

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

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

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#### REVIEW

# Three-dimensional stereophotogrammetric analysis of nasolabial soft tissue effects of rapid maxillary expansion: a systematic review of clinical trials

Analisi tridimensionale degli effetti dell'espansione mascellare rapida sui tessuti molli nasolabiali mediante stereofotogrammetria: revisione sistematica degli studi clinici

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#### **SUMMARY**

The aim of this systematic review is to analyse the quality and clinical evidence in the literature analysing, through 3D stereophotogrammetry, the nasolabial soft tissue modifications that may occur after rapid maxillary expansion (RME). This systematic literature review was based on the PRISMA-P statement and was registered in the PROSPERO database with the following protocol ID: CRD42017079875. Pubmed, Cochrane, EBSCO, Scopus, Web of Science databases were searched with no restriction of year or publication status. Selection criteria were: randomised clinical trials, controlled clinical trials, cohort studies, cross-sectional studies, case-control studies on patients with unilateral/bilateral crossbite, transverse maxillary deficiency and crowding, treated with RME and monitored by 3D stereophotogrammetry. 652 articles were retrieved in the initial search. After the review process, 11 full-text articles met inclusion criteria. After the evaluation process, 4 publications were included for the present literature review. Due to the heterogeneous methodology meta-analysis was not possible; consequently, a systematic assessment of the studies and summary of the findings from the available evidence were used to answer the research question. The maximum widening of the alar cartilage is 1.41 ± 0.95 mm, whose clinical significance is open to question. The effect of RME on the mouth width remains controversial. In Altindis et al., the difference between pre-treatment and post-treatment mouth width (1.80 mm increment in the banded RME group) was statistically significant, while in Baysal 1.86 mm was considered a non-significant value. Inconsistencies and limitations in the study population and measurement protocols were detected between studies. These data underline the necessity for updated guidelines that allow to standardise, for this type of study, sample selection, measurement methods and collection of results.

KEY WORDS: Systematic review • Face • Nose • Photogrammetry • Soft tissue • Dentofacial orthopaedics • Growth

#### RIASSUNTO

In questa revisione sistematica, è stata analizzata la letteratura per analizzare i cambiamenti tridimensionali dell'area nasolabiale indotti dall'espansione rapida del mascellare (RME) misurati attraverso la stereofotogrammetria. La presente revisione è strutturata secondo lo schema PRISMA-P ed è stata registrata sul portale PROSPERO con il seguente ID: CRD42017079875. I database Pubmed, Cochrane, EBSCO, Scopus, Web of Sciences sono stati consultati senza nessuna restrizione di anno o di status della pubblicazione. 652 articoli sono risultati dalla ricerca iniziale. A seguito del processo di revisione, 11 articoli sono risultati conformi ai criteri di inclusione. Dopo la lettura in extenso dei lavori, 4 pubblicazioni sono state incluse nella seguente revisione. I criteri di selezione sono stati: studi clinici randomizzati e controllati, studi di coorte, studi caso-controllo su pazienti con crossbite uni/bilaterale o deficit trasversale del mascellare o affollamento dentale, pazienti che hanno eseguito espansione rapida del mascellare superiore e che sono stati monitorati mediante stereofotogrammetria. La metodologia eterogenea dei lavori ha reso una meta-analisi impossibile; di conseguenza, è stata eseguita un'accurata analisi degli studi ed una puntuale schematizzazione dei risultati ai fini di rispondere al quesito clinico. La massima distensione della cartilagine alare è stata di 1,41 ± 0,95 mm, la cui rilevanza clinica è questionabile. L'effetto dell'espansione mascellare sull'ampiezza della bocca rimane controverso. In Altindis et al., l'incremento di ampiezza del cavo orale post-trattamento (1,80 mm nel gruppo con RME su bande) è considerato statisticamente significativo, mentre in Baysal et al. il valore di 1,86 mm non risulta un cambiamento statisticamente significativo. Inconsistenze e limitazioni nella popolazione degli studi e nei protocolli di misurazione sono stati individuati all'interno degli articoli. I dati emersi dovrebbero essere confermati con un protocollo metodologicamente conforme, evita

PAROLE CHIAVE: Revisione sistematica • Volto • Naso • Fotogrammetria • Tessuti molli • Ortopedia dento-facciale • Malocclusione • Crescita

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#### Introduction

#### Rationale

Rapid maxillary expansion (RME) represents an orthopaedic and orthodontic procedure aimed at increasing maxillary transverse dimension in growing patients <sup>1</sup>. In orthodontic practice, the rapid maxillary expansion treatment approach is adopted to expand the maxillary arch and resolve skeletal/dentoalveolar cross-bites as well as arch perimeter deficiency in mild to moderate crowding case <sup>2</sup>. The rationale behind the approach is that heavy orthopaedic forces applied with a jackscrew can mechanically separate the maxillary segments at the level of the midpalatal suture <sup>3</sup>.

Since the bone base and soft tissue envelope are closely related, this orthopaedic therapy may affect nasal shape and dimension <sup>4-6</sup>.

Several techniques have been described to analyse nasolabial soft tissue changes following RME therapy: direct anthropometric measurements, photometric assessment, cephalograms and cone beam computed tomography (CBCT) scans <sup>7-9</sup>.

Three-dimensional stereophotogrammetry involves the use of several digital cameras that simultaneously capture images of the same object from different viewpoints; software reconstruction algorithms integrate matching regions in both images to compute the coordinates of all the points that outline the surface frame of the 3-D object <sup>10</sup>. It is intuitive and demonstrated in the literature that 3-D stereophotogrammetry is a noninvasive gold-standard imaging modality for qualitative and quantitative soft tissue analysis of the orofacial region, because it offers better reproducibility and higher accuracy than two-dimensional representations of a three-dimensional object, such as standard 2-D cephalograms or photographs <sup>11</sup> <sup>12</sup>.

The clinical potential of 3-D photogrammetry lies in the development a realistic virtual model of the patient's head for documentation, treatment planning, prediction and long-term evaluation of treatment outcomes <sup>13-15</sup>. However, there is a paucity of knowledge documenting 3D facial changes induced by RME and an absence of reviews systematically investigating this topic.

#### Objectives

The aim of this systematic review was to investigate and summarise currently available data pertaining to the use of 3-D stereophotogrammetry for assessment of nasolabial soft tissue changes after rapid maxillary expansion. The primary question of this review is: how does RME influence the nasolabial soft tissue development in growing patients?

The secondary question is: if present, can the aesthetic impact provided by RME appliances be considered clinically significant? How can the treatment effect be clinically interpreted? What guidelines can be drawn for future research?

The null hypothesis is that there are no statistically and clinically significant nasolabial soft tissue differences after RME. The alternative hypothesis is that the included studies report statistically and clinically significant differences between facial landmarks, measured before and after RME.

#### Materials and methods

#### Protocol and registration

The protocol for this systematic review was based on the PRISMA-P statement and was registered in the International Prospective Register of Systematic Review (www.crd.york.ac.uk/PROSPERO/) with the ID number: CRD42017079875.

#### Eligibility criteria

The full search strategy focused on four categories of terms, as suggested by the PICO approach (Population: face; malocclusion; Intervention: rapid maxillary expansion, Comparison: stereophotogrammetry, Outcomes: treatment effects). Only papers that met study admittance criteria reported were accepted (Table I). We choose not to include patients with reduced naso-respiratory function in the study population for the following reasons:

- patients with respiratory disorders often present morphological alterations, which make difficult to use them as a comparator <sup>16</sup>;
- altered breathing pattern may have influence on craniofacial development; so, it can potentially bias the effects of rapid maxillary expansion <sup>17 18</sup>.

Only papers published in English were considered. No limitation concerning publication year or publication status was included.

#### Information sources and literature search

On 11 July 2017, five electronic sources were systematically consulted: Pubmed, Scopus, Cochrane Central, Web of Science, EBSCO. The same search strategy was adapted for each mesh terms database (Supplementary material 1). In addition, http://clinicaltrials.gov, Google Scholar and grey literature searches were conducted. Manual search concerned references and citation list of the included studies. The publications of the authors listed in the accepted studies were checked as well.

Table I. Study selection criteria.

#### Study selection criteria by abstract Type of the study Randomised clinical trials (RCTs), controlled clinical trials (CCTs), cohort studies, cross-sectional studies, case-control studies Studies on patients with unilateral or bilateral cross-bite, maxillary Clinical research query transverse deficiency, crowding Studies on patients who underwent rapid maxillary expansion in order to obtain a rapid increase in the upper arch available space. Follow-up three-dimensional images of the face have been acquired before and after treatment by means of stereo-photogrammetry Control sample Homogeneous patients not receiving RME treatment Study selection criteria by full-text Inclusion criteria **Exclusion criteria** Type of study, randomised clinical trials (RCTs), controlled clinical trials Type of study, case reports, case series with less than 10 patients. (CCTs), cohort studies, cross-sectional studies, case-control studies reviews, author editorials, technical papers, animal studies Clinical research query, studies on patients with unilateral or bilateral cross-Clinical research query: studies on patients with systemic disorders or bite, maxillary transverse deficiency, crowding. Studies on patients who impaired naso-respiratory function, underwent rapid maxillary expansion in order to obtain a rapid increase in studies about surgical-aided rapid maxillary expansion (SRME or the upper arch available space. Follow-up: three-dimensional images of the SARME), studies regarding the use of photography face have been acquired at least before and after treatment by means of or lateral cephalograms to evaluate soft tissue effects stereo-photogrammetry induced by RME Control sample: must include homogeneous patients not receiving RME Control sample: must NOT include healthy patients not receiving RME treatment treatment

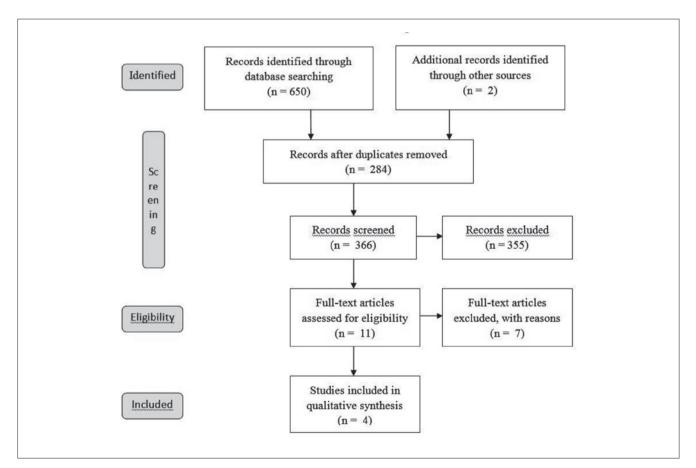


Fig. 1. PRISMA flow diagram for the identification and selection of studies.

#### Study selection and data collection

Eligibility of the articles was biphasically determined: two of the authors (ES and MDL) independently conducted the electronic search and performed a title and abstract (TIAB) screening to pre-select articles for full-text retrieval. Any disagreement was resolved in consensus with a third examiner (RP).

The articles selection process is described in the PRISMA Flow Diagram (Fig. 1).

#### Risk of bias in individual studies

The Cochrane Collaboration tool for assessing the risk of bias and Newcastle-Ottawa quality assessment scale were used by two Authors (ES and MDL) independently to rate the methodological quality of experimental and observational studies, respectively.

In order to uniformly rate the level of evidence of the included studies (confidence in effect estimates), the 3-point grading system, described by the Swedish Council on Technology Assessment in Health Care (SBU), was adopted <sup>19 20</sup>.

#### **Results**

#### Study selection

Discarding 284 duplicates with Endnote<sup>®</sup>, a total of 652 titles were considered for possible inclusion. After a title and abstract (TIAB) screening to pre-select articles for full-text retrieval, 11 papers were identified.

Among the trials available, 4 articles were met inclusion criteria listed for the systematic review. The studies rejected after full-text evaluation were recorded in the excluded studies table (Supplementary material 2), together with the reasons for exclusion.

#### Study characteristics

In Table II, the evidence is quantitatively analysed and summarised; studies are classified according to the type of appliance used and the patient's age at the time of intervention.

Homogeneous landmarks were not adopted among the selected studies, and thus a meta-analysis could not be performed.

#### Result of individual studies

The included articles of Baysal et al. <sup>21</sup>, Altındiş et al. <sup>2</sup>, Altorkat et al. <sup>22</sup> report the use of the banded appliance in similar age groups, showing different results on the alar cartilage width effects (Table II): the study of Baysal <sup>21</sup> and Altındiş <sup>2</sup> found a statistically significant increase of

the nasal width (1.16 mm and 1.42 in the banded RME group, respectively), while Altorkat et al. <sup>22</sup> reported a non-significant change of 0.4 mm. The difference between the increments is almost three times, but not clinically significant if a threshold value of 3 mm is established <sup>23</sup>.

The effect of RME on the mouth width remains controversial. In Altındiş et al. <sup>2</sup>, the difference between pretreatment and post-treatment mouth width (1.80 mm increment in the banded RME group) was statistically significant, while in Baysal et al. <sup>21</sup> 1.86 mm was not considered to be a significant value (Table III).

Altındiş et al. <sup>2</sup> found that RME produces a more protrusive effect on the upper lip. Dindaroglu <sup>23</sup> found no significant changes on the labial area. Baysal <sup>21</sup> did not find any statistically significant changes for the lips, or for the intercantal and zygoma point distances.

#### Quality of evidence assessment

According to the SBU tool, the quality of the collected evidence was moderate (grade B) in three studies <sup>221 23</sup> and low (grade C) in one <sup>22</sup>. Thus, conclusions with a limited level of evidence could be drawn from the review process. The most important sources of bias were the absence of a growth status assessment, age of the treated sample, heterogeneity of follow-up protocols and lack of blinded standardised measurement procedures.

#### Discussion

#### Summary of evidence

In conclusion, nasal soft tissues after RME present small and variable immediate changes. Altorkat et al. <sup>22</sup> reported that there are significant changes in nasal transverse dimensions after RME, while Altindis et al. did not find any significant differences between different types of appliances. In both studies, the absence of a control group makes it impossible to discriminate the nasolabial soft tissue modifications induced by RME with those occurring in a physiological growth pattern in an untreated population.

From a statistical point of view, the short-term effect of RME of morphology remains controversial. If present, the aesthetic impact provided by RME appliances may be considered as not clinically significant.

#### Limitations

The articles by both Altındiş et al. <sup>2</sup> and Altorkat et al. <sup>22</sup> did not consider gender differences in puberty timing, as other authors have done <sup>24</sup>; this seems to be in contrast with evidence supporting that the start and the advance of fusion of the midpalatal suture may be greatly influenced by gender <sup>25</sup>.

**Table II.** Patient characteristics and quality of evidence of the included studies.

Trial	Setting	Sample size	Mean age (years)	Mean time between image acquisitions	Type of appliance	Skeletal development	Quality of the evidence (SBU grading system) <sup>1</sup>
Altındiş et al., 2016 <sup>2</sup>	RCT	42 (18 M, 24 F)	ME:	NA (at the end of the three months retention period)	ns RME, modified	NA	В
		**Banded RME: 6 M, 8 F					
		Bonded RME: 7 M, 7 F					
		Modified bonded RME: 5 M, 9 F	$15.5 \pm 0.8$				
Altorkat et al., 2016 <sup>22</sup>	Case- series	14 (7 M, 7 F)	$12.6 \pm 1.8$	NA (at the end of the active phase)	Bonded RME	NA	С
Baysal et al., 2016 <sup>21</sup>	RCT	34 (18 M, 16 F) Exp: 9 M, 8 F Ctr: 9 M, 8 F	Exp: $13.4 \pm 1.2$ Ctr: $12.8 \pm 1.3$	6.1 months	Bonded RME	NA	В
Dindaroğlu et al., 2016 <sup>23</sup>	RCT	50 (26 M, 24 F) Exp: 14 M, 11 F Ctr: 12 M, 13 F	Exp:  Male: $9.6 \pm 0.9$ Female: $10.1 \pm 1.0$ Ctr:	15.6 days	Bonded RME	Not exceeding MP3 cap stage	В
			Male: 9.2 ± 0.7 Female: 9.9 ± 0.9				

<sup>&</sup>lt;sup>1</sup> Articles were graded according to the SBU criteria as follow: 1) grade A (High level of evidence): randomised controlled trials (RCTs) or prospective study with a well-defined control group; presence of defined diagnosis and endpoints; well-described diagnostic reliability tests and reproducibility tests; blinding outcome assessment. 2) grade B (Moderate level of evidence): same criteria as grade A except for the blinding outcome assessment. 3) grade C (Low level of evidence): articles that do not meet the criteria of grade A and B.

SBU tool permitted to assess the level of the available evidence of the systematic review accordingly to the following classification: 1) strong: at least two studies of level A; 2) moderate: one study of level A and at least two studies of level B; 3) limited: at least two studies of level B; 4) scarce: fewer than two studies of level B.

Moreover, the authors did not classify the sample according to growth status: earlier beginning, peak, or end of the pubertal height growth spurt groups may present different soft-tissue nasolabial changes after RME <sup>26</sup>. Even if there is evidence supporting that growth increments of the soft

tissue profile are at an unimportant level in such a short period <sup>27</sup>, age is not a reliable indicator of the maturational stage of the midpalatal suture <sup>25</sup>.

Clinical experience and bone biology studies highlight that the stage of sutural maturation might be related to

Table III. Definitions of soft tissue landmarks and comparison of mean differences between the included studies.

Comparisons of treatment changes among the groups (mm)						
Abbreviation	Definition	Altındiş et al. <sup>2</sup>	Altorkat et al. 21	Baysal et al. 22		
AIR-AIL	Distance between left and right alar: point located at left and right labial commissure	1.35 ± 1.08	1.6 (1.00 – 2.02)	1.42 ± 0.96		
ChR-ChL	Distance between left and right chelion: most lateral point on left and right alar contour	$1.80 \pm 1.85$	-	$1.86 \pm 1.35$		

<sup>\*</sup> Please note: the study of Dindaroğlu et al. <sup>23</sup> does not report linear distances (AIR-AIL and ChR-ChL), but volumetric 3-D deviations. Therefore, Dindaroğlu's data are not included in this table.

<sup>&</sup>quot;Please note: in Altındiş et al. 2, only the banded type appliance RME group was included in this review. NA: Not Assessed

the success of orthopaedic expansion, emphasising that conventional RME treatment is indicated before the circumpubertal period <sup>28</sup>; in the studies of Altındiş et al. <sup>2</sup> and Altorkat et al. <sup>21</sup> the mean age is 12.7 and 12.6 years, in Baysal et al. <sup>22</sup> is 13.4 years, and thus it can be expected that patients would show more dentoalveolar than skeletal effects after RME treatment <sup>29</sup>.

The longest follow-up evaluation in the included studies was six months <sup>2</sup>; additional studies are needed to gain a better understanding of the long-term effects of RME treatment on nasolabial soft tissues.

The inconsistency between nasal width values may be related to the fact that post-treatment 3-D stereophotogrammetry is scheduled at different time periods (Table IV).

No single study focused on inter-examiner reliability. This concept is crucial: none of the investigations mentioned the reference plane used to identify the soft tissue anthropometric landmarks. This bias should be masked if the examiner is still the same, but there could be significant differences in landmark positioning between different points of view.

All studies assessed intra-examiner reliability; however, inter-examiner reliability and blinding of the investigator who identified the facial landmarks are not reported. These methodological issues may cause bias in the results. In Dindaroğlu's analysis, the 3D deviation around the nasolabial area is automatically calculated by the software: this protocol reduces operator-related bias due to landmark identification error <sup>23</sup>.

Statistically, the alar cartilage and mouth width of the included studies does not reach the clinically significant increment of 3 mm. However, in the study of Altorkat et al. <sup>21</sup>, the "3 mm" cut-off parameter was made on the basis of a cephalometric study concerning skeletal modifications due to RME, even if it is not demonstrated that nasolabial soft tissue changes follow hard tissue modifications <sup>30</sup>.

#### **Conclusions**

RME appliances produce slight clinically non-significant nasolabial soft tissue changes. RME is an effective therapeutic option for patients with maxillary transversal deficiency. Most of patients who seek orthodontic treatment are dissatisfied with their appearance. The treatment protocol that considers the impact of orthopaedic treatment on facial morphology represents an improved standard of care for patients <sup>31</sup>. This aspect of the treatment cannot be overstated. If the RME induced noticeable impairment, this strong discontent may continue throughout the patient's life. Advances in 3D-imaging techniques achieve

high accuracy and reproducibility for capturing and superimposing facial images and measure changes in soft tissue position three dimensionally <sup>32-34</sup>. The novel use of stereophotogrammetry includes the quantification and assessment of immediate changes of the mid facial third following rapid maxillary expansion <sup>35</sup>. An increasing number of reviews is available in the current literature, so that high emphasis should be put on the methodological quality of the clinical trials. It is true that the strength of the evidence lies in the study design: in orthodontic practice, it is even more difficult than other disciplines to compare a multitude of variables.

#### Recommendations for further research

Updated guidelines for future research are outlined according to the PICOS approach:

Population: it should be staged according to the skeletal development status; even if Johnson et al. <sup>24</sup> showed that non-significant differences were noted between pre-pubertal and post-pubertal groups, they noted a significant increase in greater alar cartilage width between treated and untreated groups in a prepubertal male population from the beginning of the treatment to the 6-month follow-up.

Intervention: is it curious that we found only articles dealing with tooth-borne expanders; it could be interesting to compare soft-tissue changes bone-anchored (BAME) and traditional tooth-anchored rapid maxillary expanders (TAME). Lagravere at al. <sup>36</sup> pointed out that the difference in terms of skeletal expansion is almost null between TAME and BAME, and Nada et al. <sup>37</sup> stated that toothborne and bone-borne surgically assisted rapid maxillary expansion devices showed comparable results.

Comparison: we would strengthen the need for long-term follow-up studies; photometric studies show that differences between pre-pubertal and post-pubertal patients are significant in the short-term period, but may change during growth <sup>38</sup>. The sample should include homogeneous untreated patients and non-healthy individuals to investigate the differential growth pattern of nasolabial soft tissues.

Outcome: bias avoidance is fundamental for the development of a randomised controlled clinical trial. It is fundamental to standardise the anatomic landmark positioning because the methodology of the point selection results to be a critical step of the morphometric analysis. The anatomical structures are visually identified by the examiner; therefore, accuracy and reproducibility of the measurements reflects the precision of the point determination; experience and blinding of the investigators play a key role in the analysis of facial morphology <sup>39</sup>.

Table IV. Risk of hias assessment

Study	Rating scale Cochrane's collaboration tool for assessing the risk of bias				
Baysal 2016 <sup>21</sup>					
Items	Low risk	High risk	Unclear risk of bias		
Randomisation	Х				
Allocation	Χ				
Blinding participant and personnel		Χ			
Blinding outcome assessor		Χ			
Missing outcome data	Χ				
Selective reporting	Χ				
Other bias			Χ		
		(skeletal maturation; age	e of 13 years; 6-month follow-up)		

Dindaroğlu 2016 <sup>23</sup>	Cochrane's collaboration tool for assessing the risk of bias			
Items	Low risk	High risk	Unclear risk of bias	
Randomisation	Χ			
Allocation			Χ	
Blinding participant and personnel		Χ		
Blinding outcome assessor		Χ		
Missing outcome data	Χ			
Selective reporting			X	
Other bias		Χ		
		(15-days follow-up)		

Altındiş 2016 <sup>2</sup>	Cochrane	Cochrane's collaboration tool for assessing the risk of bias				
Items	Low risk High risk		Unclear risk of bias			
Randomisation	Χ					
Allocation			X			
Blinding participant and personnel		Х				
Blinding outcome assessor		Χ				
Missing outcome data	Χ					
Selective reporting			Χ			
Other bias	3-month follow-up	(age of 12.6 years)	x (absence of skeletal maturation indicators)			

			maioatoro)	
Altorkat 2016 <sup>21</sup>	Newcastle-Ottawa Quality Assessment Scale			
	0 star	1 star	2 stars	
Representativeness	X			
Selection	X			
Sample size		Χ		
Non-respondent		Х		
Exposure	X			
Comparability	X			
Outcome assessment	X			
Statistical test	X			
Statistical test	X			

Study: stereophotogrammetry is the most versatile method for quantitative longitudinal assessment of craniofacial dimensions and shapes in children 40 41. It is a noninvasive method that allows a routine clinical assessment of facial

changes induced by orthodontic appliances. The versatility of this technique offers the opportunity to have a longitudinal monitoring of the facial soft-tissue development <sup>41</sup>. Accordingly, we would strengthen the importance

to obtain 3-D images following a standardised protocol: image acquisition should be performed after the active phase of RME, after the retention period and one-two years thereafter, in order to have a clear idea of the soft-tissue remodeling in growing patients.

#### **Conflict of interest statement**

None declared.

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#### **Supplementary material**

Supplementary material 1. Full electronic search strategy.

Database	Search strategy
Pubmed (free text words)	((((((((orthodontics*[All Fields]) OR jaw*[All Fields]) OR face*[All Fields]) OR (growth and development*[All Fields])) OR malocclusion*[All Fields]))) AND ((((((female*[All Fields]) OR male*[All Fields])) OR adolescent*[All Fields]) OR epidemiologic studies*[All Fields])) AND (((((diagnosis*[All Fields])) OR determination*[All Fields])) OR assessment*[All Fields]) OR evaluation*[All Fields])) OR treatment outcomes*[All Fields]))) AND (photogrammetry*[All Fields])
Pubmed MeSh	((((((((orthodontics*[MeSh]) OR jaw*[MeSh]) OR face*[MeSh]) OR (growth and development*[MeSh])) OR malocclusion*[MeSh]))) AND ((((((female*[MeSh]) OR male*[MeSh]))) OR child*[MeSh]) OR adult*[MeSh]) OR adolescent*[MeSh]) OR epidemiologic studies*[MeSh]))) AND (((((diagnosis*[MeSh]) OR determination*[MeSh]))) OR assessment*[MeSh]) OR evaluation*[MeSh]) OR treatment outcomes*[MeSh]))) AND (photogrammetry*[MeSh])
Scopus	((TITLE-ABS-KEY (orthodontics*)) OR (TITLE-ABS-KEY ( jaw*)) OR (TITLE-ABS-KEY (face*)) OR (TITLE-ABS-KEY (growth AND development*)) OR (TITLE-ABS-KEY (malocclusion*))) AND ((TITLE-ABS-KEY (femalo*)) OR (TITLE-ABS-KEY (malocclusion*)) OR (TITLE-ABS-KEY (malocclusion*)) OR (TITLE-ABS-KEY (epidemiologic AND studies*))) AND ((TITLE-ABS-KEY (diagnosis*)) OR (TITLE-ABS-KEY (assessment*)) OR (TITLE-ABS-KEY (evaluation*)) OR (TITLE-ABS-KEY (determination*)) OR (TITLE-ABS-KEY (treatment AND outcomes*))) AND (TITLE-ABS-KEY (photogrammetry*))
Cochrane Central (Free Text Words)	(orthodontics* OR jaw* OR face* OR growth and development* OR malocclusion*) AND (male* OR female* OR child* OR adult* OR adolescent* OR epidemiologic studies*) AND (diagnosis* OR assessment* OR evaluation OR determination* OR treatment outcomes*) AND photogrammetry*
Cochrane Central MeSh	((MeSH orthodontics) OR (MeSH jaw) OR (MeSH face) OR (MeSH Growth AND Development) OR (MeSH Malocclusion)) AND ((MeSH diagnosis) OR (MeSH Outcomes AND Process Assessment) OR (MeSH Evaluation Studies as Topic) OR (MeSH Treatment outcome)) AND ((MeSH male) OR (MeSH female) OR (MeSH child) OR (MeSH adult) OR (MeSH Adolescent) OR (MeSH Epidemiologic Studies)) AND (MeSH Photogrammetry)
Web of Science	(TS=(orthodontics*) OR TS=(jaw*) OR TS=(face*) OR TS=(growth and development*) OR TS=(malocclusion*)) AND (TS=(male*) OR TS=(female*) OR TS=(child*) OR TS=(adult*) OR TS=(adolescent*) OR TS=(epidemiologic studies*)) AND (TS=(diagnosis*) OR TS=(assessment*) OR TS=(evaluation) OR TS=(determination*) OR TS=(treatment outcomes*)) AND (TS=(photogrammetry*))
EBSCO MeSh	(MH orthodontics* OR MH jaw* OR MH face* OR MH jaw diseases* OR MH ( growth and embryonic development*) OR MH malocclusion*) AND (MH Photogrammetry*) AND (MH male* OR MH female* OR MH child* OR MH adult* OR MH child development: 5 years* OR MH child development: 6-11 years* OR MH child development: 11-17 years* OR MH experimental studies*) AND (MH diagnosis* OR MH outcome assessment* OR MH evaluation* OR MH treatment outcomes*)

 $\textbf{Supplementary material 2.} \ \textit{Table showing references of excluded studies with rationale for exclusion.}$ 

References	Rationale for exclusion
Bishara et al., 1995	3D analysis not performed
Cummins et al., 1995	3D analysis not performed
Kamonji, 1980	3D analysis not performed
Kim et al., 2016	Patients not treated with RME
Matzler et al., 2014	Patients not treated with RME
Rune et al., 1980	3D analysis on hard tissue and not on soft tissue
Singh, 2002	Patients not treated with RME



#### HEAD AND NECK

### Unravelling the risk factors that underlie oral and oropharyngeal surgery in elderly

Chiarire i fattori di rischio che sottendono la chirurgia del cavo orale e dell'orofaringe negli anziani

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#### **SUMMARY**

Oral squamous cell carcinoma (OSCC) diagnoses in elderly patients are expected to double in the next 20 years. Current guidelines suggest surgery as a preferred approach, but elderly patients are hardly considered suitable to challenging surgical treatments. Using a multicentric retrospective analysis, we evaluated the outcomes of 99 patients affected by OSCC and aged at least 70, who underwent to either transoral procedures (TP), open neck resection without (OR) or with reconstruction (ORR). In our cohort, overall survival was significantly hampered by concomitant diseases and postsurgical complications, whose development is driven by the former. Thus, our findings support the growing acceptance that chronological age alone should not be a sufficient contraindication for aggressive surgery in the treatment of OSCC. However, elderly patients affected by OSCC are undoubtedly delicate surgical candidates and accurate selection prior to surgery with curative intent is mandatory.

KEY WORDS: Oral cancer • Elderly • Reconstructive surgery • Complications • Free flap • Quality of life

#### **RIASSUNTO**

Nei prossimi vent'anni è previsto che il numero di diagnosi di carcinoma del cavo orale nel paziente anziano raddoppi. L'approccio chirurgico resta la terapia d'elezione sebbene sia dibattuto se esso possa essere praticabile negli anziani anche nei casi più demolitivi. Attraverso un'analisi retrospettiva multicentrica, abbiamo valutato 99 pazienti ultra-settantenni affetti da carcinoma della cavità orale sottoposti a chirurgia transorale, o resezione open con o senza ricostruzione. Nella nostra coorte, la sopravvivenza dei pazienti è stata negativamente influenzata dalla presenza di comorbidità e dallo sviluppo di complicanze post-operatorie. Inoltre, la comparsa di tali complicanze è stata posta in diretta correlazione con la presenza di una o più patologie concomitanti nel quadro clinico del paziente. Tuttavia, sebbene il paziente anziano sia un candidato delicato per approccio chirurgico ed un'accurata selezione sia quindi necessaria, i nostri risultati suggeriscono che l'età anagrafica non debba essere considerata una controindicazione sufficiente ad escludere a priori pazienti anziani candidati a trattamento chirurgico.

PAROLE CHIAVE: Cancro del cavo orale • Anziani • Chirurgia ricostruttiva • Complicanze • Lembi liberi • Qualità di vita

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#### Introduction

Alarming epidemiological data have been reported for many tumour histotypes, particularly for head and neck squamous cell carcinomas (HNSCC), including oral (OSCC). Indeed, an increase in diagnosis from the present ~300,000 cases worldwide to ~500,000 is expected within 2035 (+65%). More worryingly, the ~115,000 OSCC currently diagnosed in elderly patients (≥ 65 years

old) are expected to double (about +104%) in the next 20 years, while those in younger will "only" increase by about 40% <sup>1</sup>.

Current guidelines for treatment of OSCC require surgery as the preferred approach, whereas they suggest radiotherapy or chemoradiotherapy for advanced-stage cancer in the presence of adverse features <sup>2</sup>. Photodynamic therapy may be otherwise considered as an approach for the management of previously-treated patients or for those

who are not suitable for conventional therapies. Therefore, complex reconstructive surgeries have been used more and more frequently in the last two decades to improve the post-treatment quality of life. However, this trend determines an extension of surgical times, as well as a general need to carefully select patients, which is based on the most serious comorbidity to reduce complications and overall costs. In this scenario, elderly patients are not considered to be good candidates to undergo more challenging treatments, e.g. highly invasive resective/reconstructive surgery and complex chemotherapy schedule <sup>3</sup>.

To provide surgeons with a model to choose the most appropriate treatment options, we retrospectively analysed 99 patients aged at least 70, suffering for OSCC, and treated with radical intent with 3 different types of surgery: transoral procedures (TP), open neck resection without reconstruction (OR) and open neck resection with reconstruction (ORR). Major outcomes as well as the incidence of post-treatment complications were evaluated, whereas predictive factors involved in their occurrence were identified.

#### Materials and methods

#### Patients and surgery

After informed consent was obtained, all patients underwent surgery for OSCC at the Policlinico Hospital in Modena or at the Martini - San Luigi Gonzaga Hospitals of Turin between January 1, 2001, and December 31, 2012. Data collection from the medical charts included demographic information such as age and sex, TNM staging, tumour site and subsite, tumour histology, physical status according to the American Society of Anesthesiologists (ASA) 4, age at the surgical time, type of surgery and neck dissection, type of reconstruction, duration of surgery, duration of hospitalisation (including days in intensive care unit, ICU), comorbidities and perioperative complications. The assessed comorbidities were diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), cardiac diseases (including chronic heart failure, arrhythmia and coronary artery disease), hepatic, metabolic and cerebrovascular diseases.

In the present retrospective study, age at the time of surgery ≥ 70 years <sup>5-7</sup>, histological diagnosis of OSCC and surgical treatment with curative intent (as single modality or as part of a multimodality approach) were considered as inclusion criteria.

The chart data of 99 patients were retrieved. The choice of the treatment was based on tumour stage and site, as well as comorbidities, but non-considering chronological age as a discriminatory factor. Procedures were classifiable as tran-

**Table I.** Characteristics of the 99 elderly patients undergoing head and neck surgery according to age, sex and pathological status.

							No. of patients (%)
Age, y							
Mean							$77.0 \pm 5.6$
Range							70-93
70-79							70/99 (70.7%)
≥ 80							29/99 (29.3%)
Sex							
Male							60/99 (60.6%)
Female							39/99 (39.4%)
Pathological status*							
	NO	N1	N2a	N2b	N2c	N3	
pT1	23	6	1	4			34/98 (34.7%)
pT2	24	4	1	3	1	1	34/98 (34.7%)
pT3	3	4		4			11/98 (11.2%)
pT4	10	2	1	6			19/98 (19.4%)

<sup>\*</sup> We considered 98 patients because one patient was lacking pTNM.

Table II. Patient stratification accordingly to the lesion subsites.

	No. of patients (%)
Oral cavity	74/99 (74.7%)
Gingiva	9/74 (12.2%)
Lips	10/74 (13.5%)
Tongue	30/74 (40.5%)
Oral mucosa	16/74 (21.6%)
Hard palate	2/74 (2.7%)
Floor of the mouth	7/74 (9.5%)
Oropharynx	25/99 (25.3%)
Anterior wall	7/25 (28.0%)
Lateral wall	13/25 (52.0%)
Superior wall	5/25 (20.0%)

soral procedures (TP), meaning mini-microinvasive surgeries as well as the non-surgical photodynamic therapy, in 14 of 99 patients (14.1%), open neck resection without reconstruction (OR) in 59 of 99 patients (59.6%) and open neck resection with reconstruction (ORR) in 26 of 99 patients (26.3%).

Characteristics of the patient cohort are summarised in Table I, while stratification according to tumour site and sub-site is reported in Table II.

#### Statistical analysis

The length of time from the date of diagnosis to the date of death (overall survival, OS) or to the date of death for disease (disease-specific survival, DSS) was estimated using Kaplan-Meier curves. At the end of the study, the dates of last consultation for patients still alive were used for type-I censoring. Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare Kaplan-Meier estimates between groups (number of comorbidities, tumour site, type of surgery and postoperative complications). The CHAID (Chi-square Automatic Interaction Detection) method <sup>8</sup> was used to detect the optimal subdivision to maximise the differences in response within the different variables.

Univariate regression with colinearity analysis was used to evaluate independent risk factors (e.g. age at the surgery  $\geq 80^9$ , gender, presence of comorbidities, tumour stage, type of surgery and duration of surgery) for development of perioperative and postoperative complications (within 30 days). Those significantly associated were included in a multivariable logistic regression model.

Kaplan-Meier curves, log-rank and Gehan-Breslow-Wilcoxon tests were performed with Graphpad Prism version 6.0e (GraphPad Software, San Diego, CA, USA), whereas CHAID analysis, univariate regression with colinearity analysis and multivariate logistic regression were performed with IBM® SPSS® Statistics version 23 (IBM Corp., Armonk, NY, USA). All analyses were considered statistically significant at p < 0.05.

#### **Results**

#### Patient comorbidities

Concomitant diseases were present in 69 of 99 (69.7%) elderly patients, of whom 32 (32.3%) were affected by multiple ( $\geq$  2) comorbidities. The most frequent were hypertension (50.5%), cardiovascular disease (25.2%), diabetes mellitus (19.2%) and chronic obstructive pulmonary disease (COPD) (12.1%). The severity of each comorbidity was scored and recorded according to the American Society of Anesthesiologists (ASA) physical status classification system  $^{4\,10}$  (Table III).

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

	No. of patients (%)
ASA	
1	9/97 (9.3%)
2	34/97 (35.1%)
3	43/97 (44.3%)
4	10/97 (10.3%)
5	1/97 (1.0%)

#### Surgery and postoperative morbidity

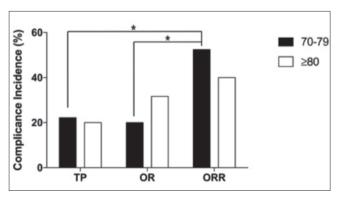
The mean surgical time was  $3.4 \pm 2.3$  h, ranging from 0.5 h to 10.5 h in patients aged 70-79 years and from 0.5 h to 6.5 h in those  $\geq 80$  years (p = 0.156).

Amongst treated patients, 31 (14 OR and 17 ORR) were postoperatively transferred to the intensive care unit (ICU) where they resided for an average time between 1.6 days (70-79 years old) and 1.1 days (age  $\geq$  80 years; p = 0.675). Transfer to the ICU was decided by the anesthesiologist and was based on duration of surgery, preoperative ASA score and complications occurred during surgery. Generally, the mean length of hospitalisation was 21.0 days in 70-79 patients and 18.7 in those aged  $\geq$  80 years (p = 0.537). Patients were discharged when completely cured and autonomous in major activities (swallowing, breathing or cannula management).

Perioperative or postoperative complications affected 30 of 99 patients (30.3%) of whom 21 of 70 (30.0%) in the age range 70-79 and 9 of 29 (31.0%) in  $\geq$  80 years (p = 0.890).

Furthermore, stratifying patients for the type of surgery, no differences between groups were observed, although open techniques followed by reconstruction displayed a significantly higher incidence of complications than with other techniques in patients 70-79 years old (p < 0.05, Fig. 1).

In the 70-79 year group, 4 patients suffered systemic complications, 9 had local complications (mainly bleedings, fistulas and wound infections) and 5 developed both systemic and local complications. One patient suffered of multiple systemic complications, whereas 1 patient had 2 local complications. Two patients (9.5%) died postoperatively. In the elderly aged  $\geq$  80, 4 patients developed a systemic complication, 1 patient had 2 systemic complications, whereas 4 patients suffered of local complication. One patient (11.1%) died postoperatively (Table IV). Fi-



**Fig. 1.** Incidence of complications on patients treated by transoral procedure (TP), open neck resection (OR), or open neck resection with reconstruction (ORR).  $^*$  = p < 0.05.

**Table IV.** Complications in patients.

Complications		Number of	events (%)
		70-79	≥ 80
Local	Fistula	3/21 (14.3%)	1/9 (11.1%)
	Infections	5/21 (23.8%)	0/9 (0.0%)
	Haemorrhage	2/21 (9.5%)	1/9 (11.1%)
	Haematoma	0/21 (0.0%)	0/9 (0.0%)
	Necrosis	1/21 (4.8%)	1/9 (11.1%)
	Dehiscence	3/21 (14.3%)	1/9 (11.1%)
	Wound diastasis	0/21 (0.0%)	1/9 (11.1%)
	Seroma	3/21 (14.3%)	0/9 (0.0%)
Systemic	Pneumonia	2/21 (9.5%)	2/9 (22.2%)
	Cardiovascular*	6/21 (28.6%)	1/9 (11.1%)
	Psychiatric	3/21 (14.3%)	1/9 (11.1%)
	Death	2/21 (9.5%)	1/9 (11.1%)
	Nephropathy	0/21 (5.6%)	0/9 (0.0%)
	Cerebrovascular event	1/21 (4.8%)	0/9 (0.0%)
	Hyperglycaemia	1/21 (4.8%)	1/9 (11.1%)
	Sepsis	0/21 (0.0%)	0/9 (0.0%)

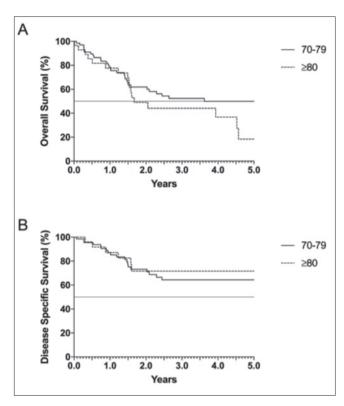
<sup>\*</sup> Cardiovascular complications included acute miocardial infarction, arrhythmia, and cardiac arrest.

nally, 27 of 99 patients (27.3%) underwent a second surgical procedure, whereas 9 of 99 patients (9.1%) underwent a third salvage surgery.

### Correlation of age, comorbidities, tumour site, type of surgery and complications with patient survival

Patients were followed for a mean period of 2.52 years (range 6 days – 9.3 years). At the last follow-up, 40 of 99 patients (40.4%) were alive without disease, 26 died with disease (26.3%) and 24 died for other reasons than head and neck cancer (24.2%), whereas 8 were alive with disease (8.1%). The remaining patient was lost to follow-up (1.0%). At 5 years, overall survival (OS, 41.1%) was not significantly affected by patient age at the surgery. In fact, OS was 49.9% in those 70-79 years old and 18.4% in those aged  $\geq$  80 years (p = 0.176; for early events p = 0.433), with 50% mortality at 3.6 and 1.7 years, respectively (Fig. 2A). Likewise, 5-year disease-specific survival (DSS, 66.1%) was 64.4% in 70-79 year old patients and 71.6% in the older ones (Fig. 2B; p = 0.677).

Furthermore, by stratifying chart data, we found that the presence of  $\geq 2$  comorbidities at diagnosis significantly worsened life expectancy of patients (p < 0.05). In these cases, OS was 23.9% (50% mortality at 1.5 years), whereas it was 53.4% and 48.2% (50% mortality at 3.9 years), respectively, in patients without or with 1 comorbidity (Fig. 3a). Otherwise, the anatomical localisation of the pathol-

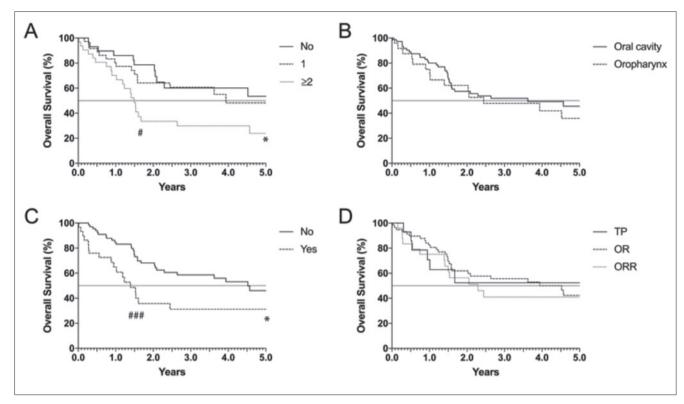


**Fig. 2.** Overall survival **(A)** and disease-specific survival **(B)** over a 5-year period in 99 patients with oral squamous cell carcinoma.

ogy had a marginal role (p = 0.510, Fig. 3b): patients with tumours in the oral cavity had 45.5% OS (50% mortality at 3.6 years), whereas those in which the pathology involved the oropharynx had 35.9% (50% mortality at 2.4 years). Regarding treatment, OS was affected by the presence of post-operative complications, although the choice of surgical technique did not play a direct role. In fact, 5-year OS of patients who experienced perioperative and post-operative complications was 31.2% (50% mortality at 1.4 years), which is significantly lower (p < 0.05; for early events p < 0.01) compared to 46.1% (50% mortality at 4.5 years) of the other patients (Fig. 3c). Otherwise, patients treated by a more invasive ORR had 5-year OS of 41.0% vs. 42.3% and 52.4% of those treated by OR and TP, respectively (p = 0.754) (Fig. 3d).

#### Risk analysis on the development of complications

Even if no variables evaluated displayed colinearity, age ≥ 80 years, gender, previous treatments, ASA physical status classification and duration of surgery did not show statistically significant correlations at univariate regression with the onset of perioperative and postoperative complications. On the contrary, they were correlated with the presence of concomitant diseases, tumour stage and type of surgery.



**Fig. 3.** Overall survival over a 5-year period of patients stratified for: presence of comorbidities at the diagnosis **(A)**, tumour site **(B)**, experience of peri- and/ or post-operative complications **(C)**, or employed surgical procedure **(D)**. \* p < 0.05 (Log-Rank test); # p < 0.05, ### p < 0.001 (Gehan-Breslow-Wilcoxon test for early events). TP, transoral procedure; OR, open neck resection; ORR, open neck resection with reconstruction.

In fact, patients affected by  $\geq 2$  comorbidities were prone to develop complications with a risk of 53.1%, which is significantly higher than those with 1 concomitant disease (27.1%, p < 0.05) or without any comorbidities (10%, p < 0.001). Similarly, patients who were diagnosed with early stage tumours had a lower risk (13.0% stage I and 16.7% stage II) to incur complications than those with advanced-stage disease (43.8% stage III and 45.7% stage IV, p < 0.01). Finally, patients undergoing ORR had an higher risk (p < 0.05) of developing complications (50.0%) compared to those treated by OR (23.7%) or TP (21.4%).

Concomitant diseases, tumour stage and type of surgery were included together with the non-statistically significant age parameter in the following multivariate logistic regression model (p < 0.001, Likelihood Ratio  $\Lambda$  test):

$$P = \frac{1}{1 + e^{-[1.253 + 0.446(a) - 0.741(b) + 0.385(c) - 2.887(d) - 1.677(e) - 2.070(f) - 1.459(g) - 0.313(h)]}}$$

where: (a) = patient aged 70-79; (b) = treatment by OR; (c) = treatment by ORR; (d) = absence of comorbidities; (e) = presence of 1 comorbidity; (f) = stage-I

neoplasm; (g) = stage-II neoplasm; (h) stage-III neoplasm.

In the regression model (Table V), the type of surgery was not statistically significant for the predisposition to develop complications (p = 0.170). Their rate was determined accordingly, stratified for both concomitant diseases and pathology stage, and reported in Table VI.

#### **Discussion**

Worldwide, the progressively aging population makes treatment of elderly patients more frequent than in the past. Nevertheless, the elderly have the tendency to be often considered as a population that should be treated by less invasive/time-consuming procedures. Furthermore, full scientific agreement about not considering age by itself as a risk factor for incidence of surgical complications in the elderly it is still lacking <sup>11-18</sup>. Consequently, aggressive surgery on older patients has been generally infrequent until now <sup>19</sup>. However, it has been recently demonstrated for the treatment of laryngeal cancer that the employment of more invasive surgical procedures can also be adequate to treat older patients, albeit with some recommendations <sup>20</sup>.

**Table V.** Multivariate regression analyses for the development of post-operative complications.

	-2 Log (Λ)	$\chi^2$	df	Р
Advanced stage	67.085	9.684	3	0.021
Comorbidities	73.974	16.572	2	0.000
Invasive surgical techniques	60.948	3.547	2	0.170
Age ≥ 80	57.942	0.541	1	0.462

 $\Lambda$ , likelihood ratio;  $\chi^2$ , chi squared; df, degrees of freedom.

Table VI. Complication risks (%).

		No. of comorbidities				
		0	1	≥ 2		
Tumour stage		1.8 - 5.4	5.9 - 11.4	17.4 - 50.3		
		2.1 - 9.4	6.8 - 25.9	27.9 - 44.9		
	$\parallel \parallel$	9.6	18.6 - 52.3	55.0 - 85.5		
	IV	8.5 - 30.9	23.8 - 60.0	62.5 - 88.9		

This finding could also be relevant for oral cancer. In the elderly, indeed, it is almost always (95%) diagnosed as squamous cell carcinoma (OSCC) 21 22, a tumour histotype characterised by an intrinsic resistance to non-surgical approaches like radiotherapy and chemotherapy (including the newest proton therapy and "target therapy") <sup>23-25</sup>. The clinical evolution of OSCC has led to a rapid and strong decline in both life quality and expectancy, and includes pain, dysphagia, odynophagia, bleeding, fetor ex ore, teeth loss, inability to swallow and tumour externalisation from mouth and facial skin with consequent irreparable, permanent socially disfiguring impairment. The functional, cosmetic and psychological repercussions suffered by OSCC patients frequently result in significant burden for them, their families and society. Generally, their nutritional status is poor and depression is frequent, with important somatic problems that often cause social isolation.

In this context, surgery can be considered the only reliable approach and is, hence, the treatment of choice for all tumour stages <sup>2</sup>. Thus, the exclusion criteria of patients with diagnosis of OSCC from surgery (including more invasive techniques) should be finely defined, avoiding the *a priori* exclusion of older patients to more challenging therapeutic options because wrongly considered as frail <sup>10 19</sup>.

In this retrospective study, we considered a cohort of old (70-79 years) and very old ( $\geq$  80 years) patients <sup>9</sup> affected by OSCC, in order to understand whether age represents *per se* a contraindication to treatment with open invasive surgery. Both old and very old populations were treated by one of three different approaches (transoral procedures, TP, open neck resection, OR, and open neck re-

section with reconstruction, ORR), chosen according to tumour stage and site, as well as comorbidities. The distribution of patients to surgical techniques was homogeneous between the two groups. Likewise, no differences were detected among groups after comparison between surgical time, number of ICU and hospitalisation days and incidence of complications. No significant differences were detected in terms of overall survival (OS) at 5 years from surgery, though a poorer 18.4% was detected in  $\geq$  80 year old patients vs 49.9% of those 70-79 years (p = 0.176). This non-significant difference was likely due to physiological instead of pathological causes, since during the same period disease-specific survival (DSS) was at some extent better (71.6%) in  $\geq$  80 years than in those 70-79 (64.4%, p = 0.677) years. This finding is further corroborated if we consider younger cohorts. In fact, following 489 patients (median age = 62) affected by oral tumours (40% in advanced stage), Rogers and co-workers <sup>26</sup> achieved 74% DSS after 5 years from surgical treatment. Furthermore, they reviewed the results from other cohorts in which the 5-year DSS varied from 49% to 84%. Combining the data, we can deduce an overall cohort of 805 patients with a DSS of 73.4% that is completely superimposable (p = 0.871) with our full-cohort DSS (66.1%). By patient stratification, we detected that OS was affected by both comorbidities at diagnosis and post-operative complications. Patients with ≥ 2 comorbidities had 23.9% OS vs. ~50% seen in the others. Similarly, patients who developed complications had 31.2% OS compared to the 46.1% of those who did not (p < 0.05), although the phenomenon was more evident in the first post-operative years (p < 0.001). Otherwise, tumour localisation as well as the choice of surgical approach did not have an apparent role in OS, even if we detected a higher incidence of complications (p < 0.05) in those 70-79 years undergoing a more extended ORR approach. As recently stated by Grammatica and coworkers, reconstruction still remains a complex procedure that affects the development of both local and systemic perioperative complications <sup>27</sup>.

As a confirmatory result, at univariate analysis the factors involved in the development of complications for our patient cohort were the presence of comorbidities, tumour stage and type of surgery employed, rapidly discharging any implication role of age, gender, previous treatments, ASA score and duration of surgical treatment. Nevertheless, at multivariate analysis, the role of each surgical approach became statistically negligible, highlighting a predominant involvement of tumour stage and above all the presence of concomitant diseases. Patients without comorbidities had a small to moderate risk in developing post-operative complications, even facing more ad-

vanced pathologies (stage III/IV, 8.5-30.9% risk). At any rate, the risk is already increased for patients facing very early stage tumours, but with  $\geq 2$  concomitant diseases (I/II, 17.4-50.3% risk).

As final digression, we would conclude that no differences in terms of functional outcomes (oral diet, speech intelligibility, and mouth opening) were detected among old and very old patients. Even if in our cohort much chart data did not report functional outcomes and for this reason results can only be considered as preliminary, they seem to be in accordance with the results of Nao and co-workers  $^{28}$ , although they compared younger patients ( $< 70 \text{ vs} \ge 70 \text{ years}$ ).

#### **Conclusions**

Up to now, it is widely accepted that elderly OSCC patients could not be treated with the standard of care because of medical prejudices related to advanced age. Nevertheless, our findings support the growing acceptance that chronological age alone should not be a sufficient contraindication for aggressive surgical therapy for OSCC. Instead, the presence of comorbidities at diagnosis might play a pivotal role in the choice of the more appropriate treatment of elderly patients. In multivariate analysis, indeed, comorbidities correlated with the development of post-surgical complications, thus foreclosing access to many treatment options. For these reasons, elderly patients affected by OSCC are undoubtedly delicate surgical candidates and accurate selection based on our results prior to surgery for curative intentions is mandatory.

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

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#### Conflict of interest statement

None declared.

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#### HEAD AND NECK

### Predictors of recurrence after surgical treatment of idiopathic progressive subglottic stenosis

Predittori di recidiva dopo trattamento chirurgico delle stenosi idiopatiche subglottiche progressive

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#### SUMMARY

Idiopathic progressive subglottic stenosis is a rare cause of tracheal narrowing. Partial cricotracheal resection and anastomosis can cure idiopathic stenosis, even if some patients may require multiple interventions and experience voice and swallowing deterioration. We investigated risk factors for retreatment and assessed the impact of crico-tracheal resection on functional parameters. We conducted a retrospective multicentric study on 44 female patients (mean age 52.6 ± 13.1 years) affected by idiopathic stenosis and treated by crico-tracheal resection between 2002 and 2016. Functional outcomes after crico-tracheal resection were assessed by the airway-dyspnoea-voice-swallowing score (range 1-5, with "1" expressing normal and "5" completely altered function). Previous treatments, grade of stenosis, site, airway comorbidities, age and resection length were tested as predictors of postoperative complications and number of additional treatments, using bivariate and multivariate analysis. The overall decannulation rate was 97.3%. The dyspnoea score improved (mean variation  $1.4 \pm 1.0$ ; p < 0.001), while voice and swallowing were negatively affected (mean variation  $1.6 \pm 0.9$  and  $0.5 \pm 0.7$ , respectively; p < 0.001). Airway comorbidities were associated with a higher rate of complications (p < 0.05). Retreatments were more frequent in patients with postoperative complications (p < 0.05). The length of resection correlated with the number of subsequent treatments (R = 0.52; p < 0.01). At multivariate analysis, post-operative complications were predicted by comorbidities and disease stage (p < 0.05); number of retreatments was linked to the length of resection (p < 0.05) as well as with the application of mitomycin C (p < 0.001). Crico-tracheal resection for idiopathic progressive subglottic stenosis offers good functional results in terms of airway patency. These data suggest that a higher complication rate can be expected in patients affected by comorbidities. Moreover, more extensive surgical resection seems to be associated with the occurrence and number of subsequent retreatments. On the contrary, the local application of an anti-proliferative drug does not seem to be of use in preventing recurrences.

KEY WORDS: Idiopathic subglottic stenosis • Partial cricotracheal resection • Complications • Recurrence

#### **RIASSUNTO**

La stenosi idiopatica subglottica progressiva rappresenta una rara causa di restringimento della laringe. La resezione parziale con successiva anastomosi può potenzialmente essere curativa; nonostante ciò alcuni pazienti richiedono un numero elevato di ritrattamenti e possono sviluppare disfonia e disfagia in seguito all'intervento. In questo studio abbiamo investigato i fattori di rischio per il ritrattamento e abbiamo valutato l'impatto della resezione crico-tracheale sui parametri funzionali. È stata condotta un'analisi multicentrica retrospettiva su 44 pazienti di sesso femminile (età media  $52.6 \pm 13.1$  anni), sottoposti a resezione crico-tracheale tra il 2002 e il 2016. Gli esiti funzionali sono stati valutati utilizzando la scala "vie aeree-dispnea-voce-disfagia" dove ognuno di questi parametri è stato valutato con un punteggio da 1 a 5, ove 1 esprime una funzione normale e 5 una funzione completamente compromessa. L'esistenza di trattamenti pregressi, il grado di stenosi, il sito della stenosi, la presenza di comorbidità delle vie aeree, l'età e la lunghezza del segmento resecato sono stati testati all'analisi bivariata e multivariata come predittori di complicanze e di trattamenti aggiuntivi. Il trattamento ha permesso la decannulazione del paziente nel 97,3% dei casi. L'indice di dispnea è migliorato (variazione media  $1,4 \pm 1,0$ ; p < 0,001), mentre quelli relativi alla voce e alla deglutizione sono peggiorati (variazione media  $1,6 \pm 0,9$  and  $0,5 \pm 0,7$ , rispettivamente; p < 0,001). I pazienti affetti da comorbidità delle vie aeree hanno presentato un tasso più alto di complicanze (p < 0,05). La lunghezza del segmento resecato ha dimostrato una correlazione diretta con il numero dei ritrattamenti (R = 0.52; p < 0.01). All'analisi multivariata, le complicazioni post-operatorie erano predette dall'esistenza di comorbidità e dallo stadio di malattia (p < 0.05); il numero dei ritrattamenti era associato alla lunghezza del tratto resecuto (p < 0.05) e all'applicazione di Mitomicina C (p < 0,001). La resezione crico-tracheale offre dei buoni risultati funzionali per la cura della stenosi idiopatica subglottica progressiva, in termini di pervietà delle vie aeree. I nostri dati suggeriscono che i pazienti affetti da comorbidità possono presentare un'incidenza più alta di complicazioni. Inoltre, resezioni chirurgiche più estese sembrano essere associate all'incidenza e al numero dei ritrattamenti. Al contrario, l'applicazione di sostanza anti-proliferativa non sembra essere utile nella prevenzione delle recidive.

PAROLE CHIAVE: Stenosi idiopatica subglottica • Resezione cricotracheale parziale • Complicazioni • Recidiva

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#### Introduction

Idiopathic progressive subglottic stenosis (IPSS) is a rare, acquired cause of upper airway related dyspnoea, whose pathologic hallmark is represented by progressive scarring of the subglottic larynx and upper trachea. Even though its pathogenic mechanisms remain obscure, onset of IPSS has been linked with severe coughing, gastrooesophageal reflux disease (GERD) or to autoimmune inflammatory mechanisms. These mechanisms have been proposed as possible triggers of an inflammatory process that is later sustained by unclear mechanisms 1-4. Moreover, a distinctive hallmark of IPSS is represented by its almost exclusive predilection for peri-menopausal women, with a median age of 47 years 5. Respiratory distress usually has an insidious onset, but it eventually progresses from exertional dyspnoea to respiratory symptoms even at rest and stridor. The disease shows usually a slow but constant progression and all patients eventually require surgical treatment to restore respiratory function and quality of life 467. Different surgical options have been advocated for IPSS management, ranging from endoscopic to openneck approaches 4 6-8. Recent studies seem to favour the latter, as laryngotracheal reconstruction techniques have shown better long-term results and lower recurrence rates compared with transoral surgery 6 9-13. In fact, patients treated by endoscopic balloon dilatation alone needed to be repeatedly treated to maintain functional airway patency 7; this leads to a negative impact on the overall quality of life, without attaining proper cure 14. Similar results have been observed by CO2 laser-assisted IPSS resection 15. Conversely, partial cricotracheal resection and anastomosis (PCTRA) can potentially achieve complete and permanent restoration of airway function <sup>5</sup>.

However, a significant percentage of patients show multiple relapses, even in case of apparent total resection of the affected segment <sup>7 8</sup>. In light of this, we investigated the risk factors for post-operative complications and re-operation in IPSS treated by PCTRA as well as the impact of the procedure on functional parameters such as breathing, phonation and swallowing in a large multicentre series of subjects managed by a common therapeutic strategy.

#### Materials and methods

#### Patient population

We retrospectively analysed clinical data of 44 female patients (mean age 52.6 years; range 31-79) affected by IPSS and treated by PCTRA at the Department of Otorhinolaryngology, Katharinenhospital, Stuttgart, Germany between July 2010 and June 2016 and in the Departments

of Otorhinolaryngology Head and Neck Surgery, Universities of Brescia and Genoa, Italy between June 2002 and August 2014. The inclusion criteria were: no history of intubation at least 2 years before symptoms onset, no previous tracheotomy, no concurrent head and neck trauma, airway infection, or systemic autoimmune diseases.

All patients signed a written informed consent form, which was reviewed and approved by the respective local Ethics Committees and included the utilisation of anonymised patient data for research purposes.

#### Endoscopic work-up

The endoscopic evaluation included a detailed static and dynamic analysis of the airways <sup>16</sup>. Pre-operative assessment was performed under direct laryngoscopy, in spontaneous ventilation using 0° and 30° rigid telescopes (Karl Storz, Tuttlingen, Germany) to examine passive vocal fold mobility, as well as the precise stenosis site and its craniocaudal extension. Subsequently, adequate laryngeal exposure in microlaryngoscopy was obtained with different laryngoscopes such as the Sataloff (Microfrance® iXomed, Saint Aubin Le Monial, France), Dedo or Dedo-Ossoff (Pilling, Philadelphia, PA, USA) to precisely evaluate and measure the extension, consistency and grade of IPSS. A biopsy was always performed to rule out an autoimmune background of the disease process.

#### Operative technique

In all patients, PCTRA was performed as a single-stage surgical procedure aimed at treating stenosis of the sub-glottic larynx and trachea by complete resection of the affected airway segment, including the anterior cricoid arch, the mucosal layer of the cricoid plate potentially up to the cricoarytenoid joints and, when needed, the first tracheal ring(s) in order to reestablish its continuity in a single step by thyro-crico-tracheal anastomosis <sup>17</sup>. At the end of the procedure, all patients were primarily extubated and then monitored at in an intensive care unit.

Functional outcomes, complications frequency and need for retreatment after PCTRA

Functional outcomes were assessed with the Airway-Dyspnoea-Voice-Swallowing score (ADVS) <sup>18</sup>. This scale consists of 4 functional domains, including airway (A), dyspnea (D), voice (V), and swallowing (S). All parts of the scoring system have a 1 to 5 ordinal progressive scale, with "1" expressing normal and "5" completely impaired function. This scoring was obtained before and after intervention.

Variables including previous treatments, grade and localisation of IPSS, airway comorbidities, age and resection length were all tested as predictors of post-operative complications and number of additional treatments needed to cure the patient.

#### Statistical analysis

A T-test for paired samples was used to compare pre- and post-operative ADVS scores between patients. Correlation of previous treatments, grade and localisation of IPSS, airway comorbidities, age and resection length with post-operative complications and number of additional treatments was tested by bivariate analysis using Pearson's product-moment correlation coefficient index. Significant correlations were then inserted and tested using a multivariate model (MANOVA). A p value < 0.05 was considered statistically significant. The SPSS program (SPSS, v. 21.0, IBM, Armonk NY, USA) was used for statistical analysis.

#### **Results**

#### Clinical outcomes after PCTRA

The operation-specific decannulation rate following PCTRA was 97.3%, resulting in a permanent tracheostomy in one patient due to a major post-operative complication. However, 6 subjects (13.6%) were submitted to post-operative temporary tracheotomy (mean duration 9.3 days; range 2-18), because of serious complications (2 oedema, 1 haematoma, 2 tracheal

necrosis and 1 inversion of vocal fold motility), which arose 5-17 days after the intervention (median = 11 days).

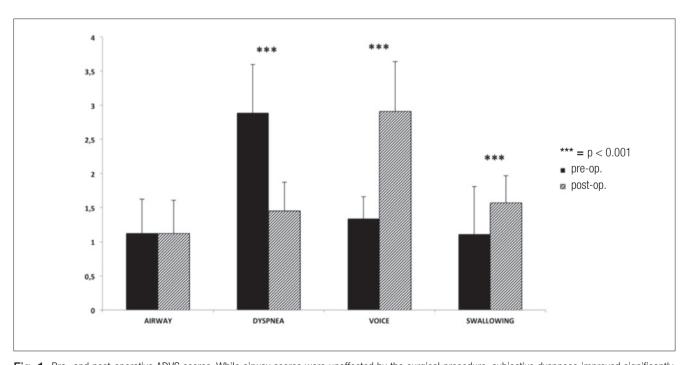
This, however, had no influence on the airway score  $(1.12 \pm 0.5 \text{ before PCTRA} \ vs \ 1.12 \pm 0.5 \text{ after PCTRA}$ , Fig. 1). The dyspnoea score improved significantly  $(2.89 \pm 0.72 \text{ before PCTRA} \ vs \ 1.45 \pm 0.66 \text{ after PCTRA}$ ; p < 0.001, Fig. 1), as most of patients showed significant improvement in symptoms. In fact, no patient presented post-operative resting dyspnoea.

On average, voice was negatively affected in all patients  $(1.34 \pm 0.71)$  before PCTRA vs  $2.91 \pm 0.42$  after PCTRA; p < 0.001, Fig. 1), as the majority of patients passed from slight or absent voice problems to post-operative dysphonia due to cricothyroid muscles and cricoid arch resection with ensuing loss of vocal pitch modulation. As a result, most subjects experienced significant difficulties in being heard or understood in loud environments.

Similarly, swallowing scores were negatively affected (1.11  $\pm$  0.32 before PCTRA vs 1.57  $\pm$  0.73 after PCTRA; p < 0.001, Fig. 1). After surgery, the majority of patients showed the onset of mild subjective swallowing difficulties even though they were able to eat a normal diet, in comparison to intact swallowing prior to surgery.

#### Post-operative complications

Notably, all patients affected by airway comorbidities (asthma, chronic obstructive pulmonary disease, unilateral vocal



**Fig. 1.** Pre- and post-operative ADVS scores. While airway scores were unaffected by the surgical procedure, subjective dyspnoea improved significantly. However, this came at the cost of a relative deterioration in voice and swallowing scores.

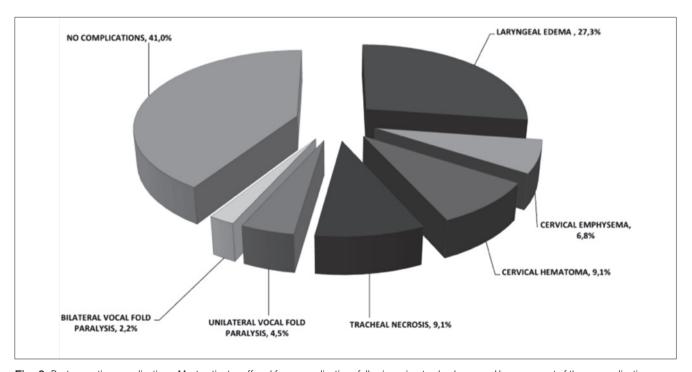
fold palsy) encountered post-operative complications. By contrast, adverse events occurred in 52.6% of patients without pre-existing airway conditions (p < 0.05 vs the remaining patients). The most commonly observed post-operative complication was laryngeal oedema, affecting 12 (27.3%) patients, and resulting in short-term orotracheal intubation in 5 cases, endoscopic removal of fibrin tissue or injection of triamcinolone acetonide (Volon A. Dermapharm AG) in 5, endoscopic balloon dilatation in one and short-term tracheotomy in one. Three (6.8%) subjects experienced post-operative cervical emphysema followed by anastomotic revision in 2 cases and short-term orotracheal intubation in one. Cervical haematoma occurred in 4 patients (9.1%), and required neck surgical re-exploration in 2. The most severe observed complication, in the form of tracheal necrosis, occurred in 4 (9.1%) patients, resulting in temporary endoluminal tracheal stent in one case, temporary tracheotomy in 2 and permanent tracheotomy in another. Unilateral vocal cord paralysis occurred in 2 (4.5%) subjects, and was managed by intracordal injection of Calcium Hydroxyapatite (Radiesse, Merz Aesthetics) in both cases. Temporary bilateral vocal fold paresis occurred in only one (2.3%) patient and was treated by a reversible endoscopic unilateral arytenoid lateropexy according to Lichtenberger's technique <sup>19</sup>. See Figure 2 for details.

#### Additional treatments

Twenty-six (59.1%) patients required additional endoscopic treatments (mean  $3.2 \pm 2.3$ ; range 1-9), but no further open-surgical procedure. The endoscopic revisions included balloon dilatations (Inspira Air Technology, Acclarent) and topical injection of triamcinolone acetonide in 9 cases, and balloon dilatation with topical application of mitomycin C (2 mg/ml for 2 minutes) in 12 cases. Granulation tissue was removed in 11 subjects. See Figure 3 for details. Retreatments were significantly more frequent in patients who presented post-operative complications (2.2  $\pm$  1.7 vs 3.7  $\pm$  2.5; p < 0.05). Moreover, length of resection directly correlated with the number of subsequent treatments (R = 0.52; p < 0.01, Fig. 4). Topical application of mitomycin C did not improve the clinical outcome; on the contrary, patients receiving mitomycin C had to be re-treated more frequently compared with those who did not  $(4.1 \pm 3 \text{ vs } 1.1 \pm 1.7; \text{ p} < 0.001)$ . This finding was independent from clinical stage as well as from length of resected segments.

#### **MANOVA**

At multivariate analysis, onset of post-operative complications was predicted by the presence of pre-operative comorbidities (RR 7.2; p < 0.05) as well by disease stage (RR = 5.1, respectively; p < 0.05). Conversely,



**Fig. 2.** Post-operative complications. Most patients suffered from complications following crico-tracheal surgery. However, most of these complications were mild and reversible; only one patient suffered long-term damage.

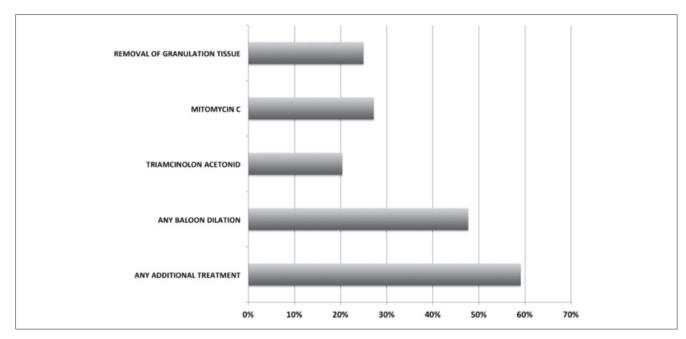
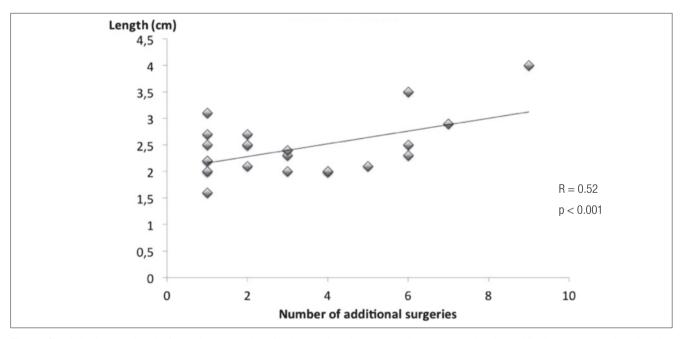


Fig. 3. Frequency of retreatments. None of the patients required re-intervention with open surgery. However, endoscopic treatments were necessary in about half of patients. Local application of anti-proliferative drugs produced no appreciable effect.



**Fig. 4.** Correlation between length of resection and number of re-interventions. Longer resections were associated to recidivating stenosis, perhaps implying that a more extensive resection is more likely to trigger further inflammatory reactions.

history of previous treatment did not influence the surgery outcome.

Clinical stage at baseline and history of previous surgeries did not predict the need or the number of additional procedures. However, number of subsequent retreatment was predicted by the length of resected segment (RR = 2.4; p < 0.05).

Regarding functional outcomes, the length of the resected segment was strongly associated with the post-operative subjective dyspnoea score (p < 0.01).

Application of mitomycin C was directly and strongly associated with occurrence of retreatments (p < 0.001) as well as with the number of additional surgical procedures (p = 0.001).

#### Discussion

The present research confirms that the success rate for PC-TRA is extremely high, similar to previous series <sup>5</sup>. However, it also highlights that successful decannulation can come through this technique at a cost. In fact, patients were relieved of dyspnoea, but their phonatory and swallowing function were negatively affected. Moreover, there was a significant percentage of patients in which the stenosis recurs. Actually, when compared to other stenosis aetiologies, IPSS patients have longer duration of symptoms and a tendency to require multiple treatments <sup>20 21</sup>. In fact, idiopathic stenosis appears to be sustained by a chronic inflammatory syndrome, at least partially dependent on hormone receptor unbalance 20-22; in IPSS, surgery may thus alleviate the symptoms, but not fully remove the underlying cause. Nonetheless, our data help to shed light on the reasons underlying the tendency to relapse. In fact, it appears that pre-operative presence of any type of airway comorbidities may set the stage for the insurgence of post-operative complications, which in turn could promote the tendency to relapse. A greater size of the removed segment can also increase the risk of recurrence, other than possibly affecting negatively the chance of dyspnoea improvement. Even though fully eliminating the affected segment and maintaining a safe resection margin is the objective of the PCTRA procedure, the available data suggests that IPSS is an abnormal inflammatory reaction triggered by an unapparent stimulus <sup>23-25</sup>. In this context, treatment with PC-TRA may per se constitute a trigger, capable of inducing an inflammatory response in a previously unaffected (but otherwise susceptible) airway segment. In longer resections, force applied to the suture margins, as well as wider and lengthier tissue manipulation could negatively impact the repair process and constitute a stimulus for the abovementioned inflammatory reaction. This reasoning could also explain the inefficacy of the adjuvant local application of mitomycin, in accordance with the recent literature <sup>26</sup>. Actually, patients treated with this drug presented a worse outcome, which does not seem to be dependent on selection bias (as the mitomycin subgroup had neither a higher stage nor a greater prevalence of comorbidities), but could be rather linked to respiratory epithelium damage following local mitomycin application as well as to impaired wound healing and fibrin accumulation <sup>27</sup>.

Given these considerations, the occurrence of voice and

swallowing deterioration, the longer post-operative recovery and the higher risk of complications linked with PTCRA, the surgeon may be tempted to favor an endoscopic treatment. However, the best possibility for cure lies in the first surgery, as the patient can expect better long-term results in terms of airway stability and patency. Moreover, patients operated by endoscopic procedures will have to face more treatments and generally worse long-term outcomes. However, patients with a relatively high risk of perioperative complications, active airway comorbidities and in whom deterioration of the phonatory and swallowing functions is not acceptable could receive greater benefits from an endoscopic approach, embracing PCTRA only after multiple failed transoral attempts or worsening of airway problems. It is then of utmost importance to thoroughly counsel the patient about intra- and post-operative risks and complications, including the possibility of additional endoscopic treatments and/or revision procedures 5. Moreover, patients should be warned about the frequent alterations of voice, which are more likely to occur when an open procedure is employed. In fact, they should be reassured that they will have a functional voice, but some changes may be noticed in comparison with pre-operative function. This study has some intrinsic limitations: it is a retrospective evaluation of patients treated at three different centres over a prolonged period of time. However, diagnostic work-up, treatment philosophy, surgical technique, instrumentation and follow-up policy were comparable. Moreover, follow-up time was variable, as some patients treated in the early 2000s stopped attending visits after a

#### **Conclusions**

the scores in the three subgroups.

Surgical treatment by PCTRA is effective in treating IPSS; however, life-long surveillance is necessary as the majority of patients will experience disease relapse during the course of follow-up. Accurate evaluation of the clinical history and careful assessment of airway related comorbidities are of great value in predicting, reducing, and properly managing perioperative complications, as well as the occurrence of relapse, in IPSS. The goals of PCTRA should be the restoration of airway physiologic patency, while reducing to

long remission period and, conversely, some patients were

recruited at relatively recent times. Finally, evaluation

of functional parameters was based on the self-reported

symptoms' heftiness. This evaluation was selected so as to

avoid bias due to different calibration and availability of

instrumentation in the three different centers. This could

have caused difference in symptoms reporting; however,

no statistically significant variations were detected among

a minimum voice and swallowing-related sequelae and the complication rate. At present, this approach remains of special relevance in management of IPSS and the one that allows the highest rates of both short and long-term success.

#### Conflict of interest statement

None declared.

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#### LARYNGOLOGY

## Relationship between socio-demographic characteristics and vocal fold nodules, polyps and oedema

Relazione fra edema della laringe, noduli e polipi delle corde vocali e caratteristiche socio-demografiche

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#### **SUMMARY**

The aim of our study was to compare socio-demographic characteristics of vocal fold nodules, polyps and oedema. The study included patients diagnosed for the first time with vocal fold nodules, polyps and oedema at the Communication Disorders Care Center of Clinic for Otorhinolaryngology and Maxillofacial Surgery in Clinical Center of Serbia, Belgrade. Diagnosis was made on the basis of symptoms, clinical otorhinolaryngological and phoniatric examination and endovideolaryngostroboscopic findings. A self-administered questionnaire was used to collect the following data: socio-demographic status, exposure to occupational noise and air pollution, occupational voice demands, health habits, symptoms of the present voice problems and voice problems in the family. By multivariate logistic regression analyses, nodules and oedema were more frequent in women than men in comparison with polyps (p < 0.001). Patients with nodules and polyps were younger than those with oedema (p < 0.001). Patients with nodules were more frequently lecturers, singers and actors compared with polyp patients (p = 0.006), had occupational voice demands more frequently than patients with oedema (p = 0.037) and were less frequently smokers than patients with polyps (p = 0.043) and those with oedema (p < 0.001). Patients with oedema were more frequently current smokers than patients with nodules and those with polyps (p = 0.040) and those with oedema (p = 0.001). Voice problems in the family was more frequently reported by oedema patients than by patients with polyps (p = 0.005). These findings are in agreement with majority of previous studies and may be of help in investigations on the aetiology of the disease.

KEY WORDS: Vocal fold nodules • Polyps • Edema • Epidemiological study

#### **RIASSUNTO**

Scopo del nostro studio è stato quello di paragonare le caratteristiche socio-demografiche dei pazienti con noduli, polipi ed edema delle corde vocali. Lo studio ha incluso pazienti con una prima diagnosi di noduli, polipi od edema delle corde vocali presso il Centro di Disordini della Comunicazione della Clinica Otorinolaringoiatrica e Maxillo Facciale di Belgrado, Serbia. La diagnosi è stata posta sulla base dei sintomi, della visita ORL e foniatrica con videolaringostroboscopia. È stato utilizzato un questionario per la raccolta dei seguenti dati: status socio-demografico, esposizione al rumore nell'ambiente lavorativo ed inquinamento dell'aria, utilizzo della voce nelle attività lavorative, abitudini di vita, sintomi riferibili alla disfonia attuale ed eventuali disfonici in famiglia. Un'analisi multivariata ha evidenziato come i noduli e l'edema siano più frequenti nelle donne rispetto agli uomini se paragonate ai polipi (p < 0,001). I pazienti con noduli sono risultati essere più giovani di quelli con edema (p < 0,001). Quelli con noduli erano più frequentemente conferenzieri, cantanti od attori se paragonati a quelli con i polipi (p = 0,006), avevano una storia di abuso vocale più frequentemente rispetto ai pazienti con edema (p = 0,037) ed erano meno frequentemente fumatori rispetto ai pazienti con polipi (p = 0,043) e a quelli con edema (p < 0,001). I pazienti con edema erano più frequentemente fumatori rispetto ai pazienti con noduli e polipi (p < 0,001). La faringodinia come sintomo principale era più frequentemente nei pazienti con noduli rispetto a quelli con i polipi (p = 0,040) o con edema (p = 0,001). I problemi di voce in famiglia erano più frequentemente riportati fra i pazienti con edema rispetto a quelli con polipi (p = 0,040) o con edema (p = 0,001). I problemi di voce in famiglia erano più frequentemente riportati fra i pazienti con edema rispetto a quelli con polipi (p = 0,040) o con edema (p = 0,001). I problemi di voce in famiglia erano più frequentemente ripo

PAROLE CHIAVE: Noduli corde vocali • Polipi corde vocali • Edema corde vocali • Studio epidemiologico

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#### Introduction

Vocal fold nodules, polyps and oedema are classified as vocal fold masses, also known as exudation lesions of Reinke space <sup>1 2</sup>. The aetiology, pathogenesis, histology and clinical aspects of these lesions are still rather controversial, as well as their management.

It has been considered that both genetic and environmental factors play a role in the development of vocal fold (VF) disease <sup>3 4</sup>. Gender, age, education level, occupations, vocal abuse or misuse, cigarette smoking, alcohol consumption, unfavourable microclimate conditions at work and comorbidities such as gastro-oesophageal reflux, infections, allergy and thyroid diseases are recongised risk factors <sup>5-13</sup>.

Investigations of factors related to VF nodules, polyps and oedema show some differences between these three forms of VF disease. For example, in the study by Nagata et al. <sup>5</sup> polyps were frequent in middle-aged subjects of both sexes, whereas nodules were more common in boys and middle-aged women. Smoking was more frequently associated with VF oedema than with nodules and polyps <sup>7</sup>. These and similar findings raised the question of whether VF nodules, polyps and oedema were the same entity. Although only genetic studies and studies at molecular level might definitively answer the question, it is of help to understand the main differences among VF nodules, polyps and oedema in terms of socio-demographic characteristics.

The aim of our study was to compare the socio-demographic characteristics of vocal fold nodules, polyps and oedema.

#### Materials and methods

The study included patients diagnosed for the first time with VF nodules, polyps and oedema at the Communication Disorders Care Center of Clinic for Otorhinolaryngology and Maxillofacial Surgery in Clinical Center of Serbia, Belgrade, during October 2014 - March 2015.

Diagnosis was made on the basis of symptoms, clinical otorhinolaryngological and phoniatric examination and endovideolaryngostroboscopic findings. The diagnosis was established by multidisciplinary team consisted of two phoniatricians, two laryngologists and two logopaedics with at least 20 years of experience in the field of communication disorders. Endovideolaryngostroboscopy was a key tool because it allows all members of the team to take a part in examination at the same time. Inclusion criteria were age over 18 years and voluntary participation. Exclusion criteria were neurological and psychiatric illness, malignant disease, severe hearing loss, transsexual conflict, professional voice needing urgent phonosurgery

and no treated comorbidities (reflux, allergy, thyroid end lung disease).

Using a self-administered questionnaire, the following data were collected: gender, age, height and weight, marital status, educational level, occupation, working experience, exposure to occupational noise and air pollution, additional job, occupational voice demands, family income, physical activity, cigarette smoking, alcohol consumption, comorbidity, symptoms of present voice problems and duration in months and voice problems in the family. Body mass index (BMI) was calculated as weight (kg) divided by height (m<sup>2</sup>). With reference to smoking, each patient was classified as a nonsmoker, former smoker or current smoker. A current smoker was defined as a person who smoked at least one cigarette per day in the 12 months before the disease or who quit smoking within that year. A former smoker was defined as a person who quit for more than a year before the disease occurrence. Regarding alcohol consumption, patients were divided into two groups: ever drinkers and non-drinkers (those who during their life drank less than 12 alcoholic beverages) 14. Physical activity comprised any kind of unprofessional physical activity for 30 min per day during the previous month. Persons who exercised more than once a week were considered physically active and the others physically inactive.

For statistical analysis univariate and multivariate logistic regression methods were used. All test variables with statistical significance of  $p \le 0.10$  in the univariate model were included in the multivariate model. Significance was considered with a p value < 0.05. Statistical analysis was performed using the SPSS 20 package.

#### Results

Of 205 patients with exudative lesions of Reinke's space, 72 (35.12%) were with nodules, 70 (34.14%) with polyps and 63 (30.63%) with oedema.

Characteristics of patients with nodules, polyps and oedema, and differences between these three groups according to univariate logistic regression analysis, are presented in Tables I-III.

When compared with VF polyp patients, those with VF nodules were significantly more frequent in women, younger, not married and with university education. In comparison with VF oedema patients, those with VF nodules were significantly younger, not married, with university education and with high family income. Patients with VF polyps, compared with VF oedema patients, were significantly more frequent in younger men (Table I).

According to data in Table II, patients with VF nodules, compared with VF polyps, significantly differed in occu-

**Table I.** Socio-demographic characteristics of patients with vocal fold nodules, polyps and oedema.

Variable		Patients with	71 31		p value * for	
	VF nodules (n = 72)	VF polyps (n = 70)	VF oedema (n = 63)	VF nodules <i>vs</i> VF polyps	VF nodules <i>vs</i> VF oedema	VF polyps <i>vs</i> VF oedema
	N (%)	N (%)	N (%)			
<b>Gender</b> Male Female	3 (4.2) 69 (95.8)	37 (52.9) 33 (47.1)	7 (11.1) 56 (88.9)	< 0.001	0.139	< 0.001
<b>Age (years)</b> ≤ 40 > 40	55 (76.4) 17 (23.6)	32 (45.7) 38 (54.3)	6 (9.5) 57 (90.5)	< 0.001	< 0.001	< 0.001
Married	37 (51.4)	53 (75.7)	46 (73.0)	0.003	0.011	0.722
<b>Education</b> Elementary to high school Faculty	34 (47.2) 38 (52.8)	45 (64.3) 25 (35.7)	47 (74.6) 16 (25.4)	0.042	0.010	0.200
<b>Income</b> Low Middle High	1 (1.4) 38 (52.8) 33 (45.8)	2 (2.9) 45 (64.3) 23 (32.9)	3 (4.8) 41 (65.1) 19 (30.2)	0.104	0.042	0.614

VF: vocal fold; \*: according to univariate logistic regression analysis.

pation, had significantly shorter working experience, were significantly more exposed to noise in the working place and more frequently with considerable and immense occupational voice demands.

In comparison with VF oedema patients, VF nodule patients also significantly differed in occupation, had signif-

icantly shorter working experience and were significantly more frequent in patients with considerable and immense voice demands.

Patients with polyps and those with VF oedema significantly differed only in the working experience, which was shorter in patients with VF polyps.

Table II. Type of occupation, occupational conditions and professional voice use in patients with vocal fold nodules, polyps and edema.

Variable	Patients with			p value * for		
	VF nodules (n = 72)	VF polyps (n = 70)	VF oedema (n = 63)	VF nodules <i>vs</i> VF polyps	VF nodules <i>vs</i> VF oedema	VF polyps <i>vs</i> VF oedema
	N (%)	N (%)	N (%)			
Type of occupation						
Singer, Actor	9 (12.5)	3 (4.3)	2 (3.2)			
Lecturer	20 (27.8)	4 (5.7)	4 (6.3)			
Physical worker	3 (4.2)	7 (10.0)	11 (17.5)	0.003	0.044	0.238
Administrative worker	23 (31.9)	40 (57.1)	23 (36.5)	0.000	0.0	0.200
Health worker	6 (8.3)	5 (7.2)	3 (4.8)			
Unemployed	9 (12.5)	3 (4.3)	1 (1.6)			
Retired	2 (2.8)	8 (11.4)	19 (30.2)			
Working experience (years)	=(0 0)	00 (50 0)	10 (0= 0)			
< 20	51 (81.0)	39 (58.2)	16 (25.8)	0.006	< 0.001	< 0.001
≥ 20	12 (19.0)	28 (41.8)	46 (74.2)			
Has additional job	27 (37.5)	20 (28.4)	19 (30.2)	0.259	0.370	0.841
Noise in the working place	49 (68.1)	35 (50.0)	34 (54.0)	0.030	0.095	0648
Polluted air in the working place	36 (50.0)	35 (50.0)	30 (47.6)	0.782	1.000	0.784
Occupational voice demands				0.002	< 0.001	0.078
No	18 (25.0)	28 (40.0)	35 (55.5)			
Increased	17 (23.6)	26 (37.1)	19 (30.2)			
Considerable	25 (34.7)	12 (17.1)	7 (11.1)			
Immense	12 (16.7)	4 (5.7)	2 (3.2)			

VF: vocal fold; \*: according to univariate logistic regression analysis.

Table III shows health habits, body mass index, and data from personal and family history of patients with nodules, polyps and oedema.

Patients with VF nodules and those with VF polyps significantly differed only in smoking and BMI. Ever smoking and current smoking were more frequent among patients with VF polyps, who also were more frequently overweight and obese.

According to comparison with VF nodule patients, those with VF oedema were significantly more frequently ever smokers and current smokers, were less frequently physically active and more frequently overweight and obese. They also had hoarseness less frequently as the main presenting symptom and longer duration of symptoms before visiting physician. Altogether other diseases were more frequent among oedema patients, but single disease, allergy, reflux and thyroid diseases were more frequent among VF nodule patients, and cardiovascular diseases among VF oedema patients.

In comparison with VF polyp patients, those with VF oedema were significantly more frequent in ever smok-

ers and current smokers, were less frequently physically active, had less frequently hoarseness as the main symptom and had longer duration of symptoms before visiting a physician. Patients with VF oedema significantly more frequently reported family history positive on voice problems.

Variables with statistical significance of p  $\leq$  0.10 according to univariate analysis were included in multivariate analysis. According to multivariate logistic regression analyses (Table IV) there were significant differences between groups for several characteristics. Patients with nodules and oedema were more frequent in women than men in comparison with polyp patients (p < 0.001). Patients with nodules and polyps were younger than oedema patients (p < 0.001). Patients with nodules were more frequently lecturers, singers and actors compared with polyp patients (p = 0.006), had occupational voice demands (considerable and immense) more frequently than patients with oedema (p = 0.037) and were less frequently smokers than patients with polyps (p = 0.043) and those with oedema (p < 0.001). Patients with oedema were more frequently

Table III. Smoking, alcohol consumption, recreational physical activity, body mass index, and personal and family history of patients with vocal fold nodules, polyps and oedema.

Variable		Patients with			p value * for	
	VF nodules (n = 72)	VF polyps (n = 70)	VF oedema (n = 63)	VF nodules <i>vs</i> VF polyps	VF nodules <i>vs</i> VF oedema	VF polyps <i>vs</i> VF oedema
	N (%)	N (%)	N (%)			
Smoking status Non smoker Former smoker Current smoker	35 (48.6) 21 (29.2) 16 (22.2)	21 (30.0) 23 (32.9) 26 (37.1)	1 (1.6) 8 (12.7) 54 (85.7)	0.017	< 0.001	0.002
Alcohol consumption	18 (25.0)	27 (38.6)	16 (25.4)	0.084	0.958	0.107
Physically active (recreation)	56 (77.8)	50 (71.4)	32 (50.8)	0.386	0.001	0.015
<b>Body mass index</b> Normal weight Overweight or obese	56 (77.8) 16 (22.2)	35 (50.0) 35 (50.0)	27 (42.9) 36 (57.1)	0.001	< 0.001	0.847
Present disease symptoms Hoarseness Dyspnea Other	62 (86.1) 1 (1.4) 9 (12.5)	55 (78.6) 1 (1.4) 14 (20.0)	38 (60.3) 3 (4.8) 22 (34.9)	0.229	0.001	0.033
Duration of symptoms (months) $\leq 12$ $> 12$	60 (83.30) 12 (16.7)	50 (71.4) 20 (28.6)	29 (46.0) 34 (54.0)	0.093	< 0.001	0.003
Has some other diseases	36 (50.0)	41 (58.6)	45 (71.9)	0.306	0.012	0.123
Type of other disease Allergy Reflux Thyroid Cardiovascular Other	7 (19.4) 10 (27.8) 7 (19.4) 5 (13.9) 7 (19.4)	5 (12.2) 12 (29.3) 7 (17.1) 7 (17.1) 10 (24.4)	3 (6.7) 6 (13.3) 8 (17.6) 17 (37.8) 11 (24.4)	0.414	0.016	0.093
Voice problems in the family	11 (15.3)	8 (11.4)	18 (28.6)	0.502	0.064	0.016

VF: vocal fold; \*: according to univariate logistic regression analysis.

Table IV. Characteristics which significantly differed between patients with vocal fold nodules, polyps and oedema, according to multivariate logistic regression analysis.

Variable VF nodule patients <i>vs</i> VF polyp patients		VF nodule patients <i>vs</i> VF oedema patients		VF polyp patients <i>vs</i> VF oedema patients		
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Gender (women/ men)	30.30 (8.13-111.11)	p < 0.001.			0.07 (0.02-0.24)	< 0.001
Age (≤ 40 years/> 40 years)			14.03 (3.58-54.92)	p < 0.001	17.27 (4.36-68.36)	< 0.001
Occupation *	2.50 (1.30-4.76)	0.006				
Occupational voice demands †			2.04 (1.04-4.0)	0.037		
Smoker (no; former; current)	0.59 (90.35-0.98)	0.043	0.15 (0.06-0.37)	< 0.001	0.19 (0.08-0.43).	< 0.001
Symptoms of the present disease (hoarseness/dyspnoea and others)	2.93 (1.05-8.20)	0.040	13.49 (2.75-66.15)	0.001		
Voice problems in the family (yes/no)					0.13 (0.03-0.53)	0.005

VF: vocal fold; OR: odds ratio; Cl: confidence intervals.

current smokers than patients with nodules and those with polyps (p < 0.001). Hoarseness as the main symptom of the present disease was more frequent among patients with nodules than among patients with polyps (p = 0.040) and those with oedema (p = 0.001). Voice problems in the family were more frequently reported by oedema patients than by those with polyps (p = 0.005).

#### Discussion

It is still a paradigm how to classify vocal fold nodules, polyps and edema <sup>15</sup>. Although it seems reasonable to place all of the three together, there are some differences between them. In the present study, patients with nodules, polyps and oedema significantly differed in seven characteristics: gender, age, occupation, occupational voice demands, smoking, family history of voice problems and symptoms.

Age and gender related risks for specific voice disorders have been highlighted by other authors <sup>16</sup> <sup>17</sup>. In our investigation, the three groups were strictly divided. VF nodule patients were predominantly at the age of 40 and under, and VF oedema patients at the age of 41 and over. The VF polyps group was more balanced, with 32 patients with an age of 40 and under, and 38 patients with an age of 41 and over. In the investigation by Yoon Se Lee et al. <sup>18</sup> the age range for vocal fold polyps in the group of 41 males and 51 females was 22-72 years, with an average of 51.

The reasons for this age distribution are still not clear, but from a socio-demographic point of view it seems that VF nodules are a disease of the young, and that VF oedema is a disease of an older population because of large differences in vocal and health behaviour of these two groups. In our investigation, in the VF polyps group 52.9% of patients were men, compared to only 4.2% in the VF nodules group and 11.1% in the VF oedema group. This gender difference may be related to many factors, both genetic and psychological, but also with environmental factors <sup>3</sup>. It would seem that gender and age are of importance in determination in which direction one exudative lesion of Reinke's space will develop. Women with vocal folds in the presence of risk factors will develop nodules rather than polyps. Older women with vocal folds in the presence of risk factors will develop oedema rather than polyps. The reasons for this are still unclear, probably lying at the molecular level, and likely associated with contributing factors such as occupational voice demands, smoking and delay of seeking medicine attention.

The type of occupation has also been recognised as a risk factor for VF disease <sup>8</sup>. In fact, the type of occupation is related to voice demands and air pollution. The incidence of vocal fold nodules and polyps correlates with vocal overuse <sup>19</sup>. Increased vocal use, predominantly linked to the VF polyps group, was connected with professions such as army and police commanders, street and other sale persons, receptionists, medical stuff and speech and

<sup>\*:</sup> unemployed or retired; physical, administrative or health worker; singer, actor, lecturer.

<sup>†:</sup> no; increased; considerable; immense.

language therapists, lawyers, judges, hair dressers. Considerable vocal use, mostly linked to VF nodules group, was registered in teaching stuff, telephone operators, clerks, politicians, sport trainer and managers. For example, in a study from Spain, the prevalence of voice disorders among teachers was 14% for nodular lesions, 2% for polyps and 1.2% for Reinke's oedema 20. In the study conduted by Krecicki et al. 8, women formed the majority, and teachers formed the largest occupational group (30%). Immense vocal use, also linked to the VF nodules group, is present in singers, actors, TV and radio speakers and showmen 19. In our investigation, VF nodules were linked to voice overuse (considerable and immense occupational voice demands). Alvarez also found that voice abuse or misuse was the main factor in patients with VF nodules 21.

There is general acceptance of a close relationship between chronic cigarette smoke exposure and onset of voice pathology, especially Reinke's oedema 7. In the study by Krecicki et al. 8 most VF oedema patients (86%) were smokers. According to the investigation by Alvarez et al. 21 smoking was the main symptom in polyps and oedema. In our study, smokers were most frequent among VF oedema patients. Up to 98.4% of patients with oedema were ever smokers, and 85.7% were current smokers. Among patients with VF polyps, 70.0% were smokers (37.1% current smokers), which was less than among patients with oedema but more than among those with nodules. However, there are few basic investigations on this subject, and the existing studies do not give firm evidence about the effects of smoking on formation of vocal fold oedema 22 23.

In the present study, family history positive for vocal problems was reported by 11.4% to 28.6% patients, and was most frequent in oedema patients. It has been considered that genetic factors play role in the development of VF nodules, polyps and oedema <sup>34</sup>. There is a possibility that various genes are associated with each of VF disorders – nodules, polyps, edema – and that their expression is influenced by various environmental factors. However, there is also possibility of recall differences between compared groups.

In patients with VF oedema, symptoms other than hoarseness were more frequent (39.7%) than in the other two groups of patients. This can be explained since in a large number of patients with oedema, symptoms lasted more than 12 months before they visited a physician.

In summary, on the basis of mutual comparisons of patients with VF nodules, polyps and oedema, the main characteristics of these three types of vocal fold were as follows: patients with nodules were most frequently

women ≤ 40 years old, with a high-risk occupation (lecturer, singer, actor), with considerable and intensive occupational voice demands, with a similar proportion of ever smokers and non-smokers, and hoarseness as a dominant symptom; patients with polyps were almost equally distributed by gender and age, were most frequently administrative workers, frequently ever smokers and current smokers and had hoarseness as a dominant symptom; patients with oedema were most frequently women 41 or more years old, without or with slightly increased occupational voice demands, almost all were ever smokers and large proportion were current smokers, more than a quarter of them had positive family history on voice problems, and a considerable number had symptoms other than hoarseness.

Besides limitations related to collection of data by the use of the questionnaire, the main limitation is the relatively small number of patients.

#### **Conclusions**

Mutual comparisons of patients with VF nodules, polyps and oedema showed that they differed in several main characteristics. These findings are in agreement with the majority of existing studies and may be of help in future investigations on the aetiology of the disease.

#### **Conflict of interest statement**

None declared.

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#### RHINOLOGY

## The effect of passive smoking on bacterial colonisation of the upper airways and selected laboratory parameters in children

L'effetto del fumo passivo sulla colonizzazione batterica delle alte vie aeree e su determinati parametri di laboratorio nei bambini

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#### **SUMMARY**

Exposure to tobacco smoke is associated with a higher risk of respiratory tract diseases. The aim of this study was to determine the influence of passive smoking on selected characteristics of children with adenoid hypertrophy. Sixty-one children with adenoid hypertrophy were enrolled in the prospective study. Differences in bacterial colonisation of middle nasal meatus and nasopharynx and changes in selected laboratory immune and inflammatory markers according to the tobacco smoke exposure were analysed. Exposure to tobacco smoke was associated with significantly higher colonisation of pathogenic bacteria and polymicrobial growth of pathogenic bacteria ( $\geq 2$  bacteria) in middle nasal meatus compared to non-exposed children (P = 0.045, P = 0.032, respectively). Identification of pathogenic bacteria in the middle nasal meatus did not correlate with isolation of pathogenic bacteria in the nasopharynx in either group of children. Parameters of humoral immunity in serum, IgA and IgG, were detected at higher concentrations in children exposed to tobacco smoke (P = 0.047, P = 0.031, respectively). Differences in selected parameters of cellular immunity in peripheral blood according to passive smoking were not observed. Tobacco smoke exposure is related to increased colonisation by pathogenic bacteria in middle nasal meatus and elevation of IgA and IgG in peripheral blood, but does not seem to influence markers of cellular immunity parameters in children with adenoid hypertrophy. Avoidance of passive smoking could be recommended as a universal preventive strategy against microbial colonisation of the upper airways and development of various inflammatory diseases in children, e.g. adenoid hypertrophy.

KEY WORDS: Mucosal microbiota • Passive smoking • Pathogenic bacteria • Upper airways • Immunity

#### **RIASSUNTO**

L'esposizione al fumo di sigaretta è associato ad un alto rischio di sviluppare malattie del tratto respiratorio. L'obiettivo di questo studio è stato quello di determinare l'influenza del fumo passivo su determinate caratteristiche dei bambini con ipertrofia adenoidea. Sessantuno bambini con ipertrofia adenoidea sono stati arruolati in questo studio prospettico. Sono stati analizzati differenze nella colonizzazione batterica del meato medio e del nasofaringe e cambiamenti di determinati parametri di laboratorio immunologici e di marker dell'infiammazione in relazione all'esposizione al fumo di tabacco. L'esposizione al fumo è stata associata in maniera significativa alla colonizzazione di batteri patogeni e alla crescita polimicrobica di batteri patogeni (≥ 2 batteri) nel meato nasale medio, rispetto ai bambini non esposti (P = 0,045, P = 0,032, rispettivamente). L'identificazioene di batteri patogeni nel meato medio non è stata accompagnata all'isolamento di batteri patogeni nel nasofaringe di entrambi i gruppi di bambini. Parametri sierici dell'immunità umorale, quali IgA e IgG, sono risultati notevolmente più elevati nei bambini esposti (P = 0,047, P = 0,031, rispettivamente). Tuttavia non sono state trovate differenze nei parametri sierici riguardanti l'immunità cellulare. In conclusione l'esposizione al fumo di tabacco sembra essere correlata ad un incremento della colonizzazione da parte di batteri patogeni del meato medio e ad un aumento delle IgA e delle IgG nel sangue periferico, mentre non sembra influenzare i markers dell'immunità cellulare nei bambini con ipertrofia adenoidea. Evitare il fumo passivo dovrebbe essere raccomandato come strategia preventiva universale contro la colonizzazione microbica delle alte vie aeree e lo sviluppo di svariate malattie infiammatorie dei bambini, come ad esempio l'ipertrofia adenoidea.

PAROLE CHIAVE: Microbiota • Fumo passivo • Batteri patogeni • Alte vie respiratorie • Immunità

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#### Introduction

Exposure to environmental tobacco smoke (ETS) is associated with a variety of health effects, including cancer, cardiovascular diseases and/or respiratory illnesses. Tobacco is also a major burden to people who do not smoke. As developing individuals, children are particularly vulnerable to the negative effects of second-hand smoke (SHS). Furthermore, they are unable to influence their own degree of exposure. Worldwide, at least 40% of children are regularly exposed to SHS predisposing them to upper and lower respiratory infections as well as asthma 12. Moreover, long-term exposure to ETS creates a state of permanent inflammation and an imbalance in the lipid profile that leads to lipid accumulation in the blood vessels of the heart and aorta. Children with long-term exposure to ETS may have an elevated risk for the development of premature coronary artery disease <sup>3</sup>. Simonetti et al. <sup>4</sup> found that in healthy children, parental smoking is an independent risk factor for higher blood pressure, adding to other familial and environmental risk factors.

Mucosal microbiota of the upper airways is very important for health and diseases and its development begins suddenly after the birth. Changes in airway microbiota are associated with acute and chronic consequences. There are many positive factors influencing the correct composition of microbiota, e.g. breastfeeding <sup>5</sup>. On the other hand, negative changes of mucosal microbiota may contribute to the development of pathological conditions such as sinusitis, otitis media or chronic airway inflammation <sup>6</sup>. Passive smoking changes the microbial colonisation of the airways 7. It has been shown that nasopharyngeal microbiota is related to the frequency of upper respiratory infection and sinusitis and can be a determinant for infection spread to the lower airways 689. It has been suggested that commensal colonisation may interfere with pathogen colonisation 10. Adenoids serve as a bacterial reservoir for upper airway infections and their removal is followed by changes in upper airway microbiota and a decrease in the rate of respiratory infections 11.

In our prospective study, we aimed to evaluate the modifying effect of passive smoking on selected parameters in children with adenoid hypertrophy indicated for endoscopic adenotomy due to mechanic upper airway obstruction or recurrent respiratory tract infections. Moreover, we studied the effects of passive smoking on the composition of upper airway mucosal microbiota in the nasopharynx and middle nasal meatus.

# Materials and methods

Design of the study

The prospective study was conducted with 61 children divided into 2 groups according to tobacco smoke exposure. All children enrolled in the study were scheduled to endoscopic adenotomy for adenoid hypertrophy (due to mechanic obstruction of upper airways or recurrent respiratory tract infections) at the Department of Otorhinolaryngology, Head and Neck Surgery, Comenius University, Jessenius Faculty of Medicine, University Hospital in Martin, Slovakia.

Children treated with systemic or local antibiotics within the 2 weeks before enrolment, recent respiratory infection, increased level of C-reactive protein and those with recurrent tonsillitis were excluded from the study.

Smoking exposure was recorded according to the questionnaires. Differences in bacterial colonisation of the middle nasal meatus and nasopharynx and changes in humoral and cellular immunity according to tobacco smoke exposure were analysed.

The study was approved by the Ethics Committee of Jessenius Medical Faculty, Comenius University in Martin, Slovakia (EK 1515/2014). An informed consent form was signed by all parents of participating children.

#### Smoking exposure

Only exposure to parental smoking was recorded as parents were considered to be the closest individuals caring for the child. The level of exposure when smokers were other than the parents (e.g. grandparent or sibling) and parent was a non-smoker could not be evaluated and those cases were excluded from the study. Exposure to smoke other than tobacco smoke was not recorded. All the children were from urban areas.

#### Cultivation studies

Middle nasal meatus and nasopharyngeal swab specimens were obtained under endoscopic control by using sterile cotton-wool swabs and transported in Stuart's transport medium to the microbiological laboratory within 2 to 4 hours. The swab was inoculated on Sheep blood agar (Columbia Bio-Rad, Bratislava, Slovakia) and Chocolate agar with bacitracin disc, Mac Conckey agar (Bio-Rad, Bratislava, Slovakia), and placed into a 7% CO<sub>2</sub> incubator at 37° C. Plates were examined after 18 to 24 hours of incubation. The incubation was further extended to 48 hours to detect slow-growing microbes. Identification of colonies at a genus or species level was based upon typical colony morphology by subculture, Gram stain, standard

rapid tests (catalase, pyrrolidonyl aminopeptidase - PYR and oxidase tests), identification by latex agglutination tests and biochemical tests. All pathogenic strains were tested for their susceptibility to antimicrobial agents using the agar diffusion method (by EUCAST) with commercial discs (Oxoid).

Examination of immune parameters in peripheral blood Various parameters and markers of cellular and humoral immunity were evaluated. Venous blood samples were drawn from a peripheral arm vein, collected into an evacuated tube and treated with either EDTA or sodium heparin. The sampling was performed on the day before surgery. White and red components of the blood count were examined by sampling with an 18-parameter haematological ANALYSER Beyer Advia 60 (Siemens AG, Munich, Germany) using the company's reagents. Differential counts of leukocytes, as well as subpopulations of lymphocytes and NK cells, were assessed immediately after sampling. Cells were counted on the flow cytometer FC500 (Beckmann Coulter, Brea, CA, USA) after staining with monoclonal antibodies (Immunotech, Prague, Czech Republic) according to the manufacturer's instructions. A four-colour fluorescent protocol was used with the following composition: CD4+CD19-FITC/ CD8+CD16+CD56-PE/CD3-PC5/CD45-PC7. The absolute counts of all cell populations were calculated from the examined blood count. The following populations, based on the CD45<sup>+</sup> leukocyte gate, were quantified from the CD4 vs. side scatter (SS) cytogram: lymphocytes (low SS), T lymphocytes (CD3+), T helpers (CD3+CD4+), T cytotoxic cells (CD3+8+), B lymphocytes (CD19+) and NK cells (CD3-8+16+56+). Absolute and relative counts of NK cells were also examined on the cytometer using separate analysis parameters (CD8-FITC/CD16+CD56PE/CD-3PC5/CD45PC7). Serum four immunoglobulin isotypes (IgG, IgA, IgM, total IgE) were also examined.

#### Statistical analysis

Frequencies of categorical data were tabulated and evaluated with a chi-square test using Yates's correction. For other data, median and interquartile range was calculated and tested with the Kruskal-Wallis or Mann-Whitney tests. The statistical analysis was performed with STA-TISTICA Cz 10. All conclusions were based on a significance level of P < 0.05.

### Results

Among the 61 children in this study, 23 (37%) were exposed to SHS (14 male, 9 female, mean age  $5.5 \pm 3$  years,

range 2-16). Thirty-eight (63%) children had non-smoking parents (29 male, 9 female, aged  $5.2 \pm 2.8$  years, range 2-16). Bacterial growth was present in 50 of the 61 samples (82%) from the middle nasal meatus and 60 of the 61 samples (98%) from the nasopharynx. Microorganisms isolated from the middle nasal meatus and nasopharynx are presented in Tables I and II. Coagulase-negative Staphylococcus species, Corynebacterium species, Streptococcus viridans and Neisseria species are considered as commensals of the upper respiratory tract. Other species of identified bacteria in our study were considered as pathogens. The pathogenic bacteria in our patients were present in 29 samples (58%) in the middle nasal meatus and 43 (72%) in the nasopharynx (P = 0.133). We found significantly more intense colonisation by pathogenic bacteria in the middle nasal meatus in children exposed to SHS than in children with non-smoking parents (P = 0.045). Polymicrobial growth of pathogens (defined as detection of at least 2 or more pathogens from one sampling site) in the middle nasal meatus was also significantly increased in children exposed to SHS (P = 0.032) (Fig. 1A). In the nasopharynx, there were no significant differences in the presence of commensals, pathogenic bacteria, or polymicrobial growth between children exposed and not exposed to tobacco smoke (Fig. 1B). In children exposed to SHS, Streptococcus pneumoniae was significantly more often isolated from the middle nasal meatus and nasopharynx (P = 0.031, P = 0.004, respectively). Other pathogens, such as Staphylococcus aureus, Haemophilus influenzae and Moraxella catarrhalis, were more often colonised in the middle nasal meatus in children exposed to SHS (P = 0.031, P = 0.001, P = 0.05, respectively) (Table I). Those differences were not observed in the nasopharynx. Identification of pathogenic bacteria in the middle nasal meatus did not correlate with isolation of pathogenic bacteria in the nasopharynx in either group of children. Gramnegative pathogens were isolated significantly more often from the middle nasal meatus in children exposed to SHS compare to gram-positive bacteria (P = 0.018). There were no significant differences in the presence of grampositive and gram-negative bacteria in the nasopharynx between children exposed and not exposed to tobacco smoke (P = 0.723).

Analysing the differences in selected immunological parameters according to the exposure to tobacco smoke, a possible association with passive smoking was found. Significant higher levels of IgA and IgG in peripheral blood were detected in children exposed to SHS compared to children whose parents were non-smokers (P = 0.047, P = 0.031, respectively). Differences in the markers of cellular immunity were not found (Table III).

**Table I.** Bacterial species isolated from middle nasal meatus.

Bacteria	SHS exposed (n = 18)	SHS non-exposed (n = 32)	Р
Gram-positive			
Coagulase-negative Staphylococcus	5 (28%)	10 (31%)	0.667
Corynebacterium species	4 (22%)	7 (30%)	0.621
Streptococcus viridans	3 (16%)	7 (30%)	0.136
Streptococcus pneumoniae	4 (22%)	1 (3%)	0.031
Streptococcus agalactiae	0	0	NA
Streptococcus β-hemolyticus	1 (5%)	0	0.361
Staphylococcus aureus	4 (22%)	1 (3%)	0.031
Staphylococcus aureus MRSA	0	0	NA
Gram-negative			
Neisseria species	2 (11%)	3 (9%)	0.599
Haemophilus influenzae	9 (50%)	2 (6%)	0.001
Moraxella catarrhalis	6 (33%)	4 (12%)	0.051
Polymicrobial growth*	6 (33%)	1 (3%)	0.032

SHS: second hand smoke; MRSA: methicillin-resistant Staphylococcus aureus; n: number of patient; NA: not applicable.

Table II. Bacterial species isolated from nasopharynx.

Bacteria	SHS exposed (n = 23)	SHS non-exposed (n = 37)	Р
Gram-positive			
Coagulase-negative Staphylococcus	1 (4%)	4 (11%)	0.379
Corynebacterium species	1 (4%)	1 (3%)	0.693
Streptococcus viridans	18 (78%)	26 (70%)	0.703
Streptococcus pneumoniae	8 (35%)	2 (5%)	0.004
Streptococcus agalactiae	0	1 (3%)	0.617
Streptococcus β-hemolyticus	1 (4%)	0	0.383
Staphylococcus aureus	6 (26%)	9 (24%)	0.576
Staphylococcus aureus MRSA	0	0	NA
Gram-negative			
Neisseria species	7 (30%)	15 (40%)	0.607
Haemophilus influenzae	10 (43%)	15 (40%)	0.521
Moraxella catarrhalis	5 (22%)	7 (19%)	0.791
Polymicrobial growth*	8 (35%)	14 (38%)	0.978

SHS: second hand smoke; MRSA: methicillin-resistant Staphylococcus aureus; n: number of patient; NA: not applicable.

# **Discussion**

Exposure to tobacco smoke has many harmful effects on the health status of exposed children. In our prospective study in a group of children with adenoid hypertrophy, we analysed the influence of passive smoking on mucosal microbiota and selected laboratory parameters. We were able to detect various significant changes and differences associated with exposure to tobacco smoke. Passive smoking was associated with increased colonisation with pathogenic bacteria and polymicrobial growth in the upper airways. Due to chronic stimulation of mucosal immunity, children exposed to tobacco smoke had higher serum levels of IgG and IgA, although no changes were observed in the cellular part of immunity.

Second-hand tobacco smoke consists of exhaled smoke

<sup>\*</sup> Detection of  $\geq 2$  pathogenic bacteria from one sampling site in one patient.

<sup>\*</sup> Detection of  $\geq 2$  pathogenic bacteria from one sampling site in one patient.

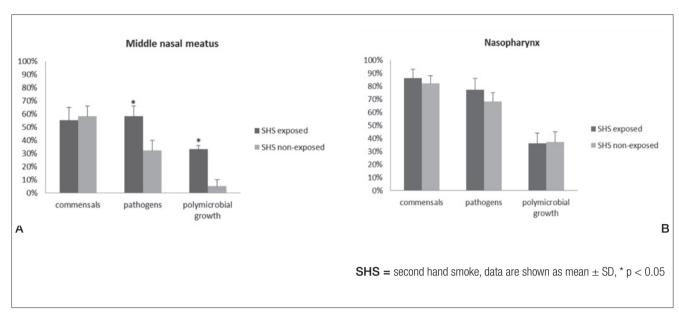


Fig. 1. Differences in microbial isolation and tobacco smoke exposure.

Table III. Differences in humoral and cellular immunity according to the second hand smoke exposure. Data are shown as mean  $\pm$  SD.

Immune parameter	SHS exposed	SHS non-exposed	Р
IgG [g/L]	$9.87 \pm 2.56$	$8.43 \pm 1.79$	0.031
<b>IgA</b> [g/L]	$1.13 \pm 0.39$	$0.86 \pm 0.46$	0.047
IgM [g/L]	$0.95 \pm 0.38$	$0.89 \pm 0.38$	0.477
<b>C3</b> [g/L]	$1.16 \pm 0.19$	$1.16 \pm 0.22$	0.952
<b>C4</b> [g/L]	$0.25 \pm 0.13$	$0.21 \pm 0.07$	0.249
IgE [IU/L]	$58.94 \pm 76.73$	$32.09 \pm 29.63$	0.566
Leucocytes [10 <sup>6</sup> /L]	$7.77 \pm 1.46$	$7.80 \pm 2.82$	0.340
Neutrophils [106/L]	$3.15 \pm 1.08$	$3.04 \pm 0.83$	0.979
Lymphocytes [10 <sup>6</sup> /L]	$3.66 \pm 0.84$	$3.84 \pm 2.15$	0.548
Monocytes [10 <sup>6</sup> /L]	$0.65 \pm 0.19$	$0.70 \pm 0.27$	0.603
Eosinophils [10 <sup>6</sup> /L]	$0.39 \pm 0.36$	$0.25 \pm 0.15$	0.566
Basophils [106/L]	$0.05 \pm 0.05$	$0.05 \pm 0.05$	0.862
CD3+ T lymphocytes [109/L]	$2508.77 \pm 701.03$	$2589.93 \pm 146.70$	0.430
CD19+ B lymphocytes [109/L]	$627.38 \pm 185.84$	$656.72 \pm 345.82$	0.786
CD3+CD4+ T lymphocytes [109/L]	$1330.46 \pm 377.87$	$1374.03 \pm 645.44$	0.596
CD3+CD8+ T lymphocytes [109/L]	$1026.69 \pm 399.34$	$990.52 \pm 694.42$	0.169
CD15+CD56+ NK cells [109/L]	$462.69 \pm 242.76$	$527.66 \pm 438.57$	0.849
CD4:CD8 ratio	$1.39 \pm 0.32$	$1.48 \pm 0.47$	0.751

Ig: immunoglobulin; C3 and C4: parts of complement system; NK cells: natural killer cells.

as well as side-stream smoke that is released from the burning cigarette between inhalations, which has a very similar composition. In children, exposure to smoking is associated with upper and lower respiratory tract diseases, such as acute otitis media, asthma, wheezing, cough, bronchitis, pneumonia and impaired pulmonary function <sup>12</sup>. Both smoking and exposure to tobacco smoke in the household are associated with carriage of bacteria, such as *Neisseria meningitidis* <sup>13</sup>. In children, the intensity of exposure to environmental smoking correlates with

respiratory infection rates, especially if the parent smokes in the same room as the child <sup>14</sup>. In young children, *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* are the most common bacterial pathogens that cause respiratory infections, such as acute otitis media and pneumonia, as well as invasive infections, such as bacteraemia and meningitis <sup>7</sup>. Adenoid hypertrophy is a common pathological condition in early childhood and is frequently associated with upper respiratory tract obstruction (leading to e.g. obstructive sleep apnoea syndrome) <sup>15</sup> and recurrent respiratory tract infections. Based on our results, passive smoking had a negative influence on selected parameters in children with adenoid hypertrophy, and could therefore represent an avoidable factor that can complicate the clinical status of these children.

Colonisation of organisms is the first step toward development of respiratory diseases. Therefore, recognition of risk factors for colonisation is important. However, data are sparse with regards to the influence of smoking on rates of nasal and nasopharyngeal colonisation with these organisms in children and adults. In the present study, we demonstrated that children exposed to smoking by parents had a significantly higher rate of pathogenic bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Staphylococcus aureus) carriage than did children who were not exposed to tobacco smoke. The increased carriage rate in individuals exposed to tobacco smoke was seen in the middle nasal meatus, but not in nasopharyngeal specimens. The differences between these two sites were found also by Rawling et al. (2013) 16. Increased nasal colonisation by pathogenic bacteria may be a predisposing factor to additional spread, resulting in lower respiratory tract infections. This could be further increased during coinfection with respiratory viruses, such as influenza viruses, in children <sup>17</sup>. In a recent study, it was shown that colonisation with Staphylococcus may be also beneficial to some extent, since it counteracts otopathogens 10. Despite the fact that we did not study the effect of bacterial colonisation and passive smoking on the frequency of respiratory infections, our findings might explain previous reports demonstrating that children exposed to environmental tobacco smoke more frequently experience respiratory infections, such as acute otitis media and pneumonia 7 14. Increased polymicrobial growth of pathogens in the upper respiratory tract in children exposed to SHS compared with children born to non-smoking parents found in our study also confirmed the role of tobacco smoke in the pathogenesis of respiratory tract infections in those children in early childhood.

The mechanism by which smoking and passive exposure

to tobacco smoke is associated with carriage of potentially pathogenic bacteria is not fully understood. One of the possible explanations is based on mucociliary transport alterations. Several studies have shown that cigarette smoke significantly reduces the ciliary beat of respiratory epithelial cells both in vitro 18 and in vivo 19. Moreover, Tamashiro et al. (2009) found that exposure of tobacco smoke impaired ciliogenesis in a dose-dependent manner in murine sinonasal epithelial cell culture <sup>20</sup>. Cigarette smoking is also associated with profound changes in the mechanisms of mucous production. Chronic exposure to tobacco smoke causes respiratory epithelium metaplasia with increased number and size of goblet cells and, consequently, increased mucous secretion in the upper respiratory tract. Furthermore, tobacco smoke also inhibits interleukin 8 and human β-defensin in sinonasal epithelial cell cultures derived from patients with CRS 21. These findings suggest that cigarette smoke may have a suppressive function on sinonasal innate immunity. Taken together, more intense colonisation of upper respiratory tract by pathogenic bacteria might be a result of impaired local defence mechanisms of respiratory mucosa. Moreover, respiratory pathogens (e.g. Streptococcus pneumoniae) are associated with increased adherence to respiratory epithelial cells in chronic exposure to cigarette smoke <sup>22</sup>.

This study also demonstrated that gram-negative bacteria were significantly more often isolated from the middle nasal meatus in children exposed to SHS compared to non-exposed children. Similar to our results, Ertel et al. (1991) showed that the respiratory system of adult smokers is preferentially colonised by gram-negative bacilli. This is explained by better resistance of gram-negative bacteria to cigarette smoke compared to gram-positive ones <sup>23</sup>.

On the other hand, only *Streptococcus pneumoniae* was found more often in the nasopharynx in children exposed to SHS compared to non-exposed children. Differences in other pathogens according to tobacco exposure were not observed. One explanation for this finding is the study population. All children in the present study underwent surgical treatment due to adenoid hypertrophy. Pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are most commonly detected bacteria in adenoid tissue <sup>24</sup>. Therefore, we assume that colonisation by pathogens was up-regulated due to adenoid hypertrophy, and thus the possible differences between tobacco exposure and pathogens in nasopharynx in children with adenoid hypertrophy could not be manifested.

In our study, we observed an effect of passive smoking on markers of systemic humoral immunity (IgG and IgA), which were increased in children regularly exposed to tobacco smoke compared to non-exposed children. There are only a few reports on the effects of passive and active smoking on humoral mucosal and systemic immunity in the literature. It has been shown that smokers may have increased 25 but also decreased concentrations of IgA in saliva <sup>26</sup>. Exposure of cigarette smoke supports the activation of innate immunity (e.g. Toll-like receptors, neutrophils) with possible effects on parameters of adaptive humoral immunity <sup>27</sup>. On the other hand, tobacco smoke increases the susceptibility of respiratory mucosa to various viruses and bacteria 28, which can contribute to the recurrent respiratory infections, chronic stimulation of mucosal immune system and its hypertrophy. Hypertrophic lymphoid tissue in the upper airways is associated with increased levels of saliva IgA 29. Maternal smoking increases chronic upper respiratory symptoms and saliva IgA levels in children <sup>30</sup>. The increased levels of IgA and IgG in peripheral blood observed in our children might be therefore attributed to the chronic stimulation of lymphoid tissue of upper airways due to recurrent respiratory infections, which can be the result of exposure to passive smoke. Moreover, this activation of humoral immunity can also be supported by chronic inflammation induced by exposure to tobacco smoke. Passive smoking was also shown to be a risk factor for the development of adenoid hypertrophy in another study 31. Recently, it was shown that adenoid tissue is related to a Th-2 deviated immune response. This could aggravate the harmful effect of passive smoking on mucosal immunity and microbial colonization 32. It was further shown that smoking induces nasopharyngeal lymphoid hyperplasia, and therefore passive smoking could also be considered as a risk factor for development of adenoid hypertrophy <sup>33</sup>. Another important contributing mechanism of passive smoking is the induction of persistent oxidative stress and endothelial dysfunction <sup>34</sup>.

# **Conclusions**

Tobacco smoke exposure is related to increased colonisation by pathogenic bacteria in the middle nasal meatus, but not in the nasopharynx. Identification of bacteria from the middle nasal meatus did not correlate with isolation of pathogenic bacteria from the nasopharynx. The upper respiratory tract is preferentially colonised by gram-negative bacteria in children exposed to second hand smoke. Chronic passive smoking alters the composition of upper airway mucosal microbiota and thus contributes to the development of several pathological conditions. Exposure to tobacco smoke leads to elevation of IgA and IgG in peripheral blood, but does not influence markers of cellular immunity in children. Therefore, it can be suggested that avoidance of passive smoking represents a universal strat-

egy for prevention of different inflammatory conditions in children and could be recommended as a standard part of complex management of children with recurrent respiratory tract infections and adenoid hypertrophy.

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#### Conflict of interest statement

None declared.

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#### MAXILLO FACIAL SURGERY

# Trans-nasal endoscopic and intra-oral combined approach for odontogenic cysts

Approccio combinato trans-nasale endoscopico e intra-orale alle cisti odontogene

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#### **SUMMARY**

Maxillary cysts are a common finding in maxillofacial surgery, dentistry and otolaryngology. Treatment is surgical; a traditional approach includes Caldwell-Luc and other intra-oral approaches. In this article, we analyse the outcomes of 9 patients operated on using a combined intra-oral and trans-nasal approach to the aforementioned disease. Although the number of patients is small, the good results of this study suggest that the combined approach might be a reliable treatment option.

KEY WORDS: Maxillary cysts • Maxillofacial surgery • Otolaryngology • Trans-nasal endoscopic surgery

#### **RIASSUNTO**

Le cisti mascellari sono un'evenienza comune nella pratica clinica degli specialisti del settore Odontoiatrico maxillo-Facciale e Otorinolaringoiatrico. Il trattamento della patologia è esclusivamente chirurgico. Tradizionalmente gli approcci chirurgici descritti per il trattamento di questa patologia sono di tipo intra-orale (ad esempio la chirurgia secondo Caldwell-Luc, mutuata dalla chirurgia per la sinusite). In questo articolo basato sulla revisione retrospettiva di 9 pazienti operati con approccio combinato per cisti del seno mascellare, abbiamo analizzato i risultati di questa procedura. Anche se il numero dei pazienti è esiguo e i risultati sono da validare su un campione più ampio, il risultato di perfetta guarigione, i dati sul tempo di ospedalizzazione e la mancanza di gravi complicazioni suggeriscono che il trattamento sia valido.

PAROLE CHIAVE: Cisti mascellari • Chirurgia maxillo-facciale • Otorinolaringoiatria • Chirurgia endoscopica trans-nasale

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#### Introduction

Odontogenic cysts are a common pathological finding in oral and maxillofacial surgery. The most common are radicular cysts, followed by dentigerous cysts and odontogenic keratocysts <sup>1</sup>.

Maxillary cysts can expand through maxillary sinus walls causing subtotal or total occupation of the sinus, and can also reach the nasal floor and nasal septum. Nasal obstruction, sinusitis, infraorbital nerve dysfunction, disruption of the normal bone profile of the maxilla, the nasal floor or the medial wall of the maxillary sinus are possible consequences <sup>2</sup>.

Imaging plays a key role in the diagnosis of maxillary odontogenic cysts, which are usually characterised by

eroding neo-formations that tend to erode the maxillary bone and/or dislocate cranially the floor of the maxillary sinus. Hypo-dense areas of these cysts are in continuity with one or more teeth, which can be included in case of follicular odontogenic cysts or in continuity with dental root/s in case of odontogenic inflammatory cysts. If these signs are present, mucocele can be excluded, since it usually does not erode the maxillary bone or alter cortical bone. Differential diagnosis between ameloblastoma and keratocyst is not simple using radiographical images alone. There are some characteristics that are suggestive and can be used during the diagnostic phase: ameloblastomas tend to erode the dental root, while odontogenic cysts tend to not do so. In the end, the only definitive diagnosis is made by biopsy.

Maxillary odontogenic cyst and neoplasm have been treated for the last decades by open trans-oral or trans-facial surgical approaches <sup>3-5</sup> keratocystic odontogenic tumour (KCOT). These procedures require a trans-oral incision and most of the affected teeth are extracted alongside with the cyst walls. Morbidity includes oroantral fistulas, need for extensive reconstruction, loss of surrounding dentition and chronic rhinosinusitis <sup>6</sup>.

Trans-nasal endoscopy has been recently described as a useful surgical option in several approaches to the facial skeleton and skull base; however, the exclusive endoscopic trans-nasal approach for odontogenic cyst is seldom possible. Endoscopy provides less invasive surgery and high definition direct view on the lesions <sup>7 8</sup>, and therefore a combined trans-nasal and trans-oral approach was chosen to treat the dental pathology in the same surgical session. This series describes the use of a combined endoscopic trans-oral and trans-nasal surgical approach for the management of large maxillary odontogenic cysts.

# Description of the clinical technique

Nine patients diagnosed with maxillary odontogenic cyst were referred to our department and operated on between March 2013 and June 2017. Informed consent was obtained from all patients. Due to the retrospective nature of the study, it was granted exemption by the Verona University institutional review board. Seven patients presented with a cyst born in the maxillary sinus, one patient presented with a cyst of the premaxilla and one presented a large lesion of the infratemporal fossa.

Oral health was accurately investigated looking for active dental pathologies such as periodontitis, caries, etc. Each patient was administered a preoperative SNOT20 questionnaire. Most patients reported few nonspecific symptoms like swelling and mild pain. However, when asked specific questions (as those present in the SNOT20) their score was suggestive for a specialist consult, and interestingly these symptoms, and the related SNOT20 score, did not correlate with severity of disease.

All patients underwent the same preoperative examination: Panorex and CT of the maxillofacial complex and paranasal sinuses; CT scans were evaluated to asses Lund-Mackay score for each subject. The radiological examination allowed to establish the precise boundaries of the lesion that the surgeon would find during the endoscopic dissection (Fig. 1).

Patients underwent surgery after a preoperative antibiotic therapy with ciprofloxacin (500 mg/day for 7 days).

Surgery started with the trans-nasal endoscopic approach. Nasal cavities and paranasal sinuses were thoroughly ex-



Fig. 1. Maxillary cyst CT scan coronal view.

plored and analysed to evaluate extension of the disease and possible presence of sinusitis. A direct 4 mm 0°,45° or 70° endoscope was used (Karl Storz GmbH & Dr. Co KG, Tuttlingen, Germany).

In case of clear pathological involvement of the paranasal sinuses, anterior and posterior ethmoidectomy and frontal sinusotomy were performed. Once the anatomical key-points were identified, a maxillary antrostomy was performed allowing the surgeon to directly reach the medial-posterior side of the lesion occupying the maxillary sinus.

The unattached portion of the maxillary cyst was delivered from the lateral and anterior side of the sinus and debulked. In order to access the inferior portion of the maxillary sinus, an endoscopic maxillary mega-antrostomy was performed in the standard fashion 9 poor mucociliary clearance may result from long-standing inflammation or scarring from previous surgery. This subset of patients often has persistent sinus disease despite medical therapy and adequate antrostomy: endoscopic maxillary mega antrostomy (EMMA).

In case of lesions invading the bony structure of the premaxilla, the nasal floor was accurately investigated to detect any mucosal or bone defect.

Once endoscopic dissection had been performed, a crestal incision was sculptured to elevate a mucoperiosteal flap and expose the lateral aspect of the maxillary bone and the underlying neoplasm. In four cases, teeth involved in the lesions were extracted at this point; the cysts were then dissected from the residual maxillary bone (Fig. 2).

In one patient, the lesion involved 10 teeth (1.5 to 2.5). In this case, the endoscope was used to magnify periapical lesions to obtain accurate dissection of the lesions from teeth.



Fig. 2. Maxillary cyst endoscopic view: the cyst is mobilised from the medial wall of the maxillary sinus.

In one patient, the lesion was located in the pterygo-palatine fossa and the posterior wall of the maxillary sinus was anteriorly displaced. Endoscopic transnasal maxillectomy type 2 was performed according to Turri-Zanoni et al. <sup>11</sup>, and a pre-lacrimal approach was considered inadequate to treat this particular case as it did not grant appropriate control over the pathology. In case of a lesion invading the posterior maxillary sinus, MRI is mandatory to evaluate involvement of the pterygoid muscles and nervous structures that are in close relationship with the fossa. In this case, the lesion had an expansive nature and did not erode the cranial base, but invaded the orbit. For these reasons, the authors decided to proceed with the combined technique trans-nasal and intra-oral approach, otherwise radical surgery was not considered possible (Figs. 3, 4).

Any residual sharp bony edge was smoothed by round burrs. An ipsilateral buccal fat pad flap was harvested in five cases to close the bony defect. The buccal fat pad flap was sutured to the residual edges of the maxilla with a multilayer suture technique. The size of the buccal fat pad flap was sufficient to achieve a complete and tension-free closure of the bony defect (Fig. 5).

In case of peri-nasal soft tissue dissection, the intervention contemplated the skeletonisation of the piriform and possibly the anterior nasal spine. It is advisable to use an alar cinch suture to obtain a surgical alar base correct repositioning <sup>10</sup>.

Postoperative antibiotic therapy with amoxicillin and clavulanic acid (3 x 875 mg + 125 mg/day for 7 days) was administered, soft diet and frequent chlorhexidine mouthwashes were suggested. Nasal pads were removed 72 hours after surgery and intraoral sutures were removed 15 days after surgery.

A CT scan was performed at 3 months after surgery to reasses the Lund-Mackay score, and a new SNOT20 questionnaire was administered at three months after surgery. In order to restore the natural clearance of the maxillary

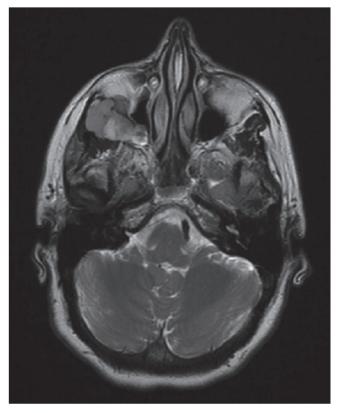


Fig. 3. Preoperative MRI.

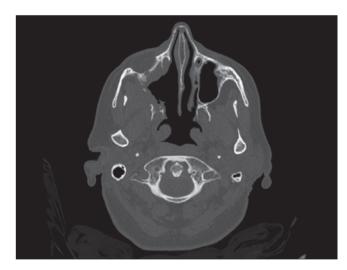
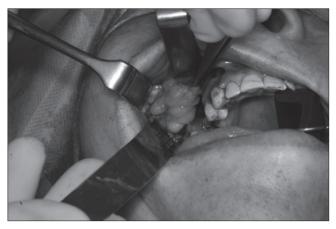


Fig. 4. Postoperatice CT scan.

sinus and prevent rhino-sinusal problems the ostium of the maxillary sinus was enlarged as suggested by present day literature <sup>11</sup>.

Postoperative Lund-MacKay scores were compared with preoperative scores and showed significant improvement. Comparison between preoperative and postoperative



**Fig. 5.** Buccal fat pad flap is mobilised and sutured to the maxillary bone to reconstruct the defect.

SNOT20 questionnaires showed a substantial reduction, with an improvement in quality of life (Table I).

Patients were followed monthly for 6 to 18 months, and no radiological complication occurred during postoperative follow-up. There were some postoperative complications such as malar oedema in all cases and malar haematoma in 6 cases. In one case the patient complained of infraorbital transient paraesthesia that spontaneously resolved at about 6 months after surgery.

#### **Conclusions**

A traditional surgical approach to odontogenic lesions is the trans-oral or trans-facial approach. Although the open approach allows a direct view of the lesions, it does not provide a clear vision of the medial and posterior sides of the lesion. Moreover, if the paranasal sinuses are not completely analysed during surgery it is possible that the lesion is not completely eradicated and therefore sinusitis could occur or relapse in a short time.

Table I. Patient data.

Patient	Gender	Age	Surgery	Final diagnosis	Location	Preoperative Lund-Macay	Postoperative Lund-Macay	Preoperative SN0T20	Postoperative SN0T20
AA	Male	48	Combined transnasal-intraoral, BFPF used	Odontogenic inflammatory cyst	Maxillary sinus, tooth 1.8	2	0	25	12
IA	Male	46	Combined transnasal-intraoral, BFPF used	Odontogenic cyst	Maxillary sinus, tooth 1.6	2	0	30	15
CA	Male	52	Combined transnasal-intraoral, Extraction 2.6-2.8	Odontogenic inflammatory cyst	Maxillary sinus, teeth 2.6-2.8	2	0	28	13
NE	Female	27	Combined transnasal-intraoral, Extraction 1.5, 1.6, mucosal scroll flap used	Odontogenic inflammatory cyst	Maxillary sinus, teeth 1.5, 1.6	2	0	32	14
RM	Female	50	Combined transnasal-intraoral, BFPF used	Odontogenic inflammatory cyst	Maxillary sinus, teeth 1.5-1.7	2	0	35	16
CZ	Male	50	Combined transnasal-intraoral, Extraction 1.7, Apicectomy 1.4	Odontogenic cyst	Maxillary sinus, teeth 1.6, 1.7	2	0	36	16
PG	Male	69	Extraction 3.6, Apicectomy 1.3, 1.4, 2.3, 2.4, mucosal scroll flap used	Giant radicular cyst	Maxillary sinus, nasal cavities, nasal septum, teeth 1.5-2.5	2	0	35	18
PM	Female	57	Combined transnasal-intraoral	Keratocyst	Maxillary sinus, infratemporal fossa	2	0	30	14
CM	Male	41	Combined transnasal-intraoral	Odontogenic inflammatory cyst	Maxillary sinus, theeth 1.6-1.7	2	0	27	13

A traditional surgical approach does not allow any type of adequate correction of nasal and paranasal sinus anatomy unless wide antrostomy is performed; however, wide antrostomy without an endoscopic approach is associated with an increased risk of postoperative complications.

Intraoral or external approaches require incisions through the oral mucosal or, in case of large lesions, directly through the skin with possible functional and/or aesthetic consequences.

On the other hand, an exclusive trans-nasal approach is characterised by some disadvantages such as the inability to remove all cyst remnants in some cases.

If a combined approach is necessary, the trans-nasal approach may decrease the extent of trans-oral dissection required to remove the entire lesion as most lesions can be removed transnasally, and small remnants may be removed transorally.

This technique has already been used for odontogenic neoplasms since it allows to perform extended resection of the neoplasm in the maxillary sinuses and consequently prevention of local recurrence <sup>12</sup>.

Several reconstruction procedures have been described to correct secondary maxillary atrophy <sup>13 14</sup> or fill the residual bony defect after odontogenic cyst removal <sup>15 16</sup>, but this technique does not require secondary reconstruction procedures. Reconstruction, when necessary, is carried out using a buccal fat pad flap during the same session.

Cooperation between maxillo-facial and otolaryngologists is strongly recommended to obtain the most comprehensive treatment for the patient affected by cysts localised in the paranasal sinuses, orbit and skull-base <sup>17-19</sup>. The present experience is based on an effective collaboration between maxillofacial and ENT surgeons skilled in both endoscopy and oral surgery.

The combined endoscopic trans-oral and trans-nasal approach grants complete coverage of any pathological situation inside the paranasal sinuses and allows the surgeon to deal with it better, due to improved visualisation. The surgeon can manage the entire premaxillary region with complete control of the residual space inside the bone, and it is also possible to directly manage any eventual defect in the nasal floor or nasal septum involvement.

The combined trans-oral and trans-nasal endoscopic approach can reach complete control of the superior, posterior wall of the maxillary sinus. If associated with a mega-antrostomy or endoscopic modified medial maxillectomy, it allows complete examination of the maxillary sinus and, if necessary, a path to the infratemporal fossa (Fig. 6).

In the present case series, there were no complications of traditional procedures such as oroantral fistulas or maxillary sinusitis. In the end, the treatment was less invasive

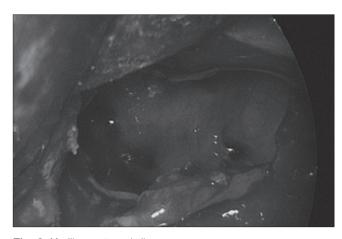


Fig. 6. Maxillary cyst eggshell.

with less morbidity. An endoscopic approach in the treatment of maxillary cysts may be helpful as both an exclusive and combined approach to obtain better magnification and a wider view of the pathology with minimally-invasive surgery. The number of patients is low and therefore our results are not statistically significant. Thus, further studies are necessary, even if the results of complete healing in all our patients, compared with a review of present literature, suggests that this treatment might be a reliable option.

#### Conflict of interest statement

None declared.

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#### AUDIOLOGY

# Cochlear implantation in far-advanced otosclerosis: hearing results and complications

Impianto cocleare nell'otosclerosi in fase avanzata: risultati uditivi e complicanze

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#### **SUMMARY**

Severe forms of otosclerosis known as far-advanced otosclerosis (FAO) can lead to severe to profound sensorineural hearing loss and can justify cochlear implantation. Because of the pathophysiology of otosclerosis, patients implanted for FAO may experience an increased rate of complications, such as facial nerve stimulation or electrode dislocation, and may have poorer hearing outcomes than expected. This retrospective study aimed to compare cochlear implantation hearing outcomes, surgical difficulties and complications in FAO patients versus non-FAO patients. Moreover, we evaluated whether high resolution computed tomography (CT scan) findings were predictive of perioperative problems, complications and hearing outcomes. FAO patients were diagnosed based on medical history, examination and CT scan. Thirty-five ears from FAO patients were compared to 38 control ears. Audiometric results were assessed at least 12 months after implantation by pure tone average, speech reception threshold, monosyllabic and disyllabic word recognition score (WRS) and Central Institute for the Deaf (CID) sentences test. Complications and surgical difficulties were compiled. CT scan findings were categorised within 3 grades of otosclerotic extension. No significant difference was found between FAO and non-FAO hearing outcomes, except that monosyllabic WRS were lower for FAO patients, especially those who underwent previous stapedotomy. Facial nerve symptomatology occurred in 8.6% of FAO patients; among these, one required explantation-reimplantation surgery. 86% of FAO implanted patients had retrofenestral extension on CT. These were associated with poorer disyllabic WRS (51% vs 68%, p < 0.05) than those with only fenestral involvement. Although not significant, high grade of severity on CT tended to be associated with surgical difficulties and complications. Cochlear implantation in FAO patients is an effective treatment technique. Though the overall complication rate is low, it tends to be higher in cases of severe extension on CT.

KEY WORDS: Cochlear implantation • Otosclerosis • Speech perception • Computed tomography • Facial nerve injuries

#### **RIASSUNTO**

Molte forme di otosclerosi, riconosciute come far-advanced otosclerosis (FAO) presentano un'ipoacusia neurosensoriale grave o profonda, e possono giustificare un impianto cocleare. A causa della fisiopatologia stessa dell'otosclerosi, i pazienti impiantati per FAO potrebbero andare incontro più frequentemente a complicanze, come stimolazione del nervo faciale, dislocazione dell'elettrodo, e potrebbero avere dei risultati uditivi peggiori rispetto a quelli attesi. Questo studio retrospettivo si è posto l'obiettivo di confrontare i risultati uditivi dell'impianto cocleare, le difficoltà chirurgiche e le complicanze tra pazienti con FAO e pazienti senza FAO. Inoltre, abbiamo valutato se la TC ad alta risoluzione fosse predittiva di problemi perioperatori, complicanze, e risultati uditivi. Trentacinque orecchie dei pazienti con FAO sono state confrontate con 38 orecchie di controllo. I risultati audiometrici sono stati valutati almeno 12 mesi dopo l'impianto attraverso la soglia media per toni puri e la soglia di ricezione del linguaggio, il "monosyllabic and disyllabic word recognition score" (WRS) e il "Central Institute for the Deaf sentences test" (CID). Sono state annotate le complicanze e le difficoltà chirurgiche. I quadri TC sono stati classificati in tre gradi di estensione otosclerotica. Non sono state riscontrate differenze significative tra i risultati audiometrici dei pazienti con FAO e dei pazienti senza FAO, ad eccezione del WRS monosillabico, più basso nei pazienti con FAO, specialmente in coloro sottoposti precedentemente a stapedotomia. Segni e sintomi riferibili a danni del nervo faciale si sono verificati nell'8,6% dei pazienti con FAO; tra questi, un solo paziente è stato sottoposto a chirurgia di espianto-reimpianto. L'86% dei pazienti con FAO impiantati avevano un'otosclerosi retrofenestrale alle immagini TC, il che si associava ad un WRS bisillabico inferiore (51% vs 68%, p < 0,05) rispetto ai pazienti con coinvolgimento esclusivamente fenestrale. Quadri TC gravi tendevano ad associarsi a difficoltà chirurgiche e complicanze, anche se non in maniera statisticamente significativa. In conclusione l'impianto cocleare nei pazienti con FAO è un'opzione di trattamento efficace. Benché il tasso di complicanze sia basso, queste tendono ad aumentare in caso di quadri severi alla TC.

PAROLE CHIAVE: Impianto cocleare • Otosclerosi • Percezione del linguaggio • Tomografia computerizzata • Danni del nervo faciale

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### Introduction

Otosclerosis is an osteodystrophy that affects the bone of the otic capsule. In a normal inner ear, this bone is supposed to be free from osteoclastic and osteoblastic phenomenon. However, otosclerosis is associated with a continuous process of osteolysis and osteogenesis leading to a peculiar histology including vascular proliferation, bone resorption and new formation of connective tissue stroma <sup>12</sup>. The mean prevalence in the Caucasian population is 1/3000. According to pathophysiological research, several aetiological factors may be involved, including heredity, genetics, hormones and viral infection <sup>3</sup>.

Otosclerosis prefers the fissula ante fenestram. When it reaches the footplate, conductive hearing loss appears: at this stage of the disease, hearing aids or stapedotomy, or both, are generally indicated to improve hearing.

In about 10% of the otosclerotic population sensorineural hearing loss occurs <sup>45</sup>, concomitant with the progression of the osteodystrophy to the lateral wall of the cochlear endosteum. One hypothesis postulates that the atrophy of the stria vascularis and spiral ligament, which leads to an ionic perturbation of the endolymph, is responsible for hair cell dysfunction <sup>26</sup>.

In 1961, House and Sheehy described FAO as a clinical diagnosis of otosclerosis associated with an air-conduction threshold above 85 dB without a measurable bone conduction threshold <sup>7</sup>. In 2011, Merkus et al. <sup>8</sup> added the necessity of a speech reception threshold (SRT) decrease. When sensorineural hearing loss is profound and WRS is under 50% at 60 dB with efficient hearing aids, the patient may meet clinical cochlear implantation criteria. Thus, at the FAO stage, management algorithms include stapedotomy in addition to efficient hearing aids, or cochlear implantation.

As shown in several studies describing hearing improvement after stapedotomy in patients with severe to profound hearing loss, stapedotomy combined with hearing aids does not lead to many complications, and is relatively low cost, efficient and effective (post-operative disyllabic WRS at 60 dB = 50.6% for Kabbara et al.) <sup>9</sup>. Moreover, stapes surgery does not preclude further cochlear implantation <sup>49 10</sup>.

Nevertheless, cochlear implantation is also effective in the management of severe to profound congenital or acquired hearing loss, including otosclerosis. Thanks to the standardisation of the procedure, the complication rate is low and audiometric outcomes continue to improve (disyllabic WRS at 60 dB = 72.8% for Kabbara et al.) <sup>9</sup>. However, among all the various aetiologies requiring cochlear implantation, FAO suffers from a relatively high rate of

complications, most commonly electrode dislocation and facial nerve stimulation. The latter may be the result of current flow from the electrode to the facial nerve because of the lower impedance of the otosclerotic bone between the facial nerve canal and the upper basal turn of the cochlea 9 11. Thus, the management of FAO patients remains difficult, as the clinician and patient must balance audiometric outcomes, complication rates and economic issues. Most studies evaluating cochlear implantation in otosclerosis have not taken into account radiologic criteria for diagnosis of disease. Therefore, the incidence of complications for cochlear implantation in the otosclerotic population might have been overestimated or underestimated due to sampling error. Typically, only post-mortem histological findings can objectively confirm a diagnosis of otosclerosis. Consequently, during a patient's lifetime a diagnosis can be suspected when certain criteria such as radiological findings are met. As the sensitivity and specificity of high resolution CT in otosclerosis are 95% and 99% respectively (according to Marx et al.) 12, the probability of having severe otosclerosis like FAO in the presence of a normal CT scan is low. CT confirms the otosclerotic focus, and can rule out other causes of conductive or mixed hearing loss with a normal tympanic membrane: fixation of the head of the malleus to the wall of the tympanic cavity, dystrophy or blocking of the ossicular chain, or inner ear malformation. Consequently, CT is now fundamental in the initial workup of otosclerosis. In addition, MRI is often performed on implant candidates to evaluate endosteal involvement and exclude a retro-cochlear pathology.

This study aimed to evaluate cochlear implantation outcomes in FAO patients whose diagnosis was supported by CT findings, and to compare audiometric outcomes, complication rates and peri-operative problems with a non-FAO control group. In addition, we analysed whether preoperative radiological findings were predictive of adverse effects and hearing outcomes.

#### Materials and methods

This is a retrospective study including adult implanted patients from our centre operated on from 1997 to 2015.

#### Patient selection

A diagnosis of FAO was made using typical clinical history of progressive hearing loss, normal otoscopic examination, audiometry showing a severe to profound hearing loss without acoustic reflex and typical CT findings. Patients with normal or absent radiologic data were excluded. Patients who previously underwent stapes surgery were included.

26 FAO patients were compared to a non-FAO control group of 30 post-lingually deafened patients selected from the same cochlear implant database. The two groups were comparable for sex, age at implantation, period of implantation and time of hearing deprivation, and the control group was implanted for other aetiologies than otosclerosis (e.g., progressive idiopathic, progressive familial, traumatic, or Menière's disease). They all had undergone standard evaluation before cochlear implantation and met criteria for implantation: a severe to profound sensorineural hearing loss associated with a speech discrimination threshold under 50% for words at 60 dB with efficient hearing aids.

#### Surgical technique

Two experienced members of our surgical team performed the surgery under general anaesthesia. Facial nerve monitoring was used in all cases. In most cases, a facial recess approach was performed in order to access the round window. When a bony wall made the access to the round window membrane difficult, it was carefully drilled out; if ossification of the basal turn was encountered, a drill-out was performed until luminal permeability was found. After local steroid injection, the electrode array was inserted into the scala tympani using minimally traumatic techniques. Finally, the internal receiver/stimulator was fixed in a subperiosteal temporal pocket and the ground electrode, if present, was placed underneath the temporalis muscle. The position of the electrode array was confirmed by skull radiography immediately after the procedure. Surgical findings such as round window ossification, incomplete insertion, or misplacement of the electrode array were recorded. Devices from four manufacturers were implanted. Only straight electrode arrays were used.

#### Outcome assessment

Demographic and clinical data such as sex, deafness aetiology, age of implantation, time of hearing deprivation and previous stapes surgery were recorded. The following audiometric data were collected in our department at least 12 months after implantation: post-operative pure tone average (mean PTA, calculated by averaging the airconduction thresholds at 500, 1000 and 2000 Hz), speech reception threshold (SRT) as the decibel level at which 50% of words could be repeated by the subject, monosyllabic and disyllabic WRS and a French translated version of the CID sentences test. Words and sentences were presented at 60 dB.

Adverse effects such as facial palsy or stimulation (even if temporary), vertigo, tinnitus, dysgeusia, or infections, as reported in the medical record during follow-up clinical appointments, were compiled. For bilaterally implanted patients, surgeries had been performed sequentially, and each ear was considered independently.

#### Imaging data

High resolution CT scans of temporal bones were analysed by three experienced neuroradiologists. FAO patients were classified in three grades as follows: grade 1, otosclerotic focus anterior to the oval window or thickened footplate; grade 2, patchy retrofenestral involvement of the disease to the cochlea or around the cochlear otic capsule; grade 3, diffuse involvement to the otic capsule. These grades correspond to the main categories of Rotteveel's <sup>13 14</sup> radiographic classification.

#### Data analysis

As demographic and audiometric data of both groups did not follow a normal distribution, we used non-parametric tests such as the Mann-Whitney U-test, Wilcoxon signed-rank test and Fisher's exact test to compare them. In order to evaluate the correlation between CT scan grade and hearing performance, we used the non-parametric Kruskal-Wallis test. Age, time of hearing deprivation and hearing outcomes are expressed as means  $\pm$  SD. The level of statistical significance was p < 0.05.

#### Results

#### Demographic data

26 patients with 35 implanted ears (9 bilaterally implanted) were included in the FAO group. Among these, 8 had previous stapedotomy. Thirty non-otosclerotic patients with 38 implanted ears (8 bilaterally implanted) were selected as controls.

Considering each ear independently, the two groups did not differ for age at implantation (59 years  $\pm$  8 in the FAO group, 55 years  $\pm$  9 in the non-FAO group, Wilcoxon test p = 0.10), sex ratio (FAO SR = 1.18, non-FAO SR = 0.9, Fisher's exact test p = 0.55), or time of hearing deprivation (3.5 years  $\pm$  7.8 in the FAO group, 1.5 years  $\pm$  3.6 in the non-FAO group, Wilcoxon test p = 0.08). Detailed demographic data are presented in Table I.

### Peri- and post-operative clinical data

Surgical difficulties were encountered in 18 of the 73 implanted ears (24.6%): 3 FAO patients (2 CT scan grade 2, 1 grade 3) necessitate round window or basal turn extra drilling until the scala tympani was properly identified, 1 FAO patient (grade 2) with electrode misplacement and 8 incomplete electrode insertions in the FAO group (1 grade 1, 2 grade 2, 5 grade 3). In addition, there were 6 incom-

plete electrode insertions in the non-FAO group. Detailed data for the FAO group are presented in Table I.

The difference in incidence of surgical difficulty between both groups was not significant (Fisher's exact test p = 0.10). In addition, no significant correlation was found between the severity of the CT scan and incidence of surgical complications (Kruskal-Wallis test p > 0.05).

Facial symptomatology occurred in both groups: temporary facial palsy occurred in 2 FAO patients, classified grade 2 and 3 on CT scan, and in one non-FAO patient. One FAO patient had persistent facial nerve stimulation even after deactivation of several electrodes; this patient required a revision surgery. He was classified grade 3 on CT scan.

**Table I.** Demographic, radiographic and surgical data for the FAO group.

N	Bilateral	Gender	Age at implantation (year)	Hearing deprivation (year)	CT grade	Incomplete insertion	Stapedotomy	Facial symptomatology	Electrode dislocation	Cochlear ossification
1	Υ	M	60	20	3	N	N	N	N	N
2	Υ	M	62	0	1	N	Υ	N	N	N
3	N	F	62	0	2	N	N	Υ	N	N
4	Υ	M	53	3	2	Υ	N	N	N	Υ
5	Υ	M	53	3	2	N	N	N	N	Υ
6	N	F	56	1	2	N	N	N	N	N
7	N	M	51	1	1	N	N	N	N	N
8	N	M	66	0	3	N	N	N	N	Υ
9	N	F	70	0	3	Υ	Υ	N	N	N
10	Υ	M	49	10	3	N	N	N	N	N
11	Υ	M	53	0,5	3	N	N	N	N	N
12	Υ	M	72	0	3	N	N	N	N	N
13	Υ	M	75	0	3	Υ	Υ	N	N	N
14	N	F	69	0	3	Υ	N	N	N	N
15	N	F	53	0	3	N	N	N	N	N
16	N	F	52	0	2	Υ	N	N	N	N
17	N	F	49	1	1	N	N	N	N	N
18	N	F	58	0	3	N	N	N	N	N
19	N	F	71	0	3	N	Υ	N	N	N
20	Υ	F	47	0	3	N	N	N	N	N
21	Υ	F	58	10	3	N	N	N	N	N
22	Υ	F	66	0	1	Υ	N	N	N	N
23	Υ	F	62	10	1	N	Υ	N	N	N
24	Υ	M	66	2	3	N	N	N	N	N
25	Υ	M	67	0	2	N	N	N	N	N
26	Υ	M	54	0	2	N	N	N	Υ	N
27	Υ	M	54	0	2	N	N	N	N	N
28	N	F	69	39	3	N	N	N	N	N
29	N	M	62	1	2	N	N	N	N	N
30	N	M	47	1	2	N	N	N	N	N
31	N	F	46	5	3	N	Υ	N	N	N
32	Υ	M	45	1	3	N	N	Υ	N	N
33	Υ	M	60	15	3	Υ	Υ	Υ	N	N
34	N	M	64	0	2	Υ	N	N	N	N
35	N	F	50	0	3	N	Υ	N	N	N

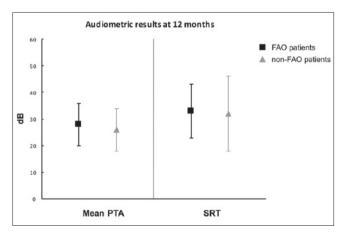
Bilateral, ears from bilaterally implanted patients; Y, Yes; N, No.

Four patients required revision surgery within a year following the initial surgery. Three of these were in the FAO group: one the day after the implant surgery for electrode dislocation in the superior semi-circular canal (grade 2), one because of facial nerve stimulation (grade 3) and one for infection 6 months after surgery. One patient in the non-FAO group also required revision surgery for infection.

Patients did not complain of dysgeusia or vertigo. Sixty-three percent of implanted patients suffered from preoperative tinnitus (26 in the FAO group, 20 in the non-FAO group), while after surgery only 37% complained of tinnitus (14 FAO patients, 13 non-FAO patients). This improvement was significant (Mann Whitney p = 0.001) but there was no association between aetiology of deafness and presence of preoperative tinnitus (Fischer exact test p > 0.05), hearing outcomes, or presence of post-operative tinnitus (Mann Whitney p > 0.05 for all comparisons).

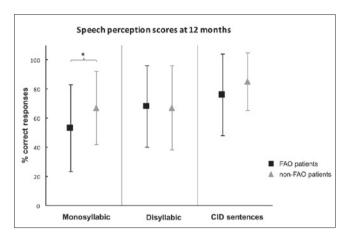
#### Hearing outcomes

Twelve months after surgery the mean PTA was  $28 \text{ dB} \pm 8$  in the FAO group and  $26 \text{ dB} \pm 8$  in the non-FAO group. The mean SRT was  $33 \text{ dB} \pm 10$  and  $32 \text{ dB} \pm 14$  in the FAO and non-FAO group, respectively (Fig. 1). In the FAO group the mean monosyllabic, disyllabic and CID sentences recognition scores were  $53\% \pm 30$ ,  $68\% \pm 28$ , and  $76\% \pm 28$ , respectively. In the non-FAO group, they were  $67\% \pm 25$ ,  $67\% \pm 29$ , and  $85\% \pm 20$ , respectively (Fig. 2). There was no statistical difference between both groups for hearing outcomes (Mann-Whitney p > 0.05 for each comparison) except for the monosyllabic WRS which was



**Fig. 1.** Audiometric results at 12 months for far-advanced otosclerosis (FAO, black squares) and non-FAO (grey triangles) patients. Mean PTA: averaged pure tone audiometric thresholds at 500, 1000 and 2000 Hz (in dB); SRT: speech reception threshold.

Comparative analysis was performed and found no significant difference between groups (Mann-Whitney, p>0.05).



**Fig. 2.** Mean speech perception scores at 12 months for far-advanced otosclerosis (FAO, black squares) and non-FAO (grey triangles) patients. The percentage of correct responses is shown for monosyllabic words, disyllabic words and Central Institute for the Deaf sentences (CID); Comparative analysis on each score revealed a significant difference between FAO and non-FAO patients for monosyllabic word recognition score (Mann-Whitney, p < 0.05).

significantly better in the non-FAO group (Mann-Whitney p = 0.042).

Within the FAO group, patients who underwent previous stapedotomy had poorer audiometric outcomes than the other FAO patients, with mean PTA 30 dB  $\pm$  4 vs 27 dB  $\pm$  8, SRT 39 dB  $\pm$  10 vs 31 dB  $\pm$  8, monosyllabic WRS 30%  $\pm$  26 vs 60%  $\pm$  27, disyllabic WRS 47%  $\pm$  35 vs 74%  $\pm$  23, and CID sentences score 54%  $\pm$  38 vs  $82\% \pm 21$ . Only the monosyllabic WRS showed a significant difference (Mann Whitney p = 0.013). This difference remained significant even when comparing FAO / previous stapedotomy to all other FAO and non-FAO patients (Mann Whitney p = 0.003). Demographic analysis revealed a slightly higher mean age at implantation in the group of FAO patients with stapedotomy than in the others: 62 years vs 57 years in FAO patients without previous stapedotomy (Mann Whitney p = 0.25) and 55 years in non-FAO patients (p = 0.07). There was no statistically significant difference in radiographic CT grade severity between patients with or without previous stapedotomy (6 grade 3, 2 grade 1, Chi Square p = 0.09).

Overall, hearing outcomes were slightly better when the electrode insertion was complete than when it was partial: mean PTA 26 dB  $\pm 7$  vs 31 dB  $\pm 8$  (Mann Whitney p = 0.07), SRT 32 dB  $\pm 13$  vs 34 dB  $\pm 7$  (p = 0.26), monosyllabic WRS 63%  $\pm 26$  vs 49%  $\pm 34$  (p = 0.13), disyllabic WRS 69%  $\pm 28$  vs 62%  $\pm 26$  (p = 0.33) and CID sentences score 84%  $\pm 22$  vs 68%  $\pm 29$  (p = 0.046).

Considering each ear independently, ears from bilaterally implanted patients had significantly better audiomet-

ric performance than ears from unilaterally implanted ones: mean PTA 24 dB  $\pm$  7 vs 30 dB  $\pm$  7 (Mann Whitney p = 0.001), SRT 27 dB  $\pm$  8 vs 37 dB  $\pm$  13 (p < 0.001), monosyllabic WRS 65%  $\pm$  25 vs 57%  $\pm$  30 (p > 0.05), disyllabic WRS 75%  $\pm$  25 vs 61%  $\pm$  29 (p = 0.037) and CID sentences score 88%  $\pm$  20 vs 74%  $\pm$  26 (p = 0.002).

#### CT findings

The CT results of the 35 otosclerotic ears are noted in Table I. Five ears (14.3%) had only fenestral disease (grade 1), 11 ears (31.4%) had a localised retrofenestral disease (grade 2) and 19 ears (54.3%) had a diffuse retrofenestral disease with or without fenestral damage (grade 3).

There were no significant differences in hearing outcomes between the 3 grades (Kruskal-Wallis p > 0.05) although patients from grades 2 and 3 showed poorer performances on all the scores. The division into fenestral (grade 1) and retrofenestral (grades 2 and 3) categories showed a significantly lower disyllabic WRS for patients with retrofenestral involvement on CT scan ( $68\% \pm 13 \ vs \ 51\% \pm 28$ , Mann-Whitney p = 0.023).

Although surgical difficulties and facial symptomatology were most encountered in CT grade 2 and 3, no significant correlation could be shown between the retrofenestral damage on CT scan and these adverse effects (Fischer's exact test p = 0.64 and p = 0.62).

#### Discussion

Our results reaffirm that cochlear implantation constitutes an efficient solution in patients with FAO. Indeed, our findings revealed no difference between FAO and non-FAO implanted patients on standard measures such as disyllabic and CID sentences at 12 months. Scores were similar to those encountered in the literature 469 15 16. However, it is noteworthy that analysis of monosyllabic WRS uncovered significant differences between groups and subgroups not otherwise revealed in other studies. We found a significantly lower monosyllabic WRS in the FAO group than in the non-FAO group, and within the former group we found a lower monosyllabic WRS for patients who underwent previous stapedotomy. The discrepancy between disyllabic and monosyllabic results can be partly explained by the well-known ceiling effect with disyllabic or sentences scores in quiet <sup>17</sup>. In our study, 23% and 35% of subjects scored 100% on the disyllabic and CID sentence recognition test, respectively, compared with only 8% of subjects who achieved the maximum score on the monosyllabic WRS. In contrast, in a small population, Castillo et al. 4 noted a statistically better monosyllabic WRS for FAO patients. Sainz et al. <sup>6</sup> found a similar trend as we have, though it was not statistically significant. In order to improve outcomes for implantation in post-stapedotomy FAO patients, it would be helpful to confirm our result in a larger sample and to determine the extent to which differences in speech understanding are related to pathophysiologic factors.

Several authors now recommend stapedotomy before potential cochlear implantation in FAO patients. This attitude has been reinforced by a recent meta-analysis on stapedotomy in cochlear implant candidates with FAO. In that study, van Loon et al. <sup>18</sup> showed that in 60 of 83 patients (72%), post-operative speech recognition scores with hearing aid were higher than 50% after stapedotomy, and those patients were actually no longer CI candidates. Their mean speech recognition score after stapedotomy was 59% (including words or sentences, monosyllabic, and disyllabic tests), which can be compared to the mean monosyllabic, disyllabic and sentences post-implantation scores reported in the present study of 53%, 68% and 76% respectively.

Regarding prognosis for patients who need cochlear implantation after stapedotomy, our results for monosyllabic WRS contradict the general consensus, based on disyllabic WRS <sup>10</sup>, that stapedotomy does not compromise further cochlear implantation <sup>9</sup>. Furthermore, it is noteworthy that in this study patients with stapedotomy were older at time of implantation and tended to present with a higher grade of severity on CT scan. This could be explained by the initial effectiveness of stapedotomy plus hearing aids that may delay cochlear implantation.

In this study, we chose stringent radiographic criteria for diagnosis of otosclerosis. As expected, our FAO patient distribution within CT grade differs from other studies as we did not consider those with normal CT scan as otosclerotic patients. Nevertheless, the trend was similar, as most of the patients (86%) who required cochlear implant had retrofenestral involvement <sup>10</sup> <sup>11</sup> <sup>13</sup> <sup>16</sup>.

To date, there is no universally accepted computed tomography classification for otosclerosis. Rotteveel's criteria rely on histological extension of the otosclerotic lesion to the footplate, cochlear endosteum, and otic capsule. This type of classification was initially created to evaluate stapedotomy as treatment of otosclerosis. Although it is inspired by several histological studies that revealed discrepancies in the association between localization of anatomical foci and hearing outcomes or facial nerve stimulation <sup>1</sup> <sup>12</sup> <sup>19</sup>, Rotteveel et al. showed no correlation between duration of sensorineural hearing loss and endosteum extension, though extension was associated with a younger age at deafness onset <sup>13</sup>. In our study, the severity

of the CT scan grade seemed to be related to poorer auditory outcomes, but this relationship was not statistically significant. However, the trend was statistically confirmed with analysis of the disyllabic WRS when CT grades were grouped into fenestral and retrofenestral categories, regardless of cochlear endosteum involvement, as proposed by Lagleyre et al. <sup>20</sup> and Marx et al. <sup>12</sup>.

The distinction between fenestral and retrofenestral involvement allowed us to show that retrofenestral involvement is a negative predictive factor for disyllabic WRS. However, this radiological distinction did not predict surgical difficulties or facial nerve symptomatology. These results are contrary to the conclusions of Semaan et al. 21, who showed in a similar study that the presence of CT scan (and especially retrofenestral) abnormalities did not predict hearing outcome in cochlear implantation for FAO. However, in that study, only 26.4% of the FAO patients had pre-operative radiographic abnormalities, which seems different from the reported sensitivity of 95% for CT scan findings of otosclerosis 12. Furthermore, their results were based on a comparison between patients with and without CT scan abnormalities; our study instead evaluates different grades of lesions among only those patients who have pathological imaging.

Surgical difficulties such as cochlear ossification, incomplete electrode insertion and electrode misplacement seemed to be encountered more frequently in the FAO group (34% vs 15%) and especially in cases of retrofenestral involvement on CT scan, but our sample may be too small to find a statistically significant correlation between these rare complications and the aetiology of deafness. Overall complication rates in this review were less than or similar to most other studies <sup>69 22</sup>.

Using solely straight electrodes, we observed facial nerve symptomatology in 8.6% of our patients with FAO, which is less than that shown in some other series  $(25-75\% ^{23} ^{24})$ , but similar to that obtained by Mosnier et al. and Sainz et al. 6 15. However, one of our FAO patients required revision surgery for resistant facial nerve stimulation; as far as we know, this type of complication is quite rare as few cases are noted in the literature 5 25 26. In addition, within the FAO group, facial nerve symptomatology occurred only in patients with retrofenestral disease on CT scan. This is concordant with the hypothetical pathophysiology of facial nerve stimulation in otosclerotic implanted patients: otic capsule involvement on CT scan might be the radiologic translation of the histologic findings of this dysplastic bone between the facial nerve canal and the upper basal turn of the cochlea leading to decreased impedance between these structures 2 11. Although not significant, this trend should be taken into account when warning otosclerotic patients of the potential risk of facial symptomatology.

Finally, we noticed higher scores from the ears of bilaterally implanted patients than from unilaterally implanted ones. We found no predictive factor in their demographic data. De Seta et al. <sup>27</sup> showed that speech performance of the poorer ear continues to improve between 1 and 5 years after bilateral simultaneous implantation, whereas such an improvement is not observed after 1 year in unilateral implantation. One possible explanation could be related to the benefit of long-term increased stimulation of cortical auditory areas in bilaterally implanted patients <sup>28</sup> <sup>29</sup>. Nonetheless, we cannot ignore that there may be a sampling bias as our bilaterally implanted candidates were usually selected from good unilateral performers.

#### **Conclusions**

Based on standard evaluation scores, cochlear implantation in far advanced otosclerosis provides as good auditory outcomes as implantation in any aetiology. Even though surgical difficulties and complication rates are still low, they tend to be higher in patients with otosclerosis, especially in cases of severe extension shown by computed tomography. Patient information should be adjusted accordingly. Cochlear implantation in FAO patients can be considered as an effective and safe rehabilitation technique and should be proposed when stapedotomy and efficient hearing aids are no longer effective.

#### Conflict of interest statement

None declared.

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#### AUDIOLOGY

# Prediction of hearing recovery in sudden deafness treated with intratympanic steroids

Previsione delle possibilità di recupero uditivo nell'ipoacusia improvvisa trattata con steroidi intratimpanici

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#### **SUMMARY**

The present study aims to obtain a probability model allowing prediction of auditory recovery in patients affected by sudden sensorineural hearing loss treated exclusively with intratympanic steroids. A monocentric retrospective chart review of 381 patients has been performed. A Probit model was used to investigate the correlation between the success of treatment (marked or total recovery according to Furuashi's criteria) and the delay between onset of disease and beginning of therapy. The age of patients and audiometric curve shapes were included in the analysis. The results show that delay is negatively correlated with variable success. Considering the entire sample, each day of delay decreases the probability of success by 3%. The prediction model shows that for each day that passes from the onset of the disease the probability of success declines in absence of the medical treatment, hence we conclude that early treatment is strongly recommended.

KEY WORDS: Hearing loss • Sensorineural • Prognosis • Recovery • Audiometry • Steroids

#### **RIASSUNTO**

Il presente studio ha lo scopo di ottenere un modello di probabilità che consenta di prevedere il recupero uditivo nei pazienti affetti da ipoacusia improvvisa neurosensoriale trattati esclusivamente con steroidi intratimpanici. È stata realizzata una revisione retrospettica dei dati di 381 pazienti. Un modello Probit è stato utilizzato per studiare la correlazione tra il successo del trattamento ("marked" or "total recovery" secondo i criteri di Furuashi) e il ritardo (Delay) tra l'insorgenza della malattia e l'inizio della terapia. Sono stati inclusi nell'analisi i dati relativi all'età dei pazienti e alle curve audiometriche. Dallo studio è emerso che la variabile Delay è negativamente correlata con la variabile successo. Considerando l'intero campione, ogni giorno di ritardo diminuisce del 3% la probabilità di successo. Il modello di previsione mostra che per ogni giorno che passa dal momento della comparsa della malattia, la probabilità di successo declina in assenza dell'intervento; possiamo quindi concludere che il trattamento precoce è fortemente raccomandato.

PAROLE CHIAVE: Ipoacusia • Neurosensoriale • Prognosi • Recupero • Audiometria • Steroidi

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#### Introduction

Idiopathic sudden sensorineural hearing loss (SSNHL) is defined as a decrease of hearing affecting 3 or more frequencies by 30 dB or greater over 72 hours or less with no identifiable aetiology.

During 2006 and 2007, the annual incidence of SSNHL was 27 per 100,000 in the United States. The incidence increased with age, ranging from 11 per 100,000 for patients younger than 18 years to 77 per 100,000 for patients

aged 65 years and older. There was an overall slight male preponderance with a male-to-female ratio of 1.07:1. This was more pronounced in patients aged 65 years and older, with a ratio of 1.30:1 <sup>1</sup>.

The aetiology and natural history of SSNHL are still obscure; many studies investigated the percentage of spontaneous recovery that ranges between 30 and 65% of cases <sup>2</sup>. However, the real number of patients that recover spontaneously from SSNHL is currently unknown, since many who recover spontaneously within the first days do not

seek medical treatment. Therefore, the boundary between spontaneous recovery and the efficacy of early medical therapy is still controversial, making the treatment of this condition a current matter of debate <sup>3 4</sup>.

Various therapies have been proposed without a universally accepted standard protocol. Corticosteroids, antiviral agents, vasodilators, hyperbaric oxygen therapy (HBOT), anticoagulants, anti-inflammatory drugs and other approaches have been suggested, alone or combined, with variable percentages of efficacy reported in literature <sup>5-9</sup>.

Despite the controversies in the medical management of SSNHL <sup>10</sup> <sup>11</sup>, systemic steroid therapy is currently the most widely accepted treatment <sup>12-14</sup>; however, the high dose required for systemic treatment can lead to early and late complications.

Intratympanic (IT) steroid therapy can potentially provide organ-specific treatment with application of high doses of drug directly in the middle ear over the round window membrane, thereby avoiding the adverse effects of systemic corticosteroid therapy <sup>15-18</sup>. The efficacy of IT steroid therapy has already been demonstrated in prospective, randomised, placebo-controlled trials <sup>15-19</sup>. Moreover, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines for SSNHL recommend that clinicians should offer IT steroid perfusion when patients have incomplete recovery from SSNHL after failure of initial management <sup>14</sup>.

The existing scientific literature sets the timeframe within which maximum recovery may occur from few days to several months, complicating the evaluation of the efficacy of treatment compared to the natural history of the disease. Early steroid treatment has been shown to give greater chances of recovery, especially if performed within the first two weeks from onset; however, timely treatment often does not happen, as *delay* in diagnosis is a common issue in SSNHL. Moreover, SSNHL can present in different audiometric curves, each having a different course of disease and response to therapy <sup>18</sup>.

To date, the influence of the time to initiation of treatment on hearing prognosis has not been clearly established. The aim of this retrospective study was to propose a probability model that allows predicting the course of auditory recovery in patients suffering from SSNHL treated with IT steroid therapy as first-line treatment. To define the model, we have analysed the course of SSNHL in all patients treated in the last 5 years in a tertiary referral centre, dividing them according to the timing of initiation of therapy, and considering 4 different audiometric curves of presentation.

#### Materials and methods

The medical charts of 401 patients diagnosed with SS-NHL in the Otolaryngology Department of our Hospital from January 2009 to January 2014 were retrospectively reviewed. Since the present was a retrospective observational study, the institutional ethics committee did not require formal approval. All patients were affected by unilateral SSNHL and treated on an outpatient basis with IT steroid therapy as first-line therapy. The following data were extracted: patient demographics; delay between onset of symptoms and beginning of therapy; audiometric data. We excluded patients lost to follow-up and patients with a subsequent diagnosis of Meniere's disease or cerebellopontine angle tumour (MRI was performed in all patients to rule out a retrocochlear pathology). Overall, 381 patients were included in the study. All patients provided informed consent for the use of clinical data.

#### Audiometric data

Patients were evaluated using standardised methods for pure tone threshold audiometry. Pure tone average (PTA) was calculated as the mean of thresholds at 6 frequencies (250; 500; 1,000; 2,000; 4,000 and 8,000 Hz). Thresholds that could not be measured due to the limit of the audiometric equipment were "dummy coded" with the highest test level of audiometric equipment (5 patients), as suggested in previous studies <sup>12 19</sup>. In the present series, this limit was set at 130 dB HL. Based on the PTA of the pre-treatment audiometric test, patients were distributed into four audiometric curve groups: up-sloping (low frequencies affected), down-sloping (high frequencies affected), flat moderate to severe (all frequencies involved with PTA between 40 and 90 dB) and profound (flat audiogram with PTA more than 90 dB).

The evaluation of hearing improvement was performed using Furuhashi criteria <sup>20</sup> (Table I). The outcomes were classified as successful treatment (complete recovery or marked improvement), slight improvement, or no recovery.

**Table I.** Furuhashi's criteria used to define audiological improvement <sup>20</sup>.

Table I. Fururiasiii's Crite	na useu to define addiological improvement 23.								
Complete recovery *	PTA ** ≤ 25 dB or identical to the contralateral, non-affected ear								
Marked improvement *	PTA improvement > 30 dB								
Slight improvement	PTA improvement between 10 and 30 dB								
No recovery	PTA improvement < 10 dB								
* O									

<sup>\*</sup> Complete recovery or marked improvement = successful treatment; \*\* PTA = six-frequency pure-tone average (250; 500; 1,000; 2,000; 4,000; 8,000 Hz).

#### Therapeutic protocol

The therapeutic protocol consisted in the IT administration of Prednisolone (Deltacortene Sol®, Bruno Farmaceutici, Rome, Italy) at a dose of 0.4 ml of 62.5 mg/ ml, once a day for 3 consecutive days. The IT injection procedure, already described in a previous study <sup>6</sup>, was performed on an outpatient basis. The integrity of the tympanic membrane was evaluated with the aid of a microscope. Local anaesthesia was performed by means of a cotton-sponge soaked with 10% lidocaine solution (Xylocaine, 10 mg/dose, AstraZeneca Korea, Seoul, Korea) placed on the tympanic membrane. The sponge was removed after 20 minutes and the external canal was cleared of any remaining fluid. Patients were placed in a supine position, with their head tilted 40-45° to the healthy side and then a 25-gauge spinal needle was introduced in the posterior-inferior quadrant of the tympanic membrane. The steroid saline solution was gently perfused into the middle ear. Following the injection, patients were asked to avoid moving their head, speaking or swallowing for 30 minutes.

#### Statistical analysis

Our dataset is a cross section of 381 observations, each one reporting information for a single patient.

The main objective was to investigate the relationship between the *success* variable and the interval between the onset of the sudden deafness and the beginning of treatment (named *delay*). The data includes only treated patients but there is heterogeneity in their behavior, and therefore we could estimate the correlation between *delay* and *success*. Given the nature of *success*, which is a dichotomous variable expressing the event of a therapeutic *success*, it seems obvious to specify a non-linear model. Hence, we used a Probit model for our cross section of individual. Our baseline specification was

$$Pr(Y(i) = 1|X(i)) = \Phi(X(i)*\beta) \{1\}$$

where Pr represents probability, and  $\Phi$  is the Cumulative Distribution Function of the standard normal distribution. The parameters  $\beta$  are estimated by maximum likelihood. X is the matrix of covariates that include age, delay and female.

Another variable has been added to the X matrix, which may help to understand the role of *delay* as a determinant of the *success* rate. We called this variable *delay-square*, which is computed as the square of *delay*.

We have defined such a covariate because we believe that the effect of delaying one day can be very heterogeneous over time. Precisely, we believe that a one-day *delay* at the second day from the onset of SSNHL cannot be compared, in terms of predicted probability of *success*, to a one-day delay occurring after 30 days from onset. What we expect is that the probability of success decreases quickly during the first days and then decreases more slowly as time passes. Thus, the variable *delay* will capture the negative linear trend of probability over time (i.e. delaying one day is expected to be always better than delaying one week) and delay-square will capture a difference in the slope of the predicted probability over time (i.e. a one day delay at the first day from the onset will decrease the probability of success by more than a one-day delay after a week from the onset). We expect to find a negative and significant sign for delay, while we expect a positive and significant sign for delay-square. Moreover, such specifications allow better determination of when the therapy will likely be unsuccessful, and therefore of how many days of delay are tolerable to provide a successful treatment.

Model {1} has been applied to several sub-samples. We have firstly developed a general model including all the observations in the sample; afterwards, we divided the sample according to the variable *pattern*. This is a categorical variable with 4 values: up-sloping, down-sloping, flat moderate to severe and profound.

#### **Results**

Three-hundred eighty-one patients were included in the present study. The mean age was  $50.7 \pm 16$  years (range: 11-92 years). The sample included 168 females (44.1%) and 213 males (65.9%), the mean *delay* was 17.5 days  $\pm$  19. A standard deviation of 19.5 days for this variable shows very heterogeneous patient behaviour. The variable *delay* has a median of 9 days and a maximum of 100; a large part of our sample presented during the first week after SSNHL onset.

Overall, the therapy had a *success* rate of 47.2%; however, a standard deviation of 0.49 for this variable suggests that the probability of having a positive outcome is a complex event that should be related to specific individual characteristics.

Table II shows the summary of statistics for the main variables used for the analysis: *age* of the patient; *delay*, indicating the number of days between the onset of SSNHL and the beginning of IT therapy; two dummy variables, *female* = 1 when the patient is female gender, and *success* = 1 when the outcome of the Furuhashi index collected at the end of the therapy showed a complete or marked recovery.

Considering the 4 different audiometric curves, we supposed that the probability of *success* may be heterogeneous within the different patterns, and thus we can use the different values of *success* rate to identify different sub-

**Table II.** Main variables analysed in the present study.

	Age	Female	Delay	Success
Mean	50.72	44.6%	17.56	47.26%
p50	50	0	9	0
Min	11	0	1	0
Max	92	1	100	1
SD	16.212	0.497	19.502	0.499

p 50: median; min: minimum value; max: maximum value; SD: standard deviation; age: age of the patient; delay: number of days between the onset of SSNHL and the beginning of IT therapy; two dummy variables, female = 1 when the patient is female gender, and success = 1 when the outcome of the Furuhashi index collected at the end of the therapy shows a complete or marked recovery.

populations. We also expect that the *delay* coefficients will be very different over the different patterns. Thus, the treatment will heterogeneously affect the different subpopulations.

Table III shows the marginal effects from the Probit regressions for the equation {1}. Marginal effect is a way of estimating how much the event *probability* changes when a given predictor is changed by one unit. In our study, the marginal effect of the covariates is defined as the change in success rate when a covariate changes by one unit. Column 1 includes the data concerning the whole sample, and columns 2 to 5 show results for the different sub-samples; precisely the sub-samples are tailored on different patterns (i.e. flat moderate to severe, up-sloping, down-sloping, profound). The results show that delay and delay-square are highly significant in columns 1 to 3, and delay is significant in columns 1 to 4. These results can be deduced by the number of observations in each sample. Therefore, it is expected that the first column shows strongly significant results.

In our sample, *females* showed a greater tendency to recover compared to men. This difference is around 10% on average in the entire sample; in the *profound* pattern group, *females* showed 30% more probability of *success* 

than men. Age appeared to be always negatively correlated with the probability of success.

The predicted probability of *success* generated by the specified model, slightly different among the different samples, is between 0.40 and 0.54. In particular, the upsloping pattern (0.54) appeared to be the one with higher chances of recovery. On the base of the aforementioned results, a probability model was realised to exploit the statistical model; Table IV shows the chances of *success* predicted by this model considering five age classes for different *delay* values. For instance, patients aged between 31 and 50 years have a probability of recovery of 77% if the treatment is initiated after one day from the onset of SSNHL, this probability decreases to 50% if the treatment begins after two weeks from SSNHL onset.

#### **Discussion**

SSNHL treatment is a matter of evolving debate. While the current standard of care is widely recognised to be corticosteroid therapy 12 13 21, the course of disease has not yet been defined with certainty. Recently, a meta-analysis was carried out to investigate the comparison between IT and systemic steroids. Han et al. compared the efficacy of combination therapy (combined IT and systemic use of steroids) with systemic steroid therapy as primary treatment for SSNHL 22. A total of 14 randomised controlled trials were selected, including 756 subjects allocated to combined therapy and 638 to systemic steroids. The analysis revealed that combined therapy seems to confer a certain degree of benefit as primary treatment of SSNHL compared with only systemic treatment. In a randomised, triple-blind, controlled trial in 2017 <sup>23</sup> on 112 patients, 32 received IT corticosteroids, 45 received systemic corticosteroids and 35 received a combination of the two. No differences were found in hearing recovery between the three therapeutic approaches. These results are in line

**Table III.** Marginal effects from the Probit regressions for the equation {1}.

Covariate	(1) ME Whole sample	(2) ME Flat moderate to severe	(3) ME Up-sloping	(4) ME Down-sloping	(5) ME Profound
Delay	- 0.028 *** (0.0489)	- 0.044 *** (0.0087)	- 0.056 ** (0.0281)	- 0.0280 ** (0.0131)	- 0.0133 (0.0197)
Delaysq	+ 0.0001 *** (0.0000)	+ 0.0003 *** (0.0001)	+ 0.0007 * (0.0004)	+ 0.0001 (0.0002)	+ 0.0000 (0.0004)
Female	+ 0.1024 * (0.0604)	+ 0.1333 (0.1006)	+ 0.1336 (0.2199)	+ 0.0157 (0.1148)	+ 0.2869 *** (0.1325)
Age	- 0.0058 *** (0.0183)	- 0.0043 (0.0031)	- 0.0259 *** (0.0107)	- 0.0066 * (0.0036)	- 0.0017 (0.0036)
Predicted probability of success	0.45	0.40	0.54	0.40	0.43

ME: marginal effect; Standard error in parentheses; \*\*\* p < 0.01; \*\* p < 0.05; \* p < 0.1.

Table IV. Probability of success predicted by the model considering five age classes and four audiometric curves, at different delay endpoints.

	DAY 1	DAY 2	Day 3 to 5	Day 6 to 10												
Age (years)	U	D	F	P	U	D	F	Р	U	D	F	Р	U	D	F	Р
16-30	1	0.85	0.94	0.7	1	0.84	0.9	0.49	0.99	0.79	0.86	0.52	0.97	0.69	0.72	0.44
31-50	0.97	0.76	0.87	0.55	0.97	0.76	0.87	0.51	0.93	0.71	0.81	0.48	0.84	0.61	0.69	0.46
51-65	0.88	0.71	0.87	0.6	0.68	0.64	0.78	0.47	0.70	0.62	0.76	0.46	0.56	0.52	0.64	0.46
Over 65	0.47	0.58	0.79	0.60	0.47	0.57	0.79	0.60	0.38	0.51	0.72	0.58	0.21	0.41	0.59	0.57
AVG	0.83	0.73	0.87	0.61	0.78	0.70	0.84	0.52	0.75	0.66	0.79	0.51	0.65	0.56	0.66	0.48

U: up-sloping audiometric curve; D: down-sloping audiometric curve; F: flat audiometric curve; P: profound audiometric curve; AVG: probability of success of treatment, the variable success ranges from 0 to 1.

with previous studies performed by our group on 265 patients in 2014 <sup>18</sup> and by Rauch et al. on 250 patients in 2011 <sup>24</sup>. In both studies, patients were treated either by IT or oral steroids, and both treatments showed the same efficacy on SSNHL.

Though SSNHL is commonly considered to be an otologic emergency, there are very few trials that report evidences regarding the urgency of medical care <sup>3 25 26</sup>. Several factors have been reported to have a prognostic impact on SSNHL. Hearing recovery appears to be related to the degree of initial hearing loss <sup>27</sup>, as well as to age and the shape of the audiogram <sup>25 26</sup>.

Many studies have analysed vertigo as a possible predictor of hearing recovery in SSNHL, assessing that subjective perception of vertigo is a predictor for worse outcome <sup>25</sup> <sup>26</sup>. Also, according to several reports, advanced age, hypertension, diabetes and hyperlipidaemia are poor prognostic factors; however, there is still no general agreement on the real influence of these factors on recovery <sup>28-35</sup>. In recent years, different studies have investigated the prognostic factors in SSNHL treated by systemic steroids. In 2015, Magnano et al. 36 found that only precocity of treatment and up-sloping hearing loss were positive prognostic factors for hearing recovery. A recent retrospective study conducted on 494 patients treated with either IT or oral steroids showed that age, severity of initial pure tone audiometry, duration from onset to treatment and initial speech discrimination were statistically significant prognostic factors related to hearing improvement in SSNHL, and that IT steroid injection as an initial single treatment is comparable to systemic oral steroid administration <sup>37</sup>.

In the present study, we proposed a prognostic model able to predict auditory recovery with respect to the precocity of medical treatment, also considering the audiometric curve shape. The decision of choosing an audiometric curve shape classification instead of Clark classification <sup>38</sup> is believed to be coherent with previous studies published from our group <sup>17 18</sup>. The results of the study and application of the statistical equation show that poorer recovery

of hearing can be expected when medical treatment is delayed.

Delay and delay-square are highly significant in the majority of samples. This suggests a nonlinear pattern for the variable delay. As we hypothesised, delay is negatively correlated with the variable success; moreover, delay-square shows a positive correlation in the entire sample. These two data together suggest that the probability of success decreases with time; however, during the first days following the onset of the SSNHL such a decrease is much more evident. Therefore, we can assume that early treatment is strongly recommended. Considering the entire sample, each day of delay decreases the probability of success by 3%. For the flat curves, the percentage is 4.4%, while for the up-sloping pattern it is 5.6%. For a downsloping pattern, the probability of success decreases with the same values of the entire sample.

The behaviour of the profound pattern is more difficult to predict due to the lack of robustness in our estimates (lower number of patients). Nevertheless, these patients showed a decrease of 1.3% in the probability of recovery for each day of delayed treatment.

Figure 1 shows a graph derived by the Probit regressions. In this graph, we plotted the predicted probability as computed using different specifications against the variable *delay*, following the Probit regression {1}. The curve is evidently much sharper in the first part of the graph, indicating that for each day that passes from the onset of SSNHL and initiation of treatment the probability of *success* decreases, and that chances of recovery lower to less than 50% after the first three weeks. The graph is reliable until the 40<sup>th</sup> day of *delay*, since the confidence interval is narrow until that point; this is due to the number of observations that is higher during the first period.

The developed predictive model not only has a theoretical value, but clinical application is also possible. Table IV identifies the probability of *success* for each age class according to the timing in which the patient begins medical treatment with IT corticosteroids.

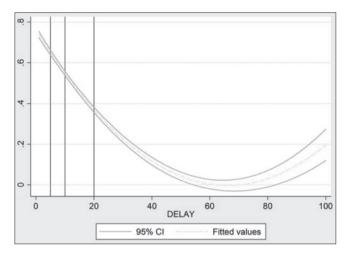


Fig. 1. Effect of delay-square variable on the entire sample.

#### **Conclusions**

The role of precocity of treatment in recovery from SS-NHL is still not clear. The statistical analysis performed herein allowed defining a probabilistic model that is able to identify the chances of recovery of patients that begin medical treatment with different timing. The prediction model shows that for each day that passes from the onset of SSNHL to the beginning of treatment, the probability of *success* decreases, strongly suggesting that early treatment is recommended.

#### **Conflict of interest statement**

None declared.

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# VESTIBOLOGY

# Report from a Consensus Conference on the treatment of Ménière's disease with betahistine: rationale, methodology and results

Risultati di una Consensus Conference sul trattamento della malattia di Ménière con betaistina

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#### **SUMMARY**

Ménière's disease is a disorder of the inner ear that causes vertigo, tinnitus, fullness and hearing loss. Although several treatments are available, the success rate is reported to be around 70%, similar to placebo. Betahistine, a weak H1 receptor agonist and an effective H3 receptor antagonist, is frequently prescribed for Ménière's disease, especially to reduce recurrent vertigo attacks. The effects of this drug on hearing and other audiological symptoms remains unclear. Given the inconclusive reports in the literature, we proposed a consensus conference on the use of betahistine in Ménière's disease. The aim was to define best practice criteria for therapy for Ménière's disease, improve clinical suitability and reduce heterogeneity of the therapeutic approach. The consensus conference on betahistine for Ménière's disease involved a group of Italian experts in vestibular disorders who were asked a series of questions prepared by opinion leaders. The Delphi method, an iterative investigation method, was used to increase consensus. Via a tele-voting system, each participant anonymously evaluated all statements using a Likert 5-point scale. Betahistine was considered useful for the treatment of dizziness and vertigo during the intercritical phase of the disease (87% agreeing answers). However, during the acute phase of the disease betahistine was considered less effective and useful only when associated with other drugs (71% agreement). Similarly, the efficacy of the drug was considered low when used to reduce progressive hearing loss, tinnitus, and ear fullness. The experts advocated the use of betahistine during the intercritical phase of Ménière's disease to reduce the number and severity of vertigo attacks. Its use seems to be at low risk of major side effects.

KEY WORDS: Ménière's disease • Betahistine • Consensus Conference • Delphi method

#### **RIASSUNTO**

La malattia di Ménière è una patologia dell'orecchio interno che causa acufene, sensazione di ovattamento auricolare, ipoacusia e vertigini. Sebbene siano disponibili numerosi tipi di trattamento, il successo terapeutico è stimato intorno al 70%, percentuale simile a quella riscontrata con l'utilizzo di placebo. La betaistina, un debole agonista dei recettori H1 e un effettivo antagonista degli H3, è frequentemente prescritta nella malattia di Ménière. Non è chiaro di quanto la betaistina sia in grado di migliorare la sintomatologia nella Ménière. Data l'inconsistenza dei report presenti in letteratura, abbiamo proposto una Consensus Conference sull'utilizzo della betaistina nella malattia di Ménière. Lo scopo è stato definire i migliori criteri clinici dell'approccio terapeutico alla malattia di Menière, migliorarne l'appropriatezza clinica e ridurre l'eterogeneità delle prescrizioni. La Consensus Conference sull'utilizzo della betaistina ha coinvolto un gruppo di esperti italiani nelle problematiche dell'apparato vestibolare, a cui è stato chiesto di rispondere ad una serie di domande preparate da opinion leaders del settore. Allo scopo di aumentare la significatività del Consensus è stato utilizzato il metodo Delphi, una modalità d'indagine interattiva. Attraverso un sistema di televoto, ogni partecipante ha valutato in maniera anonima ciascun punto secondo una scala Likert a 5 punti. La betaistina è stata considerata utile nel trattamento dei capogiri e della vertigine durante la fase intercritica della malattia (87% di concordanza nelle risposte). Tuttavia, durante la fase acuta della malattia la betaistina è stata considerata meno efficace e utile solo se associata ad altri farmaci (71% di concordanza nelle risposte). Allo stesso modo, l'efficacia del farmaco è considerata bassa quando utilizzata per contrastare la perdita progressiva dell'udito, l'acufene e la sensazione di ovattamento auricolare. In conclusione, gli esperti hanno concordato nel supportare l'uso della betaistina durante la fase intercrit

PAROLE CHIAVE: Malattia di Ménière • Betaistina • Consensus Conference • Metodo Delphi

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# Introduction

Ménière's disease (MD) is an idiopathic pathological condition of the inner ear, most often unilateral, caused by endolymphatic hydrops, which leads to symptoms such as fluctuating hearing loss, tinnitus and fullness, associated with recurrent episodes of rotational vertigo with neurovegetative symptoms 1. The current prevalence of the disease is 190/100,000 <sup>2</sup>. There is discordance regarding the gender-distribution of the disease: some authors report a higher prevalence in men<sup>3</sup>, while others described a higher prevalence in women 4; there is general agreement that MD is a disease of middle-age, with average age at onset in the fourth decade of life <sup>2</sup>. A controversial feature of the disease is represented by possible bilateral involvement, especially during the natural progression of MD. The literature on this aspect provides extremely heterogeneous data, with percentages of bilateral involvement ranging from 2% to 78% of patients 5. This broad range might depend on the definition of bilateral involvement, given that hearing abnormalities, without the appearance of complete symptomatology of MD, are frequently found in the contralateral ear 6.

Various treatment strategies have been proposed and used for MD, most of which are based on empirical criteria. Some of these therapies are widely accepted, while others are only practiced in a few centres. The differences in treatments is due to the lack of a definite aetiopathogenesis of the disease, as well as to the difficulty of carrying out clinical class A studies, given the natural fluctuation of the disease which includes long phases of remission. Reviews that analyse the response of MD patients to various therapies have reported that the success rate, roughly 70%, was not different from that obtained with placebo treatments <sup>7</sup>. Nevertheless, based on clinical pragmatism, medical treatment is the first therapeutic option for MD, taking into account cost-effectiveness and potential side effects. If a positive response to therapy is not obtained, more specific treatments may be considered. Medical treatment for MD has two components: treatment of acute attacks and prophylaxis between attacks. In the treatment of acute vertigo attacks, vestibular suppressants (i.e. dimenhydrinate, meclizine) are usually associated with antiemetic drugs. Diazepam, which has an additional beneficial anxiolytic effect, might also be administered intravenously. Steroid treatment in the acute phase, initially suggested because of the hypothesised autoimmune origin of MD, has been used to reduce the magnitude of crises as well as to promote auditory and vestibular recovery 8. Corticosteroids (e.g. prednisone 1 mg/kg) can be used both intravenously and orally in cycles of 10-14

days. Finally, osmotic diuretics (10% mannitol or glycerol) given intravenously as a slow infusion may also be used as treatment.

Treatment prescribed for the intercritical phase aims to: (i) reduce the number and severity of vertiginous crises; (ii) relieve chronic symptoms (instability and tinnitus); and (iii) prevent progression of the disease, with specific focus on hearing loss and loss of equilibrium. Maintenance therapies are able to achieve sufficient control of vertiginous crises in at least two-thirds of patients, especially when associated with a healthy lifestyle (i.e., no alcohol, no tobacco, no coffee, no stress), dietary measures (sodium restriction) and diuretics <sup>9</sup>; however, there is no effective therapy for long-term hearing preservation.

The most widely used drug for MD in Europe is betahistine, a histamine-like molecule that acts as a weak agonist for the H1 receptor and, at the same time, as an effective antagonist for the H3 receptor 10. Betahistine was first registered in 1968 and is widely used in the management of vertigo. Although its mechanism of action is only partially known, several different potential effects based on both preclinical and clinical studies have been suggested. Firstly, betahistine modulates histaminergic neurotransmission through partial agonist action at the histamine H1 receptor, combined with potent histamine H3 antagonistic properties. Secondly, betahistine has been reported to have vascular effects in both the cochlea and brain 11-14. Thirdly, betahistine is thought to have effects on neuronal excitability, with a dose-dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei 15 16. It is possible that the anti-vertigo activity of betahistine is first achieved by the drug itself, and then sustained by aminoethylpyridine, one of its metabolites <sup>17</sup>. Finally, the available evidence suggests that the histamine H3 receptor plays a key role in vestibular compensation, behavioural recovery and reduction of symptoms. Betahistine may potentially act on recovery mechanisms to provide clinical benefits by helping to improve behavioural adaptation 10. Taken together, these properties are thought to contribute to the beneficial therapeutic effects of betahistine in MD and vestibular vertigo. Although the effect of betahistine on vertigo has been assessed in many studies, it remains uncertain to what extent the compound improves symptomatology in MD and vestibular vertigo. In the past decade, only one systematic review 18 and one meta-analysis 19 were published on this topic, showing no strong evidence about the positive effects of betahistine MD. These inconclusive findings might be attributable to the methodology chosen to perform the analysis 20. Thus, there is not sufficient evidence for any

of the proposed treatments for the management of MD to be considered effective, and although several studies have been conducted, the results are inconclusive and inconsistent <sup>21</sup>.

#### **Methods**

In order to define adequate best practice criteria in MD therapy, we began with a rigorous and systematic analysis of the literature, identifying all studies on betahistine in MD. We evaluated the statistical methodology, selection criteria of patients, searching for possible biases, and determined whether a possible conflict of interest was present. Since most of the studies on betahistine were biased or inconclusive, we decided to consider expert opinion as the method of choice for clinical decision, organising a Consensus Conference (CC) with experts in the field. A CC is a series of meetings to collect opinions and decisions on new or controversial topics in science, technology and ethics, and is a useful and effective tool to synthesise current knowledge and address uncertainties <sup>22</sup>.

The CC on betahistine in MD involved a group of 78 Italian experts on vestibular disorders (see appendix), who were asked a series of questions specifically prepared by 13 opinion leaders. The opinion leader group (research team) consisted in Otolaryngologists or Audiologists with special expertise in Ménière's disease. After the questions had been formulated, selected articles were circulated to all participants, who reported their comments on a form. For each, two separate experts prepared respective statements. For controversial issues, for which no answer was found in the literature, new statements were prepared and discussed.

#### Delphi method and statement generation

To increase consensus, the CC was based on the Delphi method <sup>23</sup>. The Delphi method is an iterative investigation method, which through several stages of evaluation aims to reach the most comprehensive opinion, shared in a single statement; the Delphi method allows to systematically obtain responses to a problem from a panel of independent experts in two or three rounds with a consensus-based approach. After each round, an administrator provides a summary of the experts' answers and their rationale. The process ends when the experts' answers vary only slightly between rounds. Starting from the above-mentioned systematic review of the literature, the opinion leader group created for the panelists, relevant statements about specific scenarios associated with the employment of betahistine in Ménière's disease.

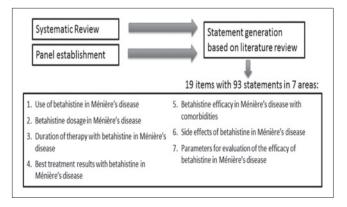
During the CC event (single day meeting in Rome on December 12<sup>th</sup> 2015), a tele-voting system allowed each

participant to anonymously evaluate all statements on a Likert 5-point scale. The answers associated with 1 and 2 of the scale were considered as a "NO", while 3, 4 and 5 were counted as "YES". Following the literature on the Delphi method, a statement was considered accepted when 70% agreement on "YES" or on "NO" was reached. Figure 1 show the process of acquisition of data from the CC.

#### Results

The entire panel of 78 Italian experts in vestibular disorders participated in the CC and evaluated the use and efficacy of betahistine in MD. With regards to prevention of vertigo spells, betahistine was considered useful (87% agreement) and a first-choice therapy between attacks (71% agreement, Fig. 2). However, betahistine was considered less effective during the acute phase of the disease and useful only when associated with other drugs (77% agreement, Fig. 3). In the management of Tumarkin's otolithic crisis, the drug was not considered efficacious (85% agreement), and useful only if associated with other agents (74% agreement). When surveyed about Tumarkin's otolithic crisis, 66% of experts had not found a useful dosage and did not rely on betahistine monotherapy to deal with this condition. The efficacy of the drug is low when used to prevent progressive auditory deterioration (82% agreement), tinnitus (79% agreement) and fullness (86% agreement).

Despite the statement affirming that betahistine is not useful during the acute phase, if the drug is used in this phase of the disease, the dosage range is between 32 and 48 mg/day (72% agreement, Fig. 4). On the contrary, 86% of experts agreed on the usefulness of the drug in the intercritical phase. While 81% of experts agreed that the dosage can vary during the different phases of the disease, the preferred overall dosage was between 32 and 48 mg/day



**Fig. 1.** Process used to select and achieve consensus for statements about betahistine in Ménière's disease. A number of statements were combined together for clarity, after the Consensus Conference.

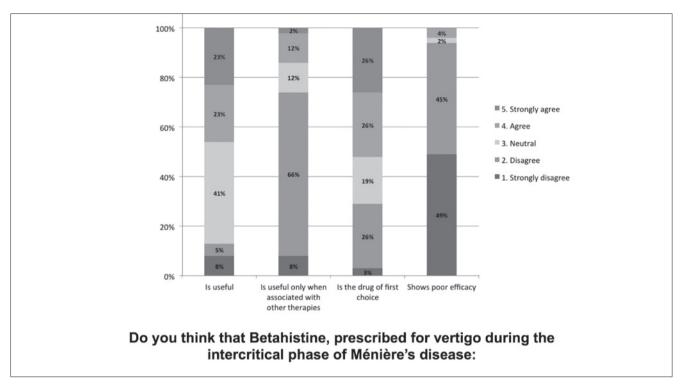


Fig. 2. Consensus conference on the use of betahistine in Ménière's disease: statements on the efficacy in the intercritical phase.

(84% agreement, Fig. 5). The experts were also surveyed about the duration of treatment in relation to the number of Ménière's crises during a 6-month interval. The experts

agreed on a 3-month treatment in cases of one to three crises per 6 months (82% agreement), while the preferred duration of treatment is 6 months (74% agreement) if a

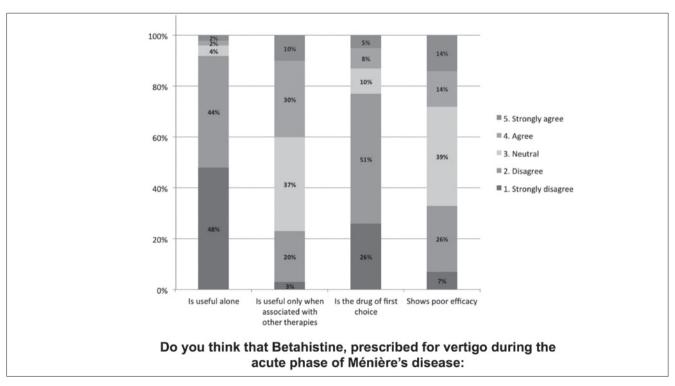


Fig. 3. Consensus conference on the use of betahistine in Ménière's disease: statements on the efficacy in the acute phase.

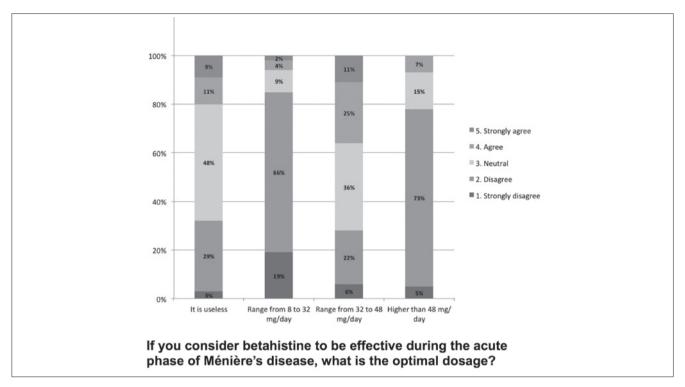


Fig. 4. Consensus conference on the use of betahistine in Ménière's disease: statements on optimal dosage in the acute phase.

patient has 4 to 10 crises in 6 months. In cases with more than 10 crises, the appropriate duration of treatment was considered to be either 6 months (69% agreement) or one

year (66% agreement). The efficacy of betahistine does not seem to depend on age: 84% of experts agreed that it can be used by adults of all ages indifferently and regard-

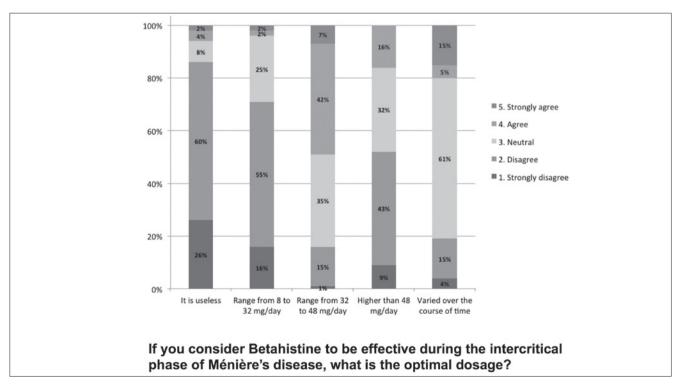


Fig. 5. Consensus conference on the use of betahistine in Ménière's disease: statements on optimal dosage in the intercritical phase.

less of gender. As far as comorbid conditions and drug interactions are concerned, in patients with MD and migraine most of the experts surveyed would use betahistine in association with an anti-migraine drug (67% agreement). In cases of comorbidity with anxious-depressive disorders, betahistine can be given in association with an anti-depressant or anxiolytic (78% agreement). Betahistine was considered to be a safe drug, with the overall frequency of side effects judged to be less than 10% (90% agreement). Gastric disturbances are the only common side effects mentioned by patients (73% agreement). Overall, to evaluate the efficacy of betahistine, the experts took into account the number and severity of crises in the preceding 6 months (93% agreement), clinical assessment of the vestibule (67% agreement) and the patients' quality of life (85% agreement).

#### Discussion

As previously discussed, the therapeutic strategies used for MD are varied and largely based on empirical criteria. The absence of a confirmed aetiopathogenesis, the difficulty in making a reliable diagnosis, together with the complexity of conducting clinical class A studies, explain the observed differences in treatments. In Europe, the most frequently prescribed drug, used mainly to reduce the frequency and severity of MD attacks, is betahistine, a weak H1 agonist and strong H3 antagonist histaminergic molecule <sup>10</sup>. Betahistine seems to have a dose-dependent role on neuronal excitability <sup>15 16</sup>, as well as on cochlear and cerebral blood flow <sup>11-14 24</sup>. In addition, its effects on H3 receptors seem to have a key role on vestibular compensation, favouring recovery and reduction of residual symptoms <sup>25</sup>.

Recent literature on the efficacy of betahistine in MD appears to be very discordant, and there is a marked lack of systematic reviews and meta-analyses. A recent Cochrane review concluded that betahistine is an acceptable treatment 18. However, the authors did not find strong evidence for the efficacy of the drug in management of dizziness, tinnitus, loss of hearing, or fullness in MD. In contrast, a meta-analysis carried out by Della Pepa et al. 19 found a role for the drug in the management of dizziness. According to a more recent meta-analysis, this lack of unequivocal evidence could be due to methodological limitations <sup>20</sup>. In that study, the authors concluded that betahistine can be considered as a safe drug, with a positive benefit/risk ratio, being effective in diseases for which dizziness and vertigo are the main symptoms. The consensus of experts consulted on betahistine, in light of their clinical practice

and daily management of patients with MD, revealed a constant use of the drug during the intercritical phase, especially in monotherapy. Betahistine is considered to be safe, suitable for all age groups and associated with a low incidence of side effects (mainly gastrointestinal symptoms). These statements, based exclusively on the clinical experience of the consensus conference participants, seems to be confirmed by a very recent Cochrane review suggesting some positive effects of betahistine in reducing vertigo symptoms without any significant side effects <sup>26</sup>. Moreover, betahistine is successfully used with other drugs in cases of comorbidity with migraine and anxiety-depressive disorders <sup>27-30</sup>. During the intercritical phase, the dosage depends on the patient's response and phase of disease, but usually ranges from 32 to 48 mg/day. The duration of treatment varies, according to the frequency of crises, from a minimum of 3 months up to a maximum of 1 year. Clinical vestibular evaluation (history and symptoms of vestibular dysfunction) and the patient's quality of life during the disease are also taken into account when evaluating the efficacy of betahistine. Betahistine is not recommended for the acute phase of MD or for Tumarkin's otolithic crises (although it can have a role if associated with other drugs), and has been found to have low efficacy in the management of auditory deterioration, tinnitus and auricular fullness.

#### **Conclusions**

The experts' clinical practice and personal experience support the use of betahistine in MD to reduce the number and severity of vertiginous crises, particularly during the intercritical phase of the disease. Betahistine does not show positive effects on auditory symptoms of MD, but its use seems to be at low risk of major side effects. However, clinical studies based on rigorous methodologies and outcome measures are needed to clearly evaluate the role of betahistine in the treatment of MD.

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#### Conflict of interest statement

None declared.

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# **Appendix**

Panel participants at Consensus Conference on the Treatment of Ménière's disease with betahistine: Alessandrini Marco, Armato Enrico, Artesi Leonardo, Balzanelli Cristiano, Barbara Maurizio, Beghi Andrea, Bentivegna Lisa, Bolognini Alfonso, Boninsegna Marco, Botticchio Rosetta, Brafa Alessandra, Brandolini Cristina, Bruno Ernesto, Bufalo Alfonsina, Bulbarelli Maurizio, Buonpane Giuseppe, Califano Luigi, Caligo Giacomo, Carrozza Emanuele, Castellucci Andrea, Cena Manuele, Coletta Mariano, Conflitti Renato, Coppo Gianfranco, Coscarella Mariangela, Cozzolino Giovanni, Cutrera Barbara, Cutri Nicola, Da Col Maurizio, Damiani Sergio, De Angelis Alfonso, Del Colle Raffaele, Dello Monaco, Maria Letizia, Falco, Carlo Emilio,

Falcone Gianluca, Ferrari Giampiero, Ferraro Guglielmo, Filiberto Daniele, Galera Francesco, Gallo Andrea, Gamba Paolo, Gianformaggio Carlo, Ingria Federico, La Placa Giacomo, Lauletta Rocco, Lucisano Sergio, Luperto Paolo, Mandara Mario, Manna Valentino, Martorana Irene Manuela, Miele Carolina, Milone Vincenzo, Mininni Francesco, Mininni Sebastiano, Mohanna Marwan, Nola Giuseppe, Pace Antonio, Padovani Davide, Pantaleoni Marco, Patrizi Mario, Perdona' Antonia, Petrillo Francesco, Petrone Domenico, Pindozzi Simona, Poletto Elisabetta, Primerano Giovanni, Raguso Michele, Rinaldi Antonio, Rizzo Davide, Saginario Vittorio, Santucci Giuseppe, Scotto Di Santillo Leonardo, Sergi Gaetano, Spasiano Roberto, Tassoni Alessandro, Tondolo Enrico, Venticinque Luciano.

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#### OTOLOGY

## Radiologic measurement of cochlea and hearing preservation rate using slim straight electrode (CI422) and round window approach

Misurazione radiologica della coclea e tasso di preservazione uditiva utilizzando elettrodo sottile a punta dritta (CI422) e approccio alla finestra rotonda

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#### **SUMMARY**

Hearing preservation surgery constitutes a considerable branch of cochlear implantation surgery and is being steadily developed and perfected. The aim of the study was to verify if insertion of a cochlear implant electrode according to individually calculated linear insertion depth improves hearing preservation. We evaluated the relations between the size of a cochlea, insertion depth angle, linear insertion depth and hearing preservation rate (HP) according to Hearing Preservation Classification in a retrospective case review of 54 patients implanted with a slim straight electrode Nucleus CI422 in 2008-2011. Group HP was 0.75 at activation, 0.67 at 12 months (for 53 patients) and 0.60 at 24 months. In 53 cases, the mean insertion depth angle was 375° (SD 17°); mean calculated cochlear duct length 35.87 mm (SD 1.95); mean calculated linear insertion depth 23.14 mm (SD 1.68). There was no significantly relevant relation between HP values and angular insertion depth or insertion depth. Preoperative measurements of cochlea and specific parameters such as linear insertion depth have no effect on hearing preservation. Poor hearing preservation in some deep insertion cases cannot be explained entirely by the electrode position.

KEY WORDS: Cochlear implant • Electrode insertion depth • Hearing preservation • Partial deafness • Round window

#### **RIASSUNTO**

La chirurgia per la preservazione dell'udito costituisce oggi un'importante branca dell'implantologia cocleare e deve essere ancora sviluppata e perfezionata. L'obiettivo di questo studio è stato quello di verificare se l'inserimento dell'elettrodo dell'impianto cocleare, eseguito secondo l'angolo di inserimento calcolato individualmente, migliorasse la preservazione uditiva. In questo studio retrospettivo comprendente 54 pazienti impiantati con un elettrodo sottile a punta dritta Nucleus Cl422 tra il 2008 e il 2011, abbiamo valutato la relazione tra la grandezza della coclea, l'angolo di inserimento e il tasso di preservazione uditiva (HP) in accordo con la Hearing Preservation Classification. Il tasso di preservazione uditiva è stato pari a 0,75 all'attivazione, 0,67 a 12 mesi (per 53 pazienti) e 0,60 a 24 mesi. Nei 53 pazienti l'angolo di inserimento medio è stato pari a 375° (SD 17°); la lunghezza media del condotto cocleare è risultata pari a 35,87 mm (SD 1,95); la profondità di inserimento pari a 23,14 mm (SD 1,68). Non è stata rilevata alcuna differenza statisticamente significativa tra i valori di HP e l'angolo di inserimento o la profondità di inserimento. La misura preoperatoria della coclea e di parametri specifici quale la profondità di inserimento non hanno effetto sulla preservazione uditiva. Bassi valori di preservazione uditiva in alcuni casi di inserimento profondo non possono essere spiegati solamente dalla posizione dell'elettrodo.

PAROLE CHIAVE: Impianto cocleare • Profondità di inserimento dell'elettrodo • Preservazione uditiva • Finestra rotonda • Sordità parziale

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#### Introduction

Hearing preservation surgery constitutes a considerable branch of cochlear implantation surgery and is being steadily developed and perfected <sup>12</sup>. There is much dis-

cussion about the terminology and groups of patients, as different authors apply different definitions to terms such as residual hearing or deep insertion.

A crucial aim of cochlear implantation, apart from deliver-

ing electric stimulation to non-functioning parts of cochlea, is to preserve low frequency preoperative hearing after surgery <sup>3</sup>. The degree of intracochlear mechanical trauma caused by surgical intervention may range from minor vascular injury, tearing of a spiral ligament, displacement or perforation of basilar membrane to fracturing of osseous spiral lamina or modiolar wall; it is associated with an acute inflammatory response 45. The cause of these problems may be not only the fault of the surgical technique and surgeon's inexperience, but may also be related to the individual anatomy of cochlea and physical parameters of electrode array and how they relate to each other. Many researchers have studied the issue of the depth of insertion of an electrode array as there is a trade-off between the expected cochlear coverage and risk of direct physical trauma caused by electrode's presence 4-9.

When analysing the placement of an electrode array of a specific length <sup>10 11</sup>, we cannot use either angular insertion depth or linear insertion as a measure of cochlear duct coverage with relation to its tonotopic organisation because of large inter-individual variability of cochlea measurements <sup>8 12-15</sup>. Additionally, several studies have shown that penetration of an electrode array into apical functioning parts of cochlea may considerably increase the risk of hearing deterioration or loss <sup>16-18</sup>. In this context, a question arises if we could use precise estimation of an individual array insertion depth in relation to the expected frequency along the organ of Corti as a tool for optimising outcomes of hearing preservation. In other words, can measuring a cochlea before surgery be helpful in increasing hearing preservation rate in cochlear implantation?

Several papers have been published investigating the relationship between depth of electrode array insertion and residual hearing preservation in cochlear implantation. There is an inherent limitation to the learning value of these reports because each relates the results obtained with different array types, different surgical approaches to cochlea, different methods of estimating the array position and, what of crucial importance, in the face of lack of a uniform classification system of hearing preservation have used various evaluation methods, and thus the results are difficult to compare 4 5 17-19. Fraysse et al. 18 presented the results of 21 adult patients implanted with a perimodiolar electrode through cochleostomy. They found no significant relationship between preservation of hearing and insertion depth angle. However, they reported considerable hearing loss in cases of deeper insertions, i.e. in smaller cochleae. Similar results have been reported by James et al. 17 in their study with a perimodiolar array implanted through a cochleostomy approach. Erixson et al. 19 studied two Med-El electrodes of different lengths, flex EAS (now Flex24)

and flex soft, and found no significant relation between angular insertion depth and hearing preservation rate, although the two deepest insertions resulted in complete hearing loss. Causon et al. <sup>5</sup> in a recent literature review analysis of reported factors found a significant relation between hearing preservation and angular insertion depth, but included several different methods of hearing preservation assessment, surgical methods and approaches, electrode arrays and physical parameters. Hassepas et al. <sup>4</sup> reported the results of 41 adults implanted with a Nucleus CI422 slim straight electrode using cochleostomy and round window technique. They focused on comparison of these two approaches in terms of insertion depths and possible scalar dislocation of array for straight electrode.

The present study is the first comprehensive approach to evaluate the relationship between the size of a cochlea, insertion depth angle and linear insertion depth and preservation of hearing assessed using the new Hearing Preservation Classification <sup>20</sup>. Study material includes the largest group of patients to date implanted with the slim straight electrode using the round window technique <sup>21</sup>. Among these patients, there were both children and adults with various degrees of low frequency hearing who had been implanted with a CI422 electrode using only two intraoperatively estimated insertion depths: 20 mm and 25 mm. There was no data on cochlea measurements prior to surgery. The objective of the study was to assess if insertions performed according to the patient's specific calculated linear insertion depth increases the rate of hearing preservation.

#### Materials and methods

Subjects

In this retrospective analysis we analysed a group of 54 patients who underwent cochlear implantation with the Nucleus CI422 slim straight electrode in our clinic between March 2008 and January 2011. Patients with structural malformations of a cochlea, retrocochlear origin of hearing loss or aetiology suggesting obliteration or ossification were excluded.

The study received the approval of the institutional bioethics committee according to Polish legal regulations (approval number IFPS/KB/04-2009). Procedures and data collection conformed with ISO 14155:2003. The study followed the principles of the Declaration of Helsinki.

#### Audiometric testing

Pure tone audiometry (PTA) tests were performed using calibrated audiometers with outputs of 90 dB HL at 125 Hz, 105 dB HL at 250 Hz, 110 dB HL at 500 Hz,

120 dB HL at 1 kHz, 120 dB HL at 2 kHz, and 115 dB HL at 4 kHz and 6 kHz. In unaided conditions, tests were performed in a double-walled sound booth using earphones. PTA using tones in the range 0.125-6 kHz was performed preoperatively and at 1, 5, 9, 12 and 24 months after activation of the speech processor. Hearing threshold evaluation in PTA was performed following the modified Hughson & Westlake procedure with 5 dB precision <sup>22</sup>. Pre- and post-operative hearing levels were categorised according to Skarzynski's definitions <sup>16</sup>.

#### *Surgery and electrode array*

Cochlear implantation was performed in the worse hearing ear in all patients. Surgery was performed using the 6-step Skarzynski procedure with a round window approach for partial treatment of deafness. All patients received the CI422 electrode, which is a 25 mm slim straight electrode with 22 half band contacts and diameters 0.3 mm at the tip and 0.6 mm at proximal end. It has two white markers, at 20 and 25 mm, to facilitate intraoperative estimation of insertion depth <sup>16 21</sup>. The decision as to how deeply an electrode should be inserted was made on the basis of the PDT classification 16, but if there is any resistance, force or lock during the insertion then it should be stopped. Otherwise, there is a risk that hearing will not be preserved. Steroids were administered according to our routine procedure in all patients: 0.1 mg/kg/day dexamethasone IV infusion in two doses per day for 3-4 days. Questionnaires with intraoperative reports on insertion depth estimation (1st marker, between markers, around 22 mm, 2<sup>nd</sup> marker) were collected.

#### Radiologic evaluation

A flat-panel high-resolution computed tomography (HRCT, Somatom Definition AS, work station Siemens MMWP) was used for imaging.

#### Diameter of the basal turn of cochlea -A

Reconstructions of the cochlea image ("cochlear view") were prepared according to the method described by Xu et al. <sup>23</sup>. The 0° reference angle was defined according to the coordinate system proposed by a consensus panel <sup>24</sup>. The diameter of basal turn – linear measurement A – was evaluated according to the method described by Cohen et al. as the largest distance from the round window through the centre of a modiolus to the opposite lateral wall of a basal turn <sup>25</sup>.

#### Angular insertion depth

The angle of insertion  $\theta$  measured along the lateral wall of cochlea was specified and estimated according to the method described by Cohen et al. <sup>25</sup>. It is an angle between the line passing through the round window and the center of modiolus and the line connecting a specific position

along the lateral wall of cochlea indicated by the electrode tip and the centre of the modiolus.

Linear insertion depth for slim straight electrode CI 422 A line tracing the outer wall of cochlea was described using the equation given by Escude <sup>14</sup>.

L = 2.62 Ax log e (1.0 +  $\theta$ /235) (Equation 1), where: log e = natural logarithm;  $\theta$  = angle between a line connecting the middle of a modiolus with a tip of an electrode and a line connecting the middle of a modiolus with a round window niche (lateral lip of sinus tympani) (Fig. 1).

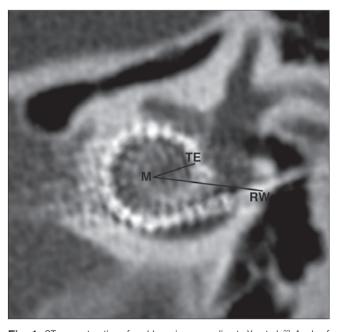
According to method proposed by Alexiades <sup>26</sup>, in order to evaluate the linear insertion depth for a particular straight array with greater precision one should allow for the length of displacement from the outer wall towards the organ of Corti. Alexiades proposed that linear measurement A should be reduced by the doubled electrode's average radius. For CI422, the average radius is 0.45 mm (range 0.3-0.6). Performing appropriate substitution to Equation 1 we obtain Equation 2 as follows:

LCI422 = 2.62 (A-0.9) x log e  $(1.0 + \theta/235)$  (Equation 2).

#### Cochlear duct length for CI 422 electrode

For cochlear duct length (CDL), we used the same evaluation method proposed by Alexiades <sup>26</sup>.

CDLlw = 4.16A + 0.18 (Equation 3). For CI 422 electrode the above equation is: CDLCI422 = 4.16 (A-0.9) + 0.18 = 4.16A-3.54 (Equation 4).



**Fig. 1.** CT reconstruction of cochlear view according to Xu et al.  $^{23}$ . Angle of insertion  $\theta$  estimated according to Escude.

#### Hearing preservation

Hearing preservation (HP) was calculated using the new Hearing Preservation classification system proposed by Skarzynski et al. <sup>20</sup>, which is based on preoperative and postoperative PTA

S (%) = [1 - {(PTApost - PTApre)/ (PTAmax - PTApre)} x 100], where: S is the hearing preservation, PTApost is the pure tone average postoperatively, PTApre is the pure tone average preoperatively and PTAmax is the limit of the audiometer.

#### Statistical analysis

Statistical analysis was performed using Statistica 10. HP analysis for implanted and non-implanted ears was performed using a non-parametric Friedman ANOVA test and the Kendall compliance coefficient. The relation between HP rate and angular insertion depth was estimated using Pearson's linear correlation. For both tests a significance level of p < 0.05 was adopted.

#### **Results**

#### Demographic data

Subjects were 54 patients aged 6 to 83 years, mean 30.05, with various degrees of high frequency sensorineural hearing loss. In this group, 26 patients were male. In 29 cases the right ear was implanted. Duration of the period of severe to profound hearing loss in study subjects ranged from 3 to 48 years, mean 13.2 (SD 2.9). In 29% subjects hearing loss had a confirmed genetic aetiology, in 60% the aetiology was unknown, in 3% deafness was caused by peri-delivery complications, in 3% due to ototoxic drug use, in 3% was post inflammatory processes and in 2% deafness was a result of birth paralysis.

#### Surgery

All implantations were successfully performed by the same surgeon. Insertion was rated as easy (very little force inside cochlea, but no problem with insertion) in 15 cases, very easy (no forces or any resistance in the cochlea) in 31 cases, acceptable (because of slight force there was slower insertion, but full depth was achieved) in 6 cases and difficult in 2 cases. Intraoperative estimation of insertion depth was as follows: in 29 cases 2<sup>nd</sup> marker, between 1<sup>st</sup> and 2<sup>nd</sup> 2 cases, and in 23 cases 1<sup>st</sup> marker.

#### Hearing preservation

In all subjects but one the PTA hearing thresholds were measured across frequencies preoperatively and over the 24-month follow-up period. One patient had temporarily fallen out of follow-up, and thus HP at 12 months was calculated for only 53 subjects. For the entire group analysed, the S value of HP was calculated and was 0.75 at activation, 0.67 at 12 months and 0.60 at 24 months.

#### Radiologic evaluation

#### Angular insertion depth $\theta$

In all cases but one reconstructions of cochlea images were successfully obtained in the early postoperative period (Fig. 1). The image quality of the excluded patient was insufficient to obtain cochlear view reconstruction. The measured insertion depth angles of array ranged from  $310^{\circ}$  to  $540^{\circ}$ , mean  $375^{\circ}$  (SD  $17^{\circ}$ ).

Cochlear duct length for CI422 electrode - CDLCI422 Calculated cochlear duct length for the CI422 electrode ranged from 30.16 mm to 40.56 mm, mean 35.87 mm (SD 1.95).

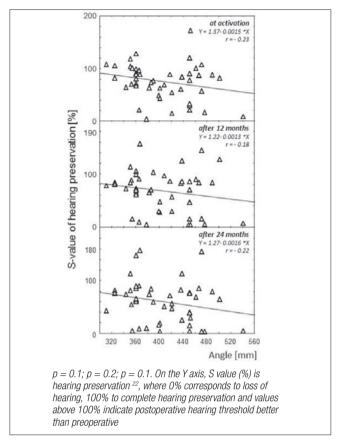
Linear insertion depth for CI422 electrode - LCI422 Calculated linear insertion depth of the CI422 electrode array in postoperative reconstructions of cochlear view ranged from 19.81 mm to 26.43 mm, mean 23.14 mm (SD 1.68).

Relationship between individual S values of HP in the studied group at activation, 12 and 24 months of followup and the individual angular insertion depths  $\theta$  was evaluated, and no statistically significant relation was found (respectively p = 0.1, p = 0.2, p = 0.1) (Fig. 2).

Likewise, the relation between the S value of HP for each subject in the group and intra-operatively estimated depth of insertion did not show any statistical significance (Fig. 3).

#### **Discussion**

Individual variability of cochlea size (Stakchovskaya 12 in the study of temporal bone specimens reports a 6.37 mm difference between the shortest and the longest cochlear duct in her material) and a large variety of residual hearing levels are the two factors that have to be considered when attempting to determine the relationship between preservation of hearing and array insertion depth <sup>12</sup>. In the relations analysed in our study, we assumed two different conditions of implantation. The first is that a surgeon does not know the cochlea size preoperatively, and the only available information is hearing status and electrode length. Secondly, a surgeon knows the diameter of the basal turn, and can thus calculate cochlear duct length, and also knows hearing status and electrode length 26. However, due to anatomical variations of cochlea dimensions the angle of insertion does not provide an actual data on frequency coverage, because in a large cochlea, as for ex-



**Fig. 2.** Relation between hearing preservation calculated at activation and at 12 months and 24 months of follow-up vs. angular depth insertion (axis Y).

ample the largest in our study group with A = 10.6 mm and CDL = 40.65 mm, an insertion to the depth of 20 mm would most probably not reach  $360^{\circ}$ , as it does in a medium sized cochlea  $^{18}$ .

Referring to Greenwood's equation describing the frequency distribution along the organ of Corti, a proportion between the cochlear duct length and the linear position of electrode enables calculating the frequency at a furthest point of a specific electrode array penetration into the scala tympani 12 27. According to our hypothesis, this information should help to avoid insertions that are too deep, which might cause low frequency hearing loss <sup>17-19</sup>. It might also be of considerable help in cases of preserved hearing in electro-acoustic stimulation, where precise estimation of a particular frequency is needed <sup>16</sup>. The first condition mentioned above is epitomised by the relation between HP rate and intrasurgical estimation of array insertion depth (Fig. 3), The second condition describes the relation between HP rate and proportion of cochlear duct length for the CI422 array (CDLCI422) and the intraoperatively estimated electrode insertion depth. We did not find this relationship to be statistically significant (Fig. 4). However, intraoperative estimation of insertion depth can be encumbered with errors resulting from such real life surgical situations such as a shortcut in the proximal part of basal turn or folding of an electrode tip <sup>28</sup> <sup>29</sup>. This is also suggested by the results published by Franke-Trieger et al. who reported 14% of cases falling outside the recommended depth in CT evaluation <sup>27</sup>.

In addition, Hassepass et al. <sup>4</sup> performed similar measurements in their study of intraoperatively approximated insertions of 22 mm. They reported mean postoperatively radiologically estimated insertion depth of 21.5 mm. However, they did not report the nominal values of ranges of linear insertion. For this reason, we introduced a mathematical calculation of the LCI422 variable based on a value of angle of insertion and cochlea size, according to Alexiades <sup>26</sup>. Herein, insertions rated as 20 mm resulted with 21.4 mm (SD 1.0) in calculations based on radiological measurement and inser-

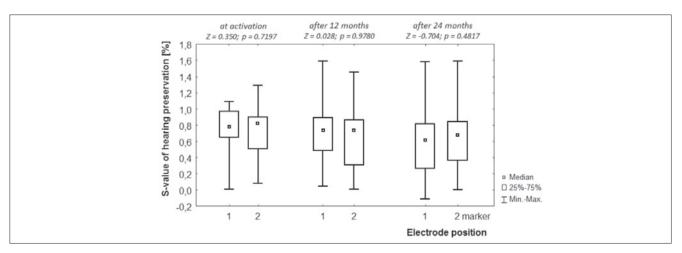
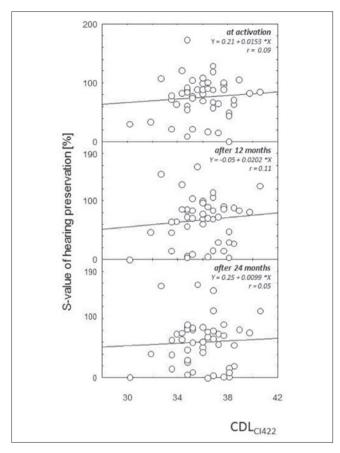
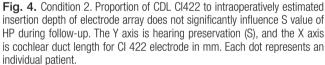


Fig. 3. Condition 1. S value of hearing preservation during follow-up is not significantly related to intraoperatively estimated insertion depth of electrode array.

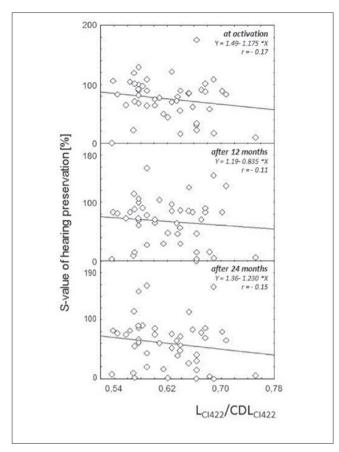




tions rated as 25 mm resulted with 23.1 mm (SD 1.8). The L CI422 /CDL CI422 proportion is independent of cochlea size, and is an individual measure of cochlear coverage. Cochlear coverage calculated based on the L CI422/CDL CI422 did not differ significantly from that calculated based on the CDL CI422 and intraoperative estimation. We did not find any significant difference between the HP and L CI422 /CDL CI422 across the study group (Fig. 5).

These relations have reference to our hypothesis, namely that HP rates in these conditions are not significantly different from one another. This does not corroborate our assumption that the preoperative measurement of cochlea size would increase the chances of high S value of HP.

A few cases where at activation we observed a minimal HP, although not complete hearing loss, were related to deep (540° or 450°) insertions. These cases slip out of the general tendency. Radiological evaluation of the electrode array did not reveal array dislocation in any case.



**Fig. 5.** Condition 2. CDL CI422/LCI422 does not have a significant influence on S value of HP during follow-up. The Y axis is hearing preservation (S), and the X axis is a quotient of Cl 422 electrode length divided by individual cochlear duct length for Cl 422 electrode. Each dot represents an individual patient.

This result is in line with those reported by other authors. Erixson et al. in a study involving 21 patients implanted with Med-El electrodes found no significant relation between the HP rate and insertion angle or insertion depth <sup>17</sup>. In their investigation, the two deepest insertions of 540° had also completely lost their hearing, although their measured linear insertions did not exceed 23.5 mm – pointing towards a conclusion that the risk of hearing loss is higher in a smaller cochleae -. A similar observation was reported by Fraysse in a study of 27 adults implanted with perimodiolar electrodes through a cochleostomy approach. Although in their estimation of the insertion depth angle they did not differentiate between a perimodiolar position of array and a lateral wall array, and for that reason is less precise, the general tendency is analogous to that observed in our study group. In their study, the greatest insertion angle was 435° and the postoperative increase of hearing threshold for 250-500 Hz averaged over 50 dB <sup>18</sup>. It also suggests that future analyses should investigate electrode types and hearing thresholds <sup>30 31</sup>.

Another important factor is the age of a patient <sup>32</sup>. In an elderly population, deeper insertions should possibly be recommended, including patients with a substantial preoperative hearing suitable for preservation <sup>33</sup>.

#### **Conclusions**

On the basis of our results we conclude that preoperative measurements of cochlea size and application of specific calculated parameters such as cochlear duct length, angle of insertion and linear insertion depth do not seem to effectively increase the probability of hearing preservation in cochlear implantation when using slim straight arrays and the round window surgical approach.

Although radiological evaluation of electrode position, including linear insertion depth, appears to provide more precise information compared to the intraoperative evaluation of electrode position, this measurement does not assure a successful and safe implantation in terms of preservation of low frequency hearing. Poor results of hearing preservation in some cases of deep insertion angles cannot be explained entirely by the electrode position.

#### Conflict of interest statement

None declared.

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#### **CASE SERIES AND REPORTS**

# Treatment-emergent central sleep apnoea after surgery for obstructive sleep apnoea

Apnee notturne centrali post chirurgia disostruttiva delle prime vie aeree nei pazienti affetti da OSAS

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#### **SUMMARY**

Central sleep apnoea (CSA) is a lack of drive to breathe during sleep, which can occur in physiologic as well as in pathologic conditions. A particular type of CSA, defined treatment-emergent CSA (TECSA), may occur after the treatment of obstructive sleep apnoea syndrome (OSAS), either with CPAP or surgery. TECSA is transitory and seems to be related to the severity of OSAS. We describe a 51-year-old man affected by severe OSAS who developed severe, transient CSA immediately after upper airways surgery. We believe that CSA was triggered by the sudden variation in nocturnal arterial PCO<sub>2</sub>, which decreased from 52.3 mmHg before surgery to 42.0 mmHg after surgery. It is conceivable that, due to long-lasting severe OSAS, our patient lowered his chemosensitivity to PCO<sub>2</sub>. Consequently, the resolution of obstructive apnoeas and the restoration of normal nocturnal values of PCO<sub>2</sub> may have reduced the nocturnal PCO<sub>2</sub> to the point of being inadequate to stimulate ventilation.

KEY WORDS: Treatment Emergent Central Sleep Apnoea • OSA • CSA • Complex Sleep Apnoea • UPPP • PCO,

#### **RIASSUNTO**

L'Apnea Centrale nel Sonno (CSA) è caratterizzata da un mancato input a compiere l'atto respiratorio durante il sonno e può verificarsi sia in condizioni fisiologiche che in condizioni patologiche. Un particolare tipo di CSA, definito come "Apnea Centrale nel Sonno Emergente dal Trattamento" (TECSA), può verificarsi dopo il trattamento della Sindrome delle Apnee Ostruttive durante il Sonno (OSAS), sia dopo ventiloterapia con CPAP che dopo intervento chirurgico. La TECSA è di solito transitoria e sembra correlata alla gravità dell'OSAS. Descriviamo un uomo di 51 anni affetto da OSAS grave, che ha sviluppato gravi e transitorie apnee centrali nel sonno, immediatamente dopo l'intervento chirurgico delle vie aeree superiori. Ipotizziamo che la CSA sia stata innescata dalla brusca variazione dei valori notturni di PCO2 arteriosa, passata da 52,3 mmHg prima dell'intervento chirurgico a 42,0 mmHg dopo l'intervento chirurgico. È ipotizzabile che, a causa della lunga durata e della severità dell'OSAS, il paziente abbia sviluppato una bassa chemiosensibilità alla PCO2 arteriosa. Di conseguenza, la risoluzione delle apnee ostruttive e il ripristino dei valori normali notturni di PCO2, potrebbero aver ridotto i valori di PCO2 notturna fino al punto di essere inadeguati per stimolare la ventilazione.

PAROLE CHIAVE: Apnea Centrale nel Sonno Emergenti dal Trattamento • OSA • CSA • UPPP • PCO,

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#### Introduction

Central sleep apnoea (CSA) is characterised by a lack of drive to breathe during sleep. CSA can occur in a variety of physiologic and pathologic conditions, which include sleep at high altitude, drug intake, neuromuscular disorders, congestive heart failure, idiopathic CSA; moreover, CSA can be associated with obstructive sleep apnoea syndrome (OSAS) <sup>1</sup>.

The present report concerns the polysomnographic findings in a 51-year-old man affected by severe OSAS, who developed severe, transient CSA immediately after upper airway surgery for OSAS.

#### Case report

A 49-year-old man referred to our sleep centre for symp-

toms of OSAS. No remarkable medical history was reported; in particular, neurologic, heart and respiratory diseases were ruled out, and he took no drugs. Body mass index (BMI) was 27.8 kg/m<sup>2</sup>, neck circumference was 42.5 cm, Mallampati class IV. Spirometry and pulmonary function tests were normal. He underwent fullnight, laboratory based nocturnal video-polysomnography (PSG). PSG montage included three EEG leads, two EOGs, submental PNG, chest and abdominal respiratory effort, airflow (nasal cannula), EKG, SpO<sub>2</sub>, body position, snoring, audio and video recording. PSG showed apnoeahypopnoea index (AHI) = 40 events/hour, and oxygen desaturation index (ODI) = 41.8 events/hour. The index of central events was 4.6. Treatment with positive airways pressure was started (CPAP = 12 cmH<sub>2</sub>0). CPAP was titrated to suppress all sleep-related pathologic respiratory events. The patient came for follow-up evaluation 24 months later, complaining of poor compliance with CPAP and persistence of symptoms, despite the use of a humidifier and the adoption of alternatively a nasal and a facial mask. A trial with a BiPAP was also attempted, without satisfactory results. He underwent a pre-surgical evaluation protocol. BMI and neck circumference were unmodified. Arterial blood gas analysis was performed in the morning, within minutes from awakening, while breathing room air. Gas analysis showed PCO<sub>2</sub> = 52.3 mmHg,  $PO_2 = 90.2 \text{ mmHg}$ , pH = 7.4. Sleep endoscopy showed

three sites of obstruction: nasal (hypertrophy of inferior turbinates); retro palatal-oropharyngeal (total antero-posterior collapse); and laryngeal (collapse of the epiglottis on the lumen of larynx). Therefore, he underwent a surgical procedure which included mucotomy with radiofrequency, uvulopalatopharyngoplasty (UPPP) and partial epiglottectomy. No surgical complications occurred. The patient presented no clinically relevant post-operative pain, and no narcotic therapy was administered. PSG performed three days after surgery (to rule out possible residual effect of anaesthetics); PSG showed a clear reduction of the obstructive events, but a striking increase of the central apnoea index (Fig. 1). At this time, the patient reported no symptoms and other subjective complaints. Central apnoeas progressively decreased in follow-up PSGs, whereas the index of obstructive+mixed events remained stable. PSG results, apnoea-hypopnoea and oxygen desaturation indexes and values of arterial blood gas analysis are reported in Table I.

#### **Discussion**

A particular type of CSA, defined treatment-emergent central sleep apnoea (TECSA) and previously known as complex sleep apnoea, has been reported during the titration CPAP in patients with OSAS <sup>2</sup>. In a large retrospective study of patients with OSAS, 6.5% had CPAP emer-

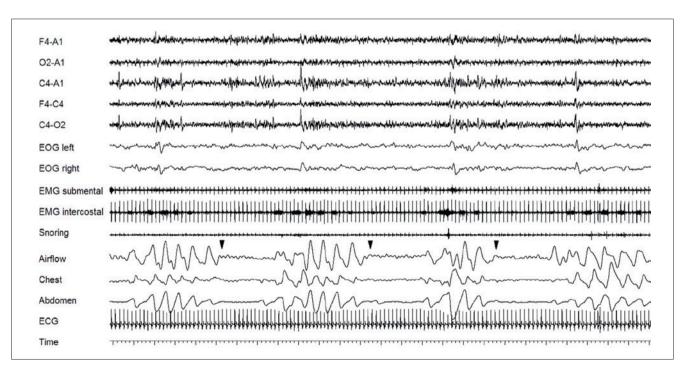


Fig. 1. PSG recording (about 2 minutes) obtained during night #3 postsurgery. Three central apnoeas are shown (arrows).

Table I. Polysomnography and arterial blood gas analysis before and after surgery.

	Before surgery	After surgery			
Polysomnography		Day #3	Day #15	Day #30	
Total Sleep Time	435	331	505	399	Minutes
Sleep Efficiency Index	96,6	95,8	88,9	98,2	%
Total Apnea-Hypopnea Index	48,2	71,2	21	14,6	Events/hour
Central events	4,6	64,1	10,4	4,7	Events/hour
Obstructive + Mixed events	43,6	7,1	10,6	9,9	Events/hour
AHI supine	45,5	69,1	18,6	27,1	Events/hour
AHI lateral	6,6	68,1	5,4	3,1	Events/hour
Oxygen Desaturations Index	42	72	21	26	Events/hour
Basal SpO <sub>2</sub>	95	96	96	97	%
Lowest SpO <sub>2</sub>	76	75	76	74	%
Arterial blood gas analysis					
PCO <sub>2</sub>	52	42		42	mmHg
$PO_2$	91	80		88	mmHg
pH	7,41	7,46		7,42	
Bicarbonates	25,8	29,9		27,2	mol/l
Base excess (blood)	2	5,4		2,4	mol/l
Base excess (extra-cellular fluid)	1,9	6,1		2,7	mol/I

gent complex sleep apnoea; however, it was generally transitory and was eliminated within eight weeks of CPAP therapy <sup>2</sup>. The occurrence of CSA during CPAP treatment is related to the severity of OSAS <sup>2</sup>. TECSA has also been occasionally described after the surgical treatment of OSAS, in particular with tracheostomy <sup>3</sup> and maxillomandibular advancement <sup>4</sup>. Central sleep apnoea has not been reported following palatal or pharyngeal surgery <sup>5-7</sup>.

The pathogenesis of CSA after the resolution of OSAS is unclear. CSA during sleep is due to abnormalities in ventilation control mechanisms, and ventilation during sleep, in particular during NREM sleep, is entirely dependent on the metabolic control systems. This means that the ventilatory drive during NREM sleep is dependent on the fluctuations of the levels of arterial PCO<sub>2</sub>.

We believe that, in our patient, transient, self-limiting CSA was triggered by the sudden variation of nocturnal PCO<sub>2</sub> that occurred immediately after surgery in a patient with reduced chemosensitivity due to long-term exposure to nocturnal hypercapnia. In fact, values of arterial PCO<sub>2</sub> on awakening decreased from 52.3 (before surgery) to 42.0 mmHg (after surgery). Severe OSAS may be associated with high levels of nocturnal arterial PCO<sub>2</sub>, due to sleep disordered breathing itself, even in the absence of other respiratory impairment <sup>8</sup>. This, in turn, can result in reduced sensitivity of brainstem chemoreceptors to PCO<sub>2</sub>. The resolution of sleep-related obstruction and restoration of nor-

mal nocturnal values of PCO<sub>2</sub> might have decreased the response of brainstem chemoceptors to PCO<sub>2</sub> to the point of apnoea <sup>1</sup>. In other words, the levels of arterial PCO<sub>2</sub> became inadequate to stimulate ventilation during sleep.

The loop-gain model provides a good explanation for breathing instability in our patient <sup>9</sup>. Loop gain is an engineering term used to quantify the gain of a system controlled by feedback loops. Respiration is in fact such a system. According to the model, a strong interaction occurs between airway caliber and ventilatory stability. It can be hypothesised that, before surgery, our patient presented a low critical pressure for upper airways closure and, consequently, obstructive apnoeas occurred. After surgery, which reduced upper airways resistance, our patient presented a high loop gain (due to reduced sensitivity to CO<sub>2</sub>) and, consequently, respiratory instability. Some weeks later, after a progressive adaptation to the new levels of nocturnal PCO<sub>2</sub>, CSA progressively decreased.

In conclusion, our observation suggests that PSG monitoring may be useful, in the days immediately after surgical intervention, in order to recognise CSA. It seems conceivable that routine assessment of complex sleep apnoea should be performed after surgery at least in patients with preoperative evidence of nocturnal hypercapnia. Moreover, monitoring the levels of arterial PCO<sub>2</sub> may help to predict, and eventually prevent, the occurrence of CSA. In our patient, no symptoms of central apnoeas were re-

ported, the condition was self-limiting and no specific treatment was needed.

#### Conflict of interest statement

None declared

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#### CASE SERIES AND REPORTS

# The EXIT (ex-utero intrapartum treatment) procedure – from the paediatric ENT perspective

Procedura EXIT (ex-utero intrapartum treatment) – prospettive otorinolaringoiatriche pediatriche

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#### **SUMMARY**

The main principle of the EXIT procedure is to maintain uteroplacental circulation with neonatal anaesthesia by controlled uterine hypotonia. This enables securing the foetal airways and decompress or resect large neck and mediastinal foetal masses. The authors present their experience with use of the EXIT procedure in 7 foetuses in whom evaluation and management of the airways were performed. In 4 patients, the neck mass was surgically removed in the neonatal period, in 1 the propranolol treatment was introduced. Two newborns died shortly after the EXIT procedure. The EXIT procedure allows the paediatric otolaryngologist to provide airway patency of newborns during delivery. Both ultrasound and MR imaging are crucial in the prenatal assessment of foetal head and neck masses. Their application in the evaluation of any foetal anomaly is essential for proper prognosis and treatment. Maternal monitoring for complications such as polyhydramnios and preterm labour are important in planning and desirability of the EXIT procedure.

KEY WORDS: EXIT procedure • Foetal neck masses • Foetal airways • Prenatal imaging • Teratoma • Lymphatic malformation

#### **RIASSUNTO**

L'obiettivo principale della procedura EXIT è sfruttare la circolazione uteroplacentare inducendo una anestesia nel neonato e controllando l'ipotonia uterina. In tal modo è possibile garantire la pervietà delle vie aeree e ridurre o resecare grandi masse fetali localizzate nel collo o nel mediastino. Gli autori, in questo lavoro, hanno presentato la loro esperienza di tale procedura in 7 feti. 4 di questi sono stati sottoposti ad asportazione della massa cervivale nel periodo neonatale; in un caso è stato effettuato un trattamento con propanololo; due feti sono morti subito dopo la procedura EXIT. La procedura EXIT permette agli otorinolaringoiatri pediatrici di assicurare la pervietà delle vie aeree durante il travaglio. Sia l'ecografia sia la Risonanza Magnetica sono indispensabili nella valutazione prenatale delle masse del distretto testa-collo, e sono di cruciale importanza per la prognosi e per il trattamento. Altresì importante, ai fini della pianificazione e fattibilità di una procedura EXIT, è il monitoraggio materno di complicanze quali il poliidramnios e il travaglio pretermine.

PAROLE CHIAVE: Procedura EXIT • Masse fetali del collo • Diagnostica prenatale • Teratoma • Malformazioni linfatiche

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#### Introduction

The EXIT (ex-utero intrapartum treatment) procedure was initially used for reversing tracheal occlusion in foetuses with CDH (Congenital Diaphragmatic Hernia). The main principle of the EXIT is to maintain uteroplacental circulation with neonatal anaesthesia by controlled uterine hypotonia <sup>1</sup>. This enables to secure the foetal airways and decompress or resect large neck and mediastinal foetal masses and provide vascular access or cannulation for the ECMO <sup>1 2</sup>. Allowing the paediatric otolaryngologist to gain adequate control of

the airway can thus improve the chances of survival in such cases.

According to Hedrick<sup>3</sup> the indications for EXIT can be based on the goal of the procedure and at the same time include the type of lesion and diagnosis. The EXIT to airway procedure requires the presence of a paediatric otolaryngologist and is attempts to evaluate and secure the airways during delivery because of the presence of a congenital neck mass with airway obstruction or CHAOS syndrome, or the necessity for reversal of tracheal occlusion. The EXIT to resection procedure involves the par-

tial or complete surgical removal of the congenital head and neck masses. The other indications are: the EXIT to ECMO (Extracorporeal Membrane Oxygenation) in congenital heart anomalies and the EXIT to separation procedure (in conjoined twins)<sup>3</sup>.

In contrary to the caesarean section, during the EXIT procedure the achievement of tocolysis is the main aim to provide placental support. After hysterotomy, the foetal head and neck and one arm are delivered and the rest of the foetal body and umbilical cord remain in the uterus to preserve heat and fluid loss <sup>45</sup>.

The authors use the airway algorithm to secure the airways as presented by Marwan et al. from Cincinnati Children's Hospital. First, direct laryngoscopy is performed. If not achieved, the next step is to intubate the foetus under control of a rigid bronchoscope with a diameter of 2.5-3.0 mm. In some cases, partial surgical reduction in the tumour mass is necessary. If the intubation is not possible, the ENT specialist performs tracheostomy. After securing the airway, surfactant is administered prophylactically to prevent barotrauma of the lungs and respiratory failure. The newborn is ventilated by the Ambu bag, and before cutting the umbilical cord, the ENT team checks the position of the tracheostomy tube using a flexible bronchoscope <sup>1</sup>.

#### Clinical cases

The authors present their experience with use of the EXIT procedure in management of 7 foetuses in whom the evaluation and management of the airways were performed. In 4 patients, the neck mass was surgically removed in the neonatal period and in one propranolol treatment was introduced. Two newborns died shortly after the EXIT procedure.

#### Case 1. Reversal of foetal tracheal occlusion

A female foetus with severe CDH and pulmonary hypoplasia underwent reversal tracheal occlusion with the PLUG (Plug the Lung Until it Grows) balloon (the FETENDO procedure was performed in London – "foetal endoscopic surgery") at a gestational age of 26 weeks. Emergency delivery by the EXIT procedure was performed at 32 weeks of gestation because of unrestrained systolic uterus function and heart rate deceleration. During rigid bronchoscopy, the balloon was removed and the neonate was intubated. The chest X-ray revealed left lung agenesis. The baby died on the 2<sup>nd</sup> day after birth for severe respiratory deficiency. Postmortem examination confirmed left pulmonary agenesis and right lung hypoplasia due to lack of efficacy of the PLUG balloon (Figs. 1, 2).



Fig. 1. Rigid bronchoscopy during the EXIT procedure with removal of the PLUG balloon.



**Fig. 2.** Postmortem examination revealed severe CDH and penetration of viscera from the abdominal cavity into the thoracic cavity, left lung agenesis and right lung hypoplasia.

Case 2. Congenital High Airway Obstruction Syndrome (CHAOS)

A female foetus was prenatally diagnosed with laryngeal atresia and polyhydramnios. Parents sought the centre in which the child could be born and undergo laryngeal reconstruction surgery. They obtained the consent of the Polish Ministry of Health to fund the labour, the EXIT procedure and laryngeal reconstruction surgery in the US. The only requirement was to maintain pregnancy to 32 weeks. Unfortunately, spontaneous delivery started at gestational week 27 with premature rupture of membranes. The emergency EXIT was performed with tracheostomy attempt. The foetus presented with hydrops fetalis and died shortly after the EXIT procedure. Postmortem examination revealed complete laryngheal and trachea agenesis.

#### Cases 3-7. Foetal neck masses

The most common indication for the EXIT procedure in our patients was foetal neck mass, most frequently lymphatic malformations and teratomas. In such cases, prenatal imaging of the neck mass related to airway structures and oesophagus is essential to optimise foetal outcome. In 5 foetuses (4 boys and 1 girl), the presence of a neck mass was prenatally diagnosed with ultrasound and MR imaging. It revealed in 2 cases lymphatic malformation, in another 2 teratoma and in 1 infantile haemangioma. In all cases the EXIT procedure was performed. Using direct laryngoscopy or rigid bronchoscopy, the airway was evaluated in all patients. In all endotracheal intubation was performed. Four children underwent complete resection of the neck mass in the neonatal period and the neonate with haemangioma was treated conservatively with propranolol (Figs. 3-5).

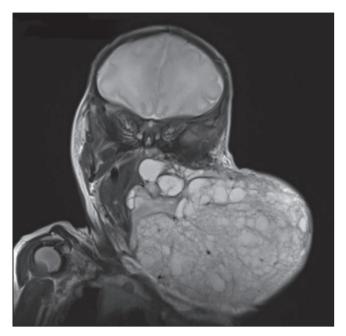


Fig. 3. Neck lymphatic malformation, postnatal MR imaging.



Fig. 4. Neck mass (teratoma) in a female newborn (before surgery).



Fig. 5. Neck mass (teratoma) in a female newborn (after surgery).

#### Discussion

The EXIT procedure was originally reserved for management of cases with severe CDH in which tracheal clipping was introduced antenatally. During delivery, the EXIT procedure and placental support provide the surgeon with additional time for removal of the clips, bronchoscopy, intubation and surfactant administration. In the cases presented, the FETENDO technique with use of the PLUG balloon (PLUG — Plug the Lung Until It Grows) was used. It was introduced into the trachea of the foetus with CDH with extreme pulmonary hypoplasia in order to increase the airway pressure resulting in an increased volume of the lung and alveoli 6-8.

CDH occurs in 1:2500 to 1:5000 live births. It has a mortality rate of 20% and the degree of associated pulmonary hypoplasia and severity of pulmonary hypertension still remain a major determinant of survival. The two factors which clearly influence postnatal mortality are the timing of the termination of gestation and the presence of additional anomalies, which can increase the mortality rate up to 90% <sup>9</sup>. Foetal surgery, because of its complexity and need for special instrumentation, is available only in a few cen-

tres that receive a sufficient number of cases. The optimal solution for cases with CDH is foetal surgery and delivery with the EXIT procedure at the same centre. As emergency delivery and the EXIT procedure were necessary too early (at 32 weeks of gestation) because of heart rate deceleration and CDH led to severe hypoplasia of both lungs, the probability of survival in the first case was poor.

In the second case presented, the problem of proper qualification to the EXIT procedure occurred. In the foetus, prenatally CHAOS (congenital high airway obstruction syndrome) was diagnosed which is a syndrome with near complete or complete intrinsic obstruction of the foetal airway. It is most commonly caused by laryngeal atresia, subglottic stenosis, laryngeal cyst, or laryngeal web. It may be associated with oesophageal atresia, cardiac anomalies, genitourinary anomalies, vertebral anomalies, imperforate anus, syndactyly and anophtalmia 1-3 8. Although the laryngeal and tracheal agenesis was not associated with other anomalies, an increase in polyhydramnios during maternal monitoring was found which worsened the prognostic criteria and therefore the foetus did not have a chance to survive. Although all large neck masses can cause airway compression, the most common indication for the EXIT procedure is cervical teratoma (2 of 5 cases presented), lymphatic malformation (2 of the presented cases), thyroid goiter, neuroblastoma, neural tube defects and rarely haemangioma (1 of the 5 cases presented) 10. Lymphatic malformations account for only about 5% of benign tumours in infants and children. About two-thirds of reported cases are found in the head and neck, usually before the age of 2 years, and some occasionally extend to the mediastinum 11 12. Cervical teratomas are uncommon neoplasms, representing 3% of teratomas in childhood; 5% of cases are localised in the head and neck region with a mortality of 40-50%. Although these lesions are histologically benign, they may be large and may cause airway obstruction (20% of cases). Prenatal ultrasound diagnosis is possible in early pregnancy (15-16 weeks) 13. According to Laje 13 both of these neck masses tend to compress the airway, but in different ways. Cervical teratomas can pull the trachea and lungs superiorly against the thoracic inlet, which can result in pulmonary hypoplasia while lymphatic malformations will not because they are softer. Cervical teratomas, in contrast to lymphatic malformations, can be invasive and destructive causing, for example, mandibular hypoplasia 15.

At the level of prenatal evaluation, the early involvement of a multidisciplinary team including neonatologist, obstetrician, anaesthesiologist, paediatric surgeon, paediatric otolaryngologist, cardiologist and radiologist is essential to correctly qualify the foetus for the EXIT procedure. Foetal ultrasonography allows visualisation

of head and neck malformations and determines their size and localisation. MRI provides information about the relationship of the foetal tumour with adjacent structures such as trachea or oesophagus. It also helps to estimate the severity of the foetal airway obstruction and reveals other anomalies <sup>2</sup> <sup>15</sup>. Maternal monitoring for complications such as polyhydramnios and preterm labour are important in planning and desirability of the EXIT procedure. Finally, the EXIT procedure allows the paediatric otolaryngologist to provide the patency to the newborn's airways during delivery.

#### Conflict of interest statement

None declared.

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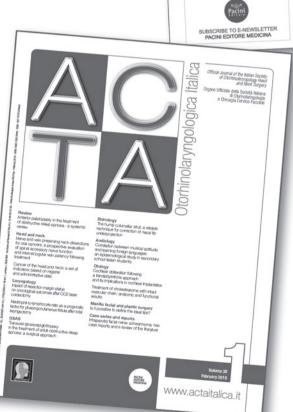
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