatoplasty thought to support optimal ventilation, reduce both bacterial and debris accumulation[4-7]. However, the "big is better" approach is often associated with a few complications which include poor cosmesis and poor hearing aid fitting amongst other things[8,9].

Two broad approaches have been reported with regards to widening the skin of the entrance of the external auditory meatus. The first approach, which in essence forms the basis of the Portman technique, uses radial incisions to create flaps arising from the outer ring of the external auditory meatus[10]. Following the excision of underlying soft tissue, the flaps are then elevated onto the bony canal. The second approach, originally described by Korner and Siebenmann but reported by others, involves dividing the ring and rotating a skin flap to cover the defect[1,11].

More recent techniques, similarly ours, have tended to favour the second approach involving rotational flaps. Osborne and Martin[12] described rotating a superiorly placed pre-tragal flap into the endaural incision following removal of some conchal bowl cartilage. Hovis *et al*[13] described a "one cut meatoplasty" involving making a single horizontal incision from the posterosuperior meatus to the antihelix to create an inferiorly based triangular conchal flap. Martin-Hirsch and Smelt described a flap starting medial to the excess conchal mucosa and extending superiorly[14]. Follow-up results of patients managed with this technique over a 9-year period have shown favourable results especially for the otitis externa group[15]. Banerjee *et al*[16] reported using an inferiorly based transposition flap which potentially has poor cosmesis as its major demerit owing to the inferoposterior widening inherent in the technique[1,14].

Other techniques which do not make use of skin flaps have been reported. Patil *et al*[1] describe a technique which involves the removal of a small triangle of skin on the entrance of the external auditory canal in addition to conchal cartilage resection. Goodyear *et al*[17] described a helical advancement technique which involves resecting a cuff of skin anterior to the helix followed by releasing the helix anteriorly to cover the defect. The authors point out that whilst this approach produces inferior cosmesis it has the advantage of producing an auto-cleaning cavity which is easy to manage in the outpatient setting[17].

In our experience of using this technique, we have not experienced any of the common complications associated with meatoplasty such as perichondritis, discharge or restenosis. Further, the patients operated on have not complained about poor cosmesis on follow-up.

CONCLUSION

We believe this previously undescribed methodology will provide an additional tool in the armamentarium of the otolaryngologist. Our modified approach demonstrated in this paper is reproducible and technically straightforward. It provides an adequate meatoplasty which promotes an auto cleaning ear that is easily accessible in clinic whilst producing an excellent cosmetic result.

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