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Review

Review of salicylate-induced hearing loss, neurotoxicity, tinnitus and neuropathophysiology

Effetti clinici e neurofisiopatologici del salicilato: ipoacusia, acufene e neurotossicità

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SUMMARY

Salicylate's ototoxic properties have been well established, inducing tinnitus and a sensory hearing loss when administered in high doses. Peripherally, acute dosing of salicylate causes frequency dependent reductions in DPOAEs and CAP amplitudes in low (<10 kHz) and high (>20 kHz) frequencies more than mid frequencies (10-20 kHz), which interestingly corresponds to the pitch of behaviourally-matched salicylate-induced tinnitus. Chronic salicylate dosing affects the peripheral system by causing a compensatory temporary enhancement in DPOAE amplitudes and up-regulation of prestin mRNA and protein expression. Despite salicylate's antioxidant properties, cultured cochlea studies indicate it also impairs spiral ganglion neurons (SGNs) by paradoxically causing an upsurge of superoxide radicals leading to apoptosis. Centrally, salicylate alters γ-aminobutyric acid (GABA) and serotonin mediated neurotransmission in the central nervous system (CNS), which results in classical and non-classical auditory regions showing hyperactivity after salicylate administration. In the auditory cortex (AC) and lateral amygdala (LA), neuron characteristic frequencies (CF) shift upward and downward to mid frequencies (10-20 kHz) altering tonotopy following salicylate administration. Additionally, current source density (CSD) analysis showed enhanced current flow into the supergranular layer of the auditory cortex after a high systemic dose of salicylate. In humans, auditory perception changes following salicylate or aspirin, including decreased word discrimination and temporal integration ability. The results of previous studies have partially identified the mechanisms that are involved in salicylate-induced tinnitus and hearing loss, however to date some interactions remain convoluted. This review discusses current knowledge of salicylate ototoxicity and interactions.

KEY WORDS: Sodium salicylate (SS) • Distortion product otoacoustic emissions (DPOAE) • Compound action potential (CAP) • Inferior colliculus (IC), • Auditory cortex (AC) • Lateral amygdala (LA) • Characteristic frequency (CF) • Current source density (CSD)

RIASSUNTO

Gli effetti ototossici del salicilato sono ben noti ed includono, ad alti dosaggi, acufene ed ipoacusia transitoria. In periferia, la somministrazione acuta di salicilato nell'animale induce una riduzione d'ampiezza dei prodotti di distorsione (DPOAE) e dei potenziali d'azione (CAP), prevalentemente per le basse (<10 kHz) e per le alte (>20 kHz) frequenze; è interessante come questa alterazione corrisponda alla tonalità dell'acufene indotto sperimentalmente. La somministrazione cronica causa invece un aumento transitorio dell'ampiezza dei DPOAEs ed una up-regulation dell'mRNA e dell'espressione proteica della prestina. In vitro la tossicità da salicilato si evidenzia prevalentemente a livello dei neuroni del ganglio spirale (SGNs) inducendo, a dispetto delle ben note proprietà antiossidanti, un rilascio paradosso di radicale superossido che avvia la catena apoptotica. Centralmente, il salicilato altera la trasmissione GABA e serotonino-mediata inducendo una iperattività di specifiche popolazioni neuronali. A livello della corteccia uditiva (AC) e dell'amigdala laterale (LA) le frequenze caratteristiche neuronali (CF) variano alterando la tonotopia fisiologica, specialmente per le frequenze centrali (10-20 kHz). Inoltre, l'analisi della densità di corrente (CSD) ha dimostrato un maggior influsso negli strati supragranulari della corteccia uditiva in seguito alla somministrazione di dosi elevate di salicilato per via sistemica.
Nell'uomo gli effetti ototossici del salicilato, oltre ad ipoacusia transitoria ed acufene, includono una diminuita discriminazione verbale e difficoltà nell'integrazione temporale. Sebbene diversi lavori in letteratura abbiano identificato i meccanismi fisiopatologici alla base delle alterazioni uditive indotte dal salicilato, ad oggi alcune interazioni rimangono poco chiare.

PAROLE CHIAVE: *Sodio salicilato (SS) • Prodotti di distorsione delle otoemissioni acustiche (DPOAE) • Potenziali d'azione composti (CAP) • Collicolo inferiore (IC) • Corteccia uditiva (AC) • Amigdala laterale (LA) • Frequenze caratteristiche (CF) • Densità di corrente (CSD)*

Introduction

The active ingredient in aspirin, salicylate, is a commonly used antipyretic, analgesic and anti-inflammatory drug. However, consumption in large doses (6-8 gm/day) [1] is widely known to induce hearing loss and tinnitus [2-4]. Originally, the influence of salicylate on the auditory system was thought to be temporary, but more recent discoveries show that prolonged, high doses of sodium salicylate (SS) can cause sustained damage within the inner ear, suppressing the neural output of the peripheral system [5]. In addition, despite salicylate's antioxidant properties, high doses *in vitro* cause a paradoxical up-regulation of the superoxide radical, leading to apoptosis in spiral ganglion neurons (SGN) [6]. Unbound salicylate concentrations in plasma have a high correlation with the severity of induced hearing loss [2 7], which saturates at ~40 dB; however, the level of salicylate in serum is somewhat less predicative [8 9]. Since high doses of salicylate can reliably induce hearing loss and tinnitus, it is commonly used to study its behavioural, anatomical, physiological and perceptual effects on the auditory system [2 10 11]. Peripherally, salicylate influences hearing sensitivity in low (<10 kHz) and high (>20 kHz) frequencies more than mid frequencies (10-20 kHz) [5]. After a high dose of salicylate, neurons in the central auditory system tuned to low characteristic frequencies (CF) in the auditory cortex (AC) shift upward and neurons tuned to very high frequencies shift downward resulting in an over representation at the mid frequencies [12]. In contrast to the suppressed neuronal output peripherally following systemic administration of SS, the AC becomes hyperactive at high levels of auditory stimulation [13-15]. Alterations to the AC may be due to salicylate's influence on γ-aminobutyric acid (GABA) and serotonin mediated neurotransmission in the central nervous system (CNS) [14 16-18]. Since salicylate is known to alter neurotransmitters located throughout the CNS, non-classical auditory structures that also respond to sound, like the amygdala, have also shown neuronal hyperactivity and CF tuning shifts following systemic administration of salicylate [19].

Despite reliable salicylate-induced threshold shifts and tinnitus generation in animal models, objective and subjective perceptual alterations in humans appear to be more variable [2 20-22]. Over the past several years knowledge about the effects that salicylate imposes on the peripheral and central auditory system has increased significantly. In this review, we will highlight several of the important changes we have identified in the cochlea and central nervous system after administering high doses of salicylate sufficient to induce tinnitus and hearing loss. In addition, we will review some *in vitro* and *in vivo* data from our lab that highlights the neurotoxic effects of salicylate.

Peripheral effects

Distortion Product Otoacoustic Emissions (DPOAE)

Acute effects
DPOAE is a measurement used to assess the function of the outer hair cells (OHC) in the cochlea. The distortion product is generated by a combination of the electromotile response of OHCs mediated by the motor protein prestin and the +80 mV endocochlear potential [23 24]. The motor protein prestin is part of a family of antiporters that transfer anionic molecules across cell membranes [25]. Prestin, which lines the lateral wall of the OHC, changes shape in response to fluctuations in the voltage across the OHC membrane. OHC depolarisation causes an axial shortening of the OHC whereas hyperpolarisation causes OHCs to elongate [26]. Sound waves lead to motion of the basilar membrane, depolarisation and hyperpolarisation of OHCs causes the axial motion of the OHCs which results in a frequency-dependent amplification of the basilar membrane in response to the incoming sound [26]. Salicylate affects the OHC electromotility response by displacing chloride and binding to the anion–binding sites on prestin, suppressing the amplification properties of the cochlea [23]. Sodium salicylate (SS) causes a frequency-dependent reduction in DPOAE [12]. Figure 1 shows the mean DPOAE input/output (I/O) response of 6 Sprague-Dawley rats under ketamine/xylazine (50/6 mg/kg) anaesthesia. Prior to SS treatment all six frequencies ($2f_1$-f_2= 4, 5.3, 8, 11, 16, 20 kHz) showed robust responses. However, 2 hours post injection (300 mg/kg, i.p.), DPOAEs decreased significantly in the low frequencies ($2f_1$-f_2 <11 kHz) and high frequencies ($2f_1$-f_2 >16 kHz) but had less influence on the mid frequencies ($2f_1$-f_2 11 -20 kHz) [12]. While salicylate caused a significant reduction in DPOAEs indicating a sensory hearing loss, animal behavioural models have also indicated that this dose reliably induces tinnitus [3 27-29]. The significant reduction in low and high frequency responses could lead to mid-frequency expansion of the tonotopic map of the AC. Interestingly, animal models have indicated that salicylate induced a mid-frequency perception of tinnitus [30], consistent with the frequency-dependent reduction in DPOAE [12].

Chronic effects
Chronic salicylate treatment also influences the motor protein prestin. Chronic treatment with SS enhanced DPOAE amplitudes and caused an up-regulation in prestin mRNA and protein expression [5 31]. Rats were chronically treated over two time periods consisting of four days, with a two day rebound period in between. During each period, the animals were treated with a systemic injection (300 mg/kg/day) of SS and DPOAEs were measured 2-hours post administration. Changes in DPOAE amplitudes were nor-

Distortion Product Otoacoustic Emissions I/O Function
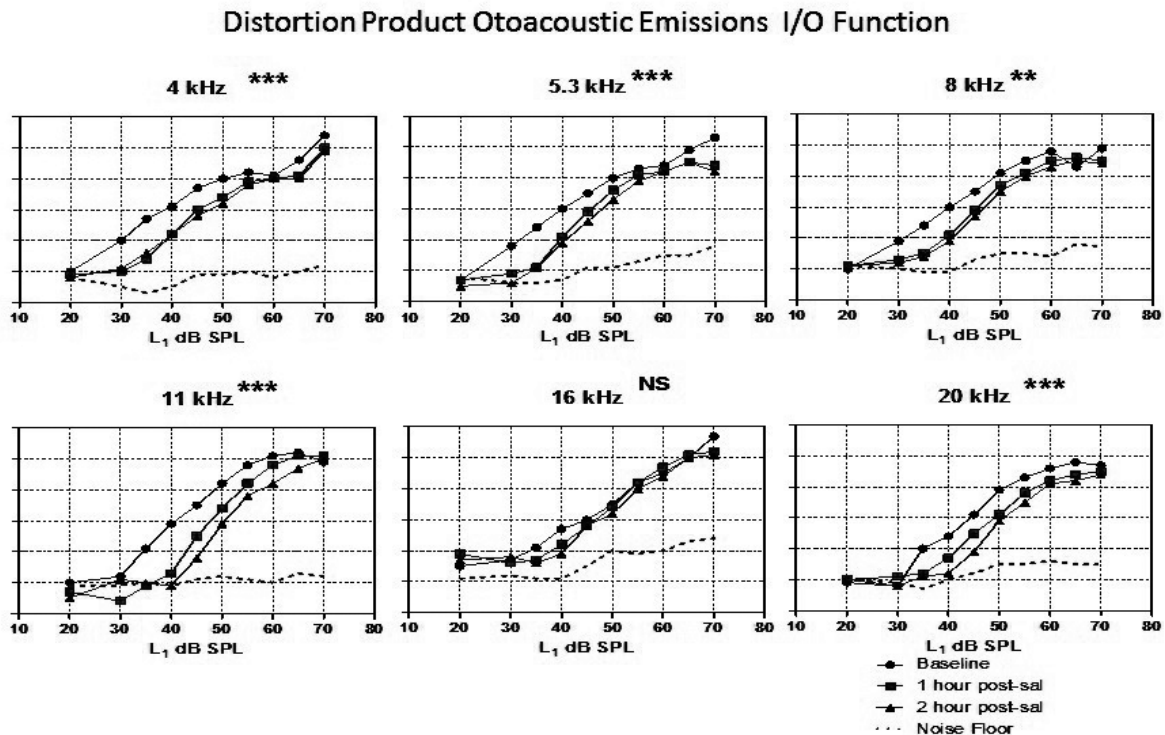
Fig. 1. Schematic of mean DPOAE amplitudes plotted as a function of L_1 intensity pre- salicylate treatment, 1 h post-salicylate treatment, and 2 h post salicylate treatment (300 mg/kg i.p.). Frequencies (4, 5.3, 8, 11, 16, & 20 kHz) indicated above each panel represent $2f_1$-f_2. Acute systemic salicylate administration significantly reduced DPOAE amplitudes in low (4, 5.3, 8, and 11 kHz) and high (20 kHz) frequencies but not at mid (16 kHz) frequencies. (** P=0.01, *** P=0.001, ns=not significant).

malised to pre-treatment amplitudes. During both treatment periods, DPOAE amplitudes were significantly reduced. However, each treatment period was followed by a significant rebound enhancement of DPOAE amplitudes compared to pre-treatment amplitudes [5]. There was no change in DPOAE amplitudes after a long duration treatment with salicylate at moderate levels (200 mg/kg/day, five days a week, for three weeks) [5].

Interestingly, chronic salicylate treatment increases prestin mRNA expression. Adult guinea pigs received a systemic injection of SS (200-250mg/kg) twice a day for 2 weeks. Prestin mRNA expression progressively increased following daily administrations. Western blots indicated an increase in the prestin protein [31]. Four weeks after cessation of SS treatment prestin mRNA levels returned to normal [31]. These results indicate that as a result of chronic high doses of salicylate, the electromotile function of the OHCs is enhanced, leading to greater cochlear amplification. Some have hypothesised that tinnitus may be generated as a result of an imbalance between IHC and OHC activity [32]. The up-regulation in prestin seen in the OHCs as a result of chronic high dosing of salicylate may cause such an imbalance and contribute to the perception of tinnitus. Indeed, chronic low therapeutic doses of aspirin can cause tinnitus alone without hearing loss [2][33]. However, currently, there are no studies that have indicated an up-regulation of prestin protein as a result of a chronic, low

doses of salicylate. Taken together, these results indicate that chronic high doses of salicylate administration can have long lasting effects on cochlear sensory cells, contributing to sensory hearing loss, tinnitus and possibly plastic changes to the central auditory system.

Compound Action Potential (CAP)

Acute effects

The first negative peak (N1) of the electrical response from the round window of the cochlea in response to a click or tone burst is the compound action potential (CAP), which reflects the synchronous onset response of type I auditory nerve fibres that directly connect to inner hair cells (IHC) (Fig. 2). Salicylate is known to depress the cochlear CAP [5][12]. Figure 3 shows changes that occur in the CAP I/O function to tone bursts (4, 12, 16, & 30 kHz) in rats under ketamine/xylazine anaesthesia (50/6 mg/kg, i.p.). Sprague-Dawley rats were treated with SS (300 mg/kg, i.p.) or the equivalent dose of saline, and two hours later the CAP was measured by placing a silver electrode on the round window. The amplification produced by the OHCs results in a non-linear CAP I/O function prior to salicylate treatment (compare to dashed lines in Fig. 3 which represent a linear relationship). The influence of salicylate on the electromotility of OHCs in-

duced a significant threshold shift (I/O functions shifted to the right 20-30 dB), reduced the CAP amplitude and creates a more linear I/O function. The non-linear relationship was affected most at low (4 kHz) and high frequencies (30 kHz) and least at mid frequencies, indicating that cochlear amplification was still largely functional at the mid-frequencies [5]. These results are consistent with

Fig. 2. High-pass filtered (>11 kHz) CAP response to a 12 kHz tone burst. Bars represent N1; response amplitude represents activity stemming from type 1 auditory nerve fibres. N1 is measured to represent CAP amplitudes.

Fig. 3. CAP I/O function pre- (dotted) and 2 hours post-SS (solid) treatment. Dotted grey lines represent linear relationships to the CAP I/O function; the distance between the linear lines and CAP I/O functions represents the amount of residual amplification from the OHCs (demonstrated in 30 kHz I/O panel). At low (4 kHz) and high (40 kHz) frequencies the CAP I/O function becomes more linear than mid frequencies (12 & 16 kHz). The threshold shift is greater in the low and high frequencies (~ 30 dB SPL) compared to the mid frequencies (~20 dB SPL). CAP I/O functions demonstrate salicylate-induced hearing loss affects the OHC amplification properties in a frequency dependent manner, which is consistent with previous findings in DPOAE I/O functions. CAP amplitudes at high stimulation levels are reduced even though little amplification is needed. This is indicative that salicylate may also affect SGNs.

DPOAE data indicating a frequency-dependent reduction in cochlear amplification. Importantly, CAP amplitudes are reduced at high stimulation levels, particularly at 4 and 30 kHz (e.g. amplitude decreased from ~90 μV to ~20 μV at 80 dB SPL), where little cochlear amplification is necessary. This indicates that salicylate also imposes an acute effect on the IHC and/or SGN [6][34].

Chronic effects

High doses of aspirin and SS have long been thought to exert only temporary effects on the auditory system; however, recent studies suggest that high doses may induce permanent changes. Most *in vitro* and *in vivo* studies indicate that prolonged treatment with high doses of SS does not damage sensory hair cells *in vitro* or *in vivo*; however, it can affect SGNs [6][34][35]. To determine the effect of chronic salicylate treatment on the CAP, 6 rats were administered 200 mg/kg (i.p.) of SS 5 days a week for 3 consecutive weeks and a control group was given saline [5]. CAP I/O functions were measured four weeks after cessation of treatment. The SS-treated group showed a slight, but significant reduction in CAP amplitudes compared to the control group. CAP I/O functions were still non-linear in both groups indicating normal OHC function. However, when amplitudes were compared as a function of frequency, low and high frequencies were reduced more than mid-frequencies, consistent with the acute effects of SS on OHC functions [5]. Since the CAP was reduced in the chronic treatment group, but sensory cells appeared normal, these results imply that SS induced functional or structural damage to SGN. These results are consistent with auditory brainstem response (ABR) data showing a reduction of ABR amplitudes predominantly at low and high frequencies at high stimulation levels after chronic treatment with high doses of SS [5].

Cochlear Microphonic (CM) and Summating Potential (SP)

The effects of high doses of SS on the CM and SP have also been studied after systemic or local application of SS. The CM, generated predominantly by the OHCs in cooperation with +80 mV endocochlear potential, largely reflects the flow of potassium ions through the stereocilia on the apical pole of the OHCs in response to acoustic stimulation [36]. The SP, a sustained DC

potential evoked by sound stimulation, is predominantly generated by IHCs along with a smaller contribution from OHCs [37]. The effects of salicylate on the CM and SP in the guinea pig cochlea have been investigated by cochlear perfusions with salicylate followed by recording neural responses to tones [38]. The CM in response to a 10 kHz tone burst was largely unaffected by cochlear perfusion of salicylate [38]; however, others have found an increase in the CM response to a 1 kHz tone [39]. No significant change in the SP was seen following cochlear perfusion in the guinea pig. This functional data suggest that intracochlear perfusion of SS has little effect on hair cells.

Spiral Ganglion Neuron (SGN)

Recent research has demonstrated that high doses of SS can damage the SGN without concurrent damage to cochlear sensory cells [34] [35]. In order to evaluate the effects of

salicylate on the SGN, postnatal day 3 organotypic cultures were treated with SS for 48 hours. Hair cells were labelled with Alexa-488 conjugated phalloidin and auditory nerve fibres were immunolabeled with a monoclonal antibody targeting class III β-tubulin. SS treatment did not induce hair cell loss even at the highest dose of 10 mM; however, the peripheral fibres projecting out from the SGN to the sensory cells were decreased in number and showed many blebs and breaks which were positively correlated with increases in the dose of SS [34]. Figure 4-A shows the peripheral fibers from SGNs cultured under normal conditions (Figure 4-A1) and after being exposed for 96 h to 3 mM (Figure 4-A2), 5 mM (Figure 4-A3) and 10 mM (Figure 4-A4) SS. Nerve fibers exposed to SS showed fragmentation, blebs, and breaks that increased with the concentration of SS. The mean cochleograms in Figure 4-B shows the percentages of missing OHC and IHC in control cultures and cultures treated with 3, 5 or
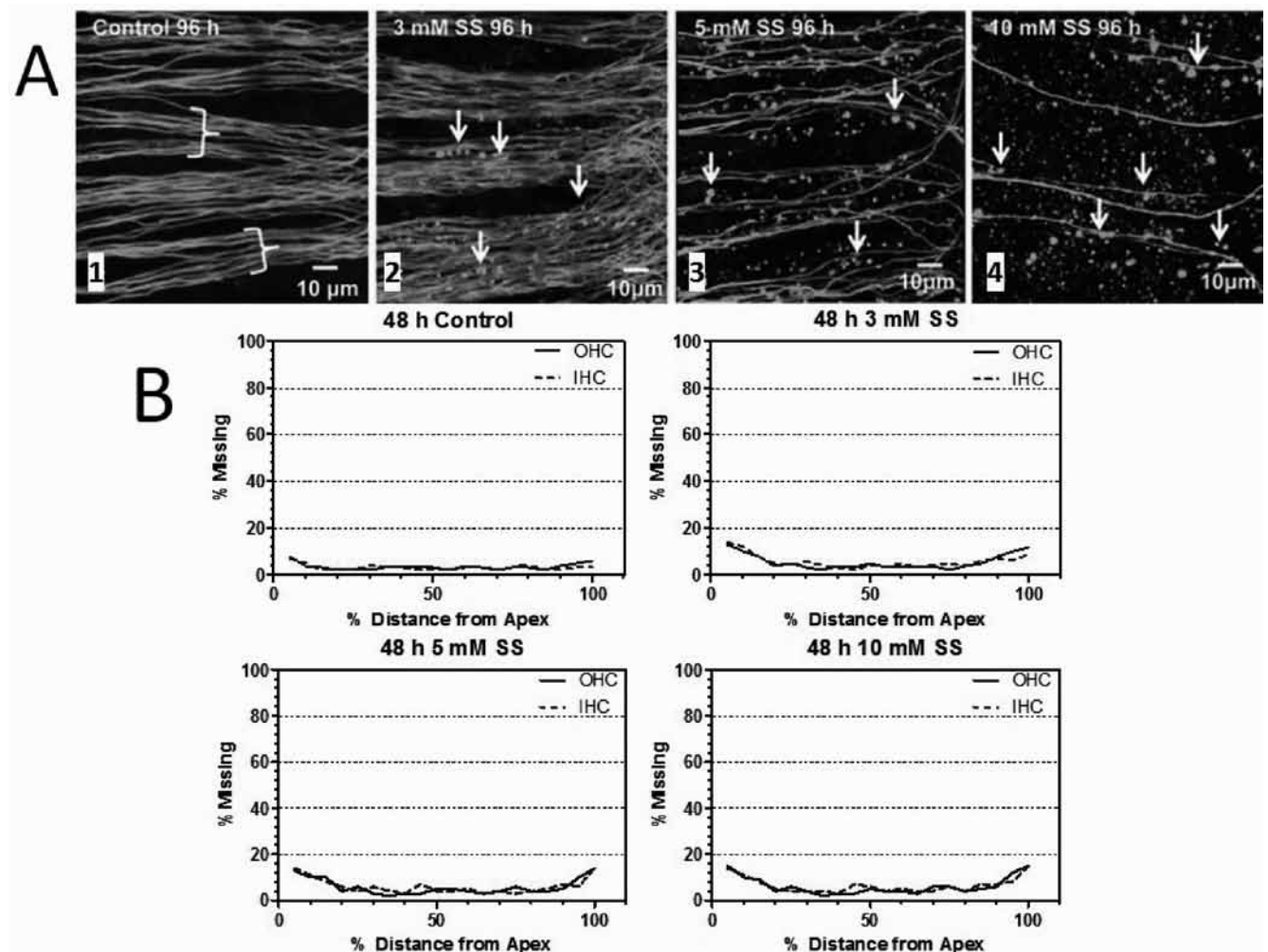
Fig. 4. (A) SGN fibres from the middle turn of the cochlea immunolabelled with primary antibody against β-tubulin and secondary antibody conjugated to Alexa Fluor 488 in control cultures and in 3, 5 and 10 mM SS for 96 hours. In control cultures, nerve fibres demonstrate thick healthy fascicles. With increasing concentrations of SS the nerve fibres show increasingly more fragmentations and blebs (white arrows), and ultimately nerve fiber disappearance in a dose dependent manner. Image obtained from Deng 2013, with permission. (B) Cochleogram representing the percentage of sensory cell loss in control cultures and cultures treated with 3, 5 and 10 mM SS for 48 hours. SGN fibres are degenerated when exposed to SS in a dose dependent manner; however, sensory cells appear structurally unaffected.

10 mM SS. These results indicate that even the highest dose of SS does not destroy hair cells [6]. In addition, recent *in vivo* studies indicate that high doses of SS can lead to SGN degeneration through caspase-mediated apoptosis [40]. Paradoxically, salicylate is a potent antioxidant with neuro- and oto-protective properties [41][42]. However, high doses of salicylate cause an upsurge of the highly toxic superoxide radical in SGNs but not neighbouring sensory and supporting cells [6]. Little or no dihydroethidium (DHE) staining, which labels the superoxide radical, was observed in control cultures. In cochlear cultures treated with 10 mM SS for 48 hours, a significant amount of DHE staining was observed in SGNs, but not in neighbouring sensory or support cells [6]. When cultures were treated with 10 mM SS plus 100 μM PyP, a cell permeable superoxide scavenger, they showed significantly less SGN damage than those treated with SS alone [6]. Thus, for reasons yet unknown, high doses of SS exert their toxic effects on SGN by selectively increasing the production of the superoxide radical in SGN, but not other cells in the inner ear.

Auditory Nerve (AN)
Auditory nerve fibre recordings following high doses of SS treatment have yielded variable results, which may be a result of the dosage, route of administration or species differences. In cats, a significant increase in spontaneous auditory nerve firing was observed following an extremely high dose of SS (400 mg/kg, i.v.) [43]. In contrast, in gerbils, a slight but significant reduction in auditory nerve firing rate following a moderate dose of SS (200 mg/kg i.p.) was observed in fibres with low characteristic frequencies (CFs), but not in fibres with high CFs [44]. However, cross comparisons between these species is unreliable due to the cats' inability to effectively metabolise salicylate [45][46]. The effects of chronic treatment of salicylate on spontaneous auditory nerve activity has also been evaluated [47]. The average spectrum of electrophysiological cochleoneural activity (ASECA), a measurement of auditory nerve activity, was recorded from the round window in guinea pigs over several weeks of salicylate administration (200 mg/kg/day, i.m.). Initially, the ASECA decreased in the followings hours after salicylate administration; however, after several days this suppression was alleviated and returned to normal levels. Over the following weeks the ASECA progressively increased; furthermore, after cessation of treatment the ASECA reversed and progressively decreased to the values measured initially [47]. The increase in auditory nerve spontaneous activity seen in these studies was suggested as the neural correlate of tinnitus [47][48]; however, the decrease seen in other reports raises questions about this model.
Taken together, the results indicate that salicylate's effect on the peripheral auditory system results primarily in a reduction of auditory sensitivity (threshold shift) caused

by the frequency-dependent suppression of OHC electromotility. Salicylate's influence on hearing sensitivity was previously thought to be temporary; however, recent data suggest that prolonged treatment with high doses of salicylate may lead to sustained OHC dysfunction [5] and degeneration of SGNs [6][34]. While some studies have reported an increase in spontaneous activity in the auditory nerve after SS treatment others have reported a decrease or no change [44]. Thus, it remains an open question as to what role auditory nerve spontaneous rates play in tinnitus perception, particularly since severe cochlear damage largely abolishes spontaneous activity [49].

Central effects

Inferior Colliculus (IC)
The IC was one of the earliest auditory brain regions used to investigate salicylate's effects on the central nervous system (CNS). The main inhibitory neurotransmitter in the CNS, γ-aminobutyric-acid (GABA), plays an important role in IC function. GABA-mediated inhibition plays a major role in shaping frequency tuning, binaural processing, and intensity coding in the IC [16][50-52]. Moreover, SS appears to modulate GABAergic activity indirectly by imposing suppressive effects on serotonergic-influenced GABAergic synaptic transmission [18].
Electrophysiological responses in the IC do not show sound-evoked hyperactivity following salicylate administration unlike higher levels in the central auditory system (Fig. 6-A) [13]. However, because the IC response amplitudes are nearly normal at suprathreshold levels whereas the CAP responses are reduced, these results imply that
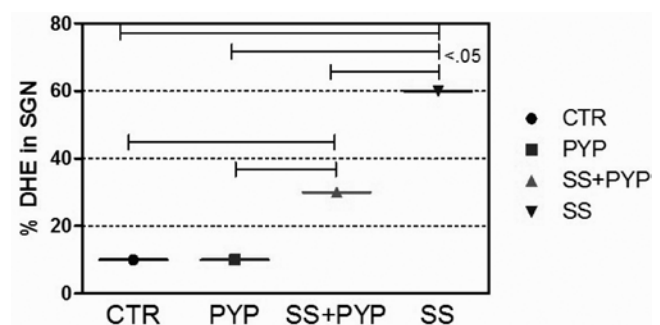
Fig. 5. The amount of DHE-positive staining in SGNs in control cultures, cultures treated with 100 μM PyP alone, 100 μM PyP plus 10 mM SS, and 10 mM SS alone. There was no significant difference between the control cultures and cultures treated with PyP alone. The percentage of DHE-positive staining in cultures treated with 100 μM PyP plus 10 mM SS was significantly larger then than the control or PyP alone cultures (P<0.05). Cultures treated with 10 mM SS alone showed significantly more DHE-positive staining than control, PyP alone and PyP plus SS cultures. This demonstrates that cochlear cultures that were exposed to 10 mM SS alone for 48 hours showed a significant upsurge in superoxide radical. When 100 μM PyP was combined with 10 mM SS there was significantly less superoxide present in the cochlea cultures. This indicates that PyP can protect against SS-induced upsurges in superoxide radicals that can lead to SGN apoptosis.
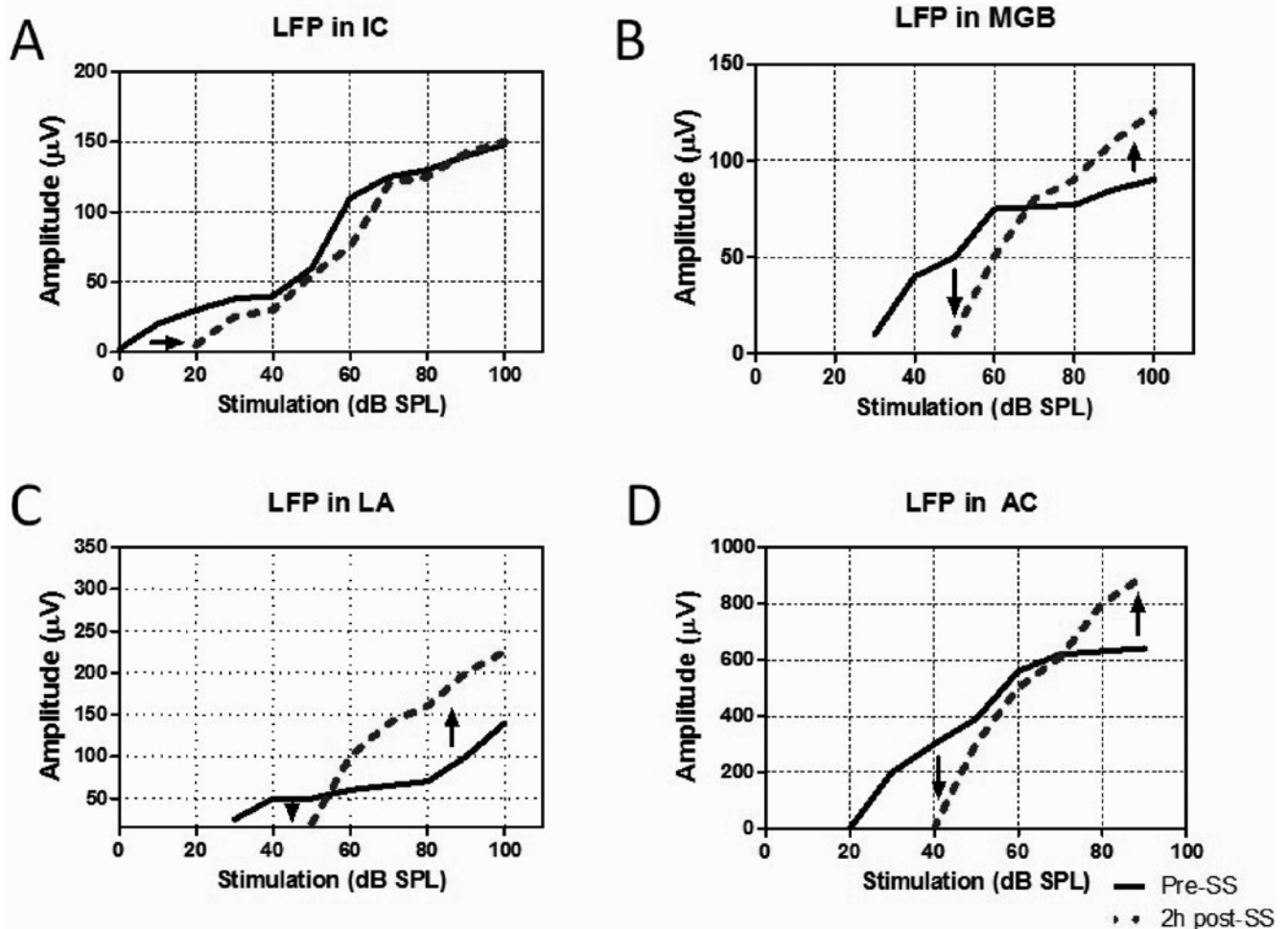
Fig. 6. The effects of systemic salicylate on the LFP of the IC, MGB, LA, and AC. (A) LFP in the IC pre- and 2 hours post- systemic administration of SS (250 mg/kg i.p.). Salicylate did not change the amplitudes recorded from the IC; however, an approximately 20 dB SPL threshold shift occurred. The threshold shift is most likely due to salicylates suppressive effects on OHC electromotive amplification. (B) LFP in the MGB pre- and 2 hour post- systemic administration of SS (300 mg/kg i.p.). There was an approximately 20 dB SPL threshold shift. At low stimulation levels LFP amplitudes were reduced. This could most likely be attributed to SS suppressive effects in the peripheral system. At high stimulation levels LFP amplitudes were enhanced. This can most likely be attributed to salicyte's inhibitory effects on GABAergic activity. (C) LFP in the lateral amygdala pre- and 2 hour post- systemic administration of SS (300 mg/kg i.p.). Results were similar to that seen in the MGB, approximately 20 dB SPL threshold shift, reduced LFP amplitudes at low stimulation levels, and enhanced LFP amplitudes with high stimulation. (D) LFP in the auditory cortex pre- and 2 hour post- systemic administration of SS (300 mg/kg i.p.). Again, the results are similar to those seen in the MGB and LA.

some compensatory increase in gain occurs after the auditory nerve to restore the IC amplitudes to their normal levels. Furthermore, electrophysiological recordings have indicated an increase in spontaneous activity in the external nucleus of the IC (eIC) following salicylate administration in guinea pigs [53]. In contrast, when recording from the central nucleus of the IC (ICc) in anaesthetised mice, acute salicylate administration reduced spontaneous activity in low frequency neurons [54] similar to what has been reported in gerbil auditory nerve [44]. Thus, different subdivisions of the IC appear to respond differently to high doses of SS.

Medial Geniculate Body (MGB)
The MGB of the thalamus is thought to play an essential role in sensory gating of auditory stimuli, and therefore

has been considered a possible contributor to tinnitus perception [55]. Extracellular recordings *in vitro* have indicated that salicylate can drastically alter the spontaneous firing rate of neurons in the MGB, although the direction of change is complex. Approximately 52.4% of neurons increased their firing rate after SS treatment while firing rates decreased in approximately 47.6% of neurons [56]. Salicylate also induces a slight increase in c-fos expression, an activity related protein, in the MGB [11]. In order to further evaluate the effects of salicylate in the MGB we measured the local field potentials (LFP) pre- and post-salicylate (300 mg/kg, i.p.). Figure 6-B shows the LFP I/O function to tone-bursts pre- and 2 hours post-salicylate. Salicylate induced a threshold shift of approximately 20 dB SPL, consistent with CAP threshold shifts. The LFP amplitudes were also decreased at low stimulus levels but

rapidly increased at high intensities. Preliminary recordings from multiunit clusters in the MGB also showed an overall increase in discharge rate post-SS treatment. Since the MGB provides excitatory inputs to the primary auditory cortex (A1), changes in the MGB are likely to significantly impact activity in A1.

Auditory Cortex (AC)

The preceding results have demonstrated that not only does salicylate suppress the neural output of the peripheral auditory system [5], but also alters activity in the CNS [11-14]. The cortex is highly plastic and shows remarkably robust changes in response to systemic salicylate as illustrated by the upsurge in c-fos immunolabelling, a marker of neural activity [11]. However, electrophysiological studies have found mixed results. In some cases, spontaneous firing rates in A1 and the anterior auditory field (AAF) decreased slightly post-salicylate [14 30] whereas the secondary auditory cortex (A2) showed an increase [57]. The A1 neurons mainly receive afferent inputs from the lemniscal pathway and A2 neurons receive afferent information from the extralemniscal pathway [58]. The reduction in A1 spontaneous firing rate following SS treatment may therefore be primarily due to the suppression of neural output from the cochlea and classical auditory pathway whereas the enhanced spontaneous firing seen in A2 may reflect the changes occurring at both auditory and non-auditory loci in the CNS. LFPs, which mainly reflect the pre-synaptic inputs, and spike discharges from multiunit clusters, which mainly reflect the outputs from AC, have been evaluated after systemic SS treatment (300 mg/kg i.p.) in anaesthetised rats. SS enhanced both the sound evoked LFP and multiunit spike discharges in the AC following systemic SS treatment [13 30 59]. Figure 6-D shows the sound-evoked LFP in AC as a function of stimulus intensity. At low stimulation levels the LFP is decreased and the threshold of the I/O function is elevated (shifted to the right) approximately 20 dB, which is consistent with salicylate's suppressive effects on the cochlea. In contrast to the reduced amplitudes seen in the cochlea, at high stimulation levels the amplitude of the AC LFP is enhanced compared to control amplitudes. One factor that may contribute to the enhanced AC amplitudes at suprathreshold levels is loss of GABA mediated inhibition. Evidence supporting this view comes from studies showing that systemic administration of baclofen, which increases $GABA_B$ –mediated inhibition, isoflurane anaesthesia which increases $GABA_A$ –mediated inhibition, or vigabatrin, which increases the GABA neurotransmitter concentration, can each suppress salicylate-induced hyperactivity in the AC [14]. These results support the hypothesis that the salicylate-induced hyperactivity seen in the AC and MGB may be due to a reduction in GABA-mediated inhibition [16 18].

Under normal circumstances, GABAergic circuits help to sharpen the frequency tuning of neurons in the AC. However, when GABA-mediated activity is pharmacologically suppressed frequency receptive fields (FRFs) may shift or expand. When bicuculline (BIC), a $GABA_A$ antagonist, was iontophoretically applied to the AC of chinchillas, it resulted in an expansion of neuronal frequency tuning [60]. The FRFs in the AC are also altered by high doses of salicylate, consistent with salicylate's effects on GABA [16 18]. Approximately 2.5 hours following systemic SS treatment, there was a frequency-dependent shift in CF and a widening of AC tuning curves [12]. This resulted in an over-representation of mid frequencies (10-20 kHz), which has previously been reported as a possible perceptive frequency for salicylate-induced tinnitus [30]. Figure 7-A shows the CF (x-axis) and CF threshold (y-axis) of each AC neuron pre-salicylate and Figure 7-B shows the CF and CF-threshold at 2 hours post-salicylate (300 mg/kg, i.p.). Many low-CF neurons up-shifted their CF to 10-20 kHz whereas many very high CF units down-shifted their high CF toward 10-20 kHz. The dramatic shift in FRFs in A1 could be a result of two factors. First, DPOAE and CAP data show a frequency-selective reduction in cochlear amplification that was greatest at very high and very low frequencies and least at mid-frequencies [5], which may alter the FRF within A1. Second, the salicylate-induced reduction of cortical inhibition may contribute to the broadening and CF shifts of AC neurons [18 60].

Similar to other regions of the neocortex, the auditory cortex is comprised of approximately six interconnected layers with a multitude of neuron types [61]. An *in vitro* assessment revealed significant differences in the response of different types of neurons in the AC after perfusion with 1.4 mM salicylate. The threshold current needed to evoke
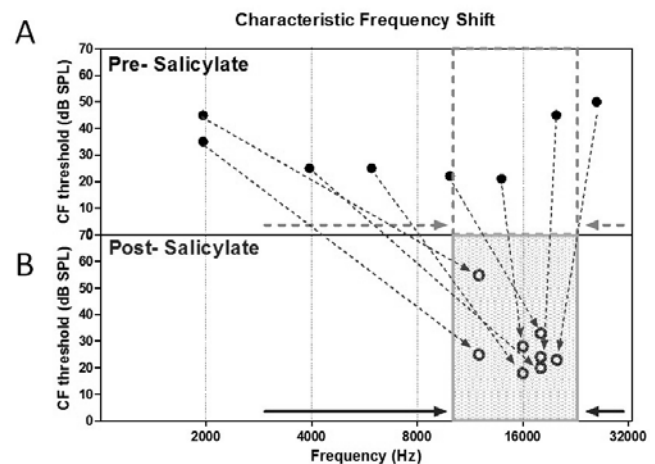
Fig. 7. (A) Characteristic frequency thresholds obtained from the auditory cortex prior to systemic administration of SS. (B) Characteristic frequency thresholds obtained from the same location as those displayed in panel A 2.5 hours post systemic administration of SS (300 mg/kg i.p.). After the injection, neurons shifted their frequency tuning upward and downward to the 10-20 kHz frequencies region, causing an over-representation in the mid frequencies around 16 kHz. This pitch has also been identified as a possible pitch for salicylate-induced tinnitus.

an action potential was significantly increased and current-evoked firing rates in fast-spiking interneurons were greatly depressed, however pyramidal neurons appeared unaffected [62]. These results indicate that salicylate preferentially impairs the function of fast-spiking GABAergic, inhibitory interneurons in specific cortical layers [62]. Current source density (CSD) analysis has also been used to study the effect of salicylate on stimulus-evoked LFP emanating from different layers of the AC *in vivo*. CSD analysis improves the spatial localisation of current sources (hyperpolarisation) and sinks (depolarisation) in different layers of the AC by taking into account the LFPs recorded from neighbouring electrodes. CSD analysis of sound-driven LFPs from the A1 region of the AC showed that systemic salicylate had much greater effects on some layers of the auditory cortex than others [63]. Under normal circumstances, CSD maps indicate a large, short latency, monosynaptic, and thalamically-driven sink in the granular layer (gSK) and a smaller, longer latency, polysynaptic, intracortically-driven sink in the supragranular layers (sSK) [63]. However, after systemic administration of

salicylate, the sink amplitudes in both gSK and sSK are enhanced significantly [63]. Additionally, the peak latency of sSK was reduced indicating more rapid processing in the supragranular layer of A1. The CSD results indicated that systemic salicylate significantly altered the intracortical microcircuits in the primary AC [63].

Local Applications of SS

To identify the central effects of salicylate independent of peripheral changes, SS was locally applied to the AC or the cochlea. Figure 8 shows the sound-driven LFP I/O functions in the AC before and after local application of SS to the cochlear round window or to the AC. When salicylate was locally applied to the round window both the CAP and AC sound-driven responses were significantly reduced and the threshold was increased approximately 25 dB [13] (Figure 8-B, C). However, when salicylate was applied locally to the auditory cortex (Figure 8-A) there was a significant enhancement of the sound-driven response in the AC, but no change in threshold [13]. Figure
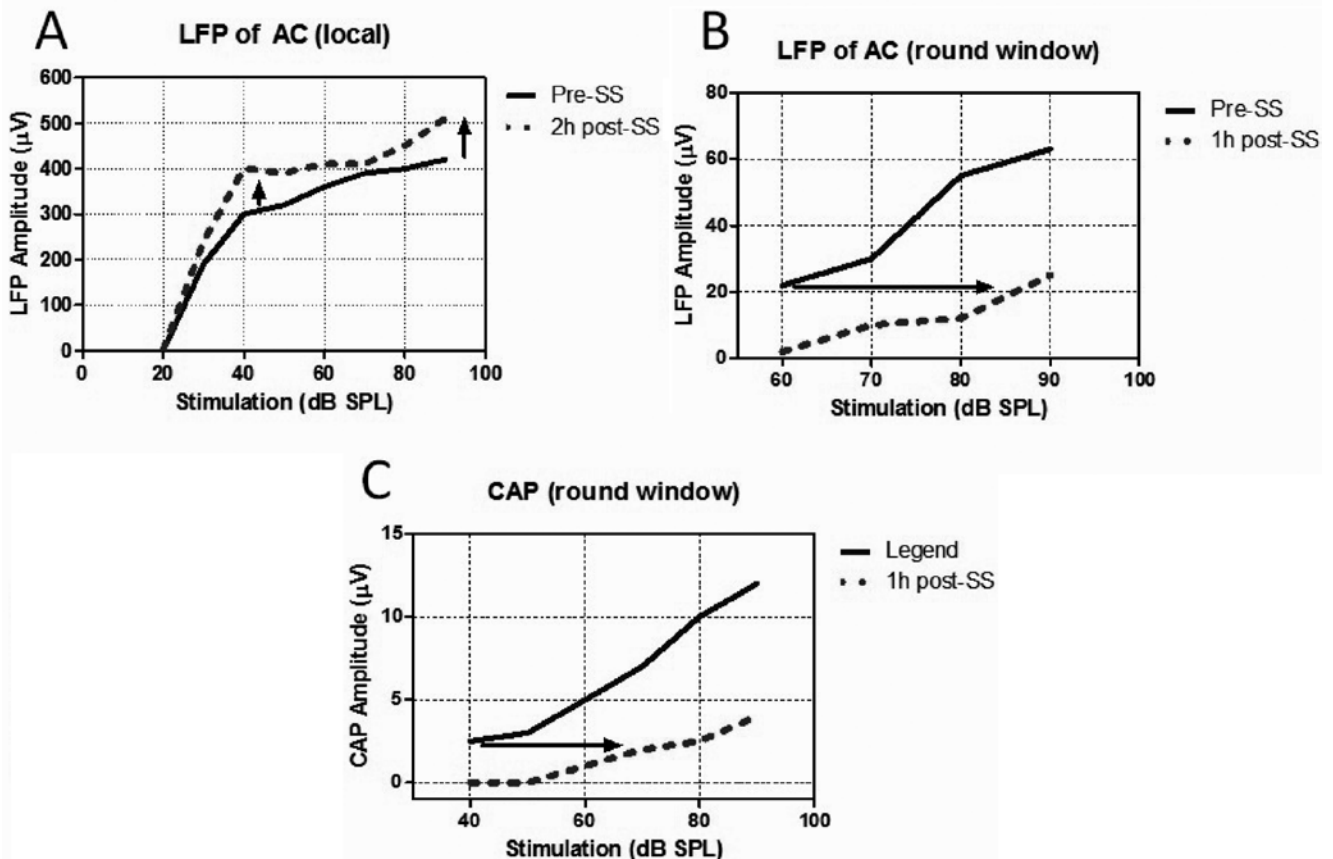
Fig. 8. Comparison of the effect of salicylate on auditory cortex LFP pre- and post-salicylate treatment with different administration routes. (A) The effect of salicylate when locally administered to the AC surface. Local administration to the AC hyper-activates the cortex with no shift in threshold or suppressed LFPs at low stimulation levels. (B) The effect of salicylate on the AC LFP when locally administered to the round window of the cochlea. Local application to the round window results in decreased LFP amplitudes and significant threshold shift in the AC. (C) The effect on CAP when salicylate is locally applied to the round window of the cochlea. The results are similar to those seen on the LFP in AC when salicylate is applied locally to the round window. This suggests that the threshold shift and suppressed LFP amplitudes seen at low stimulation levels after systemic administration of salicylate are caused by the effects of salicylate on the cochlea and the enhanced LFP amplitudes seen at high stimulation level are a result of salicylate's influence on GABAergic neurotransmission in the CNS (i.e. LFP of AC when SS is applied locally).

6-D shows the sound-driven response from the AC when salicylate was systemically administered; the threshold shift in AC observed with systemic treatment largely originates in the cochlea whereas the hyperactivity in the AC originates in the CNS.

Non-Classical Auditory Structures

Lateral Amygdala (LA)

Interestingly, nuclei outside of the classical auditory pathway respond to acoustic stimuli, and therefore may contribute to auditory functions involved with hearing sensitivity and tinnitus perception. The amygdala, part of the limbic system, plays a role in emotional regulation and attribution of emotional significance to sensory stimuli [64 65]. Since tinnitus severity is often correlated with an individual's tolerance, annoyance, stress or depression [66], the amygdala may play a role in tinnitus. Many neurons in the LA produce robust responses to acoustic stimuli and have good neuron frequency tuning; however, its tonotopic organisation is more complex than that of the AC [19 67 68]. Similar to what occurs in the AC, systemic administration of SS enhances suprathreshold, sound-driven LFPs and alters the tuning and tonotopy of FRFs [19]. Figure 6-C shows the I/O response of the LA before and after systemic salicylate treatment. At high intensity levels, the sound-driven response of the LA is hyperactive; however, at low intensities, the response is suppressed and threshold is elevated [19]. The threshold shift and suppression of low intensity sounds is a reflection of salicylate impairment of OHC amplification [5]. Interestingly, local application of salicylate to the LA enhanced suprathreshold, sound-driven activity in the AC, but did not alter threshold or responses to low intensity sounds in the AC [19]. These findings are consistent with morphological assessments showing that A1 has numerous sub-cortical pathways to areas in non-classical auditory regions such as the LA and striatum (CPu) [69]. Injection of bidirectional fluorescent axonal tracers into A1of the gerbil indicated that 76% of neural pathways extend to subcortical structures while only 24% extend to cortical structures [69]. Taken together, these findings indicate that salicylate not only affects the cochlea, but also exerts pronounced, widespread and bidirectional effects between the central auditory pathway and other regions of the CNS. Thus, the induction of salicylate-induced tinnitus may involve aberrant neural activity within as well as outside the classical auditory pathway.

Human perceptual deficits resulting from salicylate

Hearing sensitivity, tinnitus and supra-threshold measures of hearing are the three main perceptual alterations noticed when humans ingest large amounts of aspirin. Information obtained on the effect of large doses of aspirin in human subjects has mainly been obtained from suicide attempts, rheumatoid arthritis patients and some psychoacoustic studies [8].

Hearing Sensitivity

Some human studies have indicated a moderate dose of aspirin can induce a hearing loss of up to ~40 dB in subjects that received 4 gm of aspirin/ day for 3-4 days [22]. However, other studies providing similar dosage and time periods (3.9 gm for 3-4 days) have found that the subjects only incurred an average hearing loss of ~15 dB [4 8 70 71]. Aspirin appears to influence hearing sensitivity across the human auditory frequency spectrum; however, most studies have neglected to evaluate hearing above 8 kHz [8 72 73]; and some have indicated a greater threshold shift in the high frequencies [74 75]. Spontaneous otoacoustic emissions in subjects that received three 325 mg tablets every six hours for 3.75 days were completely abolished [76]. Plasma salicylate levels seem to have a good correlation with the degree of hearing loss for serum salicylate concentrations in the range of ~60-300 mg/l [22 70].

The effects of extreme doses of aspirin have been evaluated in some cases of attempted suicide. In one case, 10 gm of ingested aspirin resulted in severe hearing loss and a strong tinnitus perception within 22 hours [74]. DPOAEs were found to be present during aspirin intoxication; however, the responses were linearised, indicating reduced OHC function. After recovery, DPOAEs were within normal limits and showed a non-linear response pattern indicating that OHC function had been restored [74]. The perceptual and electrophysiological effects of extreme doses of aspirin (100 aspirin tablets) observed in a young adult male included bilateral tinnitus and hearing difficulty. Serum salicylate levels were 606 mg/l and pure tone audiometry showed a 30 dB HL bilateral hearing loss that was slightly worse in the high frequencies [77]. EcochG recordings made from electrodes on the promontory of the middle ear and reference electrodes on the forehead and mastoid process showed a recruiting, biphasic waveform, indicative of cochlear damage and a 50 dB threshold. One day post-ingestion, the patient reported a subjective decrease in tinnitus and an improvement in hearing sensitivity. The pure tone audiogram reverted back to normal and EcochG recordings showed a normal waveform with a threshold of 20 dB [77]. The previous cases suggest that aspirin can reliably impair hearing thresholds at extreme doses, but at moderate doses the effect on hearing sensitivity is more variable.

Supra-threshold effects

It is apparent that aspirin and/or salicylate cause a sensory hearing loss. It is well known that sensory hearing loss can reduce one's ability to accurately perceive speech in noise even when the signal is presented at an individual's

most comfortable level (MCL). Young & Wilson et al. (1982) investigated the effects of acetylsalicylic acid on speech discrimination ability in quiet and in the presence of filtered speech spectrum background noise. Measurements were obtained at three signal-to-noise ratios (SNRs 0, -4, and -8 dB HL) before and after high doses of aspirin. The average results from five subjects demonstrated a significant reduction in speech reception ability at the -8 SNR condition (Fig. 9-A). However, when the subject's scores were examined individually it was clearly apparent there was large individual variability (Fig. 9-B) [20]. As shown in Figure 9-B, subjects 1 and 2 both showed more difficulty discriminating speech in noise following high doses of aspirin even though they showed no significant reduction in pure tone threshold or speech discrimination in quiet following aspirin ingestion [20]. This study illustrates the variability that salicylate can have on auditory perception of supra-threshold stimuli.

Aside from speech discrimination aspirin can also affect temporal integration. Monaural thresholds were measured at 500, 1000, 4000, and 8000 Hz using tone durations between 1 and 1000 msec. Fourteen subjects given 4 g/day of acetylsalicylate for 3-4 days were evaluated before, during and after salicylate treatment [22]. Figure 10 shows the threshold difference between long and short duration tones plotted as a function of time. Under normal conditions, the threshold of a 500 msec tone is generally 15-20 dB lower than 10 msec tones (Fig. 10-B). The improvement of threshold with increasing duration is referred to as temporal summation or temporal integration. The neural mechanism for integrating acoustic energy over time is thought to arise in a neural integration process located in the central auditory system [78]. Treatment with a high dose of salicylate induces a threshold elevation, but the threshold shift is greater for long duration tones than short duration tones. Consequently, the difference in threshold between a 10 msec tone and 500 msec is generally 10 dB or less (Fig. 10-A) [22]. The slopes of the threshold-duration functions after salicylate treatment are shallower than normal. The threshold elevation
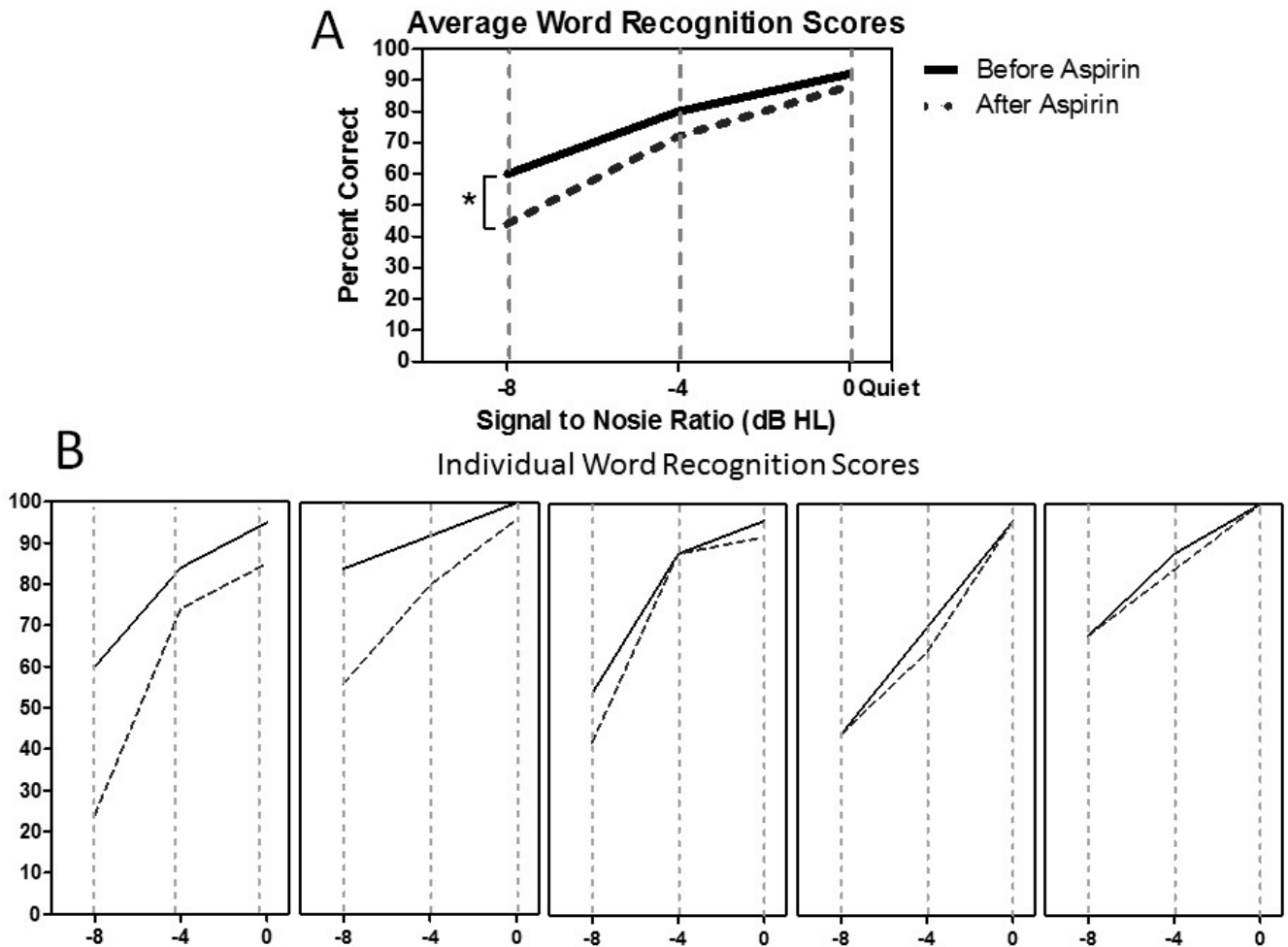
Fig. 9. (A) Mean percent correct WRS in noise as a function of SNR. After a high dose of aspirin there was a significant reduction in word discrimination ability at a SNR of -8 dB HL. (B) Individual WRS in noise as a function of SNR. When averaged together aspirin appears to have a significant reduction in word discrimination ability in noise; however, when observed individually it appears that aspirin's effect on word discrimination has large variability.
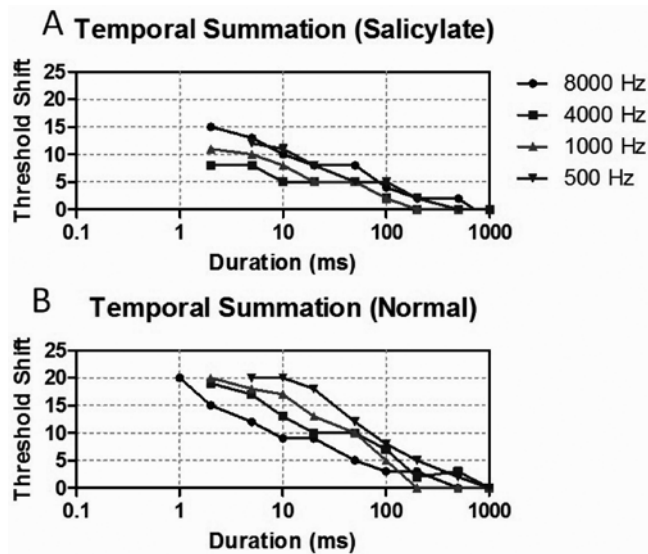
Fig. 10. Schematic of temporal summation alterations following chronic dosing (4 g/day for 3-4 days) of acetylsalicylate. Temporal summation was tested at 500, 1000, 4000 and 8000 Hz. (A) Temporal summation ability during salicylate treatment (B) temporal summation abilities after cessation of salicylate treatment. After cessation of treatment with acetylsalicylate the slope becomes steeper indicating a better threshold for long duration tones. The effects of salicylate on temporal summation is most likely directly related to its alteration in peripheral hearing sensitivity as these results are similar to those seen in presbycusis and acoustic trauma individuals.

is thought to be due to cochlear pathology while the decrease in temporal summation is thought to be due to a change in integration processes located in the central auditory system.

Salicylate has an effect on temporal resolution or the ability to detect rapid changes in an acoustic signal. One simple measure of auditory temporal resolution is the ability to detect a short duration silent interval, or gap, in an ongoing noise. In normal hearing individuals gap detection thresholds become shorter (better temporal acuity) with increase in sound intensity reaching a minimum gap value around 60 dB SPL. To determine if salicylate would impair temporal resolution, five patients were given 3.9 gm of aspirin (salicylate) a day for a period of five consecutive days. The individuals were tested on their ability to accurately identify silent gaps in a narrow band background noise centred near 0.5 kHz or 3.5 kHz. Measurements were obtained before and during aspirin administration. After salicylate, gap thresholds became longer in four of five patients, i.e. aspirin-induced hearing loss resulted in poorer (longer gap thresholds) temporal resolution [79]. These results are consistent with other studies showing presbycusis and noise-induced hearing loss result in poor temporal resolution.

Discussion

High doses of aspirin and SS have provided researchers with a powerful tool for inducing hearing loss and tinni-

tus. With short-term administration, the effects appear to be completely reversible whereas long-term administration appears to induce a unique form of damage to SGN. While salicylate and aspirin were originally believed to only affect the cochlea, more recent studies suggest that it can also have profound effects on the CNS, which should come as no surprise given that aspirin is used for relief of pain, headaches and fever. Studies of salicylate and aspirin induced ototoxicity have substantially enhanced our knowledge of auditory perception and function over the past decades and continues to be a valuable tool for investigating hearing loss and tinnitus. However, the mechanisms by which salicylate induces tinnitus, cochlear hearing loss and change the gain of the central auditory pathway are still not fully understood.

Peripheral frequency dependency

Peripherally, salicylate suppresses the electromotile response of the OHC [5] by binding to anion binding sites on the motor protein prestin [23]. This impairs hearing sensitivity in animals and humans. Salicylate's effects on OHC amplification has frequency-dependent characteristics on DPOAE and CAP measurements in rats with the greatest suppressive effects in the low and high frequencies and the least at the mid-frequencies [5,12]. However, measurements in humans have shown the greatest threshold shift at high frequencies [74,75]. During supra-threshold testing in humans, such as speech recognition in noise, the effects of salicylate vary across individuals; some subjects show compromised speech recognition at all SNR while others show almost no effect [20]. The spectrum of speech is such that consonants contain primarily high frequency sounds, while vowels contain primarily low frequencies. If high frequency hearing is compromised due to salicylate ototoxicity, then it would also compromise an individual's ability to effectively discriminate the consonant speech sounds. Surprisingly, there was no apparent correlation between the severity of salicylate-induced hearing loss at high frequencies and speech recognition scores. In addition, in humans there does not appear to be a frequency-dependent effect on temporal integration abilities measured with brief tone audiometry. However, aspirin tended to have a greater effect on low frequency gap-detection threshold than high frequency gap threshold.

Central hyperactivity and re-tuning

Salicylate's effects on the CNS seem paradoxical in light of the changes seen in the cochlea. While salicylate suppressed the neural output of the cochlea at all intensities, it enhanced LFPs and sound-driven firing rates at high intensities in the central nervous system. CSD analysis indicated that the amplified neural signal in the auditory cortex stems from changes in the intra-cortical circuits within A1 [63]. The amplitude enhancements seen at high intensities have been well established in the AC [12,13,63]

and recently in non-classical auditory structures such as the amygdala [19]. While systemic salicylate did not lead to an amplitude enhancement in the IC, the IC responses were depressed much less than those in the cochlea. One interpretation of these results is that some signal amplification occurring between the cochlea and the midbrain partially compensates for the diminished cochlear output. Since GABAergic inhibition is present in the IC and even lower levels of the auditory pathway, any salicylate-induced reduction in GABA-mediated inhibition in the brainstem would tend to enhance the incoming signal from the brainstem [13 30 80]. Systemic SS treatment also induced significant CF shifts in the AC as well as the LA, which results in an overrepresentation of mid frequencies [12 19]. High and low frequency neurons shift their best frequencies downward and upward respectively resulting in an over representation of the mid-frequencies. The mechanisms that are responsible for the salicylate-induced CF shift are not fully understood; however, it is most likely due to two factors. One is salicylate's frequency-dependent influence in the periphery which affects mid frequencies less than high and low frequencies [5]. This means that the neural signal being transmitted to central auditory structures has the lowest thresholds and largest responses in the mid frequencies. Another factor is salicylate's influence on GABAergic activity. GABA plays a major role in maintaining sharp frequency tuning [60] and salicylate has been shown to suppress serotonin-mediated GABA inhibition [18]. These results suggest that the salicylate-induced CF shifts seen in the AC and LA may be the result of frequency-dependent peripheral effects and loss of centrally mediated inhibition that creates a permissive environment for re-tuning the neural circuits in the cortex.

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Stapler suture of the pharynx after total laryngectomy

Uso della suturatrice Stapler per la chiusura del faringe, dopo laringectomia totale

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SUMMARY

The use of a stapler for pharyngeal closure during total laryngectomy was first described in 1971. It provides rapid watertight closure without surgical field contamination. The objective of our study was to compare the incidence of pharyngocutaneous fistula after total laryngectomy with manual and mechanical closures of the pharynx. This was a non-randomised, prospective clinical study conducted at two tertiary medical centres from 1996 to 2011 including consecutive patients with laryngeal tumours who underwent total laryngectomy. We compared the incidence of pharyngocutaneous fistula between two groups of patients: in 20 patients, 75 mm linear stapler closure was applied, whereas in 67 patients a manual suture was used. Clinical data were compared between groups. The groups were statistically similar in terms of gender, age, diabetes mellitus, smoking and alcohol consumption and tumour site. The group of patients who underwent stapler-assisted pharyngeal closure had a higher number of patients with previous tracheotomy (p < 0.001) and previous chemoradiation (p < 0.001). The incidence of pharyngocutaneous fistula was 30% in the mechanical closure group and 20.9% in the manual suture group (p = 0.42). In conclusion the use of the stapler does not increase the rate of fistulae.

KEY WORDS: Surgical staplers • Suture techniques • Cutaneous fistula • Laryngectomy • Laryngeal neoplasms • Carcinoma • Squamous cell

RIASSUNTO

L'uso della suturatrice meccanica Stapler per la chiusura del faringe durante la laringectomia totale è stato descritto per la prima volta nel 1971. Questa tecnica consente una rapida chiusura a buona tenuta senza contaminazione del campo operatorio. L'obiettivo del nostro studio è stato quello di confrontare l'incidenza di fistola faringo cutanea dopo laringectomia totale con chiusura manuale o meccanica del faringe. Questo studio clinico non randomizzato prospettico è stato realizzato arruolando pazienti consecutivi dal 1996 al 2011 affetti da tumore della laringe e candidati a laringectomia totale. Abbiamo confrontato l'incidenza di Fistola faringo cutanea fra due gruppi: nel primo gruppo di 20 pazienti la chiusura del faringe è stata realizzata mediante una suturatrice meccanica di 75 mm "Linear stapler", mentre nel secondo gruppo di 67 pazienti la chiusura era stata realizzata manualmente. I gruppi erano statisticamente sovrapponibili in termini di sesso, età media, prevalenza di fattori di rischio quali diabete mellito, fumo, dimensioni del tumore e assunzione di alchool. Nel gruppo di pazienti in cui la chiusura del faringe è stata realizzata con suturatrice meccanica, tuttavia, era più alto il numero di pazienti sottoposti precedentemente a tracheotomia (p < 0,001) e radio chemioterapia (p < 0,001). L'incidenza di Fistola faringocutanea nella nostra casistica era del 30% nei pazienti in cui la chiusura del faringe era stata realizzata con suturatrice meccanica e del 20,9% nei pazienti in cui la sutura era stata realizzata manualmente. Dal punto di vista statistico questa differenza non era significativa (p = 0,42). In conclusione l'uso della suturatrice meccanica stapler non aumenta il tasso di incidenza di Fistola faringo cutanea dopo laringectomia totale.

PAROLE CHIAVE: *Stapler • Tecnica di sutura • Fistola faringo cutanea • Laringectomia totale • Tumori della laringe • Carcinoma squamoso*

Introduction

Pharyngocutaneous fistula is the most common surgical complication after total laryngectomy. It is associated to a higher incidence of morbidity, hospitalisation and costs [1 2].

Although a stapler has only recently been used for pharynx closure, it has been widely applied in gastrointestinal surgeries. The use of a stapler during the resection of Zenker diverticula was described for the first time in 1969 [3].

The use of a stapler for pharyngeal closure after total laryngectomy seems to be adequate for endolaryngeal tumours [1]. It was first described in 1973 [4]. The closure is watertight and the contamination of the surgical field by secretions from mouth and pharynx decreases. As a result, the occurrence of pharyngocutaneous fistula is minimised, even in recurrent cases after radiation therapy [5]. Furthermore, pharynx closure is faster [6-9].

In spite of being a relatively simple technique with potential advantages, there is a lack of comparative studies available in the literature. Our objective was to evaluate

the incidence of pharyngocutaneous fistula after total laryngectomy comparing manual and mechanical closures of the pharynx in patients with laryngeal cancer.

Materials and methods

This survey was approved by the board of the hospitals were it was performed.

This non-randomised prospective study included consecutive patients with laryngeal squamous cell carcinoma who underwent total laryngectomy with curative intent in two tertiary reference hospitals from 1996 to 2011. The patients were operated on by the same surgical team.

Patients with hypopharyngeal carcinoma, extralaryngeal tumours or tumours involving the base of the tongue were excluded from the stapler group. However, T4a patients with only invasion of the thyroid cartilage were eligible for stapler use, since this invasion is external to the laryngeal frame and the oncological margins can be clearly verified independently of the type of pharyngeal closure employed. In the control group, patients with tension in the suture line not eligible for primary closure were excluded. Tumours were staged according to the TNM staging system adopted by AJCC and UICC.

These two groups were compared according to gender, age at the time of the operation, diabetes mellitus, smoke and alcohol habits, primary site of the lesion, previous tracheotomy, previous treatment (in case of salvage surgery), operation time, neck dissection and the development of pharyngocutaneous fistula. Clinical characteristics are presented in Table I.

There were 30 cases of residual or recurrent laryngeal tumours after organ preservation protocol, with radiation therapy doses between 6,000 and 7,020 cGy and weekly cisplatin 40 mg/m^2. The radiation therapy was interrupted at 5,040 cGy due to tumour increasing. The time between detection of therapeutic failure and salvage surgery varied from 4 weeks to 7 months. Previous chemoradiation organ sparing treatment was not employed in any patient.

Technical aspects

Patients received prophylactic antibiotics (clindamycin associated with amikacin) up to 24 hours postoperative, with the first dose during anaesthetic induction. After general anaesthesia with endotracheal intubation, tracheotomy was performed. Thus, direct microlaryngocsopy was performed in order to verify the tumour stage. Uni- or bilateral neck dissection was performed according to tumour extension and lymph node involvement with preservation of the XII nerve whenever possible. For facilitating the placement of the stapler, the pyriform sinuses and internal perichondrium of the thyroid cartilage were dissected from the lateral aspect of its lamina and the superior cornu of the thyroid cartilage, and the great cornus of the hyoid bone were cut. The epiglottic free border was pulled into the endolarynx using an Allis clamp. Thus, a 75 mm linear stapler TCL75 Ethicon® was longitudinally applied at the vallecula level, as close as possible to the thyroid cartilage lamina (Fig. 1). The double-staggered row was established by stapler activation, splitting the pharynx (closed) from the laryngeal specimen (Fig. 2). A secondary tracheo-oesophageal puncture was performed in all cases 3 months after surgery for vocal rehabilitation.

All patients were discharged from the 4th to the 7th postoperative day. In patients without any fistulas, oral feeding was started on the 10th postoperative day at the time of the nasogastric tube removal.

Statistical analysis

A p value of less than 0.05 was considered statistically significant. Univariate analysis was evaluated by χ^2 test at a confidence interval of 95%.

Results

Eighty-seven patients who underwent total laryngectomy due to laryngeal squamous cell carcino-

Table I. Clinical data of patients (n = 87).

	Mechanical suture (n = 20)	Manual suture (n = 67)	p
Gender (M/F)	19/1	61/6	0.51
Age (years)	62.0 ± 11.1	62.0 ± 11.2	1.00
Diabetes mellitus	1/20	3/67	1.00
Smoking	19/20	65/67	1.00
Alcohol assumption			
Clinical staging			
T2	4	3	< 0.001
T3	12	46	0.01
T4a	4	18	0.05
Primary tumour site			1.00
Supraglottic	3	10	
Glottic	17	57	
Hypoglottic	0	0	
Previous tracheotomy	13	17	< 0.001
Previous radiation therapy	15	15	< 0.001
Neck dissection			
No	3	3	0.003
Unilateral selective	2	2	0.04
Bilateral selective	12	12	< 0.001
Unilateral radical	1	9	0.02
Bilateral radical	2	41	< 0.001

Fig. 1. The stapler is put in place as close as possible to the thyroid cartilage lamina so as to preserve the maximum mucous by the pyriform sinuses.
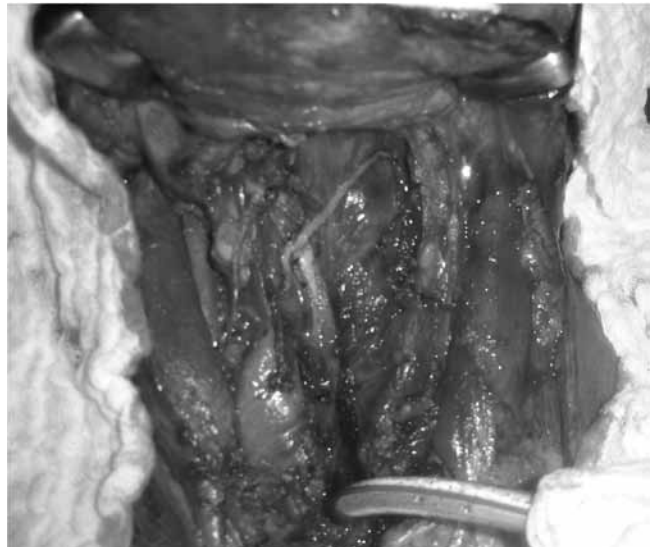
Fig. 2. The double-staggered row is established by stapler activation, splitting the pharynx from the laryngeal specimen.

ma were included in the study. Eighty patients were men (91.9%) and the age varied from 36 to 89 years, with average of 62.0 ± 11.2. The demographic and clinical characteristics of both groups are detailed in Table I.

There was no technical difficulty in the laryngeal preparation and stapler application. The groups were statistically similar in terms of gender, age, smoking and alcohol use and tumour site. Regarding the clinical staging of the primary site, there was a higher rate of patients of the stapler group staged as T2 and T3, whereas the rate of T4 tumours was higher in the manual suture group. T4 patients in the stapler group were in fact T4a patients with invasion of the thyroid cartilage only. Previous tracheotomy had been performed in 13 patients who underwent stapler closure (65%) and in 17 patients who underwent manual suture (25.4%; p < 0.001). Fifteen patients in the stapler group had undergone an organ preservation protocol (75%), whereas 15 patients in the manual closure group had undergone a similar approach (22.4%; p < 0.001). Regarding the neck approach, the majority of patients in the stapler group underwent bilateral selective neck dissection, whereas most of the other group underwent bilateral radical neck dissection.

The incidence of pharyngocutaneous fistula was 30% in the mechanical closure group and 20.9% in the manual suture group (p = 0.42).

Discussion

Pharyngocutaneous fistula is the most common complication encountered in the early postoperative period following total laryngectomy. Its incidence after head and neck surgery varies from 5% to 65% in the literature [1]. It continues to occur with distressing frequency, causing a considerable increase in morbidity, and often necessitating a greatly prolonged hospital stay and further operative procedures [6].

The limits of the indication of stapler for pharyngeal closure regarding the extension of the primary tumour must be respected. It should be confirmed by previous suspension laryngoscopy performed in the operating room [1]. The stapler is a reliable method if the limits of its indication regarding the primary tumour are considered [1] [10-13]. It is recommended that the procedure is reserved to cases in which, based on meticulous preoperative assessment with endoscopy and imaging, the endolaryngeal site of the tumour has been assessed [14] [15]. It should be considered that the tumour is not usually visualised during the resection, and a closed technique if applied improperly would compromise the oncological potential of the surgery, since it should be performed only for endolaryngeal tumours [7].

A selection bias derives from the inclusion of patients with hypopharyngeal, oropharyngeal or extralaryngeal extension in the control group (manual suture). In fact, these patients are prone to have a wider pharyngeal resection in order to assure safe oncological margins. It could be considered one important factor for developing a pharyngo-cutaneous fistula. However, patients with tension in the suture line and at an increased risk of fistula did not undergo primary closure and, as a result, were excluded from this study.

Some technical aspects should be observed. During performance of closed techniques, in some cases, it is difficult to keep the suprahyoid part of the epiglottis outside the jaws of the stapler. It has been suggested to introduce a hook or an Allis clamp into the laryngeal lumen through the trachea and, after taking the apex of the epiglottis, retract it towards the lumen, which we routinely perform. Another option is transforming the closed technique into a "semi-closed" one by creating a small opening in the mucosa of the vallecula epiglottica, through which the epiglottis can be extracted. As the linear stapler closure is

performed, the second surgeon must take care to keep the edges of such mini-pharyngotomy well above the jaws of the stapler. As this opening is small, the operating field is not contaminated by pharyngeal secretions [15].

Although the pharyngeal constrictor muscles have been considered as a sophisticated "neuromuscular compartimentalisation" [16] and many surgeons advocate a second layer closure of the constrictor muscles, this has been considered unnecessary with no change in fistula rates [17].

Favourable outcome, which includes a tension-free suture line, watertight closure of the pharynx and haemostasis with preserved viability of the mucosa, support stapler closure of the pharynx. At the end of the procedure, double-staggered rows of staples remain in the pharynx and laryngeal specimen, and minimise the risk of contamination of the surgical field by pharyngeal secretions [1 13].

The absence of pyriform sinuses, aryepiglottic and glossoepiglottic folds and vallecula involvement allow that there is no excessive resection of hypopharyngeal mucosa [5]. In our study, patients staged like this were not eligible to the stapler group and constitutes a selection bias.

The material applied on the mechanical suture has an excellent tolerance by tissues because of minimum inflammatory reaction. The absence of tissue necrosis was the main differential element between manual and mechanical sutures. In the former, necrosis is nearly inevitable, due to repeated aggression by clamps through ischaemia by surgical knots and frequent inclusion of mucosa in the suture line [5].

Although preoperative tracheotomy has been suggested a local risk factor, the majority of researchers found no significant relationship between preoperative tracheotomy and pharyngocutaneous fistula development [1 2].

Although organ preservation therapy increases the risk of fistula, there are other factors that affect their development, including the clinical and laboratory parameters of the patient, extent of the surgery, surgical technique, surgeon's expertise and postoperative care [1]. In the largest retrospective series with 1,415 patients undergoing total laryngectomy with mechanical closure of the pharynx, the rate of pharyngocutaneous fistula was 11.9%. The incidence among non-irradiated patients was 5%. After salvage surgery, the fistula incidence was 19.4% among patients irradiated up to 6,000-6,500 cGy, showing a greater possibility of fistula with progressively higher doses of radiation therapy [17]. In a retrospective analysis of 268 patients who underwent total laryngectomy, pharyngocutaneous fistula was found in 43 patients (16%). Predisposing factors for fistula included previous radiotherapy, supraglottic primary site and concurrent radical neck dissection. Among the 43 patients who developed fistula, 41.8% had previously undergone radiotherapy (p < 0.05) [18]. In our series, there were 15 patients who underwent previous chemoradiation therapy in each group. Thus, in spite of a higher rate of such patients in the stapler group (p < 0.001), there was

not a significantly increased risk for pharyngocutaneous fistula (p = 0.42).

In a series of 10 consecutive patients treated with stapler-assisted laryngectomy, primary tracheoesophageal prosthesis was applied at the time of the initial surgery under direct visualisation using a flexible esophagoscope without disrupting the stapler closure. All patients achieved alaryngeal speech and there were no complications [19]. We prefer applying this prosthesis in a secondary fashion, 3 months after the surgery.

The surgical length was decreased by an average of 43 minutes in the mechanical suture group compared to the manual closure group [9]. Data regarding the surgical time in the first operations was not available. Nonetheless, such an improvement in surgical time is clear.

In our study, the incidence of pharyngocutaneous fistula was 30% in the mechanical closure group and 20.9% in the manual suture group. However, this difference was not statistically significant (p = 0.42). We did not randomise this study because there was some difficulty in achieving extensive use of the stapler device in the beginning of the study, since it was usually applied only in gastrointestinal surgeries.

Our group of patients who underwent stapler-assisted pharyngeal closure had a higher number of patients with previous tracheotomy (p < 0.001) and previous chemoradiation therapy (p < 0.001). Even so, this procedure did no increase the rate of fistula (p = 0.42). The advantages of mechanical sutures are simple and fast application, watertight suture, prevention of field contamination, good speech and swallowing, without increasing the rate of pharyngocutaneous fistula. In spite of the cost of the stapler device, operating room expenses may also be reduced due to the decrease in operating time.

Conclusions

The use of a stapler does not increase the rate of pharyngocutaneous fistulae.

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Patients' survival after free flap reconstructive surgery of head and neck squamous cell carcinoma: a retrospective multicentre study

Sopravvivenza dopo chirurgia ricostruttiva con lembi liberi nel carcinoma spinocellulare del distretto cervico facciale: studio retrospettivo multicentrico

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SUMMARY

Head and neck squamous cell carcinoma of the (HNSCC) represents approximately 5% of malignant tumours in Italy. HNSCC are commonly treated with surgery or radiotherapy, or a combination of such therapies. The objectives of treatment are maximum cure rate balanced with organ preservation, restoration of form and function, reduction of morbidities and improvement or maintenance of the patient's quality of life. Immediate reconstructive surgery: local, regional or free flaps are now widely advised in the treatment of these patients. Microsurgical transfer requires expertise, is time and resource consuming, and as a whole requires substantial costs. These considerations introduce some concerns about the wide or indiscriminate use of free flap reconstructive surgery. When considering cost-benefit outcomes of such treatment, the main objective is undoubtedly, survival. This data is underreported in the current literature, whereas functional outcomes of free flaps have been largely diffused and accepted. This study collects data from 1178 patients treated with free flap reconstructive surgery following ablation of HNSCC in a group of Italian tertiary hospitals, all members of the Head & Neck Group affiliated with the Italian Society of Microsurgery. According to many authors, free flap surgery for HNSCC seems to be a beneficial option for treatment even in terms of survival.

KEY WORDS: Head and neck tumours • Free flap • Survival

RIASSUNTO

I tumori spinocellulari del distretto Cervico Facciale rappresentano circa il 5% dei tumori maligni in Italia. Essi sono comunemente trattati con chirurgia o radioterapia, o entrambi le terapie. La ricostruzione rappresenta un momento fondamentale della terapia nel rispetto della qualità di vita di questi pazienti. La microchirurgia ricostruttiva rappresenta la tecnica che offre i migliori risultati funzionali ma è oggetto di discussione in un rapporto costo-benefici. In questo lavoro sono raccolti ed analizzati i dati di 1178 pazienti provenienti dai membri del gruppo testa e collo, affiliato alla società Italiana di Microchirurgia, e i cui dati sono rapportati primariamente alla sopravvivenza.

PAROLE CHIAVE: *Tumori cervico-facciali • Lembi liberi • Sopravvivenza*

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents approximately 5% of malignant tumours in Italy. Well-recognised or suspected aetiological agents for most HNSCC occurrences are alcohol and tobacco consumption, oral lichen, misfit of prosthetic devices and comorbidities. Recently, human papilloma viruses have been causally associated with some oropharyngeal cancers [1]. According to the site of origin, HNSCC are commonly treated with surgery or radiotherapy, either alone or in combination; medical therapy (i.e. cytotoxic drugs, monoclonal antibodies) is often associated. The objectives of

such treatment are maximum cure rate balanced with organ preservation, restoration of form and function, reduction of morbidities and improvement or maintenance of the patient's quality of life.

Immediate reconstructive surgery is now widely advised in these patients. Local or regional flaps have a definite role in limited lesions and specific situations. Simple or composite free flaps allow *anatomical* repair of almost all defects after HNSCC ablation, whereas *functional* recovery is not always a guaranteed consequence of reconstruction. Microsurgical transfer requires expertise, is time and resource consuming, and as a whole implies significant costs [2]. These points introduce some concerns about wide or indiscriminate use of this technique. Mücke et al. [3] remark that some authors advocate that free flap reconstruction should be reserved to selected patients, namely those who are believed to have a better prognosis. Patients affected by local advanced-stage tumours have worse prognosis, but quite often they are those requiring an adequate reconstruction following extensive ablation [4]: in terms of cost-benefit analysis, these patients should receive fewer benefits from such complex surgery. However, when considering cost-benefit outcomes of such treatment, the main objective is, undoubtedly, survival. This data is underreported in the current literature, whereas functional outcomes of free flaps have been largely diffused and accepted [5 11].

The aim of this study is analysis of survival data in patients treated with free flaps following ablation of HNSCC in a group of Italian tertiary hospitals, all of which are members of the Head & Neck Group affiliated with the Italian Society of Microsurgery.

Materials and methods

Patients

Patients were recruited from centres indicated in Table I. Each participating centre was responsible for reviewing charts and collecting their own data in a database specifically constructed for this study. The study period spanned from the date in which free flap surgery was introduced in each hospital up to December, 31, 2008.

Only patients with demonstrated HNSCC were considered eligible for this case study, and those affected by other malignancies (i.e. sarcomas, malignant melanoma, salivary tumours, etc.) were deliberately excluded, in order to reduce the variability of prognostic factors. A multicentre study was proposed to acquire a larger quantity of cases available for analysis and a joint, elementary database was formed.

Subjects were included irrespective of being a candidate to free flap surgery as part of primary treatment or salvage surgery (Table II, including basic demographic data). All patients who underwent neoadjuvant chemotherapy were assigned to the previously untreated group;

Table I. Participating Centres.

Name of Centre
Istituto Nazionale Tumori, Milan
Clinica ORL, Università di Pavia, Pavia
Istituto Europeo di Oncologia, Milan
Clinica ORL, Università di Brescia
Clinica ORL, Università di Bologna
Ospedale Martini, Torino
Ospedale San Giuseppe, Milan
Ospedale Forlanini, Roma
Chirurgia Maxillo-Facciale, Università di Milano-Bicocca
Clinica ORL, Università di Ferrara

Table II. Patient characteristics (N = 1178).

Characteristics	Value (%)
Age, years	
Median	58
Range	17-85
Gender	
Male	851 (72.2)
Female	327 (27.8)
Previous treatment	
NO	791 (66.3)
Recurrence	397 (33.7)
Margins	
Clear	958 (81.3)
Involved	220 (18.7)
Site	
Oral cavity	842 (71.5)
Larynx-hypopharynx	188 (16.0)
Pharynx	83 (7.0)
Cranio-maxillo-facial	65 (5.5)
pT	
pT0/pTx	33 (2.8)
pT1	51 (4.3)
pT2	349 (29.6)
pT3	165 (14.0)
pT4	580 (49.2)
pN	
N0	559 (47.5)
N+	557 (47.3)
Nx	62 (5.2)
Adjuvant therapy	
NO	557 (47.3)
RT	434 (36.8)
CT+RT	133 (11.3)
CT	33 (2.8)
Na	21 (1.8)

for any other preoperative treatment patients had received despite the circumstance, they were attributed to the salvage surgery group.

All reconstructions were performed at the same ablative episode and, whenever possible, a two-team approach was used.

Due to the number of subsites of tumour origin, some data dispersion would have been expected, and therefore only major categories were considered and subjects were grouped according the main affected site (Table II). Similar belief about pT stratification (Table II) led us to not consider it in survival analysis.

All subjects were treated with curative intent with the aim of complete surgical ablation. Clearance of resection margins (involved or close to less than 5 mm were considered adverse event), pathological nodal status (any pN+ was defined as an adverse event) and adjuvant treatment, all recognised important prognostic factors, were also recorded and analysed.

Flap type and success rate were also investigated, but data were not reported as they were considered beyond the scope of this study.

The survival duration period was defined as the interval from surgery (see above) and the day of death from cancer or the end of follow-up (disease-specific survival, DSS).

Data analysis

Data from each participating hospital were compiled in a single database by appending them. Statistical analysis was performed with the software WinStat® for Excel (R. Fitch Software, Staufen, Germany).

The analysis was conducted according to the "intention to treat" method. Subsequently, the "worst-case scenario" (i.e. adverse event) was assumed when one of the following conditions occurred: patient lost to follow up within 2 years from surgery, in the case of "not evident disease" (NED) at the last update; patient still under control and in the case of "not evident disease" (NED) at the last update, but whose follow up period was shorter than 2 years; perioperative (within 30 days from surgery) deaths were included in the analysis and were, of course, labelled as an adverse event.

A 5-year DSS was used as the dependent variable and calculated according to the Kaplan-Meier method.

Possible predictor variables associated with DSS were: gender, previous treatment, site, clear margins, pathological nodal status and adjuvant therapy. Significant variation among groups was investigated by the log-rank test and qualitative variables were evaluated using a non-parametric test (Chi square test). DSS, instead of overall survival, was chosen as it better depicts the natural history of HNSCC.

Multiple Cox proportional hazards regression models were conducted to explore the relationship between survival and variables believed to affect outcome.

Results

A total of 1178 patients met the criteria for eligibility; most had advanced loco-regional disease (Table II). Clear margins were obtained in 958 cases (81.3%). The ability to achieve complete resection did not strictly correlate to previous treatment (p = 0.06). Monolateral or bilateral neck dissection were part of the treatment in 1116 (94.7%) cases. Pathological examination revealed that 559 (50.1%) patients had some degree of nodal involvement. A total of 551 (46.8%) patients developed recurrence after free flap surgery: of these, 22 (4.0%) were salvaged. Perioperative deaths occurred in 19 cases (1.6%). The mean and median DSS were 44.4 and 30.6 months, respectively. The probability of 5-year DSS is shown in Figure 1.

The possible influence of known prognostic factors was investigated. The probability of 5-year DSS according to sex, primary tumour region, margins of resection and adjuvant therapy are shown in Figure 2 (A, B, C, D) , to previous treatment in Figure 3 and to pathological nodal status in Figure 4.

Patients who were operated due to recurrence did worse than those of first observation, (including 48 patients who received neoadjuvant chemotherapy): their chances were 43.1% and 54.1%, respectively (p < 0.001). Considering the completeness of resection, a higher rate was obtained in the primary treatment than the relapsing group, even though the difference did not reach statistical significance (p = 0.060739). On the other hand, the primary treatment group had more pN positive cases than the relapsing group (p = 0.03285).

Involvement of regional nodes also negatively affected the outcome (40.5% vs. 62.9%, p < 0.001). Sex, age, margins of resection and adjuvant therapy were not associated with survival.
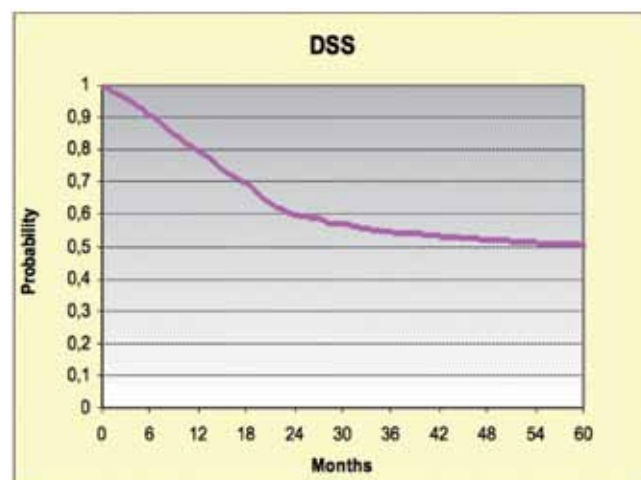
Fig. 1. Disease-specific survival calculated according to the Kaplan-Meier method.
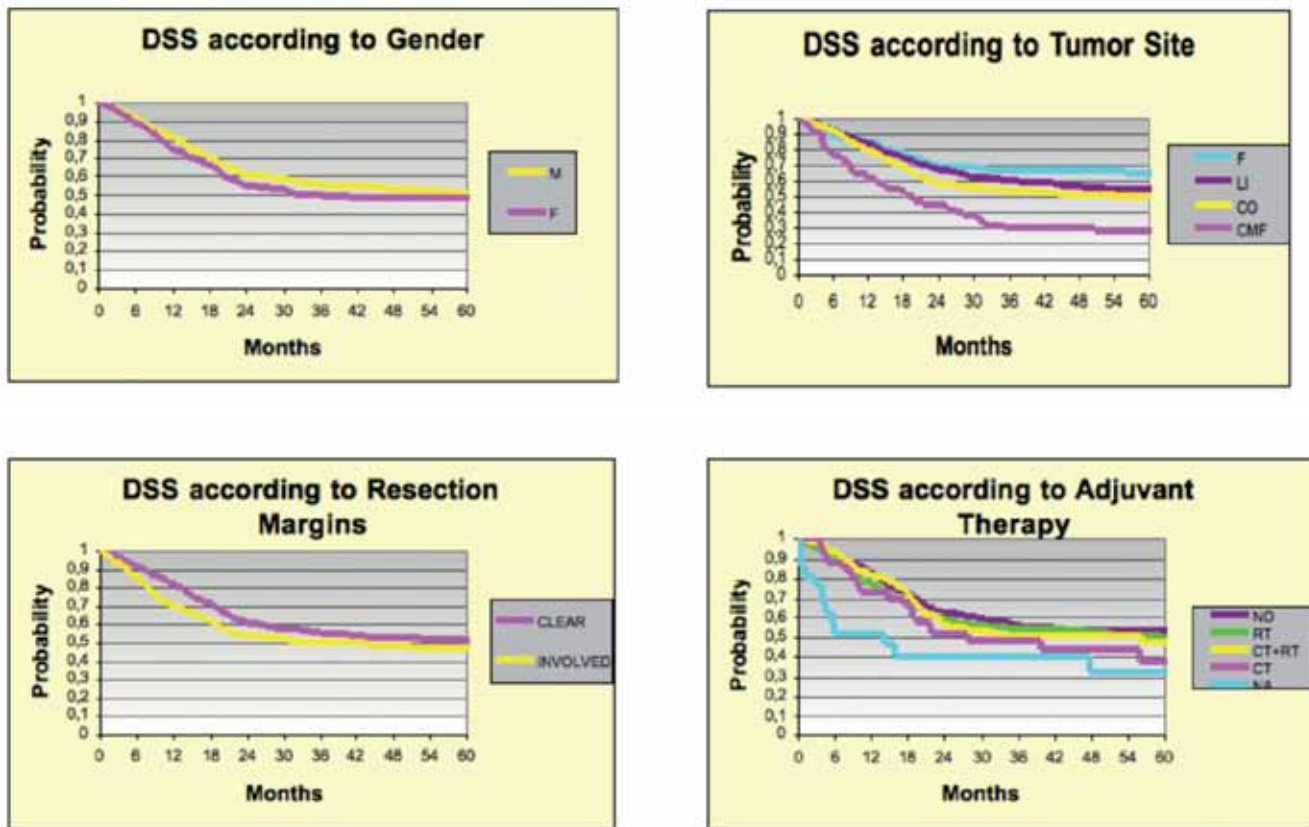
Fig. 2. The probability of 5-year DSS according to sex, primary tumour region, margins of resection and adjuvant therapy calculated according to the Kaplan-Meier method.
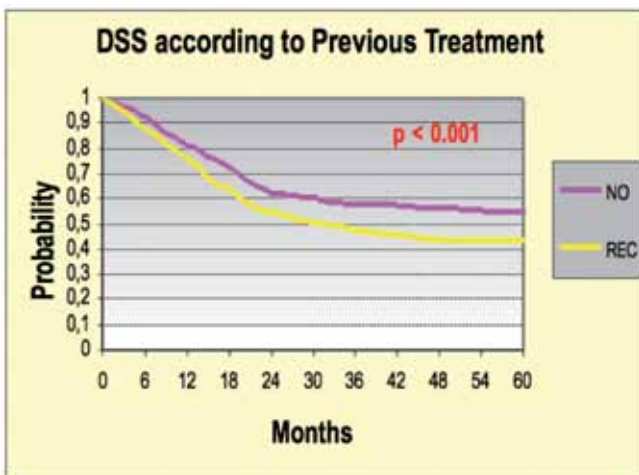
Fig. 3. The probability of 5-year DSS according to previous treatment calculated according to the Kaplan-Meier method.
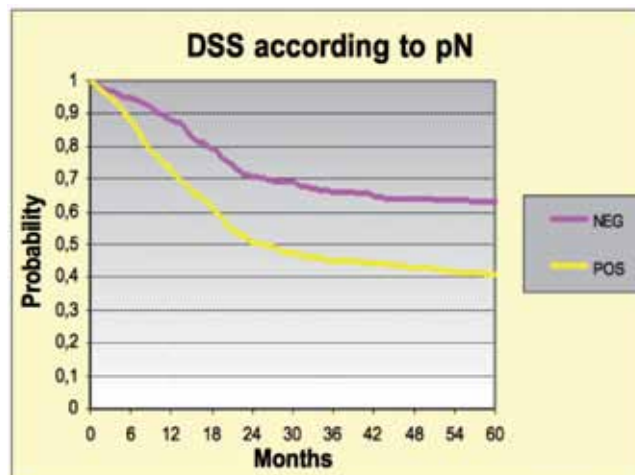
Fig. 4. The probability of 5-year DSS according to pN calculated according to the Kaplan-Meier method.

A Cox proportional hazard regression model analysis was conducted, controlling for sex, age, primary tumour region, previous treatment, margins of resection, pathological nodal status and adjuvant therapy. Female gender, previous treatment and pathologically positive nodes were associated with worse prognosis. The hazard ratios were 1.2, 1.6 and 1.9, respectively (Table III).

Discussion

Free flaps allow a wide range of quality and shape of tissues that can be used for complex anatomical and functional reconstructions. Disadvantages include expertise and higher costs of execution. This has to be taken into account when allocating resources, both at central (i.e.

Table III. Cox regression analysis.

Characteristics	P value	HR
Gender F	0.4	1.2
Recurrence	< 0.001	1.6
pN+	< 0.001	1.9
Age	0.75	
Involved margins	0.19	
Adjuvant therapy	0.4	

health authority) and local (i.e. hospital or department) levels [2], particularly considering the limited economic resources available. This might lead to selection of patients who are suitable candidates for free flap reconstruction: while excellent functional results with free flap surgery for HNSCC have been widely demonstrated [5-11], limited data are available concerning survival of these patients. This study was designed to depict an actual, panoramic view of free flap surgery for HNSCC. Intentionally, only a few, well defined prognostic factors were taken into account.

Inclusion criterion was limited to SCC because this accounts for about 90% of head and neck malignancies: the large prevalence of SCC would allow building up a large series, whose analysis is more likely to produce significant results. Indeed, this paper presents the largest series to date on this subject.

A multicentre study was proposed to acquire a larger quantity of cases available for analysis. Possible biases might have derived from different treatment policies, or expertise among the participating hospital. We tried to reduce these by involving centres that share basic principles of treatment and by building a joint, elementary database. No patients were excluded from the survival analysis, and those lost to follow-up were considered under the most pessimistic hypothesis.

Five-year DSS of the whole series was 50.4%. Sites of tumour origin were grouped in four arbitrary regions: oral cavity (OC), pharynx (PH), larynx-hypopharynx (LH) and cranio-maxillo-facial (CMF), considering that each region poses particular tasks in terms of approach, resection and reconstruction. Survival was worse (27.2%) in patients suffering from CMF tumours than other areas (PH = 65.5%, LH = 54.5%, OC = 49.7).

Gender and age did not correlate with survival. The medical literature alternatively affirms or denies such a correlation, and as such a conclusive statement seems unlikely.

Patients operated on because of relapsing tumour had lower 5-year DSS than those of the first observation (43.1% and 54.1%, respectively, p < 0.001). Differences between these groups with regards to completeness of resection and pathological N status confirms that local control remains the main goal: it also seems reasonable to suppose relapsing cancers have more aggressive local behaviour that, in turn, carries worse prognosis.

The incomplete resection rate was 18.7%, which is quite disappointing since it does not fulfill the hypothesis that availability of outstanding flaps should allow wider and safer resections. The ability of achieving complete resection slightly correlated with previous treatment (p = 0.060739). Indeed, one could theorise that resection of previously untreated cancer would be easier as the surgeon operates in a relatively unaltered field and chances of microscopically free margins would be greater than in a disordered anatomical set. However, 5-year DSS was similar between the groups with or without clear margins (51.0% vs. 47.3%, p = 0.14895). It is widely accepted that adjuvant therapy increases chances of survival. Patients with involved margins were *ipso facto* all candidates for some adjuvant therapy, when feasible (167/220, 75.9%), whereas patients with clear margins underwent adjuvant therapy less frequently (433/958, 45.2%). We suppose adjuvant radiotherapy improved survival in both groups by the same rate, but the impact was reasonably more evident for the involved margins group, as a higher proportion of patients underwent this treatment; this is a possible explanation of the minimal, not statistically significant difference between the two DSS curves.

Pathological nodal status is a powerful, largely independent prognostic factor. This study confirms this data: pN-negative patients did significantly better than pN-positive ones (62.8% vs. 40.6%; p < 0.001). Nodal metastases are thought to be an expression of intrinsic tumour offensiveness, whose treatment requires an aggressive approach (i.e. combined therapy): data from the present series lead us to suppose adjuvant therapy was only partially able to fill the survival gap between pN-negative and pN-positive patients. Survival data, to our knowledge, can only be compared to the 32% reported by Podrecca et al [11]. In that series there was a significant proportion (27.2%) of advanced tumours affecting the cranio-maxillo-facial (CMF) region, commonly believed to carry a poor prognosis, whereas in the present series tumours from CMF region accounted only for 5.5%: thus, the prognostic negative impact on the whole series is weakened. This seems a sustainable, even partial, explication of the difference between the two series.

Despite the lack of studies fully comparable to the present one, there is some published data concerning survival after free flaps for HNSCC. Lidman and Niklasson [12] reported the results of free flap surgery in primary intraoral SCC group of 79 patients, most in stage I (42%); they found a 5-year, tumour related, survival of 58%. Hanasono et al. [13] reviewed a group of previously untreated, T3-T4, oral SCC forming two subsets: patients operated without free flaps and with reconstruction (of whom, 66% were free flaps). The first group included a lower rate of advanced tumours than the reconstructed group. They reported a 5-year overall survival (OS) of 37% in the latter subset and no difference with the non-reconstructed patients (42% OS): incompleteness of resection decreased

from 18% to 7%, but no positive impact was demonstrated on survival or local relapse.

Kostrzewa et al. [14], in a series of recurrent oral and oropharyngeal SCC including a large proportion of stage III-IV tumours, reported a 5-year disease-specific survival of 43.7%. Staging, margins and previous treatment were not associated with survival. On the other hand, pathologically-affected nodes, short interval between primary treatment and salvage surgery (or between salvage surgery and relapse) were important negative prognostic factors.

Finally, Mücke et al. [3] have recently described their experience on 274 oral cavity SCC patients operated on with free flaps, comparing them with 499 patients from the same institution, but treated without reconstruction or local/regional flaps. The overall incomplete resection rate was 17.5% (specific data for each group were not reported). Patients with involved margins or relapse within six months from treatment were excluded from the survival analysis. Relapse rate was similar within the two groups. Five-year overall survival was 66.2% in the free flap subset and 58.8% in the no free flap subset. Clinical T and N stage, grading, age and free flap were identified as prognostic factors in both univariate and multivariate analysis. The matched-pair analysis showed better survival in the free flap group, but limited to T3-4 stage patients (no difference for T1-2).

Conclusions

This study investigates the *quoad vitam* outcome of a large (the largest, to our knowledge) series of HNSCC patients treated with free flaps. Efforts were made to depict the actual setting that the Head & Neck surgeon faces in his/her daily activity (limited exclusion criteria, "worst-case scenario" survival analysis). Survival rates are comparable, if not somewhat better, to those reported by different authors worldwide. Free flap surgery seems to have extended the concept of resectability, even if incompleteness of resection remains a pitfall (whose impact on survival appears to be uncertain). Salvage surgery has poorer results than primary surgery. Nodal involvement significantly decreases chances of survival. According to many authors, free flap surgery for HNSCC seems to be a beneficial option of treatment even in terms of survival. Further research is planned to refine the survival analysis. This, in turn, would help both to optimize surgical indications and to compare results to those obtainable from other therapies (i.e. chemoradiation for oro-pharyngeal SCC).

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PHONIATRY

The Pooling-score (P-score): inter- and intra-rater reliability in endoscopic assessment of the severity of dysphagia

Il Pooling-score (P-score): variabilità inter- e intra-individuale nella valutazione endoscopica della gravità della disfagia

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SUMMARY

This study evaluated the intra- and inter-rater reliability of the Pooling score (P-score) in clinical endoscopic evaluation of severity of swallowing disorder, considering excess residue in the pharynx and larynx. The score (minimum 4 - maximum 11) is obtained by the sum of the scores given to the site of the bolus, the amount and ability to control residue/bolus pooling, the latter assessed on the basis of cough, *raclage*, number of dry voluntary or reflex swallowing acts (< 2, 2-5, > 5). Four judges evaluated 30 short films of pharyngeal transit of 10 solid (1/4 of a cracker), 11 creamy (1 tablespoon of jam) and 9 liquid (1 tablespoon of 5 cc of water coloured with methlyene blue, 1 ml in 100 ml) boluses in 23 subjects (10 M/13 F, age from 31 to 76 yrs, mean age 58.56±11.76 years) with different pathologies. The films were randomly distributed on two CDs, which differed in terms of the sequence of the films, and were given to judges (after an explanatory session) at time 0, 24 hours later (time 1) and after 7 days (time 2). The inter- and intra-rater reliability of the P-score was calculated using the intra-class correlation coefficient (ICC; 3,k). The possibility that consistency of boluses could affect the scoring of the films was considered. The ICC for site, amount, management and the P-score total was found to be, respectively, 0.999, 0.997, 1.00 and 0.999. Clinical evaluation of a criterion of severity of a swallowing disorder remains a crucial point in the management of patients with pathologies that predispose to complications. The P-score, derived from static and dynamic parameters, yielded a very high correlation among the scores attributed by the four judges during observations carried out at different times. Bolus consistencies did not affect the outcome of the test: the analysis of variance, performed to verify if the scores attributed by the four judges to the parameters selected, might be influenced by the different consistencies of the boluses, was not significant. These initial data validate the clinical use of the P-score in the management of patients with deglutition disorders by a multidisciplinary team.

KEY WORDS: Deglutition disorders • Dysphagia • Diagnosis • FEES • Aspiration • Pooling • Residue • Severity

RIASSUNTO

Questo studio valuta la variabilità inter ed intra-individuale del Pooling-score (P-score) nella valutazione clinica endoscopica della gravità della disfagia, considerando i ristagni in ipofaringe e laringe. Lo score (minimo 4 massimo 11) è ottenuto dalla somma del punteggio attribuito alla sede del bolo, alla quantità ed alla capacità di controllo del bolo residuo/ristagnato, quest'ultima valutata sulla base delle reazioni volontarie o riflesse di tosse, raclage, numero di atti deglutitori a vuoto (<2, 2-5, >5). Quattro giudici hanno valutato 30 brevi filmati di transiti faringei di 10 boli solidi (1/4 di cracker), 11 cremosi (1 cucchiaio di marmellata) e 9 liquidi (1 cucchiaio da 5 cc di acqua colorata con blu di metilene, 1 ml in 100 ml di acqua) di 23 soggetti (10M/13F fra 31-76 anni, età media 58.56±11.76) affetti da patologie diverse. I filmati, distribuiti su due CD in sequenza diversa e casuale, venivano sottoposti ai giudici (previa una sessione esplicativa) nel tempo 0, a distanza di 24 ore (tempo 1) e dopo 7 giorni (tempo 2). L'affidabilità inter-individuale ed intra-individuale del P-score è stata calcolata, utilizzando l'intra-class correlation coefficient (ICC; 3,k). La possibilità che la consistenza dei boli potesse influenzare il punteggio attribuito ai filmati è stata considerata. L'ICC per i parametri sede, quantità, gestione e il P-score totale è risultato essere rispettivamente: 0.999, 0.997, 1.00 e 0.999. La valutazione clinica di un criterio di gravità di un disordine della deglutizione resta un punto cruciale nella gestione di pazienti con patologie che predispongono a complicanze. Il P-score, che deriva da parametri statici e dinamici, ha raggiunto una correlazione molto alta fra i punteggi attribuiti dai quattro giudici durante osservazioni eseguite in tempi diversi. Le consistenze del bolo non hanno influenzato l'esito del test: l'analisi della varianza, effettuata per verificare se il punteggio attribuito dai quattro giudici ai parametri selezionati potesse essere influenzato dalle diverse consistenze, è stata non significativa. Questi primi dati rendono possibile un uso clinico del P-score nella gestione di pazienti con disturbi di deglutizione in un team multidisciplinare.

PAROLE CHIAVE: *Disturbi della deglutizione • Disfagia • Diagnosi • FEES • Aspirazione • Ristagno • Residuo • Gravità*

Introduction

In patients with dysphagia due to different pathologies, predisposing to complications, the clinical severity of a swallowing disorder needs to be established [1]. Respiratory complications, related to false paths, taken by bolus or pooling of secretions, can arise in the short or long term [2]. Clinical non-instrumental assessment (clinical swallowing evaluation – CSE) [3][4] alone can fail to identify silent aspirations or micro-aspirations. In at-risk conditions for the patient, and to define physiopathology of the swallowing disorder, instrumental assessment is essential in order to plan treatment. Currently, there is no instrumental technique that clearly defines the risk of false pathways: video-fluoroscopic study of swallowing (VFSS) [5] and fiber-optic endoscopic evaluation of swallowing (FEES) [6] both yield false positives and false negatives [7]. Choosing the instrumental method that best responds to clinical questions [8] and the expertise of the clinician carrying out the procedure [9][10] become crucial factors in clinical management of patients with deglutition disorders.

Endoscopic assessment provides an exhaustive definition of anatomical details of pharyngeal and laryngeal surfaces, including secretions or bolus residues that, in usual or unusual conditions, moisten the walls (coating) or occupy containment cavities (pooling, residue). Such a evaluation is considered a clinical criterion for severity that can be linked to the risk of respiratory complications [11]. Although to date a standardised grading of pharyngeal residue is not available, this criterion is taken into account when planning treatment and management activities by a multidisciplinary team [12].

In previous publications [13-15], pooling of materials is considered in the broadest sense as any material that is present in the containment cavities of the hypopharynx and larynx, before and/or after the act of swallowing. The severity criterion proposed (Pooling score, P-score) (Table I) [14] takes into account different parameters: 1) site: identified by anatomical landmarks; 2) amount: determined in a semi-quantitative fashion by the amount of pooling materials (coating, more or less than 50% of cavity containment capacity); 3) management: the ability of the patient to clear the residue. The score refers to a specific type of consistency and volume of the bolus, changing according to these parameters. The score considers the most severe condition for each parameter, reached after a sequence of boluses of the same consistency (in our department a sequence of at least 3 boluses for each consistency).

In clinical practice, the P-score may be integrated with other parameters of clinical assessment (CSE) that are more easily determined: sensation of the pharynx, patient collaboration and age (P-SCA score). Both the scores express, as a numerical value, a continuum of severity that may be used in different ways, with correlations that still have to be verified. Therefore, a minimum score (P-score 4-5) may indicate the absence of endoscopic signs of dysphagia. A low score (P-score 6-7) may identify mild dysphagia, a medium score (P-score 8-9) moderate dysphagia and a high score (P-score 10-11) severe dysphagia.

This investigation considers the intra- and inter-rater reliability of the P-score among 4 judges with long-standing experience in the use of endoscopy. CSE parameters and the P-SCA score were not considered.

Materials and methods

Transits of 23 consecutive outpatients aged between 31 and 76 years (average age 58.56 ± 11.76), and referred to our department complaining of difficulties in swallowing, were enrolled. Sample characteristics and diseases are reported in Table II. Four judges with expertise in the FEES procedure were elected. Three judges have at least 10 years of experience, and one has 4 years of experience: they all routinely carry out at least 5 endoscopic assessments of swallowing per week.

For some of the 23 subjects, the pharyngeal transit films of more than one bolus of a different consistency was recorded to obtain a total number of 30 films: 10 solid bo-

Table I. P-score and P-SCA score.

Pooling	Endoscopic landmarks		Bedside parameters		
			Sensation	Collaboration	Age (years)
Site	Vallecula	1			
	Marginal zone	1			
	Pyriform sinus	2			
	Vestibule/vocal cords	3			
	Lower vocal cords	4	Presence = -1	Presence = -1	+1 (< 65)
Amount	Coating	1	Absence = +1	Absence = +1	+2 (65-75)
	Minimum	2			+3 (> 75)
	Maximum	3			
Management	< 2	2			
	2-5	3			
	> 5	4			
Score	**P 4-11**			**P-SCA 3-16**	

Table II. Patient characteristics and diseases.

Subject	Gender	Age	Pathology
1 PS	F	47	Globus
2 AA	F	68	Cortical ictus sequelae
3 GA	M	65	GERD
4 BA	F	62	COPD
5 CL	F	56	Dermatomyositis
6 RR	M	67	Cortical ictus sequelae
7 MM1	F	64	Laryngeal paralysis
8 XL	F	38	GERD
9 TS	F	64	Neurological degenerative
10 MM2	M	63	Cortical ictus sequelae
11 QG	M	42	Corea major
12 DA	F	71	Myasthenia
13 ME	M	52	H-N operated
14 DM	F	48	Cortical ictus sequelae
15 ME	F	46	Laryngeal paralysis
16 BG	M	62	Sjögren's syndrome
17 CC	F	76	Wallemberg sequaele
18 BF	F	73	Laryngeal paralysis
19 CR	M	51	Laryngeal paralysis
20 MP	M	71	COPD
21 RF	F	67	H-N operated
22 CL	M	31	Neurologial degenerative
23 SR	M	63	Cortical ictus sequelae

luses (1/4 of a cracker), 11 creamy boluses (1 spoonful of jam) and 9 liquid boluses (1 tablespoon with 5 cc of water dyed with methylene blue, 1 cc in 100 ml, according to the procedure used in our department). The films are short sequences of acts of swallowing that are prolonged until the bolus has been completely swallowed, or at least 5 swallows. Film length varies from a few dozen seconds to no more than 180 seconds, so the complete session lasted no more than an hour, avoiding fatigue and a decrease in concentration among judges [16].

All the films were collected on two CD copies, respectively *CD0* and *CD1*, that differed with respect to the sequence of the films. Before the session, the rationale and application of the score were explained to the judges. Each judge was given a *CD-test* containing 4 pharyngeal transits of boluses with different consistencies, in subjects who differed by the severity of dysphagia. The application of the P-score was explained personally by the first judge at an explanatory session lasting 30 min. Judges were asked to watch *CD0* immediately thereafter (time 0), *CD1* at 24 hours later (time 1) and *CD0* after 7 days (time 2) in a different order than at time 0.

Data were collected on a predefined sheet, reporting separate findings for each parameter: pooling *site*, *amount*,

management and *total P-score*. The different bolus consistencies used in our study between the pharyngeal transit films tested is a bias [17-19]. For this reason, we calculated the variance of scores attributed by judges to the parameters selected. Finally, the score can also be applied at the beginning of the observation [14]. In the films considered, material pooling at the beginning of the observation was present in only a few cases, so it was decided not to apply the score at that time, but only after the transit of the bolus through the pharynx.

The analysis of data obtained was carried out using SAS statistical software and the inter- and intra-rater reliability was calculated with the intra-class correlation coefficient (ICC; 3,k) [20].

Results

The scores attributed by judges to the *site*, *amount* and *management* of the pooled material are shown in Tables IIIa, IIIb and IIIc. The *site*, apparently simpler, was modified by both the first and fourth judges over time, reaching agreement at the last observation [ICC (3, k) 0.999]. The parameter *amount* was changed many times during observations, with differences maintained among judges [ICC (3, k) 0.997]. The parameter *management* was replicated by all judges in all three observations [ICC (3, k) 1.000]. The *total P-score* attributed by the four judges confirmed that the criterion of severity established by the first judge was essentially shared by the other three judges [ICC (3, k) 0.999] (Table IV).

The analysis of variance, performed to verify if the scores attributed by the four judges to the parameters selected, might have been influenced by the different consistency of the boluses, was not significant (interaction consistency*judge = 1.000 at times 0, 1, 2, respectively, for the three parameters of the score and P-score total). Thus, the different types of consistencies did not influence the scores attributed by judges to the 30 films.

Discussion

The evaluation of secretions or bolus pooling in the pharynx end/or larynx represents an important step in the endoscopic examination of swallowing, as it is closely correlated with respiratory complications [11]. As previously mentioned, to date, standardised grading for pharyngeal material pooling is not available: the P-score could be used in this clinical context.

From a physiopathological point of view, a swallowing disorder is the result of an imbalance between events that occur in the domain of space and time [21] [22], domains in which vector forces guarantee the efficiency of defensive strategies, which protect the airways, or clear the containment cavities of the bolus passed through them [23]. These events and forces can interact in different ways.

Table IIIa. Site (anatomical landmarks): descriptive analysis.

Time		JUDGE			
		1	**2**	**3**	**4**
		N	**N**	**N**	**N**
0	1	16	15	15	15
	2	4	5	5	5
	3	5	5	5	5
	4	5	5	5	5
1	1	15	15	15	15
	2	5	5	5	5
	3	5	5	5	6
	4	5	5	5	4
2	1	15	15	15	15
	2	5	5	5	5
	3	5	5	5	5
	4	5	5	5	5

P-score: site
ICC(3,k) 0.999

Table IIIb. Amount: descriptive analysis.

Time		JUDGE			
		1	**2**	**3**	**4**
		N	**N**	**N**	**N**
0	1	18	19	19	18
	2	8	7	7	8
	3	4	4	4	4
1	1	18	19	19	18
	2	7	7	7	8
	3	5	4	4	4
2	1	19	19	19	19
	2	6	7	7	7
	3	5	4	4	4

P-score: amount
ICC(3,k) 0.997

Table IIIc. Management: descriptive analysis.

Time		JUDGE			
		1	**2**	**3**	**4**
		N	**N**	**N**	**N**
0	2	8	8	8	8
	3	5	5	5	5
	4	17	17	17	17
1	2	8	8	8	8
	3	5	5	5	5
	4	17	17	17	17
2	2	8	8	8	8
	3	5	5	5	5
	4	17	17	17	17

P-score: management
ICC(3,k) 1.000

Time: time of observation
N: number of observation

In the domain of space, where forces are acting, the P-score identifies the pathway and flow of the bolus: the pathway is identified by the direction along the digestive or respiratory tracts, as well as false route (penetration or aspiration); the flow is indicated by the amount of bolus that does not cross the pharynx while swallowing. This amount (expressed in a semi-quantitative manner by the score) represents the difference between the total amount of the bolus taken and the amount of bolus swallowed. In the domain of time, the score identifies events that occur before or after swallowing, considering that material pooling after a previous swallow becomes a bolus for the next swallow, with a volume that is either increased or decreased. Thus, the subsequent swallowing act can clear the residue or push it below into the airway [24]. The P-score considers the sequence of swallowing acts in the "management" parameter, evaluating the fate and final amount of a bolus that persists in the pharynx/larynx after 5 empty swallows, and also gives information about the reaction of the patient to material pooling or to airway invasion. The occurrence, or absence, of dry swallowing, cough or throat clearing, in response to the residue or penetration/aspiration before, during or after swallowing, express the interaction between vectors and volumes. In this way, the number of dry swallows or clearing activities, related to the final amount of material pooling, can be assumed to be a parameter of efficiency of the entire sequence, closely linked to fatigue of muscular swallowing effectors.

These preliminary considerations can help us in the interpretation of the score attributed by the judges. The anatomical parameter (Table IIIa: site) was well identified by the 4 judges: disagreement may have been influenced by the amount and site of the residue, considering that the most severe condition has to be selected for scoring (the residue in a lower anatomical site may have been chosen with respect to a larger volume, both parameters indicating greater severity, or vice versa). In this case, site and amount are closely linked: in fact, "amount" (Table IIIb) created greater difficulties for the judges. It is worth remembering that the measurement of this parameter is semi-quantitative, and the four judges attributed a diversity of scores, which in some cases were modified during the three observations, but in other cases remained unchanged. A greater variability was seen when making a distinction between scores 2 and 3, while "coating" created fewer difficulties in score attribution.

The third parameter (management) considers the effectiveness of the manoeuvre carried out to clear the residue, regardless of whether it was spontaneous or performed upon request, and in many cases it solves the dilemma between site and volume mentioned above. This parameter (Table IIIc) was easily evaluated by all judges and in all observations, with no discrepancies. If we consider the total score (from 4 to 11), which marks the continuum of clinical severity (Table IV), it can be observed that ex-

Table IV. Severity criteria: descriptive analysis.

Time		JUDGE			
		1	**2**	**3**	**4**
		N	**N**	**N**	**N**
0	4	8	8	8	8
	5	3	3	3	3
	7	7	7	7	6
	8	4	4	4	5
	9	5	5	5	5
	10	2	2	2	2
	11	1	1	1	1
1	4	8	8	8	8
	5	3	3	3	3
	7	6	7	7	7
	8	4	4	4	4
	9	6	5	5	5
	10	2	2	2	2
	11	1	1	1	1
2	4	8	8	8	8
	5	3	3	3	3
	7	6	7	7	7
	8	5	4	4	4
	9	5	5	5	5
	10	2	2	2	2
	11	1	1	1	1

P-score: total
ICC(3,k) 0.999

Time: time of observation
N: number of observations

treme scores were replicated by the four judges in all observations, with good agreement. This was easy to identify, and maintain judgement, for subjects without pooling or patients with bulky residues. Differences emerged in the medium classes of severity where the attribution of a different partial score may affect the attribution of a different class of clinical severity. In our work, these differences, sometimes replicated at the third observation, never reached statistical significance and can be assumed to be casual.

Conclusions

One of the most difficult tasks for clinicians and management team is to determine the severity of the swallowing disorder. This criterion very often refers to the risk for the lower airways to be invaded by the bolus or by material pooling into pharyngeal or laryngeal cavities. The instrumental criterion of severity (endoscopic or radiological) needs to be contextualised according to a more general clinical criterion of severity, which should make

reference to the patient, considering that the non-instrumental assessment (CSE) tends to underestimate the risk of aspiration, whereas instrumental assessment tends to overestimate it [25]. "Severity", in this case, becomes a relative criterion, which is quantifiable by the parameters that define it. In clinical practice, aspiration is the most significant event that marks a swallowing disorder, although it is not the only one.

Endoscopic and radiological evaluations are complementary techniques [7], even if the former offers an optimal view of pharyngeal and laryngeal cavities, and particularly of material pooling [26]. Parameters related to instrumental severity, devised for radiological evaluation, might not be the best for application in the clinical endoscopic field, though they maintain their effectiveness in terms of inter- and intra-rater reliability [27][28]. Nonetheless, scores that can be easily applied in clinical practice are needed. There are several endoscopic scores reported in the literature, with severity criteria divided into 3, 4 or 5 levels. This division does not seem to interfere with the inter- and intra-rater reliability of a score [12][29]. The P-score, which considers anatomical and functional parameters, evaluates the interaction between volumetric, vectorial and temporal events, disengaging the criterion of severity from the quantitative parameter alone.

The high inter- and intra-rater reliability of the P-score was verified for anatomical, semi-quantitative and temporal parameters. Variability among judges, which was not statistically significant, was expressed with respect to the "site" and "amount", whereas "management" seems more easily determinable.

Despite the high reliability of the P-score shown herein, one critical point could be represented by the unequal subdivision of clinical severity in the sample, taken from consecutive outpatients seen in our department. The patients with the most severe clinical conditions were not able to manage all consistencies or volumes tested by those less severely affected. In the former patients, for example, it was possible to administer only a few small amounts of the bolus with a creamy consistency. Nevertheless, the statistical analysis verifies the reliability of the judges in attributing a score for each parameter of the P-score, regardless of severity, which derives from the sum of the three parameters that determine it. This should not affect the clinical use of the score, which, in contrast, seems to be able to identify patients with small differences in severity.

Further research is being undertaken to check the effectiveness of the P-score in clinical management of patients with swallowing disorders that have a different aetiology, as well as its usefulness in indicating variations after specific treatment.

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Longitudinal variations in fitting parameters for adult cochlear implant recipients

Le variazioni longitudinali dei parametri del mappaggio in pazienti adulti portatori di impianto cocleare

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SUMMARY

In patients with a cochlear implant (CI), the first critical point in processing auditory information from sound stimuli that leads to comprehension is the interface between the electrode and the cochlear nerve, which is dependent on providing appropriate current input. The purpose of this work was to evaluate the longitudinal differences in psychoacoustic fitting parameters in CI users. We studied 26 profoundly deaf adults, aged between 18 and 58 years, who had been implanted in our department between 2009 and 2011. The lowest current levels that evoked an auditory sensation (T-level) and the highest current levels that did not elicit an uncomfortable loud sensation (C-level) were recorded at the time of activation, approximately 30 days after implantation (mean 28.5 days) (T0), after one month (T1), 3 months (T3), 6 months (T6) and one year (T12). Impedance values were calculated for electrode groups: basal, middle and apical. In all cases, the same model of perimodiolar implant (Cochlear™ Nucleus® CI24RE) and the same surgical technique (cochleostomy) were used. The values of T-level and C-level showed significant incremental changes between T0 and T1 and between T1 and T3. T-levels in the basal regions of the cochlea were higher than in other sites. T-levels in the basal turn exhibited higher values consistent with a greater amount of fibrosis, as reported in other studies. Our findings suggest that fitting sessions should be scheduled more frequently during the first three months as indicated by the greater slope of T- and C- level variations during that time frame.

KEY WORDS: Cochlear implant • Adults • Fitting values

RIASSUNTO

Nei pazienti con impianto cocleare il primo punto critico del processo uditivo dallo stimolo sonoro alla comprensione può essere identificato nell'interfaccia elettrodo-coclea. Scopo di questo lavoro è quello di valutare, nei pazienti con sordità profonda e sottoposti ad impianto cocleare, le differenze longitudinali dei principali parametri psicoacustici del mappaggio. Abbiamo studiato 26 pazienti adulti di età compresa tra i 18 e 58, impiantati presso il nostro Dipartimento, nel periodo compreso tra il 2009 ed il 2011. La minima intensità di corrente necessaria ad evocare una sensazione uditiva (T-level) e la più alta intensità di corrente che non evoca sensazione acustica di fastidio (C-level) sono state registrate al momento dell'attivazione, che si è verificata circa 30 giorni dopo l'impianto (in media 28,5 giorni) (T0), dopo un mese (T1), 3 mesi (T3), 6 mesi (T6) e un anno (T12). In tutti i casi è stato utilizzato lo stesso tipo di impianto perimodiolare (Cochlear™ Nucleus® CI24RE) con la stessa tecnica chirurgica (cocleostomia). I valori di T-level e quelli di C-level mostrano variazioni significative incrementali tra T0 e T1 e tra T1 e T3. I T-level nelle regioni basali della coclea sono più alti rispetto agli elettrodi inseriti nelle partizioni cocleari mediana ed apicale. Tali valori più alti concordano con i reperti di altri autori di una prevalente neoformazione fibrosa basale. Pertanto è necessario programmare più frequentemente le sedute di mappaggio durante i primi 3 mesi, in base ad una maggiore velocità di variazione dei valori di T e C.

PAROLE CHIAVE: *Impianto cocleare • Adulti • Parametri del mappaggio*

Introduction

Cochlear implants can restore hearing function to people with a severe or profound hearing loss using an electrode system stimulating endocochlear surviving neuronal cells. Two main variables affect the performance of cochlear implants: the processor's capacity to deliver effective bursts of electrical impulses and the ability of the patient to receive such stimuli and process them appropriately.

The fitting procedure for a cochlear implant aims to establish suitable electrical stimulation levels for each channel. It includes measuring each electrode for the lowest current level that evokes an auditory sensation (T-level) and for the highest current level that does not elicit an uncomfortable loud sensation (C-level). The objective of this investigation was to evaluate time variations of these main fitting parameters in CI users. Many authors adopt

Table I. Aetiologies of profound sensorineural hearing loss in our cases (percentages are rounded).

Aetiology	Number of patients	%
Unknown	12	46
Genetic	4	15
Prenatal infections (Rubella)	1	4
Prematurity/neonatal intensive care unit stay (sepsis, hypoxia, jaundice)	5	19
Postnatal infections (meningitis, measles, chronic suppurative otitis media)	3	11
Multiple sclerosis	1	4
Total	26	

study intervals at one month after activation, followed by three months, six months and 12 months [1-3]; in some cases, intervals at 24 and 36 months are also used [4 5]. Thus, we followed the mostly widely-adopted timing criteria to better compare our data with other reports.

Materials and methods

Twenty-six profoundly hearing-impaired adults implanted by our department between 2009 and 2011 were studied. There were 16 males and 10 females ranging in age between 18 and 58 years who had either pre-lingual (n = 21) or post-lingual (n = 5) deafness: all were selected according to the latest criteria [6].

In our patients, the aetiology of deafness remained unknown in 46% of cases, while 34% was due to environmental factors, 15% to genetic causes and 4% to other clinical features. Details of the different aetiologic causes are provided in Table I.

According to the fact that the aetiology of deafness contributes to outcomes only to a very small extent [7], we did not consider separate groups in collecting the results.

The degree of deafness was bilateral and profound. Cases of bilateral implantation were excluded.

Our study protocol included assessment during device activation (T0, approximately 30 days after surgery - mean: 28.5 days), after one month (T1), 3 months (T3), 6 months (T6) and a year (T12). We chose these time points to better compare our data with existing literature reports, which adopted similar timing.

All patients received the same model of perimodiolar array (CI24RE by Cochlear LTD). Furthermore, the same surgical technique (cochleostomy) was performed on all patients; i.e. a manual and progressive introduction of the array, removal of the stylet at the end of insertion in scala tympani and always applying the recommended precautions of soft surgery for this device [8-11].

For this study, we excluded patients with incomplete insertion and/or with cochlear malformations and/or impedance values more than 20 kOhm even if occurring in only one electrode of the patient's array, and also if noted at one visit during follow-up. All patients received the same fitting using the ACE strategy at the same default fitting parameters (rate = 900 pps, pulse width = 27 μsec). The T-SPL (minimum intensity input level that results in electrical stimulation) employed was set at 25 dB. Maxima were selected according to patient preference considering subjective quality of perceived sounds: variations were noted from 8 to 12.

At the beginning of each session, electrical impedance was measured and the subjective values of T-level and C-level for each electrode were obtained. T-level was found on a channel-by-channel basis starting with an audible stimulation and reducing the energy level until the patient reported that there was no longer any sound perception. As for C-level, single channels were selected and the energy level was increased until the patient reported hearing a loud, not uncomfortable sound.

Overall mean values were evaluated for the full array and for grouped data by considering basal electrodes (E1 to E7), middle (E8 to E14) and apical (E15 to E22) named according to anatomical cochlear segments.

The progression of the values of T-level and C-level at observational periods was assessed using a repeated-measures analysis of variance (ANOVA). Post-hoc comparisons utilised the Bonferroni method of confidence interval adjustment. The probability error accepted for significant values was $p < 0.05$ after Bonferroni correction, which adds a very restrictive criteria for significance.

Speech audiometry was not considered as to its variability was mostly noted in preverbal patients, which are numerous in our cohort.

We prefer a subjective method for fitting T and C values, as we had no non-collaborating patients and to optimize compliance throughout the total time of study. An alternative method such as neural response telemetry is objective, but correlates only to a certain extent with subjective measures. In fact, in another study [12], prediction of the contour of T- and C-levels from the contour of NRT thresholds across electrodes would not be appropriate for half of subjects.

Results

Raw data showed increasing mean values for T-levels and C-levels, with a reduction of standard deviations in

Table II. Full array, n = 26, raw mean values and standard deviation for T-levels, C-levels at various times of observation are shown for activation at approximately one month after surgery (T0), after one month (T1), 3 months (T3), 6 months (T6) and a year (T12).

	T-level average	Std dev	C-level average	Std dev
T0	106.20	4.63	143.97	3.19
T1	130.74	4.14	181.26	4.04
T3	142.92	3.21	192.95	3.14
T6	143.99	2.89	195.65	2.48
T12	147.51	2.60	198.70	2.23

Figs. 1a-b. (1a) Overall variation in mean T-levels for the full array, (1b) showing the overall variation in mean C-levels for the full array, n = 26. Significant differences for the test periods are shown (p-values are Bonferroni corrected).

the final stages, T6 and T12 (Table II) comparing the results for the full complement of all electrodes for all subjects. Figures 1a and 1b illustrate these changes as mean values for T- and C-levels. The repeated measures analysis of variance showed significant differences for T-Level [F = 44.11; p < 0.001] and for C-Level [F = 93.69; p < 0.001]. The Bonferroni post-hoc comparison yielded significant incremental changes for T0 to T1 in T-level [p < 0.0001] and C-level [p < 0.0001], and from T1 to T3 in T-level [p = 0.0013] and C-level [p = 0.0023]. No significant differences were obtained for incremental changes for the T3 to T6 measurements or from T6 to T12.

The same analysis was conducted for each cochlear partition differentiating the electrodes by groups for apical, middle and basal regions compared to the entire cochlear array. The results for the apical cochlear segment for the repeated measures analysis of variance reached significant differences for T-Level [F = 44.92; p < 0.001] and C-Level [F = 81.70; p < 0.001]; Bonferroni post-hoc comparison yielded significant incremental changes from T0 to T1 in T-level [p < 0.0001] and C-level [p < 0.0001], and from T1 to T3 in T-level [p = 0.0007] and C-level [p = 0.0005]. We obtained non-significant incremental changes from T3 to T6 and from T6 to T12. In the middle cochlear array segment, the repeated measures analysis of variance showed significant differences for T-Level [F = 42.73; p < 0.001] and for C-Level [F = 96.54; p < 0.001]; Bonferroni post-hoc comparison showed significant incremental changes from T0 to T1 in T-level [p < 0.0001] and C-level [p < 0.0001], and from T1 to T3 in T-level [p = 0.0012] and C-level [p = 0.0040]. Incremental changes from T3 to T6 and from T6 to T12 were not significant. In the basal cochlear array segment, repeated measures analysis of variance revealed significant differences for T-Level [F = 33.56; p < 0.001] and C-Level [F = 77.09; p < 0.001]; Bonferroni post-hoc comparison yielded significant incremental changes from T0 to T1 in T-level [p < 0.0001] and C-level [p < 0.0001], and from T1 to T3 in T-level [p = 0.0090] and C-level [p = 0.0143]. No significant differences in incremental changes from T3 to T6 and from T6 to T12 time intervals were observed.

Table III summarises the results of comparison between the electrode groups at different follow-up points: in T0
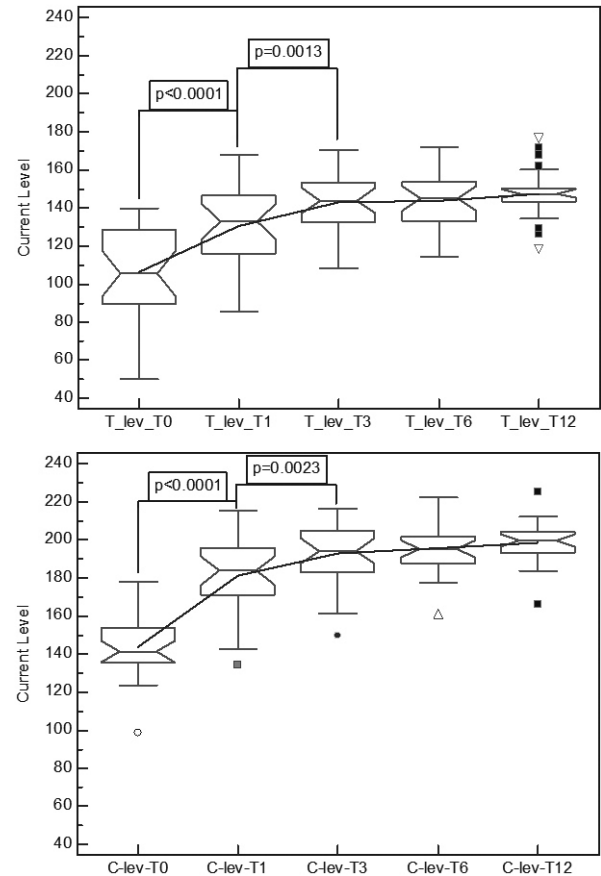
for T-Level significant differences [F = 7.82; p = 0.001] with Bonferroni post-hoc comparison significant difference in Apical vs Basal [p = 0.022] and Middle vs Basal [p = 0.0006], no statistical difference in Apical vs Middle; for C-Level significant differences [F = 4.57; p = 0.015], but with Bonferroni post-hoc comparison no significant difference in Apical vs Basal [p = 0.0847], Middle vs Basal [p = 0.371] and Apical vs Middle [p = 0.1371]; in T1 for T-Level significant differences [F = 5.39; p = 0.008] with Bonferroni post-hoc comparison no significant difference in Apical vs Basal [p = 0.1285] and Apical vs Middle [p = 1], statistical difference in Middle vs Basal [p = 0.0056]; for C-Level, no significant differences [F = 0.77; p = 0.468]; in T3, no significant differences for T-Level [F = 2.27; p = 0.114] and C-Level [F = 0.70; p = 0.503]; in T6, no significant differences for T-Level [F = 1.91; p = 0.159] and C-Level [F = 0.85; p = 0.434]; in T12, no significant differences for T-Level [F = 0.18; p = 0.833] and C-Level [F = 1.79; p = 0.177]. Figure 3 shows that the basal T-level values were slightly higher compared to middle and apical, unlike the C- level values that were always overlapping. C-level values showed no significant differences.
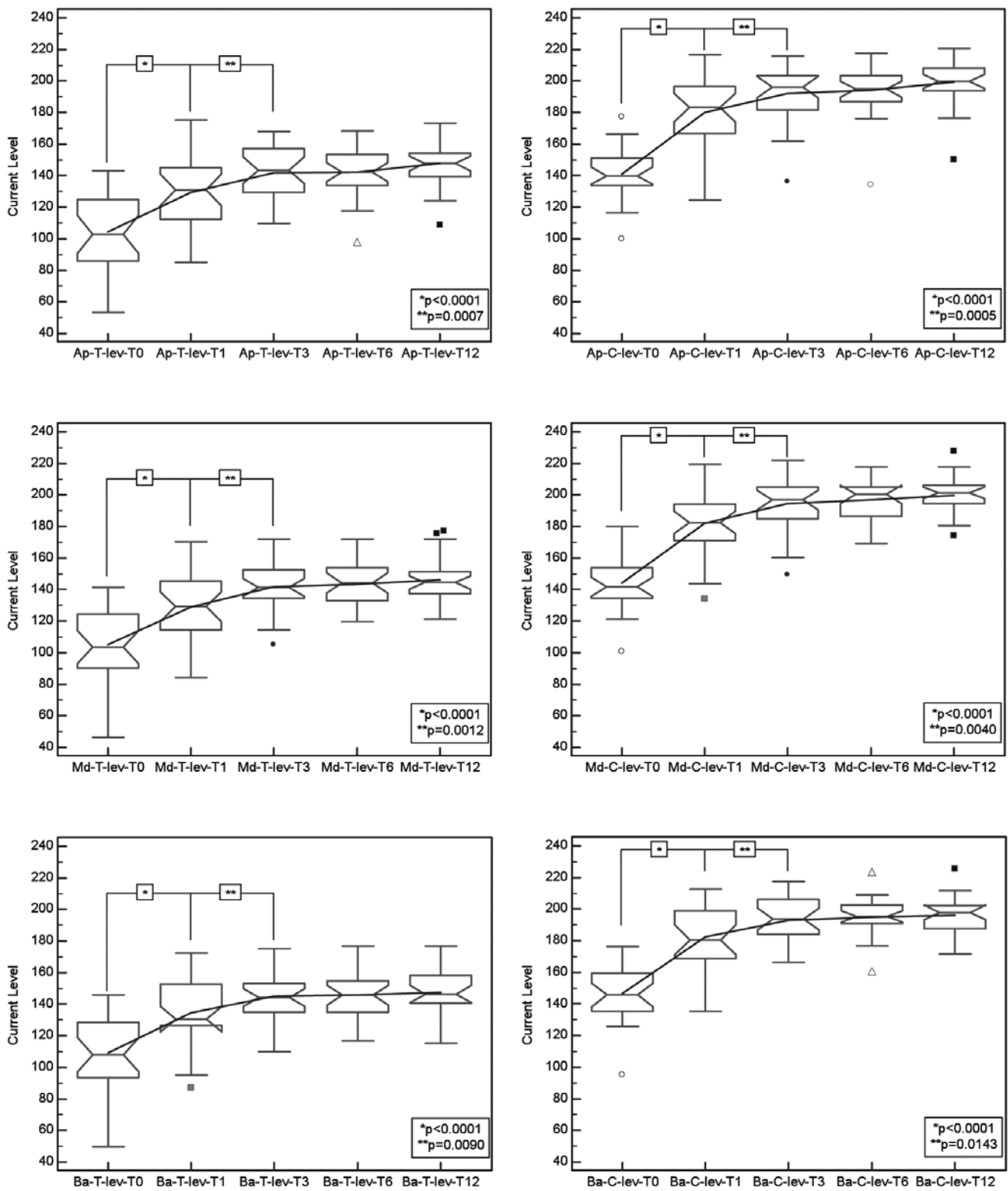
Figs. 2a-f. Time sequence of the values of T (left figures, a, c, e) and C-level (right figures, b, d, f) differentiated by apical (top figures), middle and basal (down figures) electrode groups.

Table III. Comparison between electrode groups at different follow-up times of T-and C-levels (significant difference are highlighted).

T-Level	T0	T1	T3	T6	T12
Apical vs Middle vs Basal	F = 7.82 p = 0.001	F = 5.39 p = 0.008	F = 2.27 p = 0.114	F = 1.94 p = 0.159	F = 0.18 p = 0.833
Apical vs Middle	p^a=1	p^a=1			
Middle vs Basal	p^a = 0.0006	p^a = 0.0056			
Apical vs Basal	p^a = 0.0220	p^a = 0.1290			

C-Level	T0	T1	T3	T6	T12
Apical vs Middle vs Basal	F = 4.57 p = 0.015	F = 0.77 p = 0.468	F = 0.70 p = 0.503	F = 0.85 p = 0.434	F = 1.79 p = 0.177
Apical vs Middle	p^a = 0.137				
Middle vs Basal	p^a = 0.371				
Apical vs Basal	p^a = 0.085				

[a] Bonferroni corrected

Discussion

Previous changes over time in electrical stimulation levels have been reported for adults [13-15]. In particular, Hughes [13] stated that C-levels and T-levels stabilised within 12 months of use. The results of the present study indicate that T-levels and C-levels tend to increase up to T12, with significant changes seen up to T3. Later changes observed up to T12 were not considered significant. These results appear as a slowing, although not a cessation, of change after T3. The significant difference between T1 and T12 for T- and C-levels in all electrodes may be due to a more conservative approach in setting the T1 values in patients seen at first mapping. In particular, the important interval differences observed between T1 and T12 may be due to excessive reduction of T1 values rather than a real increase in T12 values.

The non-significant values noted after T3 agree with an earlier intervention of cochlear factors of variations.

The differences noted in the basal T-level responses compared with middle and apical suggest involvement of anatomical factors in that location. Fayad [16] reported a basal prevalence of fibrosis and newly-formed bone after implantation in humans. Our results agree with such a basal anatomical modification, which can be related to the different mean basal T-levels compared to middle and apical findings.

In our patients, the same surgical technique was always implemented; therefore, the result of higher T-values in basal electrodes could be due the insertion technique compared to the round window route. Against this hypothesis, there are the histological findings of Fayad [16], who reported that five round-window surgeries compared to five cochleostomies did not yield significant differences in the amount of fibrosis, bone or, in general, of the newly-formed tissue or in residual sensorineural cells. According to Kawano [17], T-values correlate with the level of fibrous tissue and new bone, particularly with the former. The trend for average T-levels to be lower in the middle and apical segments is consistent with a more robust middle and apical turn survival of sensorineural cells and/or a closer distance between array and modiolus. Average C-levels did not exhibit any substantial differences between various electrodes at different evaluation periods. This finding agrees with a prevalence of extracochlear factors in defining C-levels; e.g. a) the prolonged activating effect of electrical stimulation on the fibres of the auditory nerve, b) the intervention of central auditory pathways, c) purely cortical factors such as learning or patient preference of a more or less robust stimulation.
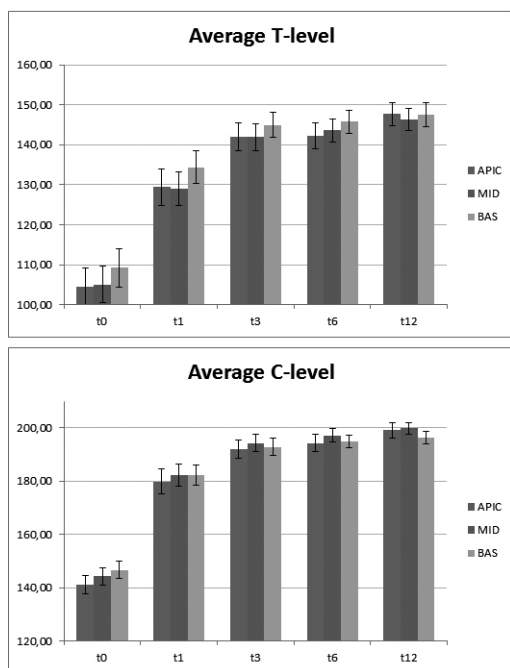
Figs. 3a-b. Time sequence of the values of T (3a) and C-level (3b) differentiated by apical, middle and basal electrodes.

Only one study [7] deals specifically with the statistical optimization of speech processor readjustment by considering fitting time intervals to maintain the maximal variation in 90% of recipients between two consecutive fittings within 6 current units.

Clinically, the data presented may be useful when scheduling patients for fitting sessions where appointments are more frequent in the first months after activation when there are more intensive fitting parameters variations.

Conclusions

T-levels in the basal turn exhibit higher values consistent with a greater amount of fibrosis, as reported in other studies. Fitting sessions should be scheduled more frequently during the first three months as indicated by the relatively greater changes seen in the slopes of early T- and C-levels.

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RHINOLOGY

Nasal septal deformities in chronic rhinosinusitis patients: clinical and radiological aspects

Aspetti clinici e radiologici delle deformità del setto nasale in pazienti affetti da rinosinusite cronica

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SUMMARY

Septal deformities are very frequent in patients suffering from chronic rhinosinusitis (CRS). The question is whether or not some types of septal deformities are involved more frequently in this process or not. The authors observed the incidence of particular types of septal deformities in a group of CRS patients using Mladina classification. The same has been done with a control group that consisted of healthy volunteers. In the literature, type 7 has been found very frequently, i.e. in nearly 30% of all CRS cases. Herein, type 7 was mostly composed of types 3 and 5. Type 3 can be accurately recognised on axial MSCT scans, while type 5 can be accurately recognised on coronal views. Concomitant septal surgery at the time of endoscopic sinus surgery is recommended.

KEY WORDS: Chronic rhinosinusitis • Nasal septum • Deformities • Incidence • Classification • MSCT

RIASSUNTO

Le deformità del setto nasale sono molto frequenti in pazienti affetti da rinosinusite cronica (CRS). La domanda è se alcune deformità possono aggravare più di altre questo processo patologico. In questo lavoro gli autori hanno studiato l'incidenza di particolari tipi di deformità in un gruppo di pazienti affetti da CRS usando la classificazione di Mladina. Lo stesso è stato fatto in un gruppo di controllo costituito da volontari sani. Il tipo 7 molto è stato riscontrato nel 30% dei casi di CRS. Tale tipo risulta essere caratterizzato dalla presenza contemporanea di diverse deformità e più frequentemente dall'associazione del tipo 3 e 5. Il tipo 3 evidenziabile accuratamente con scansioni TC assiali ed il tipo 5 con scansioni coronali. Gli autori concludono sostenendo l'importanza e l'utilità di una settoplastica da eseguirsi, in pazienti, che presentano una deformazione tipo 7, in concomitanza con la FESS.

PAROLE CHIAVE: *Rinosinusite cronica • Deformità del setto nasale • Esame TC*

Introduction

The influence of skull base shape on the onset of septal deformities of the human nose was first mentioned by Šercer as early as 1936 [1]. This author stated that septal deformities could not be found in quadrupeds since their skull base is flat, i.e. does not have any angulation at the junction of its anterior and posterior part. On the contrary, the skull base of the adult humans is angulated by an angle open downwards, i.e. towards the splanchnocranium (Huxley's angle). An approximate value of Huxley's angle is 135°. According to Šercer's opinion at that time, the angulation of the skull base results from a downward pressure of the neurocranium onto the splanchnocranium, hence causing septal deformities. Šercer called this system "cranial pincers". He also drew the attention to the fact that in newborns and small children the skull base has no angulation, but with age it gradually becomes increasingly angulated until it reaches its final shape in an adult age. This is clinically and practically supported by the fact that the incidence of septal deformities in newborns varies from 0.9% to 17% [2 3], gradually rising in small children, and continuously rising with age it finally reaches some 55% of all young adults (19-20 yr of age) [4]. A reduction of the splanchnocranium at the expense of neurocranium has also been noted, thus resulting in a prominent nose in mankind [5].

On the other hand, chronic rhinosinusitis (CRS) is a very common clinical entity. Everyday experience teaches us that septal deformities are very frequent in patients suffering from CRS. There are many reports in the literature dealing with the correlation between septal deformities and CRS, but few actually demonstrating such a correlation, thus suggesting that the correlation is perhaps not that strong and important [6-9]. The question arises here as to whether previous results are biased as because they were not based on a well defined classification of septal deformities. Our interest was whether or not some particular, targeted septal deformities are involved more frequently in this process.

To elucidate this, we needed a clear classification system. For instance, a practical and user-friendly classification of septal deformities would serve to make data standardised, uniformed, reliable and comparable. The Mladina classification [10] is such a system.

One should take into consideration that not all septal deformities can be recognised during native anterior rhinoscopy, since very posterior deformities could be simply hidden behind the more anterior anatomical parts of the nasal cavity. For this reason, decongestion and endoscopic examination of the nose are needed for reliable assessment of the possible existence of septal deformities.

The aim of this comparative study was to elucidate whether or not some particular types of septal deformities are more frequent in CRS patients.

Our multicentre study, based on native anterior rhinoscopy findings of the nose with no decongestion or even endoscopy of the nasal cavity, showed that the overall incidence of septal deformities in adult humans is very high, near 90% of the population in the world [11]. Since neither decongestion of the nasal mucosa nor nasal endoscopy were performed in that study, it could be expected that some of the so-called deep deformities remained undiscovered. This gives rise to the belief that the incidence of septal deformities in adult subjects is even higher than 90%. This finding gave rise to the assumption that septal deformities are a very common clinical entity regardless of geographical distances and locations.

Materials and methods

A group of 127 CRS patients, older than 18 yr, suffering from CRS according to EPOS criteria [12] were recruited. The EPOS 2012 criteria were used as to define a diagnosis of CRS, i.e. first of all founded on anamnestic data, clinical findings (anterior rhinoscopy before and after the decongestion, fibre endoscopy) and MSCT scans in coronal and axial projections. Previously-operated patients were excluded from the study.

All participants were patients of the ENT Department of Clinical Hospital Center Zagreb, Croatia (89 patients), or ENT Department ORL Department of Policlinico Le Scotte, Sienna, Italy (38 patients), admitted to the hospital because of sinus surgery in the period from September 2010 - September 2012. There were 78 males and 49 females, aged 18-73 yr. In both clinics, data were collected by two experienced rhinologists to ensure uniformity, relevance and reliability of the rhinoscopic and fibre endoscopic findings, as well as proper use of the Mladina classification both during physical examination (rhinoscopies, fibre endoscopy) and when assessing the appearance of nasal septums on MSCT scans.

As for the control group, the same procedures (except MSCT scans) were performed on 64 healthy volunteers with no clinical signs of CRS. There were no statistically significant differences between the CRS and control groups regarding the age and sex characteristics. All participants signed an inform consent form, and the study was approved by the relative Ethic Committees of Clinical Hospital Zagreb and Policlinico Le Scotte Siena, Italy. Statistical analysis of data collected in each centre was made with a Chi square test.

Mladina classification

There are seven types of septal deformities in this classification (Fig. 1). The first four belong to the so-called vertical deformities, meaning that deflections of the septum are defined by the sagittal plane (anterior-posterior deformities). The first two are located in the anterior valve region (type 1 and 2), the third is located next to the head of the middle turbinate, i.e. at the borderline between quadrangular and perpendicular lamina of the septal skeleton (type 3, otherwise named as "C-shaped" or "reverse C-shaped" septum). The fourth, type 4, is a double vertical deformity, i.e. it consists of type 2 on one side and type 3 on the other, thus forming so called "S" or "Z" shaped septum.

Type 5 means the unilateral basal, ascendant crest. It is located more laterally and deeper, and extends towards the lateral nasal wall (the so-called septal spur). The opposite septal side is almost always flat.

Type 6 is a unique deformity characterised by a groove between the septal cartilage and the intermaxillary bone wing. On the corresponding location of the opposite septal side, a more or less emphasised basal crest can be found.

Finally, type 7 is a variable combination of types 1-6.

Results

There were no differences in the incidence of subjects with and without a septal deformity between Italian and Croatian CRS groups (Table I). The incidence of type 7 was found to be statistically significantly higher in the group of CRS patients than in the control group (Table II). In the CRS group, it was present in almost 30% of subjects.
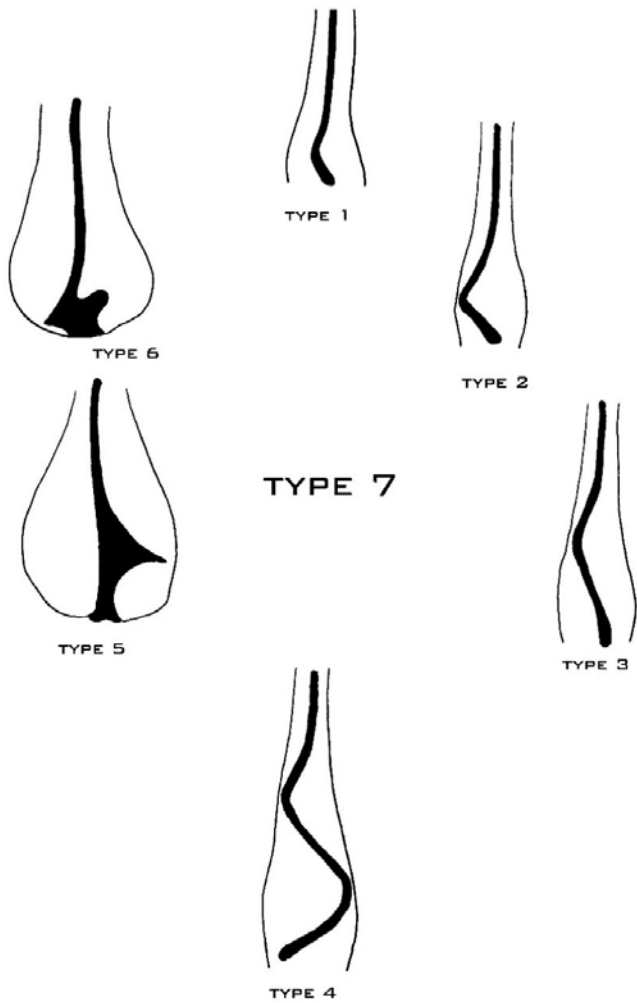
Fig. 1. Mladina classification. Types 1, 2, 3 and 4 are presented as in a bird's eye view, while type 5 and 6 are presented in an anterior-posterior view. Radiologically, the bird's eye view corresponds to axial CT scans, whereas the anterior-posterior view corresponds to coronal scans. Type 7 is in the middle of the scheme since it presents a combination of previous six types.

Table I. Incidence of septal deformities in Italian and Croatian CRS patients.

	Italy	Croatia	Statistical significance
Patients with nasal septal deformity	35 (92.10%)	81 (91.01%)	p > 0.05
Patients without nasal septal deformity	3 (7.90%)	8 (8.99%)	
Total number of patients	38 (100%)	89 (100%)	

Table II. The incidence of type 7 septal deformity in the CRS and control groups.

	CRS group	Control group	Statistical significance
Type 7 deformity	38 (29.92%)	4 (6.25%)	p < 0.05
No type 7 deformity	89 (70.07%)	60 (93.75%)	
Total number of patients	127 (100%)	64 (100%)	
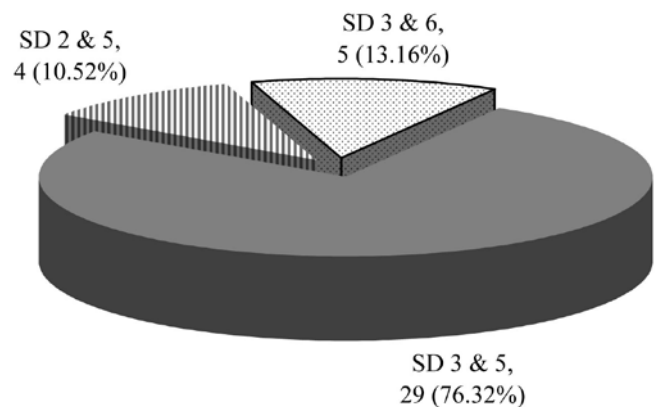
Fig. 2. The percentages of various types of septal deformities (SD) in type 7 found in CRS patients.

Type 7 is in fact a combination of some pure types of the deformities. It is well known that it usually consists of one of the so-called horizontal deformities (type 5 or 6) and one or more of the vertical deformities (types 1, 2, 3, or 4). Type 7 herein was mostly composed of types 3 and 5 (76.32%), than of types 3 and 6 (13.16%) and finally of types 2 and 5 (10.52%) (Fig. 2).

However, type 7 as a combination of some of the pure types, was not found to be the leading deformity in CRS group in general. It was present in almost one-third of those patients (29.92%), but the rest was represented by other, pure types of deformities such as: type 1 in 1.53%, type 2 in 3.05%, type 3 in 21.63%, type 4 in 6.15%, type 5 in 36.18% and type 6 in 1.53%.

Considering the incidence of type 7 in CRS group, it is obvious that the combinations that included type 5 were dominant, i.e. they were present in 86.84% of those types 7.

Radiologically, the most common types of septal deformities in CRS patients are quite easily recognisable. For instance, type 3 is a typical unilateral septal deformity, the so-called "C-shaped" or "reverse C-shaped" septum. The angulation of the deformity is located exactly at the borderline between the quadrangular and perpendicular lamina of the septal skeleton. Thus, it belongs to the group of "vertical deformities", i.e. those which concern the declinations of the septum in a sagittal plane, and is thus expected to be clearly presented and seen almost exclusively on axial MSCT scans (Fig. 3 A and B). On the other hand, type 5 definitely belongs to horizontal deformities. The deflection here does not go anterior or posterior as in types 1, 2, 3 and 4, but laterally. Because of this, type 5 as far as the MSCT is concerned, should be exclusively observed and studied by coronal scans because of its typical clinical appearance (Fig. 4 A and B).
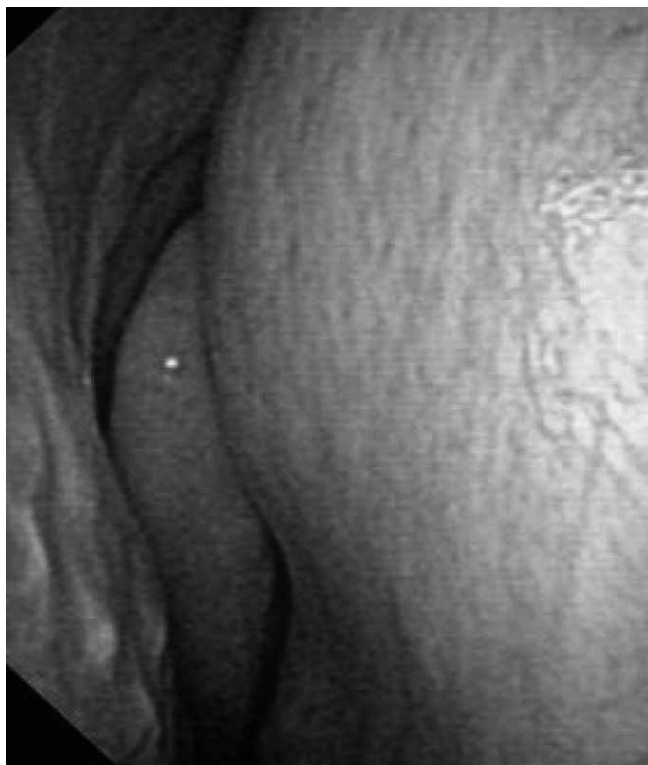
Fig. 3A. Moderate, right-sided type 3. Only lateral and inferior half of the middle turbinate can be seen after decongestion.

Fig. 3B. An axial MSCT scan of the same patient shown in Figure 3A, showing nasal septum anatomy: it is deflected at the borderline between the cartilaginous and bony septal skeleton, getting into close contact to the head of the right middle turbinate and making right nasal cavity remarkably narrower than the left one.

Discussion

A lasting question on the role of the septal deformities in CRS has been evaluated herein in a practical and clear manner: a well established international classification of septal deformities has been used in two independent CRS groups, and the results compared to a well defined control group. It was found that one of the vertical septal deformities, i.e. deformity in antero-posterior direction, was predominant. Namely, type 3, which, owing to the fact that the most prominent part of the deformity lies in the close vicinity of the head of the middle turbinate, makes one nasal cavity remarkably narrower than the other. The turbulent flow of the air-stream, which occurs

Fig. 4A. Right-sided type 5 septal deformity.

Fig. 4B. Type 5. A coronal MSCT image perfectly identifies type 5 in all cases, with no exception. Axial CT-scans are of less importance.

both because of narrow passage on one side and very wide passage on the other side, produces the epithelial metaplasia, i.e. respiratory epithelium usually becomes substituted by squamous cell epithelium [13-14]. In terms of paranasal sinus physiology, particularly in terms of normal functioning of the ostiomeatal complex, this is crucial fact: this leads directly to stasis of mucus, i.e. to long lasting, smouldering, subacute or even chronic inflammation, compromising the function and health of all sinusal compartments around it: frontal, maxillary, sphenoid and ethmoidal [7].

In addition, types 3 and 5 were found very often in the CRS group as one of the components of the otherwise frequently seen type 7.

Fortunately, this type is easily and accurately recognised when studying axial MSCT scans of the paranasal sinuses. At any rate, the second most frequent type in CRS patients was type 7, but again combined in more than two-thirds of cases of type 3 with a type 5. This was found more frequently in CRS group than in the control group (29.92% and 6.25%, respectively).

The question arises as to whether a clinician should pay attention to the septal deformities in CRS patients, and if concomitant septal surgery is warranted in addition to endoscopic sinus surgery?

In our opinion, the answer is 'yes'. Septal surgery, if performed properly, cannot produce anything negative for surgically-treated sinuses, and can only be beneficial. The duration of the surgery can be prolonged, but it is nonetheless of value since a straight septum will undoubtedly offer better aerodynamic preconditions for healthy sinuses than a deformed one.

Fortunately, septal deformities can be well recognised and accurately assessed even without rhinoscopy or fibre endoscopy of the nose by analysing MSCT scans in both axial and coronal projections. Since types 1, 2, 3 and 4 belong to the group of "vertical deformities", i.e. those which concern the declinations of the septum in a sagittal plane, they can be clearly and accurately seen and correctly recognised almost exclusively on axial MSCT scans. Coronal scans, in the case of these deformities, can allow an experienced rhinologist to get a general idea about septal morphology and the wideness of both nasal cavities, but the lateral deflections can be observed much more clearly only on axial scans only. Beyond doubt, coronal scans will show that the ipsilateral nasal cavity, where there is the septal convexity, is generally narrower than the other one.

It should be kept in mind that the irregularity cannot be reliably recognised as a type 1, 2 or type 3 since the only difference between these three types lies in the fact that types 1 and 2 are located in the region of the anterior nasal valve, while type 3 is located deeper in the nose, i.e. next to the borderline between septal cartilage and perpendicular lamina facing the head of the middle turbinate. Looking at coronal MSCT scans from anterior to poste-rior, they may give almost the same impression with the possibility to substantially confuse the observer.

Regarding types 5 and 6, two aspects are important: first, these deformities definitely belong to horizontal deformities. The deflections do not go anterior or posterior as in types 1, 2, 3 and 4, but laterally. On occasion, only the unilateral deflection can be visible, like in type 5, or the deflection involves both sides, as in type 6. Regardless, types 5 and 6, as far as MSCT is concerned, should be exclusively observed and studied by coronal scans because of their typical clinical appearance.

Conclusions

Septal deformities according to the Mladina classification can be accurately and easily recognised on MSCT of the paranasal sinuses. Type 3 can be accurately recognised on axial MSCT scans, while type 5 can be accurately recognised on coronal ones. Type 7 is found very frequently, i.e. in nearly 30% of all CRS cases. Herein, type 7 was mostly composed of types 3 and 5.

Concomitant septal surgery at the time of endoscopic sinus surgery is recommended.

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VESTIBOLOGY

Vestibular assessment in patients with vestibular schwannomas: what really matters?

Valutazione della funzione vestibolare nei pazienti affetti da Schwannomi vestibolari: cosa conta realmente?

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SUMMARY

Vestibular function is often underdiagnosed in vestibular schwannomas (VS). To evaluate it in a selected group of patients harbouring vestibular schwannomas, 64 patients were included in this study, recruited between March 2008 and June 2011 at our institution. All patients underwent Gd-enhanced MRI and complete neurotological evaluation before gamma knife surgery. Morphological measurements included Koos Classification and quantification of internal acoustic canal filling in length and diameter. Cochlear and vestibular functions were assessed considering pure tone and speech audiometry, bedside examination and caloric test by videonystagmography. A statistical analysis was performed to find possible correlations between morphological and cochleovestibular data. Patients with a higher intracanalicular length (ICL, mean value 8.59 and median 8.8 mm) of the tumour presented a higher value of UW than the subgroup with a lower length (51.9 ± 24.3% and 38.8 ± 18.1% respectively, p = 0.04), while no difference was detected for pure tone audiometry (PTA) values (50.9 ± 22.3 db and 51.1 ± 28.9 db respectively). Patients with a higher ICL also presented a higher rate of positive HIT (88% and 60% respectively, p = 0.006). Patients with a higher value of intracanalicular diameter (ICD, mean value 5.22 and median 5.15 mm) demonstrated higher values of UW (50.2 ± 29.1% and 39.3 ± 21% respectively, p = 0.03), but not different PTA (50.2 ± 29.1 db and 51.9 ± 29.9 db respectively). Finally, patients with a positive head impulse test (HIT) demonstrated significantly higher values of unilateral weakness (UW) (p = 0.001). Vestibular disorders are probably underdiagnosed in patients with VS. ICL and ICD seem to be the main parameters that correlate with vestibular function. Also, in case of small intracanalar T1 VS a slight increase of these variables can result in significant vestibular impairment. The data reported in the present study are not inconsistent with the possibility of proactive treatment of patients with VS.

KEY WORDS: Vestibular Schwannomas • Vestibular tests • Hearing loss • Gamma-Knife • Radiosurgery

RIASSUNTO

La funzionalità vestibolare è ad oggi poco studiata nei pazienti affetti da Schwannomi Vestibolari ed i deficit vestibolari spesso sottovalutati. Allo scopo di valutare tale funzione, sessantaquattro pazienti affetti da Schwannomi Vestibolari sono stati inclusi nel lavoro, reclutati tra marzo 2008 e giugno 2011 presso il nostro ospedale. Tutti i pazienti hanno eseguito una RMN encefalo con contrasto ed una valutazione cocleo-vestibolare completa prima del trattamento con Gamma-Knife. Le misurazioni morfologiche comprendevano la classificazione secondo Koos e la quantificazione della lunghezza e diametro intracanalare della lesione. La valutazione cocleovestibolare è stata effettuata con una audiometria tonale e vocale ed una valutazione vestibolare completa con videonistagmografia e stimolazione calorica. Una analisi statistica è stata condotta per valutare possibili correlazioni tra i dati morfologici della lesione ed i reperti cocleovestibolari. I pazienti con una maggiore estensione in lunghezza della lesione all'interno del canale (media 8,59, mediana 8,8 millimetri) presentavano più elevati valori di Preponderanza Labirintica alla prova termica (51,9 e 38,8 rispettivamente, p = 0,04), mentre nessuna differenza è stata trovata relativamente alla perdita uditiva all'esame audiometrico tonale (50,9 db e 51,1 db rispettivamente). I pazienti con maggiore estensione intracanalare in lunghezza presentavano anche una più alta percentuale di positività al test dell'Head Impulse (88% e 60% rispettivamente, p = 0,006). I pazienti con maggiore diametro incananalare della lesione (media 5,22, mediana 5,15 millimetri) hanno evidenziato più alti valori di Preponderanza Labirintica al test calorico (50,2 e 39,3 rispettivamente, p = 0,03) ma nessuna differenza di soglia uditiva (50,2 e 51,9 rispettivamente). Per ultimo, i pazienti con Head Impulse positivo hanno evidenziati più alti valori di Preponderanza Labirintica ai test calorici (p = 0,001). I disordini vestibolari sono probabilmente sotto-diagnosticati nei pazienti affetti da Schwannoma dell'8° nc. La lunghezza ed il diametro della lesione entro il condotto uditivo interno sono risultati i principali parametri correlabili con il danno vestibolare. Anche in caso di piccole lesioni T1, un modesto incremento della lesione potrebbe inoltre determinare un significativo peggioramento della funzione vestibolare. Questi dati suggeriscono l'utilità di una terapia attiva anche in pazienti con lesioni di piccolo volume a decorso intracanalare.

PAROLE CHIAVE: *Schwannomi 8° nervo cranico • Test vestibolari • Ipoacusia • Gamma-Knife • Radiochirurgia*

Introduction

Vestibular schwannomas (VS) are extra-axial, slow-growing benign lesions arising from the vestibular nerve. Usually the VS originates in the distal neurilemmal portion of the nerve at, or close to, the neurilemmal glial junction [1]. The median age at diagnosis is 50 years and appears in a sporadic unilateral form in the majority of cases (95%), with an incidence of about 1/100,000 per year, without any sexual prevalence [2 3]. When bilateral, it is often linked to a neurofibromatosis type 2, an autosomal dominant tumour-suppressor syndrome characterised by schwannomas, meningiomas and ependymomas that develop throughout the central and peripheral nervous systems [4 5]. They represent more than 90% of all cerebellopontine angle lesions. In 25%-45% of cases schwannomas occur in head and neck region [6].

In the last decades, with the widespread availability of MRI, the incidental diagnoses of VS has increased, while the size of newly diagnosed VS has progressively decreased. Despite the anatomical origin, many patients with VS complain of hearing loss [7 8], but only a few experience vestibular symptoms [9]. Many studies have demonstrated the correlation between tumour size and functional hearing [10 11], but the correlation between tumour extension and vestibular symptoms has still not been clarified.

In previous studies, tumour size has been demonstrated to have a correlation with caloric responses and vestibular evoked myogenic potentials (VEMPs), and above all with ocular VEMPs [12 13], although in patients with VS within the internal acoustic canal neither the nerve origin of the tumour nor tumour size show clear correlation with the results of these tests [14]. In fact, the absence of caloric responses and VEMPs from one side may be predictive of a tumour size > of 2.5 cm [15].

Three options have been proposed for VS:

Surgical treatment may be considered [16 17], although according to some authors intervention may be associated with several complications [18];

A radiosurgical approach may be alternatively taken [19 20]; according to the recent guidelines for the treatment of VS approved by the International RadioSurgery Association (IRSA) [21], stereotactic radio-surgical treatment with gamma knife (GKS) is indicated in tumours smaller than 3 cm in diameter without brainstem distortion, post-surgical residual even larger than 3 cm and growing intracanalicular tumours. Recent studies reported a tumour growth control rate after GKS treatment of 93-100% [22 23];

Since most VS have a slow growth rate, management with a "wait and see" policy has been proposed [24 25].

Some authors underline that when surgery is needed after radiosurgery, the risk of facial nerve palsy is increased [26]. Audiometric exam, rather than vestibular assessment, is at present mainly considered in therapeutic decision. The present study aims to evaluate vestibular function in a selected group of patients eligible for GKS for VS.

Materials and methods

Patient population

Between March 2008 and June 2011, 240 patients underwent GKS for VS at the Neurosurgical Department of San Raffaele Hospital in Milan. All patients were eligible for GKS according to IRSA Guidelines.

In all cases, Gd-enhanced MRI and complete otolaryngological evaluation before GKS treatment were performed. Exclusion criteria were:

- no detectable hearing before treatment;
- type 2 neurofibromatosis;
- bilateral tumours;
- Koos T4b stage;
- previous therapy on the targeted tumour;
- evidence of chronic otitis media and/or previous surgery of the middle ear;
- therapies with ototoxic drugs and/or chemotherapy;
- other lifetime vestibular disorders, with particular attention to Ménière's disease and CNS disorders.

Moreover, patients were asked to avoid consumption of any sedative drugs within the 24 hours before examination. According to these criteria, 64 patients were selected and included in the study: 42 women (66%) and 22 men (34%) with a mean age of 54.5 years (median 55.5 years, range 19-81 years). Thirty-five patients (55%) had right sided VS, and 29 (45%) left sided VS. Demographic data are summarised in Table I.

Evaluation of tumour size

Tumour volume, internal acoustic canal filling (in length and diameter) and Koos classification were assessed on MRI (Magnetom Vision model, Siemens; 1.5 Tesla) performed before GKS. The MRI imaging sequences were gadolinium contrast enhanced axial and coronal T1-weighted (2 mm thickness without gap, TR = 650, TE = 14, matrix 512 x 512 and double acquisition), 3D-CISS (reconstructed to 1.2 mm thickness without gap, TR = 4000, TE = 250, matrix 512 x 512) and axial T2 weighted (2 mm thickness without gap, TR = 3000, TE = 120, matrix 512 x 512).

The tumour volume varied between 0.01 and 9.4 ml (mean 1.34 ± 0.22 ml, median 0.73 ml). The mean intracanalicular length (ICL) was 8.59 mm (median 8.8 range 2.8-13.4 mm), and mean intracanalicular diameter (ICD) was 5.22 mm (median 5.2 range 1.1-10.8 mm). According to Koos classification, 11 lesions were stage T1, 8 stage T2, 15 stage T3a, 20 stage T3b and 10 stage T4a; no patients with 4th ventricle obstruction (Koos stage T4b) were included. Morphologic data are summarised in Table II.

Table I. Patient population.

Characteristic	# patients (%)
Sex	
Male	22 (34)
Female	42 (66)
Side	
Right	35 (55)
Left	29 (64)
Koos tumour stage	
T1	11 (17)
T2	8 (13)
T3a	15 (23)
T3b	20 (31)
T4a	10 (16)

Table II. Morphological data of lesions.

	Age y±SD	ICL mm±SD	ICD mm±SD	Volume ml±SD
Koos 1 (n=11)	51 ± 15	8.2 ± 1.9	4.7 ± 1.5	0.12 ± 0.08
Koos 2 (n=8)	47 ± 19	9.4 ± 2.2	5.6 ± 1.2	0.53 ± 0.34
Koos 3A (n=15)	55 ± 9	7 ± 2.5	4.9 ± 1.6	1.3 ± 1
Koos 3B (n=20)	55 ± 13	9.6 ± 2.5	5.1 ± 1.8	2.7 ± 2.6
Koos 4 (n=10)	57 ± 16	8.3 ± 2.8	5.6 ± 1.8	4.8 ± 2.9

ICD = intracanalicular diameter, ICL = intracanalicular length, y = years.

Cochlear and vestibular assessment

Cochlear and vestibular assessments were performed by a senior neurotologist and included:

- Clinical history for the age of onset of cochlear symptoms, presence of previous episodes of rotational vertigo and sensation of unsteadiness or imbalance.
- Pure tone audiometry for frequencies between 250 Hz and 8000 Hz; the exam was performed in a quiet room with a half octave precision. The pure-tone average (PTA) was calculated as the mean of 0.5, 1, 2, and 3 kHz thresholds.
- Speech audiometry was performed in silence, scoring by phonemes correctly repeated at several suprathreshold intensities. The CD contained phonetically balanced disyllabic lists commonly used for adult clinical testing. Speech discrimination score (SDS) was assessed; SDS was defined as the percentage of words correctly identified.
- Evaluation of vestibular system function performed by videonystagmography using the VO25 VNG system (Interacoustics, Assens, Denmark); the full vestibular examination included a study of spontaneous nystagmus, post head shaking test (HST), head impulse test (HIT) and hyperventilation tests.

- Caloric stimulation according to Fitzgerald-Hallpike was performed using an Amplaid otocalorimeter. The authors used angular slow phase velocity (SPV), as calculated during 10 sec of culmination, as the single parameter of labyrinthine function during caloric tests: data were interpreted in terms of unilateral weakness (UW) according to Jongkees' formula.

According to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines [27], hearing function was defined as class A (PTA < 30 dB and SDS > 70%), class B (PTA > 30 dB and < 50 dB and SDS > 50%), class C (PTA > 50 dB and SDS > 50%) or class D (PTA any level and SDS < 50%). Caloric vestibular function was defined as class A when UW was less than 25%, class B when between 25 and 50%, class C when between 50 and 75%, class D when UW exceeded 75%.

Statistical analysis

Continuously distributed variables were described as mean and standard deviation (SD), while median values and categorical variables were described by frequencies and percentages. The significance of any difference between groups was evaluated by a t-test for independent samples and analysis of variance (ANOVA) for repeated measures. Nominal data were compared by the chi-square test. The results were considered statistically significant for p values < 0.05.

Results

In this cohort, 18 subjects referred a previous episode of acute vertigo and 26 referred feeling unstable. Results of cochlear and vestibular findings differentiated for Koos classification are shown in Table III. Although patients with Koos 2 stage VS presented lower values of UW and PTA compared to other groups, no statistical difference was detected. Koos 4 patients referred a lower rate of lifetime rotational vertigo than other subjects. No difference was present for clinical history of imbalance.

HIT was positive in 8 subjects in Koos stage 1 (80%), 6 in Koos 2 (75%), 12 in Koos 3a (80%), 19 in Koos 3b (95%) and 7 in Koos 4a (60%). All subjects with a positive hyperventilation test also presented a positive HIT. Finally, the total population of patients with a positive HIT demonstrated higher values of UW (p = 0.001).

All vestibular and cochlear results were compared to the ICL and ICD. ICL values ranged between 2.8 and 13.4 mm (mean 8.59 ± 2.65 mm) and the median was 8.8 mm. ICD values ranged between 1.1 and 10.8 mm (mean 5.22 ± 1.68 mm) and the median was 5.15 mm. The subgroup of 30 patients with a higher ICL of the tumour presented a higher value of UW than the subgroup with a lower length (51.9 ± 24.3% and 38.8 ± 18.1% respectively, p = 0.04), while no difference was seen for PTA values (50.9 ± 22.3 db and 51.1 ± 28.9 db, respectively). Moreover, patients with a higher ICL also presented a higher rate

Table III. Cochlear and vestibular data.

	Vertigo	Imbalance	Mean PTA in decibel	Class of Hearing function	Class of vestibular function	UW%	Hypervent
Koos 1 (n = 11)	5 (45%)	5 (45%)	49 ± 27	A = 4 B = 1 C = 4 D = 2	A = 1 B = 3 C = 6 D = 1	52 ± 21	9 (82%)
Koos 2 (n = 8)	3 (37%)	4 (50%)	25 ± 13	A = 5 B = 2 C = 1	A = 4 B = 4	29 ± 14	4 (50%)
Koos 3A (n =15)	4 (27%)	3 (20%)	60 ± 30	A = 3 B = 6 C = 3 D = 3	A = 2 B = 5 C = 4 D = 4	46 ± 27	11 (73%)
Koos 3B (n = 20)	6 (30%)	9 (45%)	57 ± 35	A = 4 B = 6 C = 6 D = 4	A = 2 B = 9 C = 5 D = 4	49 ± 25	16 (80%)
Koos 4A (n = 10)	1 (10%)	5 (50%)	55 ± 34	A = 2 B = 3 C = 3 D = 2	A = 1 B = 6 C = 1 D = 2	47 ± 30	7 (70%)

PTA = Pure tone average, UW = unilateral weakness.

of positive HIT (88% and 60% respectively, p = 0.006). No difference between the two groups was detected in the hyperventilation test (72% and 70% of subjects, respectively). Finally, the subgroup of 30 patients with a higher value of ICD demonstrated higher values of UW (50.2 ± 29.1% and 39.3 ± 21% respectively, p = 0.03), but not different PTA (50.2 ± 29.1 db and 51.9 ± 29.9 db, respectively). No statistical difference for HIT was observed between these two groups (81% and 68%, respectively) and hyperventilation test (73% and 69%, respectively).

Discussion

Since VS originates from the vestibular nerve, a deficit of vestibular function should always be observed [28]; nonetheless, vestibular impairments are rarely studied in preoperative workup, and most patients came to diagnosis because of hearing loss confirmed by audiometric exam. According to previous studies, the degree of the vestibular deficit correlates with both tumour size and growth rate [29]. In our sample, only 18 subjects referred a previous episode of acute vertigo; in contrast, only 10 patients had normal vestibular assessment (15%; 1 subject in T1 stage, 4 in T2, 3 in T3a and 2 in T3b). Our data are in agreement with previously published data concerning vestibular abnormalities in patients with VS, reporting normal vestibular function in only 14% of cases. It should be also considered that only 26 subjects (40%) in our cohort referred imbalance; in our opinion, central compensation processes in slowly decreasing vestibular function may explain the significant difference with the rate of subjects presenting UW at caloric tests.

At present, the HIT proposed by Halmagyi and Curthois is widely used to detect vestibular peripheral hypofunction [30]; hyperventilation, on the other hand, is an increasingly used bedside test and alkalosis provoked by the manoeuvre can produce a nystagmus normally beating towards the healthy side, probably disrupting central compensation. In our series, the hyperventilation test was positive in 73% of patients, while other authors reported a positive result in up to 91.7% of cases [31-33]; in particular, we found no statistical difference in test responses between patients with higher or lower ICL /ICD. Moreover, according to some authors, caloric responses are well correlated with intraoperative findings and provide predictive factors for facial palsy and hearing outcome [34]. The loss of vestibular function has been correlated with tumour size, although it is not strictly associated with a deterioration of the quality of life assessed with the Dizziness Handicap Inventory questionnaire [10].

Another previous study reported a higher incidence of vertigo in patients with small and medium size VS compared to patients harbouring larger tumours (> 4 cm) [35]; in the present series, vestibular function correlated with the ICL and ICD of VS rather than with tumour volume or Koos stage. A possible explanation for this finding may be that the main mechanism of nerve injury is related to its compression inside the internal acoustic canal. On these bases, some authors proposed clinical intervention, such as vestibular rehabilitation in all patients with VS, and especially in subjects treated with surgical intervention or GKS [36].

Some authors advocate a wait-and-see strategy, especially for T1 stage VS, and focusing attention on tumour growth and hearing function [24 25 37]. On the other hand, other dem-

onstrated that the wait-and-see policy exposes patients to a high risk of tumour growth and hearing loss. Both events may occur independently in the mid-term period [38]. To the best of our knowledge, nothing has been published on vestibular function in patients proposed for wait-and-see policy. The results of this study showed that vestibular function is more influenced by ICL and ICD, rather than by total tumour volume. Consequently, it is likely that a slight increase in ICL or ICD may produce alteration in the HIT and caloric responses, reflecting a poorer result in terms of vestibular function even after successful therapy at later times. It should be also considered that previous studies reported tumour growth control in 98% of patients treated with GKS, possibly avoiding a further increase in ICL and ICD with the possibility of hearing and vestibular preservation [19].

The data reported in the present study support the possibility of proactive GKS treatment even in patients harbouring small T1 VS. Nevertheless, a prospective study analyzing data on vestibular function after GKS is needed to confirm this possibility.

Conclusions

Vestibular disorders are probably underdiagnosed in patients with VS, and complete vestibular assessment should always be performed. ICL and ICD seem to be the main parameters that correlate with vestibular function even in patients harbouring small intracanalicular VS. Particular attention should be given to ICL and ICD in small T1 VS, in which even a slight increase of these variables can affect vestibular function. The data from the present study support the role of proactive treatment even in these patients. Nevertheless, a prospective study analysing data on vestibular function after GKS is needed to confirm this possibility.

Abbreviations

VS: Vestibular Schwannomas
GKS: Gamma Knife
HIT: Head Impulse Test
UW: Unilateral Weakness
PTA: Pure Tone Audiometry
ICD: Intracanalicular Diameter
ICL: Intracanalicular Lenght
SDS: Speech Discrimination Score

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OTOLOGY

Primary squamous cell carcinoma of the external auditory canal: surgical treatment and long-term outcomes

Carcinoma spinocellulare primitivo del condotto uditivo esterno. Terapia chirurgica e risultati a lungo termine

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SUMMARY

This study was conducted on patients with squamous cell carcinoma of the external auditory canal and temporal bone treated with surgery alone or surgery plus postoperative radiotherapy. It was designed as a retrospective investigation with complete long-term follow-up covering the years from 1983 to 2008. The setting was a tertiary referral centre. Forty-one consecutive cases underwent surgery involving en bloc lateral or subtotal temporal bone resection, parotidectomy and neck dissection plus radiotherapy in advanced cases. The Pittsburgh staging system[7] was adopted. No cases were lost to follow-up, which ranged from 2 to 220 months, while for survivors ranged from 60 to 220 months and included clinical examinations and imaging. Outcome was expressed as NED (no evidence of disease), DOC (dead of other causes), DOD (dead of disease), AWD (alive with disease), disease-free survival (DFS) and disease-specific survival (DSS). Results were expressed with raw data and Kaplan Meyer curves. Patients with T1 and T2 disease had a DFS of 67% and a DSS of 92%. For T3 and T4 cases, the DFS was 41% and DSS was 48%. All treatment failures were due to local recurrences. The cases classified as T4 because the lesion extended from the cartilage canal to the periauricular soft tissues, or from the anterior wall to the parotid space, had a better outcome than the other T4 cases: this different prognosis suggests the need to stage tumours differently. Nodal disease coincided with a worse outcome due to local recurrence.

KEY WORDS: Temporal bone tumour • Carcinoma of the ear • Temporal bone resections • Lateral skull base surgery

RIASSUNTO

L'obiettivo di questo lavoro è valutare i risultati a lungo termine del trattamento chirurgico e chirurgico/radioterapico nel carcinoma spinocellulare primitivo del condotto uditivo esterno-osso temporale. Lo studio consiste in una analisi retrospettiva con follow-up a lungo termine. I casi chirurgici sono stati trattati tutti in un centro terziario di riferimento negli anni dal 1983 al 2008. Sono stati analizzati 41 casi di tumore spinocellulare primitivo del condotto uditivo esterno, trattati chirurgicamente con blocco resezione laterale o subtotale del temporale, parotidectomia, svuotamento laterocervicale elettivo o terapeutico. Abbiamo utilizzato la classificazione di Pittsburgh. Il follow-up si estende da 2 mesi a 220 mesi e, per quelli sopravvissuti, da un minimo di 60 mesi a 220 mesi. I risultati sono stati espressi come NED, DOD, DOC e AWD (non-evidenza di malattia, morto per malattia, morto per altre cause e vivo con malattia), con dati crudi e con curve di Kaplan Meyer. I T1-T2 hanno una sopravvivenza libera da malattia del 67%, ed una sopravvivenza specifica per malattia del 92%. I T3-T4 hanno una sopravvivenza libera da malattia del 41% e una sopravvivenza specifica del 48%. Tutti gli insuccessi sono avvenuti per recidiva locale. I casi stadiati come T4 per estensione da cartilagine ai tessuti molli o dalla parete anteriore alla parotide hanno avuto una miglior prognosi rispetto ai T4 con differente estensione mediale, inferiore o posteriore. Questa differenza di prognosi suggerisce la necessità di un cambio della stadiazione. Il coinvolgimento linfonodale implica una prognosi peggiore ma per recidiva locale e non regionale.

PAROLE CHIAVE: *Tumori del temporale • Carcinomi dell'orecchio • Resezioni del temporale • Chirurgia della base cranio laterale*

Introduction

Squamous cell carcinoma (SCC) of the external auditory canal is an uncommon malignancy [1 2] that arises from the external ear and spreads to the temporal bone and surrounding sites. Periauricular soft tissues, the parotid gland, temporomandibular joint and mastoid are common sites of tumour progression. The carotid canal, jugular foramen, dura, middle and posterior cranial fossae are invaded in advanced stages [2 3].

Ear pain and discharge may initially be mistaken for external otitis [5]. Late diagnosis is common and worsens prognosis. Aggressive surgery with postoperative radiation is the usual treatment [6].

A retrospective study was conducted on the outcome of our consecutive series of patients assessed preoperatively using modern imaging methods who underwent surgery between 1983 and 2008 based on a consistent skull base surgery protocol. The rationale for the surgical procedure is discussed in relation to the site and extent of the tumour and its classification. The outcome is expressed using raw data as well as Kaplan Meyer curves.

Materials and methods

Forty-four patients with primary SCC of the external auditory canal extending to the temporal bone treated between 1983 and 2008 were retrospectively reviewed. Tumours with a different histology or extending secondarily into the temporal bone were not considered. Three of the 44 patients with unresectable tumour only received palliative therapy, so 41 were the subject of the present study. This series included 35 first diagnoses and 6 recurrences (Table I). Among the former tumours, 4 arose in the radical tympanomastoidectomy cavity, and 3 cases were associated with another SCC arising in the auricle or periauricular skin.

The follow-up ranged from 2 to 220 months (mean 60 months) for the complete series, while for survivors it ranged from 60 to 220 months (mean 120 months). All surgical procedures were performed by the same surgeon using similar technique.

Table I. Site of origin of tumours.

Site of origin of tumour	Primary tumour
Bone canal	23
Cartilage canal	4
Cartilage + bone canal	4
In radical cavity	4
Recurrent tumour	6

Table II. The Pittsburgh staging system modified by Hirsch [7].

T status	Description
T1	Tumour limited to the external auditory canal without bony erosion or evidence of soft tissue extension
T2	Tumour with limited external auditory canal bony erosion (not full thickness) or radiographic finding consistent with limited (< 0.5 cm) soft tissue involvement
T3	Tumour eroding the osseous external auditory canal (full thickness) with limited (< 0.5 cm) soft tissue involvement, or tumour involving middle ear and/or mastoid
T 4	Tumour eroding the cochlear, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive (> 0.5 cm) soft tissue involvement; patients presenting with facial paralysis
N status	Lymph node involvement is a poor prognostic sign and places the patient in advanced stage (i.e. T1 N1, stage III), and T2, T3, T4 N1 (stage IV)
M status	M1 disease is stage IV and is considered a very poor prognostic sign

Diagnostic work-up and classification

The diagnostic work-up included clinical examination, imaging and biopsy. High-resolution CT and contrast-enhanced MRI were performed in 41 and 30 cases, respectively. All patients had a preoperative biopsy. The sites of origin of the tumour are listed in Table I. The modified Pittsburgh classification [7] was used for staging purposes (Table II); the early cases in the series were classified retrospectively.

Surgical indications

The framework for planning surgery involved identifying the sites and subsites of tumour growth and safe resection margins. All sites and subsites were assessed for their potential for hidden tumour diffusion and the related width of resection. Spread beyond the external auditory canal to adjacent areas, full-thickness bone erosion in the canal walls and lymph nodes that were clinically positive or suspect were all considered during the planning of the procedure. Other factors such as age, general conditions and comorbidities were also taken into account.

En bloc lateral temporal bone resection (LTBR) and en bloc subtotal temporal bone resection (STBR) were judged to be the procedures combining the widest safe resection margins with a clear and reproducible approach. No piecemeal removal was performed. The principles of skull base surgery were applied to the procedure [8]. For the LTBR, the block of the outer canal was contoured with an extended mastoidectomy and freed through a temporal craniotomy. The same craniotomy enabled the internal carotid artery to be exposed by drilling and displacing it from its canal down to the neck. The osteotomy from the carotid canal to the glenoid made it possible to free the block and preserve the continuity of the latter with the soft tissues of the parotid and neck dissection.

The STBR involved temporal and occipital craniotomies, freeing the carotid as mentioned above, and four osteotomies to deliver the block. One subtemporal osteotomy from the carotid canal to the posterior side of the petrous bone, with transection of the proximal third of the internal auditory canal and a second osteotomy through the occipital craniotomy, from the petrous bone to the jugular foramen (preserving its medial wall), a third osteotomy from the jugular fossa to the carotid canal, and a fourth from the carotid canal to the glenoid fossa through the temporal craniotomy.

The block remained continuous with the neck dissection and the parotid without violating the safe margins at this level.

Retrograde parotidectomy was performed in both LTBR and STBR. Total parotidectomy was indicated in cases of anterior growth beyond the anterior wall of the external auditory canal, while superficial parotidectomy was performed as a prophylactic measure on the intraparotid nodes in T1 and T2 cases. Parotid involvement was suspected when imaging revealed erosion of the anterior wall of the auditory canal or an enhancing mass in the parotid area.

The neck was treated in both LTBR and STBR with prophylactic selective neck dissection for clinically-negative necks and a modified type III radical neck dissection in patients with clinically-positive lymph nodes. Neck dissection was not performed in a few elderly patients who were N0, or who had an advanced tumour with a poor prognosis. If imaging showed growth of the tumour anteriorly towards the condyle of the mandible or the temporomandibular joint, then the condyle, mandible ramus or temporomandibular joint was added to the en bloc resection. Tumour growth against or infiltrating the dura demanded wide dura resection and repair with fascia. When the tumour was confined to the lateral end of the canal with no bone erosion, the LTBR lay laterally to the eardrum.

The facial nerve was handled on the basis of general principles, i.e. it was to be included in the resection when clinical examination or imaging indicated that it was involved by the tumour, or when the safe resection margin included the Fallopius. The internal carotid artery was never resected.

T1 and T2 cases underwent LTBR, superficial parotidectomy and neck dissection. T3 and T4 patients, classified as such due to spread from the cartilage canal to the periauricular soft tissues, or anteriorly through the anterior wall of the canal into the parotid space, were treated with LTBR, total parotidectomy and neck dissection. T3 and T4 cases with growth into the mastoid, or tympanum, or medial sections of the temporal bone underwent STBR, total parotidectomy and neck dissection.

Therapy

All 41 patients underwent surgery with a curative intent, but one had an incomplete STBR as the tumour was discovered to be unexpectedly advanced. LTBR was performed in 30 cases, and STBR in 11 (including the above mentioned incomplete resection). Neck dissection was part of the treatment in 33 of the 41 patients. Retrograde parotidectomy was performed in 37 cases. Postoperative radiotherapy with 50 to 70 Gy (median 60 Gy) was administered to T3-T4 cases, and to T1-T2 patients with intraoperative findings suggestive of more extensive disease, or with multiple nodal metastases or a single nodal metastasis with extracapsular spread, and to the case with undissected neck.

Follow-up

The follow-up involved clinical examination every 3 months for the first year and then every six months for four years, then yearly. Imaging with bone window CT and contrast-enhanced MRI was repeated every six months for the first year, then yearly until the 10th year.

Outcome measures

Outcome was expressed as NED (no evidence of disease), DOD (dead of disease), DOC (dead of other causes) and AWD (alive with disease), DFS (disease-free survival) and DSS (disease-specific survival) rates.

Raw data are reported because the follow-up was long and none of the patients were lost. Survivors were followed-up for 5 to 18 years (median 10 years).

DFS refers to all patients still alive and without disease (NED) after a median follow-up of 10 years (range 5-18 years) and to those who died of other causes (DOC) after a follow-up of at least 5 years. DSS refers to all patients who did not die of the disease (the whole series minus the DOD cases). Overall survival (OS) is expressed in terms of NED as none of the patients in our series were alive with disease at the end of follow-up (February 2013, after a follow-up of 5-18 years).

Results

Outcomes

The TNM staging of the surgical series is shown in Table III. Among the 36 of 41 patients who were graded, 20 were G1, 15 were G2 and one was G3. Tables III and IV

Table III. Stage-related outcome results.

T	No. of cases	NED	DOD	DOC < 5 years	DOC > 5 years	DSS%	DFS%
T1	6	2	/	3	1	**100%**	50%
T2	6	4	1	/	1	**83.3%**	83.3%
T3	8	4	2	/	2	**75%**	75%
T4	21	1	13	2	5	**38%**	29.3%
Total	41	11	16	5	9	**61%**	49%
T1+T2	12	6	1	3	2	**92%**	67%
T3+T4	29	5	15	2	7	**48%**	41%

Table IV. T stage and subsites of the external auditory canal walls originating the tumour.

T stage	No. of cases	Anterior wall	Other single wall	≥ 2 walls
T1	6	1	1	4
T2	6	3	2	1
T3	8	2	4	2
T4	21	8	2	11

show the complete case material with the T stage-related outcome and survival. The overall treatment failure rate was 39% (16/41), after a median follow-up of 10 years (range 5-18 years). The DFS (NED + DOC > 5 years, after a median 10-year follow-up, range 5-18 years) for the series as a whole was 49% (20/41), and the DSS was 61% (25/41). The failure rate for T1-T2 tumours was 8% (1/12), while for T3-T4 cases it was 52% (15/29). The T-stage related DFS and DSS are also shown in Figures 1 and 2.

All 16 failures were due to local recurrences, and one patient had a lung metastasis. In 12 patients, the tumour recurred within a mean 13.2 months (median 6 months, range 1-17 months) and all died of their disease (DOD) within 2 to 34 months. The other 4 patients survived longer: 2 had a longer time to recurrence and survived for 38 and 41 months; 2 were cases of tumour in a radical cavity and survived for 50 and 62 months.

Among the 14 DOC patients, 5 died before the fifth year of follow-up, and the other 9 died without disease after a follow-up of five years or more, and were considered cured.

Six of the 41 patients had recurrent tumour after previous treatment: their outcome was a treatment failure in 5 cases, while one died of other causes after 144 months.

The DFS rate was 17% (1/6) in the group of recurrences and 51% (18/35) in the group with a first diagnosis.

Tumours arising in a radical cavity, tumours of the canal with synchronous or metachronous SCC of the periauricular skin (regional cases) and tumours arising from the cartilage canal were considered as special subgroups. They were included among the whole series and are considered separately here in terms of their outcome.

There were 4 cases of SCC originating in an old regular cavity of a radical tympanomastoidectomy for cholesteatoma, where an area of SCC developed in the skin: 2 cases with tumour limited to the skin (considered as T1) were NED after 13 and 17 years; 2 with bone involvement (considered as T4) were DOD after 50 and 62 months (with the longest survival in the DOD group). There were 3 cases of synchronous or metachronous SCC of the auditory canal and periauricular skin: one T3 was NED at 127 months, one T3 was DOD after 16 months and one T4 was DOD after 34 months.

The eight tumours arising in the cartilage canal had the following outcome: one T2 and two T3 were NED at 113, 120 and 127 months; one T3 (also belonging to the regional SCC group) was DOD at 16 months; one T1 of the cartilage and bone canals was DOC at 33 months; three T4 (one of them was also a regional tumour) were DOD at 15, 34 and 50 months. The patients with intrinsic tumours survived, while all those with extrinsic tumours died except for one T3.

Postoperative radiotherapy
Twenty-three of the 41 patients received postoperative radiotherapy, including 19 of 29 advanced (T3-T4) cases and 4/12 T1-T2 cases. The median dosage was 60 Gy, range 50-70 Gy.
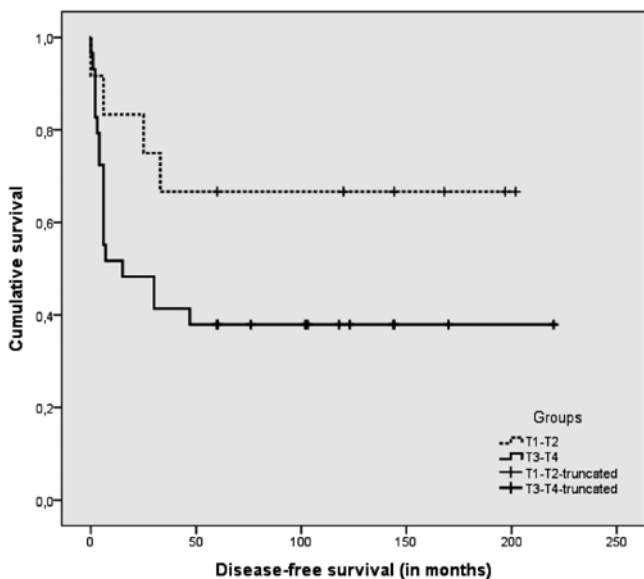

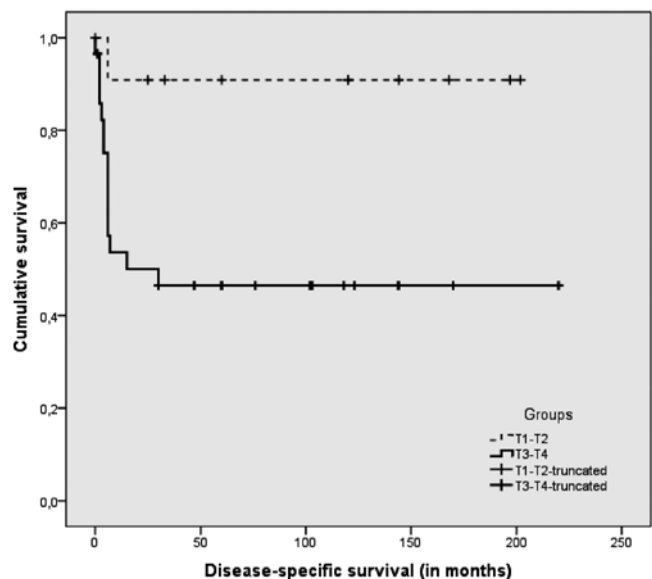**Fig. 1.** Disease-free survival (DFS) in T1-T2 *vs.* T3-T4 tumours.

Fig. 2. Disease-specific survival (DSS) in T1-T1 *vs.* T3-T4 tumours.

The indications for radiotherapy in T1-T2 patients varied: in one T2 case, intraoperative evidence of tumour aggressiveness prevailed over a negative finding at pathology; one patient had a positive node with extracapsular spread; one was a case of recurrence after primary surgery; and one case was a T1Nx with an undissected neck.

The outcome differed between the two groups treated with and without RT. Among the 4 T1-T2 cases given radiotherapy, there was one DOC after less than 5 years, and the others were all NED. Among the 19 T3-T4 cases given RT, there were 9 DOD and one DOC with a follow-up of less than 5 years, 4 DOC with a more than 5-years of follow-up and 5 NED. The DFS and DSS were 75% and 100% for the T1-T2 cases, and 47% (9/19) and 53% (10/19) for the T3-T4 cases. One of the 10 patients given no RT postoperatively had already received this treatment preoperatively, and died after 12 years of other causes (DOC > 5 years). Among the other 9 cases, one was NED, 7 were DOD and 1 was DOC < 5 years. The DFS for these patients was 20% (2/10) and the DSS was 30% (3/10).

Surgical procedures

The surgical procedures were LTBR in 30 cases and STBR in 11 (one of the latter was deliberately not completed due to uncontrollable tumour). Both types of resection were combined with retrograde parotidectomy in 37 of 41 cases. Parotidectomy was not performed in 4 cases due to patients' age or advanced tumour: one 82-year-old patient had postoperative RT and was DOC 33 months later (DOC < 5 years); two were cases of T4 recurring after surgery alone or surgery and radiotherapy (one underwent STBR and was DOD after 41 months, the other was the case of incomplete STBR, who was DOD after 14 months); and the fourth was the previously-mentioned T4 in a radical cavity who was DOD at 50 months.

LTBR was performed in T1-T2 cases and in T3-T4 disease involving the cartilage canal with periauricular extension, or the anterior wall extending into the parotid space. STBR was performed in T3-T4 cases of other origins and extensions. The DFS and DSS were 57% (17/30) and 73% (22/30) in the LTBR group, and 18% (2/11) and 27% (3/11) in the STBR group.

The treatment failed in 30% (9/30) of the LTBR group and 73% (8/11) of the STBR group.

It is worth noting the outcome in the T4 cases (Table V). The 21 patients in the T4 group included 8 cases of tumour of the anterior bone wall extending anteriorly > 0.5 cm, and 13 cases spreading medially and posteriorly to the temporal bone. The Pittsburgh classification draws no distinction between these two groups, but we found a difference in terms of survival. In the group of T4 cases with anteriorly extending disease the DFS was 62.5% (5/8 cases) and the DSS 75% (6/8), while the 13 T4 patients with a medial and posterior spread into the temporal bone had a DFS of 0% (0/13) and a DSS of 15% (2/13). If we exclude the cases with tumour in a radical cavity and recurrent tumour, a 6 case group homogeneous to the anterior extension group had similar results.

All 7 patients with pT4 disease and tumour infiltrating the dura, who underwent STBR, dura resection and fascia grafting, died of local recurrence at sites other than the dura or brain.

Nodal disease

Thirty-three of our 41 cases underwent neck dissection. The neck was clinically positive in 4 and negative in the remaining 37 patients. Pathology identified nodal disease in 9 cases, i.e. in the four clinically-positive necks and another five of the 29 cN0 cases that underwent neck dissection. The overall rate of lymph node metastases was 27% (9/33), and for occult metastases in the cN0 dissected necks was 17% (5/29). The remaining 24 cases were all pN0. The DFS in the positive neck cases was 33.% (3/9), and the DSS was 33% (3/9). In the negative neck cases, the DFS was 62.5% (15/24), and the DSS was 71% (17/24). The two disease-free patients in the N+ group were staged T1N2 and T3N2b. There were no regional recurrences in the neck, and all treatment failures were due to local recurrences.

Discussion

SCC of the external auditory canal is quite rare and the variability of the clinical pictures encountered makes it difficult to obtain homogeneous groups with sufficient statistical power. The complex anatomy and changing relationships between the tumour and contiguous tissues within a limited space make it complicated for surgery to achieve tumour-free margins. Individual surgeons take years to accumulate a number of cases, and surgical expertise changes in the meantime. All these factors limit the advances made in the treatment of this condition.

Table V. Sites of origin and outcome of T4 tumours[*].

No. of T4 cases	Site	NED	DOD	DOC < 5 years	DOC > 5 years	DFS%	DSS%
8	Anterior wall	1	2	1	4	62.5	75.
13	Other walls	/	11	2	/	0	15.3
6/13	Selected other walls[*]	/	5	1	/	0	16.6

[*] Selected other walls = tumour arising from walls other than the anterior wall, excluding recurrent or radical cavity cases.

Progress has nonetheless been made since the historical works by Lewis[9] and Conley[10], thanks to small steps forward achieved by several contributions. Staging with the Arriaga classification modified by Moody[7] is still the ground for progress.

The aim of this retrospective study was to provide outcome results based on complete long-term follow-up. The discussion focuses on the value of en bloc resection based on principles of oncological radicality and expertise in skull base surgery[8], as well as the outcome of treatment in relation to the tumour's sites and subsites of origin and direction of growth.

Outcomes

Cure rates have improved since the 1970s thanks to progress in diagnostic imaging and skull base microsurgery. In Conley's series[9], the 5-year cure rate was 18%, and in Lewis'[10] it was 25%; Moody and Hirsch[7] reported a 2- to 3-year cure rate of 20-30%. In 2005, Moffat[6] reported an overall survival rate of 43%, with a median follow-up of 7 years (range 6 months to 16 years). Later publications showed a trend towards better outcome. Yin[11] reported an overall survival of 66.8%, with 100% for T1-T2 tumours, and 67% and 29.55% for T3 and T4 cases, respectively. Adjuvant chemo-radiotherapy improved outcomes to 72%. Gidley[12] reported a 5-year survival of 48% for T1-T2 disease, and 28% for T3-T4. Dean[13] reported a 5-year DFS of 50% in a series of mainly recurrent tumours, and no worsening outcome in cases with intracranial extension. According to the author, sequential aggressive piecemeal resection in a sequential manner appeared to be more effective than the traditional en bloc approach. Morris[14] studied predictors of survival/recurrence in temporal bone resections: for 31 SCC cases of the external auditory canal, the 5-year OS was 62.2%, DSS was 67.7% and recurrence-free survival was 53.5%. Predictors were the status of the surgical margins, metastatic nodes in the neck or parotid and parotid invasion.

In our series, DFS and DSS rates were 49% and 61%, respectively. We believe that patients surviving more than 5 years without disease can reasonably be considered as cured. A follow-up of less than 2 years, as is often reported in the literature[6 15-21], seems to be too short for the purpose of assessing DFS.

When patients died of their disease, the time elapsing varied considerably, from 2 to 62 months, with the first signs of recurrence being detected after 1 to 36 months. A long-term survival with a late recurrence was seen in both the two cases of T4 in radical cavity and 2 of the 5 recurrences after surgery or RT.

T stage and outcomes

Lower-stage tumours, T1 and T2 according to the Pittsburgh staging system, had a higher rate of success after LTBR, while T3 and T4 tumours had less favourable out-come (Table III). Failures were all due to local recurrences and correlated with sites of secondary tumour growth and lymph node involvement. Tumours spreading to periauricular soft tissues and parotid space had a different effect on outcome than when they extended to the mastoid and deeper parts of the temporal bone. Tumours staged as T4 due to periauricular or anterior growth and treated with LTBR had a better outcome than T4 cases extending posteriorly, medially and inferiorly treated with STBR. For the 8 T4 cases extending anteriorly, the DFS rate was 62.5% (5/8), and DSS was 75% (6/8), while the DFS was 0% (0/13) and DSS was 15% (2/13) for the 13 T4 cases extending medially or posteriorly. Among 12 cases with extensive soft tissue *vs.* bone involvement, Ito[23] reported that only extensive bone involvement correlated with a worse prognosis. This author also mentioned[23] that Moore[24] reported a similar outcome in groups of T1, T2 and T4 cases with extensive soft tissue involvement. On the other hand, Moody[7] reported good outcome in a few cases with spread to the mastoid.

The current Pittsburgh classification[7] draws no distinction between the sites and subsites of a T4 tumour, whereas the Manolidis[22] staging system differentiates outgrowth to the parotid and infratemporal "fossa" from spread to the mastoid. Different outcomes are not further divided in the literature because the T4 stage includes all advanced tumours. It is reasonable to speculate whether further removal from the remains of an en bloc resection might be useful. STBR in our series was performed with neat, narrow cuts, leaving the carotid artery, petrous apex and neural section of the jugular foramen in place. The questions remains if a supplemental, aggressive, sequential removal[13] is indicated in such cases.

Involvement of the dura is considered an indicator of a poor prognosis[6 17-19], and this was also confirmed in our experience. It is noteworthy that our 6 cases who underwent STBR with an ample resection of the dura (and brain in one case) all developed a local recurrence away from the dura or brain. The temporal bone resection seemed to be less efficacious than on the dura.

Prognosis in T4 tumours

The different outcomes in T4 tumours extending from the cartilage canal to the periauricular soft tissues, or from the anterior bone wall to the parotid space compared to the other T4 tumours raises some questions about the anatomical and surgical factors behind these different results, and the possible need to introduce new steps in the oncological severity of the clinical picture.

Resecting tumours extending into the periauricular tissues enables safer and wider tumour-free margins to be achieved with no vital structures to sacrifice and with a choice of reconstruction techniques.

The resections under discussion are the LTBR used for T4 tumours growing into the parotid area and periauricular

tissues, and the STBR for the T4 tumours in other areas. The question is why STBR fails to prevent local recurrences of tumours having bone growth as their main feature. The natural foramina, fissures and channels for nerves and vessels have been thought to provide the routes for dissemination of the tumour: these include the branches for the auditory canal and the posterior auricular nerve for the facial nerve, the posterior auricular nerve from the vagus nerve in the jugular fossa to the Fallopius, a branch from the mandibular nerve to the auditory canal and tympanic membrane, the auriculo-temporal nerve of the mandibular nerve and the chorda tympani. The vascular channels are the numerous veins running from the mucosa and bone to the petrosal sinuses and the jugular bulb, the tympanic arteries from the carotid and the subarcuate artery.

The above-mentioned bone channels may be a crucial anatomical factor related to the severity of T4 tumours. Our experience suggests that the amount of bone invasion may be an essential factor in the prognosis of every tumour. The resection could be enlarged, but this carries a burden of morbidity for the lower cranial nerves and carotid artery, which is unacceptable to the patient and may not be supported by preoperative imaging.

The different prognostic values of the various sites of T3 and T4 tumours warrants a critical reconsideration of the current staging system that could benefit from integration of new data. In our experience, there are increasingly severe steps, depending on the sit of origin of the tumour and its secondary growth pattern, as outlined below:

1. The skin of the auditory canal.
2. Skin and bone and/or cartilage involvement, but not full thickness (the term 'full thickness' is appropriate for the anterior bone wall, while it needs to be defined for the other bone walls).
3. Anterior extension from anterior wall to parotid space, or from cartilage canal to periauricular soft tissues.
4. Extension from canal to mastoid and other sites of the temporal bone.

A tumour outgrowing the canal cannot be classified solely on quantitative measures of extension. Anatomic variations of amount and structure of bone as well as diffusion routes and critical tissues are factors affecting severity.

Our view on staging and treatment reflects the general consensus on the Arriaga-Moody [7 21] system, while introducing a few changes concerning the different severity of advanced tumours growing into soft tissue or bone as follows:

T1   Tumour in skin without bone involvement;
T2   Tumour in skin with bone/cartilage involvement, but not full thickness;
T3a   Tumour extending < 5 mm from cartilage to periauricular soft tissues, or
      Tumour strictly limited to the anterior bone wall and growing < 5 mm into the parotid space;
T3b   Same as for T3a, but extending > 5 mm;

T4a   Tumour growing into mastoid, without 7th nerve paresis;
T4b   Tumour growing into mastoid with facial paresis, or infratemporal space, or medial wall of tympanum, labyrinth, petrous bone (jugular foramen, internal carotid canal, petrous apex).

The multifaceted reality of temporal bone SCC includes several conditions that should be considered in the staging systems:

• tumour persistence or recurrence after surgery or radiotherapy;
• tumour in a radical cavity (only skin or skin plus extension to bone);
• tumour of the auditory canal as a site of synchronous or metachronous regional cancer of the auricular-periauricular skin;
• the area considered as "soft tissues" should be mentioned explicitly.

The staging system is based on the site and extent of the lesion, and the outcome of treatment, but biological markers may come into play as well. There is preliminary evidence from recent research [27] to suggest that cytoplasmic MASPIN expression is a promising prognostic indicator and that recombinant MASPIN may be a viable therapeutic agent. Such developments deserve attention as they may have a role in both staging and treatment.

Surgical procedure vis-à-vis T stage

Numerous authors agree [1 2 6 9 15 16 19] that LTBR is the appropriate procedure for T1-T2 tumours, while LTBR and STBR may be used for T3 and T4 cases. The high rate of failures is a cause of concern, however. A local recurrence may be due both to an underestimation of the tumour's extent and erroneous or ineffectual resection. Preoperative imaging may be imprecise in identifying the extent of a tumour, and microscopic tumour dissemination also needs to be better understood. The less severe outcome of T4 cases extending anteriorly may be related to a more rational surgical procedure, since retrograde parotidectomy and carotid artery dissection from the middle fossa down to the neck stay away from the area of tumour growth. The lateral approach to the carotid canal with drilling of the tympanic bone plate may endanger the safe margins around the tumour.

Our retrospective study lacks an analysis of recurrences, although it should be noted that this is also lacking in the literature. More precise data on the sites of recurrence are needed. Correlating the extent of the original tumour with the extent of the resection and the site of recurrence may shed light on the mechanism of recurrence. In this regard, MRI studies should be planned every three months for the first three years.

Since STBR so often fails, it should be established how the STBR can be enlarged. The inferior aspect of the surgical field, at the interface between the skull base and the

neck, jugular fossa and the posterior and medial aspects of the temporal bone may be where the infiltration of the tumour is undetected and uncontrolled. Once it is reached by the tumour, the periosteum may also be a source of uncontrolled spread.

Postoperative radiotherapy
Postoperative radiotherapy is commonly recommended for T3-T4 cases [1 6 11 14 17 19]. Although our experience is inconclusive concerning the benefits of RT, we prefer to use it in advanced cases.

Nodal disease and neck dissection
Lymph node involvement is acknowledged as an indicator of a poor prognosis [6 11 14 19 25] and, in our experience, outcome was poor for cases with positive nodes. Their treatment failed as a result of the disease recurring locally, and not in the neck or at distant sites. Clinical or intraoperative signs of positive nodes can be considered a sign of tumour aggressiveness and may prompt a wider resection of the tumour.

The role of neck dissection is generally accepted for cN+ cases, but is still debated for cN0 cases [6 19 25]. In the literature, there are reported rates of 4.5% to 31.8% of positive nodes after neck dissection, with a cumulative rate of 17.7% [6]. We found 27% of pN+ cases, including 4 patients with clinically positive nodes, and 5 with clinically negative nodes.

The rate of micrometastases in clinically-negative necks was 17%. We found a DFS of 22% in the group of 9 patients with positive nodes, and 6 of these died due to local failures. In the group with pathologically-negative nodes, the DFS was 62.5% (10/24). A 17% rate of micrometastases is considered too low to convincingly support the recommendation that elective neck dissection be performed in the cN0 neck [25], but there is no evidence to support the decision not to treat the neck, either in our experience or in the literature [6 19 25 26], and so prophylactic neck dissection may be advisable as the safer option. The type of neck dissection to perform in the clinically-negative neck is a debated issue [6 19 25 26]. A planned dissection of levels Ib to III enables en bloc resection of the tumour, parotid and lymph nodes. The risk of metastases at level IV should be considered in cases with positive nodes at higher levels, or in tumours recurring after surgery and/or radiotherapy. Extending the dissection to include level V is generally recommended [25] in cases of therapeutic neck dissection and intraoperative positive nodes. Intraoperative frozen section pathology is mandatory [25].

Conclusions

Skull base surgical principles and expertise were applied to en bloc resection, plus radiotherapy in advanced cases, to treat squamous cell carcinoma of the external auditory canal extending in various ways to the temporal bone and periauricular tissues. The minimum follow-up was 5 years (mean 10, range 5-18 years) for all cases, demonstrating the validity of long-term outcomes reported herein.

Most of the results reported in the literature were confirmed, e.g. the high rate of recovery for lesions lying within the bone or cartilage walls of the canal, the still limited success of treatment for tumours outgrowing the canal walls, and the dismal prognosis in advanced cases, for which postoperative radiotherapy is recommended due to poor prognosis.

In our series, all treatment failures were due to local recurrences, suggesting that the resection was not achieving free margins despite the pathology findings. Nodal disease was a marker of tumour severity and poor prognosis with local recurrences, possibly warranting more aggressive treatment. Enlarging the resection entails a disproportionate increase in the morbidity of the procedure, however, and it may be more appropriate to associate surgery with other therapies such as chemotherapy and SCC targeted therapy. Although it is uncommon, the risk of a positive node going undetected might tilt the balance in favour of prophylactic neck dissection in cN0 cases.

It is generally agreed that prognosis is worse for tumours outgrowing the canal than for those lying within the canal walls. In our experience, the difference also lies in worse outcome for tumours extending into the temporal bone, rather than for tumours growing into soft tissues and the parotid space. The amount of tumour growth in bone seems to correlate with poorer outcome, and appears to be the most important prognostic factor. This difference may raise the question of whether the current staging of T4 tumours needs to be revised.

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Dealing with paediatric cholesteatoma: how we changed our management

Il colesteatoma in età pediatrica: come si è modificato il trattamento nella nostra esperienza

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SUMMARY

We reviewed our series of surgeries for paediatric cholesteatoma to assess outcomes and functional results considering the extension of disease and surgical techniques. Between January 2003 and December 2009, 36 patients (range 6-14 years) were operated on for cholesteatoma. We considered the sites involved by the cholesteatoma (mastoid, antrum, attic, middle ear, Eustachian tube), surgical techniques used (intact canal wall, canal wall down) and how our habits changed over the years; moreover, we evaluated ossicular chain conditions and how we managed the ossiculoplasty. As outcomes, we considered the percentage of residual and recurrent cholesteatoma for each technique and hearing function (air bone gap closure, high frequencies bone conduction hearing loss) at follow-up. Intact canal wall was performed in 20 patients and canal wall down in 13 patients, in 9 as first surgery. In both groups, we observed improvement of the air bone gap; in the intact canal wall group, a residual cholesteatoma was observed in 6 patients whereas, during follow-up, 2 patients who underwent a canal wall down showed a recurrent cholesteatoma that was treated in an outpatient setting. Eradication of cholesteatoma and restoration of hearing function in paediatric patients present unique surgical challenges. Our experience shows an increased choice of intact canal wall over the years. Therefore, it is important for the surgeon to counsel parents about the probable need for multiple surgeries, especially if an intact canal wall mastoidectomy is performed.

KEY WORDS: Paediatric cholesteatoma • Intact canal wall technique • Canal wall down technique • Ossiculoplasty • Middle ear endoscopy • Recurrence • Hearing threshold

RIASSUNTO

Abbiamo analizzato i risultati nella nostra casistica riguardo al trattamento chirurgico del colesteatoma in età pediatrica considerando l'estensione della patologia e la tecnica chirurgica impiegata. Nel periodo compreso tra gennaio 2003 e dicembre 2009 abbiamo trattato 36 bambini e nell'analisi abbiamo valutato le sedi coinvolte dal colesteatoma (mastoide, antro, attico, cassa del timpano, tuba di Eustachio), la tecnica chirurgica impiegata (timpano plastica chiusa e aperta) e come il loro impiego si sia modificato nel corso degli anni; inoltre abbiamo valutato le condizioni della catena ossiculare e come abbiamo effettuato l'ossiculoplastica. Nell'analisi dei risultati abbiamo valutato il colesteatoma residuo e ricorrente per ciascuna tecnica e la funzionalità uditiva (riduzione dell'ipoacusia trasmissiva, ipoacusia neurosensoriale per le alte frequenze). La timpanoplastica chiusa è stata effettuata in 20 pazienti mentre quella aperta in 13 e per 9 di questi come primo intervento. Con entrambe le tecniche abbiamo ottenuto una riduzione dell'ipoacusia trasmissiva; un colesteatoma residuo è stato individuato in 6 pazienti trattati con timpanoplastica chiusa, mentre 2 patienti sottoposti a timpanoplastica aperta hanno presentetato durante il follow-up un coclesteatoma ricorrente. L'eradicazione del colesteatoma e il ripristino della funzionalità uditiva presentano maggiori problematiche nell'età pediatrica. La nostra esperienza fa emergere un maggior impiego della timpanoplastica chiusa nel corso degli anni. Perciò è importante che il chirurgo informi i genitori della possibilità di dover ricorrere a più interventi chirurgici durante la crescita del bambino, qualora si opti per una tecnica chiusa.

PAROLE CHIAVE: *Colesteatoma pediatrico • Timpanoplastica chiusa • Timpanoplastica aperta • Ossiculoplastica • Endoscopia dell'orecchio medio • Recidiva • Funzionalità uditiva*

Introduction

Middle ear cholesteatoma can be defined as abnormal collections of squamous epithelium and keratin debris that usually involves the middle ear and mastoid, and can be congenital or acquired; in the latter, it may be primary or secondary. Retraction pockets in the tympanic membrane, resulting from an atelectatic process, after a long standing Eustachian tube dysfunction, is the most common cause of acquired cholesteatoma in children. These pockets may form in the pars flaccida or, more frequently, in the upper posterior portion of the pars tensa [1]. Well pneumatised mastoids allow for more extensive disease compared with more sclerotic mastoid bones in adults [2 3]. Cholesteatoma

in children often involves the entire mastoid and meso-tympanum. For this reason, surgery in children is more difficult than in adults and results are commonly considered to be poorer.

Early surgical treatment is necessary for paediatric cholesteatoma to thoroughly eliminate epithelial and bone disease, to prevent recurrent disease, to produce a dry and safe ear and to restore serviceable hearing. The two main techniques employed to reach these goals are the canal wall-down (CWD) technique and the intact canal wall (ICW) technique [4]. The CWD technique provides lower recurrence rates, but it often requires regular cavity cleaning and is associated with recurrent infection, water intolerance, caloric-induced vertigo and the diminished ability to wear a hearing aid. The ICW technique preserves the normal bony anatomy, avoids the disadvantages associated with cavities, and has shown better hearing results, although it has a significantly higher recurrence rate [5 6]. More recently, other authors have proposed a CWD technique in conjunction with a mastoid obliteration using material such as fascia, vascularised musculoperiosteal flaps, cartilage and bone pate, reducing the final cavity volume and maintaining the cavity shape to render the ear free of discharge and maximise self-cleansing [7 8]. Accordingly, there are no universally accepted opinions about the choice of surgical technique for cholesteatoma, especially in children.

In spite of reported data, the evaluation of the outcome of middle ear cholesteatoma surgery in children is difficult because the literature studies differ in terms of age range, patient selection criteria, expertise of surgeons, follow-up times and hearing documentation [9].

We reviewed the charts of our paediatric cholesteatoma patients to evaluate clinical findings, extension of disease, surgical treatment, recurrences, state of the ossicular chain and hearing results. We focused our analysis on how technological improvements have changed our management philosophy and surgical technique.

Materials and methods

Thirty-six children underwent surgery for middle ear cholesteatoma between January 2003 and December 2009 at our Institution. In our analysis, we considered the surgical technique employed (ICW vs. CWD), in how many cases an ICW was converted in a CWD and how, over the years, we employed the two techniques.

Based on intraoperative findings, we evaluated the number of sites involved by the cholesteatoma (mastoid cavity, antrum, attic, mesotympanum, Eustachian tube), and the ossicular chain involvement in terms of erosion or absence of the ossicles. We also considered the technique used for ossiculoplasty, which was often delayed at second look in staged ICW procedures (after 9-12 months). CWD procedures were never staged.

We also analysed the number of residual and recurrent cholesteatomas: in case of residual cholesteatoma larger than a small pearl involving an insidious site, such as sinus tympani, we employed a CWD technique.

Follow-up examinations were carried out by otomicroscopic checks and audiometric tests. Considering hearing function, we evaluated the variation between pre-operative and post-operative air-bone gap (ABG) for frequencies between 250 and 4000 Hz. We also considered the variation of high frequency bone conduction (BC) at 2 and 4 kHz to exclude sensorineural damage due to surgical procedures.

Data was processed using GraphPad Software Prism for Macintosh (Version 4.0c). Statistical analysis was done using the Student t-test to compare differences between pre-operative and post-operative ABG and BC thresholds. A p value < 0.05 was considered statistically significant.

Results

Thirty-six children, aged between 6 and 14 years (mean: 10 years; standard deviation: 3 years), were treated; the average follow-up was 38 months (range 13-96 months); during this period three children were lost to follow-up and their data was not included. Nineteen patients were male and 14 female; the left ear was involved by the pathology in 20 cases and the right ear in the remaining 13 cases.

Pre-operative ABG of all patients was 29 dB on average, and during follow-up it showed a mean improvement of 8 dB. High frequency BC decreased by 3 dB (15 dB per-op and 18 dB post-op).

We observed that, during the period considered in the analysis, ICW techniques increased at the expense of CWD techniques (Fig. 1).

Pre-operative ABG was 31.69 dB (± 3.525) in the CWD population and 26.80 dB (± 2.662) in ICW-treated patients; differences between the two groups did not show statistical significance (p = 0.2699), suggesting no differences in preoperative audiological function.
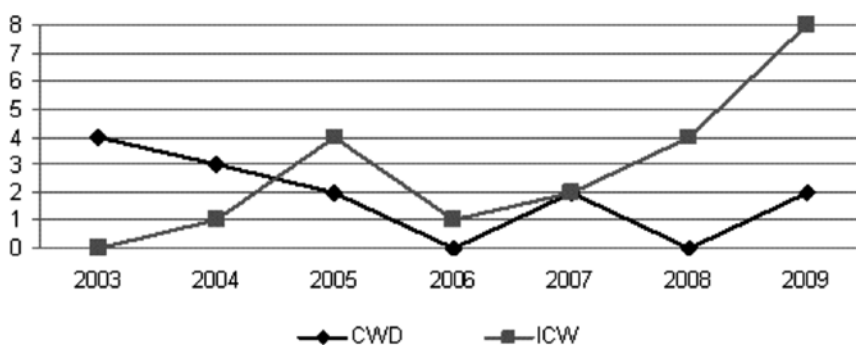

Fig. 1. Number of CWD and ICW techniques over the years.

Table I. Clinical intraoperative findings with cholesteatoma sites of involvement and ossicular chain conditions.

	ICW				CWD			
Patients	Sites	Malleus	Incus	Stapes	Sites	Malleus	Incus	Stapes
1	2	p	e	p	2	e	e	e
2	4	e	e	e	4	e	e	e
3	3	p	e	e	4	p	e	e
4	2	p	e	e	4	e	e	p
5	1	e	e	p	3	p	e	e
6	1	p	e	p	2	p	e	e
7	1	p	e	p	3	p	e	e
8	2	p	e	p	1	p	e	p
9	3	p	e	p	2	p	e	p
10	2	p	e	p	3	p	e	p
11	2	p	e	p	5	p	e	e
12	2	p	e	p	4	e	e	e
13	3	e	e	e	3	e	e	e
14	3	e	e	e				
15	5	p	e	e				
16	2	p	e	e				
17	4	p	e	p				
18	1	p	p	p				
19	2	p	p	p				
20	5	p	p	p				

p: present; e: eroded.

Clinical intraoperative findings with sites of involvement and ossicular chain conditions are reported in Table I. The ICW technique was used as first choice in 20 patients. The cholesteatoma had grown in 2.5 sites on average; the malleus was eroded/absent in 4 cases, the incus in 17 cases and the stapes in 7 cases. The ossicular chain was completely normal and not involved by the cholesteatoma in 3 patients. We observed only one case of erosion of the bony canal of the facial nerve. We performed ossiculoplasty during the first procedure in 11 cases using the body incus remodelled; we delayed ossicloplasty at the second stage in 6 patients, and we used tragal and conchal cartilage in 2 patients, and a titanium total ossicular replacement prosthesis (TORP) in 4 cases. During the second look staged procedure, there were 6 cases (30%) of residual cholesteatoma; during follow-up we did not observe any recurrent cholesteatoma. Median pre-operative ABG was 26.80 dB ($\pm$ 2.662) and post-operative ABG was 18.60 dB ($\pm$ 2.947) showing a significant median improvement of 8.200 $\pm$ 3.972 dB (0.1567 to 16.24, IC95%, p = 0,0458): at the last audiometric test, 85% of patients showed an ABG between 0 and 20 dB (Fig. 2). The decrease of post-operative high-frequency BC was 3 dB (14 dB pre-op *vs.* 17 dB post-op), which was not statistically significant (p = 0.0636).

The CWD technique was employed as first choice in 9 patients; in remaining 4 it was performed after a CWU for the presence of a dangerous residual cholesteatoma. The cholesteatoma had grown in 3 sites on average; the malleus was eroded/absent in 5 cases, the incus in all cases and the stapes in 9 cases. In two cases, a facial nerve bony canal dehiscence was noted and the second intra-tym-
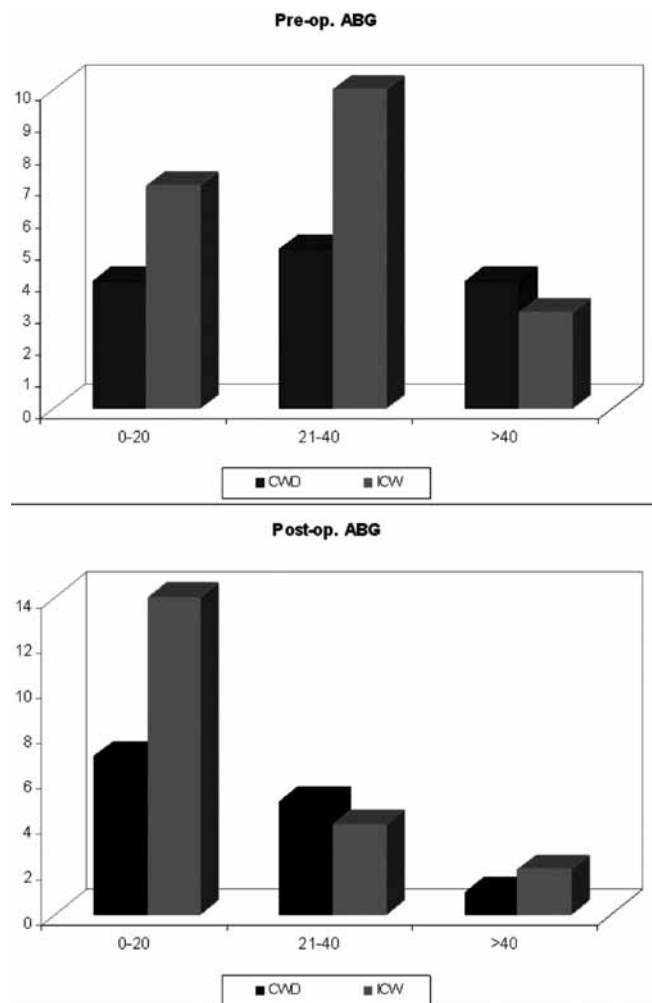

Pre-op. ABG

Post-op. ABG

Fig. 2. Pre- and post-operative ABG in the CWD and ICW groups.

panic part was involved. Ossiculoplasty was performed with the remodelled incus remnant in 6 cases, with tragal/conchal cartilage in 4 cases, with a titanium TORP in 2 cases and with the remodelled malleus in 1 case. During follow-up, two recurrent cholesteatomas were observed that were treated in an outpatient setting. Median pre-operative ABG was 31.69 dB (± 3.525) and post operative ABG was 24.38 dB (± 2.807), with a median improvement of 7.308 ± 4.506 dB that was not statistically significant (-1.993 to 16.61, IC95%, p = 0.1179): 54% of patients showed an ABG between 0 and 20 dB at the last audiometric test (Fig. 2). The decrease of post-operative high-frequency BC was 4 dB (15 dB *vs.* 19 dB) that was not statistically significant (p = 0.1320).

Fig. 3 shows the median variation of AC and BC for each frequency in both ICW and CWD patients.

Discussion

The most debated topics about paediatric cholesteatoma surgery concern the timing for surgery, choice of surgical technique and outcomes. Some authors believe that paediatric cholesteatoma is more aggressive than in adults, influencing the therapeutic approach and leading to worse clinical outcomes [10-14], whereas others have reported less osteolysis and fewer complications [15-17].

Previously, we reported on a series of 60 children (median age 9 years) treated between 1997 and 2002. We obtained good hearing function and excellent disease eradication employing the CWD technique: indeed, recurrent cholesteatoma was observed in 27% of patients and 57% of patients presented a post-operative ABG of 20 dB or less [6].
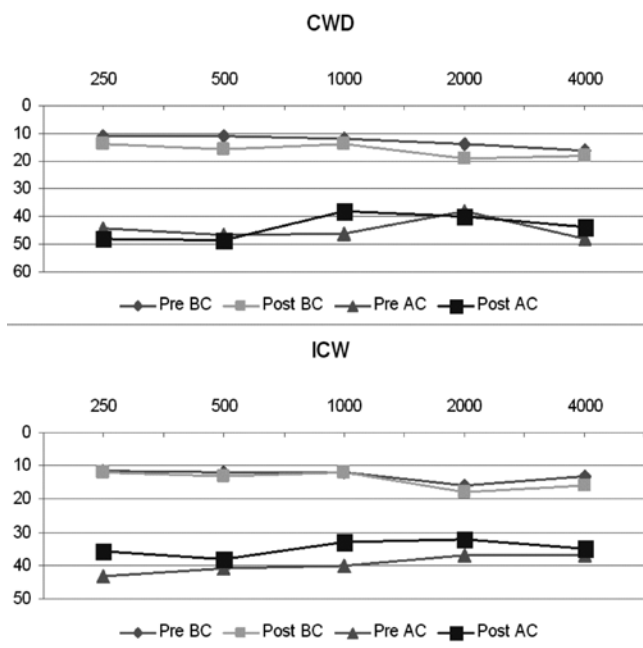
During the following years, the number of CWD procedures decreased and the ICW procedures increased, without a worsening of outcomes. A recurrent cholesteatoma was observed in 2 cases (15%) with the CWD technique, whereas a residual cholesteatoma in 4 cases (20%) using ICW. These results can also be related to a more conservative behaviour: if at the second look surgery a residual cholesteatoma showed a dimension larger than a pearl or involved hidden middle ear sites, such as the sinus tympani, we performed a CWD. We also performed CWD in cases of recurrent cholesteatoma after ICW. This allowed for better control of disease and spared patients from undergoing multiple surgeries. Moreover, we never obliterated the cavities in paediatric patients as we felt that this technique provides few long term advantages and can delay diagnosis of a recurrence. Technological advances have allowed the use of endoscopes even in ear surgery (Fig. 4). Initially, the endoscope was used only to visualise anatomical abnormalities or disease-related anatomical changes during a classical microscopic procedure [18].

Fig. 3. Median pre- and postoperative hearing threshold in the CWD and ICW groups.
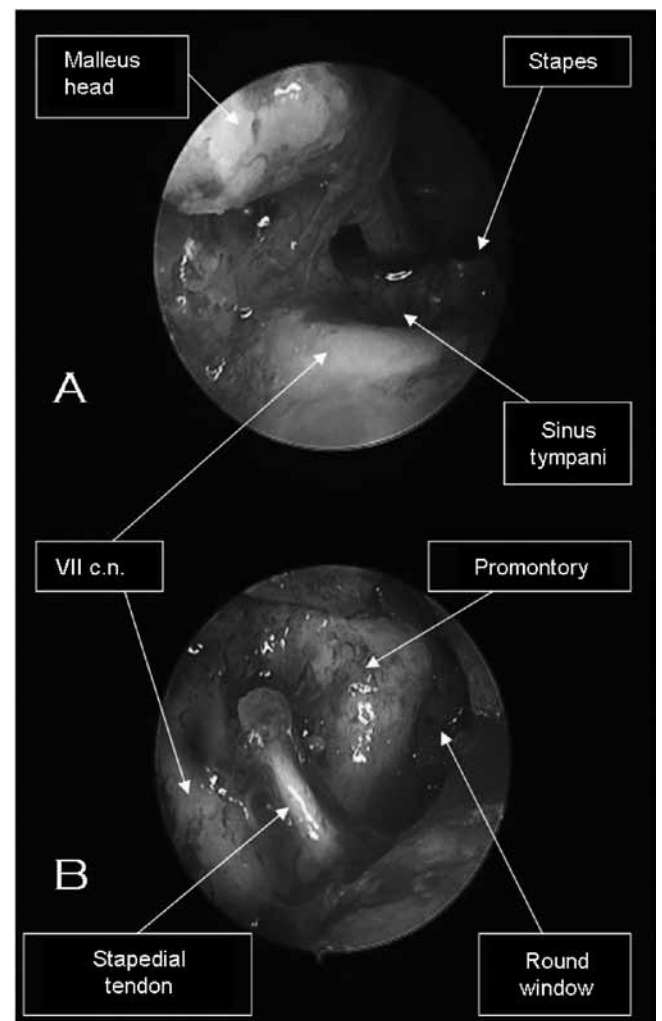

Fig. 4. Endoscopic pictures through the mastoid antrum (A) and the external auditory canal (B); such high quality images allow exploring hidden sites such as the sinus tympani.

Nowadays, endoscopes are taking an important role during certain stages of the surgical procedure itself by reducing the risk of leaving tissue remnants. Moreover, they allow exposure of hidden sites that are difficult to explore only with the microscope [19-21].

Moreover, during paediatric surgical procedures the use of endoscopes has expanded: Rosenberg [22] explored the middle ear after an ICW procedure and concluded that an open second-look mastoidectomy may be avoided if minimal or no recurrent cholesteatoma is found during endoscopic exploration. Good and Isaacson [23] used a rigid endoscope to evaluate the middle ears of a paediatric population during a surgical procedure after all visible cholesteatoma had been removed under the operating microscope, and the removal continued until all disease visualised with the endoscope was removed. Using the endoscope, they detected incompletely removed cholesteatoma in 24% of cases. At planned exploratory procedures, residual disease was found in 18% of ears judged free of cholesteatoma by both otomicroscopy and otoendoscopy at the first surgical procedure. They concluded that, even if otoendoscopy is clearly useful in detecting incompletely removed cholesteatoma, a planned exploratory procedures is required.

However, factors that should be kept in mind for choosing the best surgical technique for paediatric cholesteatoma include: intraoperative view of disease extension, mastoid pneumatisation, mucosal and ossicular chain conditions, which can be only supposed with the preoperative radiological scans, and Eustachian tube function.

The ICW technique shows unquestionable advantages compared to CWD such as the need for less postoperative therapy and better hearing function; on the other hand, these advantages cannot justify the need for a child to undergo multiple surgical procedures, due to the higher percentage of residual and recurrent cholesteatoma reported with the ICW technique.

CWD is now reserved for larger cholesteatoma or for unfavourable anatomic conditions. The choice to perform a CWD is often intraoperative and related to anatomical conditions that do not allow safe cholesteatoma removal (a low-lying middle cranial fossa dura and an anteriorly positioned sigmoid sinus which create a small mastoid and limit access into the anterior epitympanum) or for the presence of a perilymphatic fistula.

Patients submitted to CWD did not improve hearing loss in a statistically significant manner, but showed an ABG between 0 and 20 in 54% of cases and a sensorineural hearing loss similar to patients submitted to ICW (4 *vs.* 3 dB). We reserved CWD for large cholesteatoma as revealed by the number of anatomical sites involved and by greater ossicular chain involvement.

Considering functional outcomes, there is no agreement about the need to preserve the posterior canal wall to obtain a good hearing function [24], and preoperative hearing function seems to be more important, which may be a sign of either smaller or larger ossicular chain involvement [25 26]. Indeed, pre-operative status and the surgical technique for the ossiculoplasty are the most important factors influencing postoperative hearing function. Even today, incus transposition, if not totally involved by cholesteatoma, is the technique of choice; in the remaining cases different solutions, such as cartilage and biocompatible materials, are needed.

Conclusions

Eradication of cholesteatoma and restoration of hearing function in paediatric patients present unique surgical challenges. The balance between these two goals is related to the incidence of recidivism, the degree of ossicular damage and the experimental evidence that this disease exhibits a more aggressive behaviour than in adults. Fortunately, intratemporal and intracranial complications, such as inner ear fistula, facial nerve paralysis and epidural or intracerebral abscess, are rare in children.

Therefore, the surgeon must counsel parents on the probable need for multiple surgeries, especially if an ICW mastoidectomy is performed. The more intriguing prospects of paediatric cholesteatoma should focus on standardisation of the endoscopic approach and on its real advantages in removal of remnant cholesteatoma with ICW; experimental studies have the possibility to detect new histological markers that could help in predicting recurrences. In the light of the above-mentioned data, an individualised approach is needed for the treatment of paediatric cholesteatoma, and the choice of surgical technique should be based on anatomical, biological, radiological and social factors.

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LETTER TO THE EDITOR

Videolaryngoscopy for teaching and supervising rigid bronchoscopy in paediatric patients

Impiego della videolaringoscopia per l'insegnamento e la supervisione della broncoscopia rigida in pazienti pediatrici

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Dear Editor,
Rigid bronchoscopy is frequently used by otolaryngologists to evaluate the trachea and bronchi in paediatric patients. Bronchoscopes are introduced through vocal cords under direct vision laryngoscopy [1]. Poor glottic exposure leads to multiple intubation attempts with the rigid bronchoscope and, subsequently, may be associated with oxygen desaturation or airway and dental injuries [2]. Teaching and supervising otolaryngology residents to intubate the trachea with a rigid bronchoscope under direct vision laryngoscopy is difficult in paediatric patients. Low lung vital capacity and high oxygen consumption in small children also limits residents' training time. Furthermore, as airway spaces are narrow, instructors cannot see what the trainees are visualising, cannot recognise the trainee's problems and have to perform tracheal intubation themselves. This may delay the learning curve of rigid bronchoscopy in otolaryngology residency programmes.
The C-MAC videolaryngoscope (Karl Storz, Tuttlingen, Germany) is a relatively new device using modified Macintosh or Miller blades. It provides the possibility of obtaining both direct view of the larynx and a camera view displayed on a monitor screen [2][3]. This device not only improves visualisation of the vocal cords, but also allows an operator assistant to follow the intubation process on the monitor, and to help in optimising the glottic view by external laryngeal manipulations [4]. The C-MAC videolaryngoscope has already been used as a teaching tool for tracheal intubation in children [3][5][6]. In this report, we describe the use of a C-MAC videolaryngoscope as a device for training and supervising otolaryngology residents to intubate the trachea with a rigid bronchoscope in paediatric patients.
Twenty consecutive patients aged between 3 months and 2 years and scheduled for rigid bronchoscopy under general anaesthesia were included in this case series. Institutional approval and parental informed consent was obtained. In the operating theatre, all patients had standard monitoring including three-lead electrocardiography, pulse oximetry, non-invasive blood pressure measurement and end-tidal capnography. Following general anaesthesia through mask induction with sevoflurane, an intravenous access was secured and 4% lidocaine was topically applied with an atomizer to anaesthetise the vocal cords. A second year otolaryngology resident placed the patient's head in moderate extension and exposed the larynx using a C-MAC videolaryngoscope with an appropriate-sized straight Miller blade. The resident introduced the tip of the rigid bronchoscope into the oral cavity, and gently directed it towards the laryngeal inlet and through the vocal cords. During the procedure, the resident was following his own manoeuvres on the monitor screen of the videolaryngoscope. Once the rigid bronchoscope was secured in the trachea, the blade of the videolaryngoscope was removed and bronchoscopy was continued following standard procedures. The resident was supervised by a senior otolaryngologist who continuously observed the exposure of the larynx and manipulation of the rigid bronchoscope on the videolaryngoscope monitor screen and provided instructions as required.
Three otolaryngology residents and one instructor were involved in this pilot study. The rigid bronchoscope was successfully inserted in the trachea without multiple attempts in all patients. Episodes of arterial oxygen desaturation ($SpO_2 < 90\%$), teeth injuries or soft tissue lesions were not observed in any patient. The otolaryngology residents and instructors expressed their satisfaction regarding the use of C-MAC videolaryngoscope as learning and teaching tool for intubation of the trachea with a rigid bronchoscope.
In conclusion, this report shows that a C-MAC videolaryngoscope is an effective tool for training otolaryngology residents to intubate the trachea with a rigid bronchoscope in paediatric patients. It optimises visualisation of the vocal cord by the resident, facilitates manipulation of the bronchoscope and reduces the risk of dental or soft

tissue injury. In addition, the videolaryngoscope gives the instructor the opportunity to directly observe the resident's manoeuvres and to provide advice as needed.

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Auricular involvement of a multifocal non-AIDS Kaposi's sarcoma: a case report

Un caso di sarcoma di Kaposi, multifocale non-HIV correlato, dell'orecchio esterno

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SUMMARY

Kaposi's sarcoma (KS) is a multicentric, malignant neoplastic vascular disease, mainly involving skin and mucosae, characterised by the proliferation of endothelial cells. The aetiology of KS still is unknown. Nonetheless, it has been reported that several epidemiological and environmental factors may play a role in its pathogenesis. Viral factors (i.e. human herpes virus 8, HHV-8) have also been claimed to play a role in the onset of KS. Four main clinical presentations of KS have been described: classic (sporadic), African (endemic), iatrogenic (immunosuppression-associated) and AIDS-associated (epidemic). The authors present a case of KS involving the external ear of a HIV-negative patient with a history of non-Hodgkin lymphoma and tuberculosis.

KEY WORDS: Kaposi's sarcoma • External ear • Lymphoproliferative disorders

RIASSUNTO

Il Sarcoma di Kaposi (KS) è una patologia neoplastica maligna su base vascolare, che principalmente coinvolge la cute e le mucose, caratterizzata dalla proliferazione di cellule endoteliali. L'eziologia del KS è ancora sconosciuta, sebbene sia stato riportato che fattori epidemiologici, ambientali e virali (es Herpes virus umano 8, HHV-8) possano avere un ruolo nella patogenesi di tale affezione. Ad oggi, sono state descritte quattro forme principali di KS: classico (sporadico), africano (endemico), iatrogeno (associato a stati di immuno-soppressione) ed AIDS-relato (epidemico). Gli Autori presentano un caso di KS con coinvolgimento del condotto uditivo esterno, in una paziente HIV-negativa con storia di linfoma non-Hodgkin e tubercolosi.

PAROLE CHIAVE: *Sarcoma di Kaposi • Orecchio esterno • Disordini linfoproliferativi*

Introduction

Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi[1]. KS is an angioproliferative disorder characterised by proliferation of spindle-shaped cells (SC), neoangiogenesis, inflammation and oedema, categorised as an intermediate neoplasm due to the absence of conventional features of malignancy[2-4]. The clinical appearance of KS is classically described as pink, red, purple, or violaceous macules, papules or raised plaques, although nodular and more distinctly neoplastic-looking forms have also been described[5].

The pathogenesis of KS is now recognised to be multifactorial. It is influenced by genetic and environmental factors and is related to a state of immunosuppression. Moreover, the lesion is associated with a rhadinovirus, namely human herpes virus 8 (HHV-8)[6]. HHV-8 DNA sequences have been found in approximately 95% of KS lesions in patients with both AIDS and non-AIDS KS[7].

The transmission modalities of HHV-8 are still unknown, even if the higher incidence of KS in HIV homosexual males suggests a possible sexual transmission (through faeces). Moreover, HIV patients with KS mainly have oral cavity and rectal lesions, which seems to suggest local direct spreading. A limited number of review articles focus on the incidence of non-AIDS KS in the head and neck area[8][9]. The oral cavity is the most common site of presentation, and in these cases the KS lesion is usually coexistent with others[10].

The clinical appearance of KS is classically described as pink, red, purple or violaceous macules, papules or raised plaques; at later stages they can become nodular or exophytic and sometimes becomes ulcerous. Oral lesions can ulcerate more often than skin lesions. Particularly due to ulceration, lesions within the oral cavity may manifest with pain, burning and bleeding.

We describe a case of KS of the pinna and external auditory canal that developed in an HIV-negative patient with a history of tuberculosis and non-Hodgkin lymphoma.

Case report

We report the case of a female patient aged 72 years, referred to the Audiology Department of the University Hospital of Ferrara, for the evaluation of a slow-growing, violaceous, macular lesion in the right pinna and external auditory canal (Fig. 1). The patient complained of itching and occasional discharge from the external auditory canal. Right otoscopic examination revealed the presence of a violaceous and thickened macular lesion with keratosis of the concha that also involved the antero-inferior wall of the external auditory canal until about 4 mm from the tympanic membrane. The tympanic membrane was intact. Left otoscopic examination was normal. The remainder of the ENT examination was unremarkable, and in particular the oral cavity was normal and no cervical nodes were present. Pure tone audiometry showed right sensorineural hearing loss in the high frequency range (4-8 kHz).

At the time of examination, other cutaneous lesions were also present on the right arm (Fig. 2) and the postero-medial surface of the left leg.

The clinical history of the patient included peripheral polyneuropathy, miliary tuberculosis (pleural, intestinal and vesical), ankylosing spondylitis, pulmonary hypertension and chronic pericarditis. She also suffered from T-cell non-Hodgkin lymphoma for which she had been treated with 4 cycles of chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone).

KS was diagnosed 8 months before by biopsying a lesion in the left leg. The exam showed the presence of a biphasic vascular spindle-cell growth occupying the entire thickness of the dermis.

Laboratory tests revealed that the patient was seropositive for human herpes virus type 4 (HHV-4; EBV) and HHV-8; she was HIV seronegative. The patient was taking prednisone, 5 mg/day, as maintenance therapy for non-Hodgkin lymphoma.

Fig. 1. Lesion of the external ear involving the concha.

Fig. 2. Multiple skin lesions on the right arm.

The external ear lesion was treated with a local disinfectant and with periodical toilette under microscopic guidance (local medication with gentamicin and betamethasone), thus avoiding the onset of infections and accumulation of debris in the external auricular canal. This led to rapid clearing of ear symptoms, while the macular lesion did not resolve.

At follow-up, after 18 months, no other localisations have appeared in the external ear.

Discussion

Four main clinical presentations of KS have been described: classic (sporadic), African (endemic), iatrogenic (immunosuppression-associated) and AIDS-associated (epidemic). Lesions are bluish-red macules or nodules and usually have multiple cutaneous localisations, but also lymph nodes and viscera have been described at the sites of presentation [11]. The literature focuses particularly on HIV-related KS. In contrast, the other types of KS are underrepresented. About 60% of non-AIDS KS are localised on the skin (lower and upper limbs or trunk), and the head and neck is rarely involved [12-15]. The most recurrent sub-localisation of the head and neck is the oral cavity. The oropharyngeal and conjunctiva mucosa have been observed in immunosuppressed-associated KS. The incidence of auricular lesions is lower, but in recent years has increased likely due to the greater use of immunosuppressive agents (i.e. organ transplantations, diffusion of chemotherapy) [11 16 17]. At onset, they can appear as violaceous maculae that can become nodules or ulcerous. Normally the sites of tumour are coexistent and multifocal. For non-AIDS related KS, the male to female ratio is significantly lower [15]. Nevertheless, the mean age was also over 50 years. While most cases seen in Europe and North America occur in elderly men of Italian or Eastern European Jewish ancestry, the neoplasm also occurs in several other distinct populations:

young black African adult males, prepubescent children, renal allograft recipients and other patients receiving immunosuppressive therapy [18].

The aetiology of KS is unknown. However, it has been reported that several epidemiologic and environmental factors, as well as immunosuppression, play a role in the development and clinical course of the disease. In the last decade, epidemiologic and biologic evidence has suggested that a recently discovered herpes virus, namely KS herpes virus or HHV-8, is a required infectious cofactor responsible for all known forms of KS [18]. In particular, in non-AIDS associated KS immunodeficiency of any kind, iatrogenic, due to malignancy, tuberculosis [19] or chemotherapy has been claimed to be the main causal factor in the development of KS [20]. In the case presented, the previous history of miliary tuberculosis as well as previous chemotherapy could be related to the development of KS, as sources of immunodepression.

KS has a similar histopathologic appearance in all clinical subtypes. The early lesion (patch stage) is characterised by a proliferation of small veins and capillaries around one or more dilated vessels. A pronounced mononuclear inflammatory cell infiltrate, including mast cells, is often noted, as are scattered erythrocytes and hemosiderin deposits. There may be inconspicuous perivascular proliferation of spindle cells, but cellular atypia is minimal.

More advanced lesions are nodular and show increased numbers of small capillaries or dilated vascular channels interspersed with proliferating sheets of sarcomatous or atypical spindle cells, often with large numbers of extravasated erythrocytes and abundant hemosiderin deposition [11].

Main therapeutic options for KS include systemic treatments (i.e. chemotherapy or biological therapy particularly with recombinant interferon-α [IFN-α]), due to its immunomodulating and anti-angiogenetic properties [21] and local treatments (i.e. surgical excision; radiotherapy) mainly indicated for selected, small lesions. Optimal therapy for KS patients is still undecided in the literature as systemic therapy can be given in disseminated, progressive or symptomatic KS, while surgical excision and radiotherapy can be reserved for local disease [22]. It has been advocated that new advances in understanding the pathogenesis of KS, particularly the role of angiogenesis and growth factors, may help in the future development of additional therapies and in establishing a standardised protocol [22].

Conclusions

Auricular involvement in KS is relatively rare: we found 4 previously-reported cases of KS involvement of the external ear [11 16 17 23]. In 1983, Stearns described a case of KS arising as a primary lesion in the external auditory mea-

tus, treated with surgical excision [11]. In 1998, Delbruck described a case of external auditory canal KS with extension to mastoid, treated with radiotherapy [16]. Another case report concerns a solitary lesion of KS occurring in the helix of the ear in a healthy young patient, treated with surgical excision [17]. The last case described is a KS that developed in an HIV-negative patient affected by tuberculosis, which completely regressed with antituberculous therapy [23].

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Calendar of events – Italian and International Meetings and Courses

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

MAY-DECEMBER 2014

SKIN CANCER OF THE HEAD AND NECK COURSE • *May 1, 2014 • Utrecht – The Netherlands*
INTERCONTINENTAL RHINOPLASTY • *May 2-3, 2014 • Utrecht – The Netherlands*

Websites: http://reconstruction-skin-cancer.com – http://intercontinental-rhinoplasty.nl

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V INTERNATIONAL WORKSHOP ON ENDOSCOPIC EAR SURGERY • *May 5-7, 2014 • Modena – Italy*

Course Directors: Livio Presutti, Daniele Marchioni. Website: http://www.meetandwork.it/livesurgerymodena

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2nd ANNOUNCEMENT OTOLOGY JUBILEE: 150 YEARS OF THE ARCHIV FUR OHORENHEILKUNDE
Past-Present-Future in Otology & Neurology • *May 7-10, 2014 • Halle/Saale – Germany*

Website: www.otology-jubilee.com

CURSO DE DISECCIÓN ENDOSCÓPICA DE LOS SENOS PARANASALES
ENDOSCOPIC SINUS SURGICAL DISSECTION COURSE • *May 8-10, 2014 • Barcelona – Spain*

Instituto de Otología García-Ibáñez, C/ Dr. Roux, 91, 08017 – Barcelona. Tel. 93 205 02 04 ¬ Fax 93 205 43 67 – E-mail: gi.fundacion@gmail.com, fundacion@iogi.org

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BALBUZIE - IL TRATTAMENTO TRA STUDIO E HOMEWORK • *May 9-10, 2014 • Turin – Italy*

Coordinatore Scientifico: Mario D'Ambrosio. Organizing Secretariat: Centro Congressi Internazionale Srl, via San Francesco da Paola 37, 10123 Torino. Tel. +39 011 2446911 – Fax +39 011 2446950 – E-mail: info@congressiefiere.com – Website: www.congressiefiere.com

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GIORNATA DI AGGIORNAMENTO AICEF - 6ª edizione • *May 10, 2014 • Ravenna – Italy*

Scientific Secretariat: Domenico Minghetti, E-mail: minghetti@tin.it – Patrizia Schiavon, E-mail: patrizia.schiavon@gmail.com. Website: www.lopezcongressi.it

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3rd IRANIAN CONGRESS ON COCHLEAR IMPLANT & RELATED SCIENCE
May 10-12, 2014 • Tehran – Iran

IRANCI 2014 Secretariat: Tel. - Fax 098-21-8860-0006 – E-mail: info@irancochlear.com – Website: www.irancochlear.com

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101° CONGRESSO NAZIONALE SIO – Società italiana di Otorinolaringoiatria e Cervicofacciale
May 28-31, 2014 • Catania – Italy

President: A. Serra. Website: www.sio2014.org – www.eac.it

CURSO DE DISECCIÓN ENDOSCÓPICA DE LOS SENOS PARANASALES - ENDOSCOPIC SINUS SURGICAL DISSECTION COURSE • *May 29-31, 2014 • Barcelona – Spain*

Instituto de Otología García-Ibáñez, Isabel, C/ Dr. Roux, 91, 08017 Barcelona. Tel. 93 205 02 04 – Fax 93 205 43 67 – E-mail: gi.fundacion@gmail.com, fundacion@iogi.org

CORSO BASE DI OTORADIOLOGIA • *June 4-6, 2014* • *Rovereto – Italy*

Coordinatore Scientifico: M. Neri. Organizing Secretariat: Mytime Training & Technology srl, via San Carlo da Sezze 18, 04100 Latina – Tel. +39 0773 662630 – E-mail: segreteria@mytimetandt.it – Website: www.mytimetandt.it

HEAL 2014 (HEaring Across the Lifespan): "EARLY INTERVENTION: THE KEY TO BETTER HEARING CARE" *June 5-7, 2014* • *Cernobbio (Lake Como) – Italy*

Website: http://www.heal2014.org

CORSI DI VIDEOCHIRURGIA ENDOSCOPICA NASO-SINUSALE E DEL BASICRANIO • *Milan – Italy* *June 9-13, 2014 (corso intermedio)* *October 27-31, 2014 (corso avanzato)*

Course Director: Alberto Dragonetti – Scientific Secretariat: Gabriella Mantini, Valentina Casoli- Tel. +39 02 64444545 – Fax +39 02 64444003 – E-mail: gabriella.mantini@ospedaleniguarda.it. Organizing Secretariat: Eurocompany Srl, via Canova 19, 20145 Milano. Tel. +39 02 315532 – Fax +39 02 33609213 – E-mail: corsieconvegni@eurocompany.mi.it

TEMPORAL BONE DISSECTION COURSES 2014 • *June 10-13, December 9-12, 2014* • *Brazil*

Website: www.forl.org.br/courses

4th HANDS ON DISSECTION ADVANCED COURSE: "FROM REMOVAL TO RECONSTRUCTION IN HEAD AND NECK CANCERS" • *June 17-20, 2014* • *Paris – France*

Directors: Marco Benazzo, Department of Otolaryngology HN Surgery, University of Pavia, Italy; Fausto Giuseppe Chiesa, Department of Otolaryngology HN Surgery, IEO Milan, Italy. Organizing Secretariat: Bquadro Congressi srl, via S. Giovanni in Borgo 4, 27100 Pavia. Tel. +39 0382 302859 – Fax +39 0382 27697 – E-mail: bolla@bquadro-congressi.it.

CURSO DE MICROCIRUGÍA DEL OÍDO Y DISECCIÓN DEL HUESO TEMPORAL **TEMPORAL BONE SURGICAL DISSECTION COURSE** *June 18-20, 2014 - November 2014, date to be announced* • *Barcelona – Spain*

Instituto de Otología García-Ibáñez, Conchi Castilla, C/ Dr. Roux, 91, 08017 – Barcelona. Tel. 93 205 02 04 ¬ Fax 93 205 43 67 – E-mail: iogi@iogi.org

24th CONGRESS OF EUROPEAN RHINOLOGIC SOCIETY (ERS) and 32nd INTERNATIONAL SYMPOSIUM OF INFECTION AND ALLERGY OF THE NOSE. THE NOSE AS INTERFACE *June 22-26, 2014* • *Amsterdam – The Netherlands*

President: W.J. Fokkens. Website: www.ers-isian2014.com – E-mail: ers-isian2014@kenes.com

5th WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF HEAD AND NECK ONCOLOGIC SOCIETIES (IFHNOS) – ANNUAL MEETING OF THE AMERICAN HEAD AND NECK SOCIETY (AHNS) *July 26-30, 2014* • *New York – USA*

Congress Chairman: Jatin Shah. Program Chairman: Bevan Yueh. Websites: www.ifhnos2014.org, www.ahns2014.org

4th INTERNATIONAL COURSE ON ENDOCRINE SURGERY - INTRAOPERATIVE MONITORING OF LARYNGEAL NERVES IN THYROID SURGERY • *June 27, 2014* • *Stresa (Lake Maggiore, VB) – Italy*

Organizing Secretariat: Summeet Srl, via P. Maspero 5, 21100 Varese. Tel. +39 0332 231416 – Fax +39 0332 317748 – E-mail: mb.calveri@summeet.it – Website: www.summeet.it

BEST EVIDENCE ENT 2014 • *August 2-5, 2014* • *Wisconsin – USA*

Course Directors: John S. Rhee, David R. Friedland, Charles J. Harkins. Department of Otolaryngology 9200 West Wisconsin Avenue Milwaukee, WI 53226

26th INTERNATIONAL COURSE ON ENDOSCOPIC SURGERY OF THE PARANASAL SINUSES AND SKULL BASE *August 27-30, 2014* • *Ghent – Belgium*

Course Director: Claus Bachert. Website: www.fess-course.be

40° CONGRESSO CONVENTUS SOCIETAS ORL LATINA • *September 1-5, 2014* • *Baia de Luanda – Angola*

Info: Departamento de ORL da Facultdade de Medicina da Universidade Agostino Neto Hospital Josina Machel-Maria Pia Av. 1° Congresso do MPLA. Tel. 00244-923784901/914381304 – E-mail: mfilipe@snet.co.ao, drma-tuba@gmail.com

XL CONVENTUS SOCIETAS ORL LATINA CONGRESSO • *September 3-5, 2014 • Luanda – Angola*

Website: www.conventussocietasorllatina-luanda2014.org

ORL ENDO 2014 • *Modena – Italy*
Chirurgia endoscopica dell'orecchio medio (Middle ear endoscopic surgery) • *September 9-10, 2014*
Chirurgia endoscopica dei seni paranasali (Endoscopic sinus surgery) • *November 11-12, 2014*

Course Director: Livio Presutti. Scientific Secretariat: Angelo Ghidini, Daniele Marchioni. Tel. +39 059 4222402 - 4223022 – E-mail: Ghidini.angelo@policlinico.mo.it, Marchioni.daniele@policlinico.mo.it - Website: www.meetand-work.it/orl-endo2014

CORSO DI CHIRURGIA ENDOSCOPICA RINOSINUSALE, RINOSETTOPLASTICA E FILLERS -
LIVE SURGERY, III EDIZIONE • *September 11-13, 2014 • Atripalda (AV) – Italy*

Website: www.avellinose.it Organizing Secretariat: Lingo Communications Srl, via Cinthia - p.co San Paolo, is 25 80126 Napoli. Tel. +39 081 7663737 – Fax +39 081 7675661 – E-mail: ecm@lingomed.it

7th INSTRUCTIONAL WORKSHOP – CONSENSUS IN AUDITORY IMPLANTS "EUPOREAN GUIDELINES IN OTOLOGY AND NEURO-OTOLOGY" • *September 13-16, 2014 • Siena – Italy*

Website: www.eaono2014.org

IV CORSO TEORICO-PRATICO DI AUDIOLOGIA E VESTIBOLOGIA
September 22-24, 2014 • Benevento – Italy

Course Director: L. Califano. Scientific Secretariat: Luigi Califano, Maria Grazia Melillo – E-mail: luigi.califano@tin.it, vertigobn@hotmail.com

EUROPEAN UNION OF HEARING AID ACOUSTICIANS (EUHA) 59th INTERNATIONAL CONGRESS OF HEARING AID ACOUSTICIANS (EUHA) • *October 15-17, 2014 • Hanover – Germany*

Website: www.euha.org

5th ASIAN FACIAL PLASTIC SURGERY SOCIETY CONGRESS • *October 15-19, 2014 • Cappadocia – Turkey*

Website: www.afpss2014.org

CONSENSUS CONFERENCE ON SALIVARY GLAND TUMORS. ADENOID-CYSTIC CARCINOMA AND HIGH-GRADE NEOPLASMS • *October 23-24, 2014 • Brescia – Italy*

Organizing Secretariat: Servizi C.E.C. Srl, via Verdi 18, 24121 Bergamo, Italy. Tel. +39 035 249899 – Fax +39 035 237852 – Website: www.servizicec.it

CORSO DI APPROFONDIMENTO IN OTORADIOLOGIA • *November 11-14, 2014 • Rovereto – Italy*

Coordinatore Scientifico: M. Neri. Organizing Secretariat: Mytime Training & Technology srl, via San Carlo da Sezze 18, 04100 Latina – Tel. +39 0773 662630 – E-mail: segreteria@mytimetandt.it – Website: www.mytimetandt.it