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Elective neck dissection during salvage surgery after radiotherapy in patients with head and neck squamous cell carcinoma

IFN- γ and other serum cytokines in head and neck squamous cell carcinomas

Long-term outcomes of alternating chemoradiotherapy in patients with advanced nasopharyngeal cancer

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REVIEW

The efficacy of telerehabilitation in dysphagic patients: a systematic review

L'efficacia della teleriabilitazione in pazienti con disfagia: una revisione sistematica

S. NORDIO¹, T. INNOCENTI², M. AGOSTINI¹, F. MENEGHELLO¹, I. BATTEL¹

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SUMMARY

Telerehabilitation is the use of telecommunications technology for rehabilitation. Recently, some studies have shown positive effects of telerehabilitation of swallowing disorders, yet there are no systematic reviews verifying the evidence. The aim of this review is to assess the effects of telerehabilitation in the field of dysphagia as an alternative to face-to-face patient care, considering swallowing recovery and/or quality of life in different patient populations. We searched the Cochrane Library, MEDLINE, EMBASE, Google Scholar, Google Search and the grey literature from inception until December 2016 for publications written in English (keywords: telerehabilitation, telemedicine, dysphagia, swallowing disorders), which resulted in 330 records. Abstract screening and data extraction was carried out independently by two reviewers. Four papers were selected to read in full, and the methodological quality of the studies included was evaluated using Cochrane Collaboration's tool for assessing risk of bias. One study met our inclusion criteria (Wall et al. 2016), which showed that telerehabilitation improves adherence to treatment compared to patient-directed intervention. Although adherence is an important factor that influences the treatment outcome, clinical outcomes have to be examined in randomised controlled trials in order to reach evidence in this field. Lastly, this systematic review did not demonstrate the efficacy of telerehabilitation compared with face-to-face therapy.

KEY WORDS: Dysphagia • Swallowing disorders • Telemedicine • Telerehabilitation

RIASSUNTO

La teleriabilitazione consiste nell'utilizzo della tecnologia delle telecomunicazioni per la riabilitazione. Recentemente, alcuni studi hanno mostrato gli effetti positivi della teleriabilitazione sui disturbi di deglutizione, ma non esistono revisioni sistematiche che ne verifichino l'efficacia. L'obiettivo di questa revisione è quello di valutare gli effetti della teleriabilitazione nel campo della disfagia in alternativa alla cura del paziente face-to-face, rispetto al recupero del disturbo deglutitorio e/o alla qualità della vita in diverse popolazioni di pazienti. Sono stati considerati i seguenti database: Cochrane Library, MEDLINE, EMBASE, Google Scholar, Google Search e la letteratura grigia fino al dicembre 2016 per pubblicazioni scritte in inglese (parole chiave: teleriabilitazione, telemedicina, disfagia, disturbi della deglutizione), che hanno rilevato 330 articoli. Lo screening degli abstract e l'estrazione dei dati sono stati eseguiti in modo indipendente da due revisori. Sono stati scelti 4 articoli per la lettura integrale; la qualità metodologica degli studi inclusi ed il risk of bias sono stati valutati utilizzando lo strumento della Cochrane "Cochrane Collaboration's tool for assessing risk of bias". Un solo studio ha soddisfatto i nostri criteri di inclusione (Wall et al. 2016), dimostrando che la teleriabilitazione migliora l'aderenza al trattamento da parte del paziente. Anche se l'aderenza rappresenta un fattore importante che influenza l'esito del trattamento stesso, i risultati dovrebbero essere esaminati in trial clinici randomizzati controllati che prendano in esame anche outcome quali il grado di severità della disfagia, al fine di ottenere prove attendibili di efficacia. In conclusione, tale revisione sistematica non dimostra l'efficacia della teleriabilitazione rispetto alla terapia face-to-face per quanto riguarda il miglioramento dei disturbi di deglutizione.

PAROLE CHIAVE: Disfagia • Disturbi di deglutizione • Telemedicina • Teleriabilitazione

Acta Otorhinolaryngol Ital 2018;38:79-85

Introduction

Dysphagia is a swallowing disorder that increases the risk of morbidity and mortality¹. It is well documented that early intervention is crucial for preventing malnutrition and pneumo-

nia². Nevertheless, dysphagia management is often impeded by factors such as distance from healthcare services, especially in patients who live in rural or remote areas, and timely access that could lead to an increase in dysphagia severity³. Recently, a study showed the effects on use of telerehabili-

tation modality to facilitate dysphagia interventions, particularly in relation to the assessment ⁴.

Telerehabilitation is the provision of rehabilitation services to patients at a remote location using information and communication technologies ⁵. In the last decade, rapid developments in telecommunications have increased the possibility of health care delivery. Telerehabilitation involves the remote delivery of different rehabilitation services via telecommunications technology ⁶. The benefits of telerehabilitation include the delivery of prolonged and intensive therapies tailored to patients' needs at home while at the same time making significant cost savings ⁷. Several authors observed that the use of telerehabilitation leads to high levels of patient-reported satisfaction, reinforcing the hypothesis that the delivery of rehabilitative services at a distance is a feasible alternative to routine care ^{8,9}.

Despite the growing use of telerehabilitation in the field of physiotherapy and occupational therapy ¹⁰, studies concerning its application in speech and language therapy are still limited. In particular, in this field the majority have focused on hearing and language disorders, and only few have addressed swallowing disorders ¹¹. Perlman and Witthawaskul ¹² and Malandraki et al. ¹³ demonstrated that remote dysphagia consultations are feasible and relatively accessible from a technological standpoint. For patients with chronic and progressive neurological disorders (e.g. Parkinson's disease), periodic monitoring of communication and swallowing is important to assist them in maintaining these functions. An additional advantage of telerehabilitation in speech and language pathology is the potential to facilitate generalisation of treatment to the individual's everyday life. It is well established that early rehabilitative interventions can prevent and decrease the incidence of pneumonia in dysphagic patients ¹⁴.

Objectives

The aim of this systematic review is to verify the effectiveness of telerehabilitation programmes compared to face-to-face rehabilitation treatments, in terms of swallowing recovery and/or quality of life concerning feeding.

Materials and methods

Search strategy

The review was published in PROSPERO (International Prospective register of systematic reviews) with the registration number CRD42016051662. We used the PRISMA 2009 checklist ¹⁵ (Fig. 1) to establish the protocol.

We searched MEDLINE, Embase and The Cochrane Cen-

tral Register of Controlled Trials (CENTRAL) from inception until December 2016 for publications written in English, using the key words: telemedicine, telerehabilitation, telemonitoring, telehealth, deglutition disorders, eating disorders, swallowing, swallowing disorders, dysphagia. Details of search terms and strategies specific for each database are available in Appendix 1.

We also searched grey literature such as Google Scholar, reference lists of articles, from inception until December 2016. We identified published and unpublished trials, by hand searching the reference lists from relevant articles.

Selection criteria

Studies were eligible for inclusion if they tested telerehabilitation for the recovery of swallowing functions in patients affected by dysphagia due to any type of impairment or disease, including randomised controlled trials (RCT) and quasi-randomised controlled trials with or without blinding of examiner(s). We excluded studies on patients with swallowing disorders due to malocclusion and atypical deglutition. We considered studies focusing on swallowing interventions using telerehabilitation, which includes therapeutic exercises, compensative manoeuvre, monitoring and counselling. In the context of this systematic review, telerehabilitation was considered as:

- provided by means of any kind of technological device;
- allowing healthcare professional/patient interaction both on-line (via a videoconferencing system, the therapist connects to the patient's device, taking control and interacting directly, giving rehabilitation session exactly as it is in the presence of the patient) or off-line (the patient performs the rehabilitation activities prescribed independently using the device);
- provided by healthcare professionals or caregivers through remote supervision.

Data collection and analysis

Two authors (SN and IB) independently screened the titles and abstracts of the 330 records retrieved from the search strategy, applying the selection criteria previously described. The full text of the possible eligible records were retrieved and analysed for final inclusion in this systematic review. Any disagreement was resolved through discussion and contacting a third author (TI), if needed. Two authors (SN and IB) independently extracted the data from the included study, using a standard form, in which the items extracted were: details of the participants (i.e. age, gender, type of disease); inclusion/exclusion criteria for patients' eligibility; duration, intensity and frequency of interventions and controls; description of telerehabilitation programme; outcomes assessed.

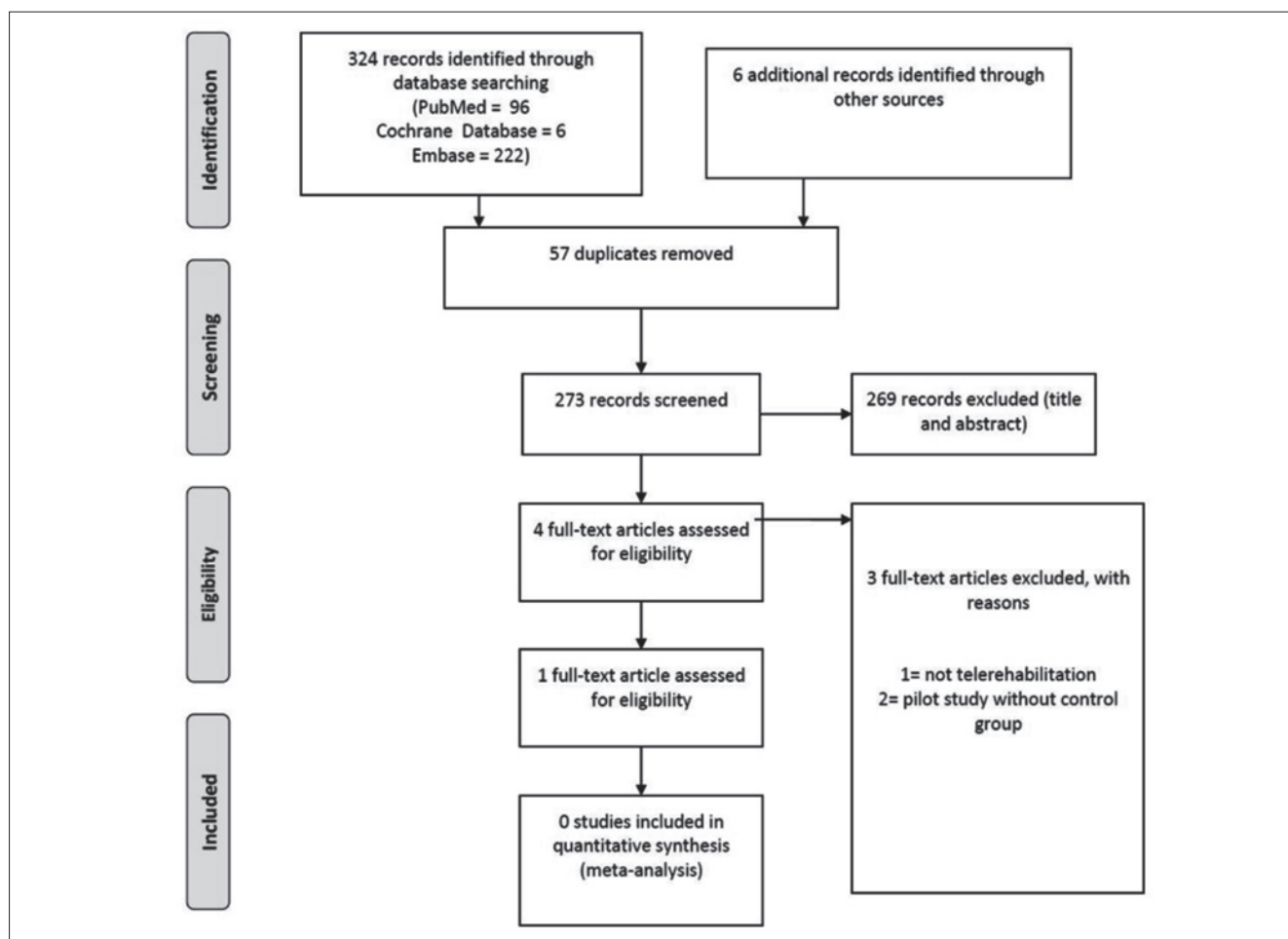


Fig. 1. Prisma flow chart.

Quality assessment

Two authors (SN and IB) independently evaluated the methodological quality of the included studies, using the Cochrane Collaboration's tool for assessing risk of bias¹⁶. Quality assessment of studies was focused on areas of bias which might overestimate the effectiveness of interventions. The domains considered as relevant: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data, selective reporting, other sources of bias.

Results

Selection of studies

The literature search retrieved 330 records (i.e. MEDLINE = 96; embase = 222; CENTRAL = 6; grey literature = 6). After the removal of 57 duplicates, we screened the title and abstract of 273 references and selected 4 pa-

pers, for which we assessed the full text for final inclusion. Among these, 3 papers were excluded for the following reasons. Two studies did not have a control group^{17,18}. One study was excluded because it was not a proper telerehabilitation intervention¹⁹; the authors conducted video-assisted swallowing therapy, but there was not a remote device for telerehabilitation.

Finally, only one RCT²⁰ presented the criteria for inclusion in this review (Fig. 1). Hence, it was not possible to carry out a meta-analysis, and we so carried out only a descriptive analysis of the study selected.

Characteristics of the included study

The main characteristics of the RCT included are described in Table I. Wall et al.'s²⁰ study included 79 patients with oropharyngeal squamous cell carcinoma, comparing 3 groups and examining adherence to a prophylactic swallowing therapy protocol ("Pharyngocise" therapy protocol 21), across three different service delivery models: clini-

Table I. Characteristics of the studies included.

Author Year Design	No. and characteristics of participants	Groups and types of interventions	Endpoint(s)	Assessments and follow-up	Results
Wall LR et al. 2016 RCT	79 adults 8 drop out 63 M, 8 F M = 56.92 years Inclusion criteria: adult patients diagnosed with oropharyngeal squamous cell carcinoma and planned for non- surgical curative intent. Exclusion criteria: severe cognitive deficits, non-English speaking, significant vision, hearing or physical dexterity impairments deemed by the radiation oncology physician at a level that prohibited participation	3 subgroups of 26 patients attending "pharyngocise" therapy protocol: 1 clinician-directed face- to-face therapy; 2 technology assisted therapy model using a purpose- built asynchronous telepractice application, Swallow-it; 3 independent patient self- directed therapy. Duration: 5 days for 6 weeks. Total: 240 cycles	Adherence to prophylactic swallowing exercise protocol. It was measured differently depending on the treatment: • daily in purpose- built exercise log books; • numbers of completed cycles into the Swallow-it system	Adherence was measured every week for six weeks	Significant decline in adherence over time ($p < 0.001$) in all groups, without significant differences among groups. For weeks 1-3: 1 clinician-directed versus Swallow-it does not show any significant difference ($p = 0.466$); 2 clinician-directed model showed significantly better adherence than patient self-directed therapy ($p = 0.014$); 3 Swallow-it presented a trend of higher adherence than patients-direct, but not significant difference ($p = 0.064$). For weeks 4-6: there was no significant difference between the groups ($p = 0.391$)

cian-directed face-to-face therapy, a technology-assisted therapy model using a telepractice application (Swallow-it), and at least an independent patient-directed therapy. The duration of the therapy was five sessions for six weeks. Adherence was measured at the end of every week.

Risk of bias assessment

Figure 2 summarises the assessment of the methodological quality of the study, which is an RCT. There is no risk of selection bias due to an adequate random sequence generation and allocation of the randomisation sequence. We found performance and detection bias due to absence of blindness, and attrition bias due to unbalanced dropouts between the groups. In addition, intention to treat analysis was not applied. The risk of reporting bias is unclear because the study protocol is not available and there is insufficient information to permit judgement of partition of primary and secondary outcomes.

Effects of interventions

The authors found a significant decline in adherence over time ($p < 0.001$) in all groups, and no significant difference in the overall percent of exercise completed by the

service-delivery group ($p = 0.107$). Regarding adherence for weeks 1-3, the results are as follows: the clinician-directed model showed significantly greater adherence than patient self-directed therapy ($p = 0.014$), while clinician-directed versus Swallow-it did not show any significant difference ($p = 0.466$). Finally, Swallow-it presented a trend towards higher adherence than patient-directed, but the difference was not significant ($p = 0.064$). For weeks 4-6, they found adherence was not significantly different between groups ($p = 0.391$).

Discussion

Despite the emerging number of telerehabilitation studies on dysphagic patients¹⁷⁻¹⁹, we found only one study that was eligible for inclusion in this systematic review²⁰. The aims of the included study were to verify the adherence to a prophylactic swallowing exercise protocol and if clinical and demographic factors influence adherence. Thus, this study did not report any swallowing outcomes and/or swallowing improvements, which are essential to verify the effectiveness of a treatment. They found that clinician-directed treatment obtained the highest adherence compared with telerehabilitation (Swallow-it) and

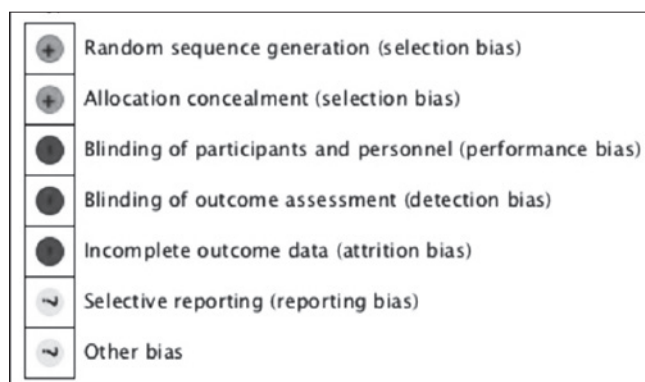


Fig. 2. Risk of bias assessment (from Wall et al., 2016²⁰, mod.).

patient-direct therapy. Nevertheless, there was a trend for greater adherence in telerehabilitation than patient-direct. This finding suggests that patients may be more motivated and encouraged when they have access to a telepractice service model instead of independent therapy. Although adherence represents an important value for positive treatment outcomes, this study had some methodological limitations. First, the criteria for adherence assessment varied depending on the treatments, resulting in difficulties comparing outcomes. Moreover, in the patient-directed group, adherence was calculated subjectively through the number of exercises reported by each patient in log books, thus increasing the risk of bias. The multivariable analysis was based only on variables taken prior to chemotherapy, and so other variables could have influenced adherence. In addition, during data collection, there were some dropouts that resulted in heterogeneous sample sizes.

The results of our systematic review suggest that telerehabilitation in the field of dysphagia treatment is at an initial phase. We considered it important to highlight the value of this topic in the field of deglutition disorders, with objective data from a systematic review, because of the relevance of technological tools for telerehabilitation that could be implemented in future studies.

Several limitations of this review should be acknowledged. First of all, most of the studies in telerehabilitation concerning dysphagia are characterised by small sample sizes, large variability of illnesses included, heterogeneity of treatments and outcomes and the consistent presence of biases. The limitation of small samples is common in the rehabilitation literature concerning dysphagia, because of the different diagnoses that can cause it, the large range of severity and disability experienced by patients and the long time needed to observe changes in clinical outcomes⁷. In addition, we chose to distinguish

telerehabilitation from other telemedicine applications (e.g. telemonitoring, teleradiology) because of the possibility of providing therapeutic interventions, remotely controlled by healthcare professionals, with rehabilitation intent. Moreover, we only considered trials reported in English, which restricted the raw dataset of records used for screening.

Conclusions

The systematic review did not provide final evidence on the efficacy of telerehabilitation in dysphagia recovery. Undoubtedly, in the last years telerehabilitation is becoming an interesting model of care even in speech and language therapy, which has been examined by several studies^{3 11}. Specifically, telemedicine offers an innovative approach to increase access to clinical rehabilitation medicine services and to guarantee adequate services to people with swallowing disorders, which require periods of intensive treatment followed by long-term management. Further, it is considered more motivating to receive rehabilitation in a patient's own environment⁸. For these reasons, though face-to-face intervention has always been considered the 'gold standard' of care, it is necessary to consider alternative types of service delivery as supplement or replacement of face-to-face treatments in some cases. Considering telerehabilitation in other fields, encouraging data can be seen, and the only one RCT²⁰ paper we found by the systematic review suggests good compliance of patients who attended telerehabilitation. Notwithstanding, additional research in the field of dysphagia is needed to define the benefits and risks associated with assisting patients in telerehabilitation modality. Future trials need to have a more robust design and evaluate the effectiveness of treatments based on specific clinical outcomes and quality of life, in different populations of patients with different type and severity of dysphagia, and associated with cost accountability and cost effectiveness analysis.

Acknowledgements

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References

- Gonzalez-Fernandez M, Daniels SK. *Dysphagia in stroke and neurologic disease*. *Phys Med Rehabil Clin N Am* 2008;19:867-88.
- Bours GJ, Speyer R, Lemmens J, et al. *Bedside screening tests vs videofluoroscopy or fiberoptic endoscopic evaluation of*

- swallowing to detect dysphagia in patients with neurological disorders: systematic review. *J Adv Nurs* 2009;65:477-93.
- ³ Mashima PA, Brown JE. *Remote management of voice and swallowing disorders*. *Otolaryngol Clin North Am* 2011;44:1305-16.
 - ⁴ Ward EC, Burns CL, Theodoros DG, et al. *Impact of dysphagia severity on clinical decision making via telerehabilitation*. *Telemed J E Health* 2014;20:296-303.
 - ⁵ Brennan DM, Mawson S, Brownsell S. *Telerehabilitation: enabling the remote delivery of healthcare, rehabilitation, and self management*. *Stud Health Technol Inform* 2009;145:231-48.
 - ⁶ Rogante M, Grigioni M, Cordella D, et al. *Ten years of telerehabilitation: a literature overview of technologies and clinical applications*. *Neuro Rehabil* 2010;27:287-304.
 - ⁷ Dansky KH, Palmer L, Shea D, et al. *Cost analysis of telehomecare*. *Telemed J E Health* 2001;7:225-32.
 - ⁸ Piron L, Turolla A, Tonin P, et al. *Satisfaction with care in post-stroke patients undergoing a telerehabilitation programme at home*. *J Telemed Telecare* 2008;14:257-60.
 - ⁹ Laver KE, Schoene D, Crotty M, et al. *Telerehabilitation services for stroke*. *Cochrane Database Syst Rev* 2013;12:CD010255.
 - ¹⁰ Agostini M, Moja L, Banzi R, et al. *Telerehabilitation and recovery of motor function: a systematic review and meta-analysis*. *J Telemed Telecare* 2015;21:202-13.
 - ¹¹ Molini-Avejonas DR, Rondon-Melo S, Amato CA, et al. *A systematic review of the use of telehealth in speech, language and hearing sciences*. *J Telemed Telecare* 2015;21:367-76.
 - ¹² Perlman AL, Witthawaskul W. *Real-time remote telefluoroscopic assessment of patients with dysphagia*. *Dysphagia* 2002;17:162-7.
 - ¹³ Malandraki GA, McCullough G, He X, et al. *Teledynamic evaluation of oropharyngeal swallowing*. *J Speech Lang Hear Res* 2011;54:1497-505.
 - ¹⁴ Daniels SK, Pathak S, Rosenbek JC, et al. *Rapid aspiration screening for suspected stroke. Part 1: Development and Validation*. *Arch Phys Med Rehabil* 2016;97:1440-8.
 - ¹⁵ Moher D, Shamseer L, Clarke M, et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement*. *Syst Rev* 2015;4:1.
 - ¹⁶ Higgins JP, Altman DG, Gotzsche PC, et al. *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials*. *BMJ* 2011;343:d5928.
 - ¹⁷ Wall LR, Ward EC, Cartmill B, et al. *Examining user perceptions of SwallowIT: a pilot study of a new telepractice application for delivering intensive swallowing therapy to head and neck cancer patients*. *J Telemed Telecare* 2017;23:53-9.
 - ¹⁸ Clawson B, Selden M, Lacks M, et al. *Complex pediatric feeding disorders: using teleconferencing technology to improve access to a treatment program*. *Pediatr Nurs* 2008;34:213-6.
 - ¹⁹ Manor Y, Mootanah R, Freud D, et al. *Video-assisted swallowing therapy for patients with Parkinson's disease*. *Parkinsonism Relat Disord* 2013;19:207-11.
 - ²⁰ Wall LR, Ward EC, Cartmill B, et al. *Adherence to a prophylactic swallowing therapy program during (chemo) radiotherapy: impact of service-delivery model and patient factors*. *Dysphagia* 2016;32:279-92.
 - ²¹ Carnaby-Mann G, Crary MA, Schmalfuss I, et al. *"Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy*. *Int J Radiat Oncol Biol Phys* 2012;83:210-9.

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Appendix 1. Electronic searches

MEDLINE

Telemedicine (Mesh) OR Telerehabilitation (Mesh) OR Telerehabilitation OR Telemedicine OR Telemonitoring OR Telehealth AND Deglutition Disorders (Mesh) OR Deglutition disorders OR Eating disorders OR Swallowing OR Swallowing disorders OR Dysphagia

EMBASE

Telemedicine OR Telerehabilitation OR Telemonitoring OR Telehealth AND Deglutition disorders OR Eating disorders OR swallowing OR Swallowing disorders OR Dysphagia

THE COCHRANE LIBRARY

Results of the free words research were collected together:

- dysphagia telerehabilitation;
- eating disorders telerehabilitation;
- deglutition disorders and swallowing disorders telerehabilitation;
- eating disorders telemedicine;
- swallowing disorders and deglutition disorders telemedicine;
- dysphagia disorders telemedicine.

HEAD AND NECK

Elective neck dissection during salvage surgery after radiotherapy in patients with head and neck squamous cell carcinoma

Svuotamento linfonodale cervicale elettivo nella chirurgia di salvataggio dopo radioterapia in pazienti con carcinoma a cellule squamose del distretto testa-collo

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SUMMARY

Elective neck dissection in patients with recurrent head and neck squamous cell carcinoma (HNSCC) without evidence of neck disease (crN0) is poorly defined. A retrospective review was carried out on 165 crN0 patients treated with salvage surgery and elective neck dissection. Multivariate Cox analysis and recursive partitioning analysis were used to evaluate prognostic factors. The frequency of occult neck node metastases in the neck dissection (rpN+) was 16.4%. The risk of occult metastases for glottic rpT1-T2 recurrences was 5.9%, for glottic rpT3-T4 recurrences 13.2%, for non-glottic rpT1-T2 recurrences 16.1% and for locally advanced (rpT3-T4) non-glottic recurrences 31.1%. Patients with occult neck node metastases (rpN+) had a 5-year adjusted survival rate of 38.1%, while patients without nodal disease (rpN0) had a 5-year adjusted survival rate of 71.1% ($p = 0.0001$). Elective neck dissection can be omitted in crN0 patients with rT1-T2 glottic recurrence. We consider it advisable to perform elective neck dissection in all other situations.

KEY WORDS: Salvage surgery • Elective neck dissection • Occult neck node metastases • Head and neck cancer

RIASSUNTO

Lo svuotamento linfonodale cervicale elettivo in pazienti con recidiva di carcinoma a cellule squamose del distretto testa-collo, senza evidenza clinico-radiologica di metastasi linfonodale (crN0), è scarsamente descritto in letteratura. Per questa ragione è stata condotta una revisione retrospettiva di una coorte di 165 pazienti crN0, sottoposti a chirurgia di salvataggio e svuotamento cervicale elettivo. Per la valutazione dei fattori prognostici sono state utilizzate l'analisi multivariata di Cox e l'analisi di partizione ricorsiva. Successivamente allo svuotamento cervicale, la frequenza di metastasi linfonodali occulte (rpN+) è stata del 16,4%. Il rischio di metastasi occulte, in caso di tumori glottici recidivanti, è stato del 5,9% per le categorie rpT1-T2, e del 13,2% per le categorie rpT3-T4. Per quanto riguarda i tumori non-glottici recidivanti, il rischio di metastasi occulte è stato del 16,1% per le categorie rpT1-T2, mentre in caso di neoplasie localmente avanzate (rpT3-T4) è stato del 31,1%. La sopravvivenza a 5 anni dei pazienti con metastasi linfonodali occulte (rpN+) è stata del 38,1%, mentre la sopravvivenza a 5 anni dei pazienti che non hanno presentato invasione linfonodale (rpN0) è stata del 71,1% (con una differenza statisticamente significativa, $p = 0,0001$). Lo svuotamento cervicale potrebbe essere omesso in pazienti con neoplasia glottica recidiva crN0 rT1-T2. Al contrario, alla luce di questi risultati, riteniamo che sia consigliabile eseguire questa tecnica in tutte le altre situazioni.

PAROLE CHIAVE: Chirurgia di salvataggio • Svuoatamento laterocervicale • Metastasi cervicali occulte • Tumore del distretto testa-collo

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Introduction

There is no doubt about the benefits of performing therapeutic neck dissection during salvage surgery in patients

with local recurrence of head and neck squamous cell carcinoma (HNSCC) after radiotherapy or chemoradiotherapy and evidence of cervical metastases (crN+). However,

the convenience of elective neck dissection in patients with local recurrence of HNSCC and no evidence of regional disease (crN0) remains unclear.

Some authors recommend performing elective neck dissection on crN0 patients during salvage surgery¹⁻⁴. Others consider it appropriate to carry out elective neck dissection only in patients with locally advanced recurrence or clinically positive nodes at the time of initial diagnosis of the tumour^{5,6}. On the other hand, a group of authors do not consider it necessary to systematically perform neck dissection in crN0 patients with HNSCC local recurrence during salvage surgery due to: (i) low percentage of occult neck node metastases in these patients; (ii) good regional control achieved in patients kept under observation; (iii) increase in postoperative complications related to performing neck dissection⁷⁻¹⁴.

The goal of our study was to determine the risk of occult nodal metastases in HNSCC patients with local recurrence without evidence of neck disease (crN0), and to define the utility of performing elective neck dissection during salvage surgery in this group of patients.

Materials and methods

We conducted a retrospective study using a database that has prospectively collected data on epidemiology, treatment and follow-up of all patients with HNSCC treated at our centre since 1985¹⁵. Eligible patients met the following criteria: (1) pathological diagnosis of HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx treated with radical intention between 1992 and 2012; (2) primary tumour treated with radiotherapy or chemoradiotherapy; (3) not having undergone a neck dissection during primary treatment of the tumour; (4) pathologically confirmed recurrence of the tumour at the primary site; (5) clinical and radiological N0 at the time of salvage surgery; (6) salvage surgery of the local recurrence with an elective neck dissection; (7) minimum follow-up of 2 years after salvage surgery unless recurrence or death. Patients were staged using the 7th edition of the TNM classification at the time of initial treatment and at the time of salvage surgery¹⁶. An oncology panel evaluated all patients and recommended salvage surgery and neck dissection. All procedures were reviewed by the Institutional Review Board of our centre. The study conforms to the principles outlined in the Declaration of Helsinki.

All patients included had a radiologic screening of the N0 neck. A CT scan was routinely used for patients with a laryngeal or hypopharyngeal tumour, while for patients with an oral cavity or an oropharyngeal tumour MRI was used preferentially. In all cases, the radiologic report ex-

cluded the presence of positive or suspicious neck nodes. None of our patients was studied with PET-CT.

In our centre, elective neck dissection was performed systematically in patients with local recurrence when salvage surgery was carried out using an open cervical approach. One hundred and sixty-five patients who met the inclusion criteria were included in the study. Table I shows location of the primary tumour, local and regional extension of the primary tumour, local and regional management during primary treatment, local extension of the recurrence and salvage surgery. For early glottic carcinomas, the field of radiotherapy was limited to the central neck, avoiding prophylactic irradiation of the cervical neck nodes. One hundred and three patients received radiotherapy over the neck nodes during the treatment of the primary head and neck tumour. Patients with N0 primary tumour (n = 69) received 50 to 55 Gy as a total dose of radiotherapy over the neck. The group of N+ patients (n = 34) received 65 to 72 Gy. Local recurrences were diagnosed during the first 2 years of follow-up after treatment of the primary tumour in 83.8% of cases.

Table I. Characteristics of patients included in the study.

		N	(%)
Sex	Men	157	(95.2%)
	Women	8	(4.8%)
Age: mean / standard deviation	58.9 / 10.1 years		
Primary tumour location	Oral cavity	14	(8.5%)
	Oropharynx	18	(10.9%)
	Hypopharynx	7	(4.2%)
	Supraglottis	36	(21.8%)
Primary tumour local extension	Glottis	90	(54.5%)
	T1-2	112	(67.9%)
	T3-4	53	(32.1%)
Primary tumour regional extension	N0	131	(79.4%)
	N+	34	(20.6%)
Primary tumour treatment	RT	145	(87.9%)
	CT-RT	20	(12.1%)
Primary tumour neck management	Observation	62	(37.6%)
	Radiotherapy	103	(62.4%)
Recurrence local extension	rT1-2	82	(49.7%)
	rT3-4	83	(50.3%)
Salvage surgery	Total laryngectomy	88	(53.3%)
	Laryngopharyngectomy	20	(12.1%)
	Partial laryngectomy	29	(17.6%)
	Pelviglossectomy	19	(11.7%)
	Bucopharyngectomy	9	(5.5%)

All patients underwent an elective neck dissection during salvage surgery. A total of 221 selective neck dissections at levels II-IV, 26 of levels I-III and 13 of levels II-III were carried out. For patients with a glottic tumour with subglottic extension (n = 13) a dissection of the paratracheal nodes (level VI) was also included. Bilateral neck dissection was performed in 57.6% of patients.

We used the Chi-square or Fisher's exact test in univariate analysis, and a logistic regression model in the multivariate analysis. Patients were classified according to a recursive partitioning analysis with a classification and regression tree (CRT) method, considering the appearance of occult neck node metastases in the neck dissection (rpN+) as the dependent variable. Location of the primary tumour, local and regional extension of the primary tumour, local extension of the recurrence, and initial management of the neck were considered as independent variables. We reviewed the pathologic reports of neck dissections of the rpN+ patients, collecting data about the size of the positive neck nodes. Micrometastases were defined as microscopic deposits of malignant cells smaller than 2-3 mm in diameter.

Survival curves were calculated using the Kaplan-Meier technique. Differences in survival were compared using the log-rank test.

Results

Occult neck node metastases were found during neck dissection (crN0/rpN+) in 27 patients (16.4%). Of the 27 patients with positive neck dissection, 14 (51.9%) were found to have only one pathological neck node (rpN1), 10 (37.0%) had 2 or more ipsilateral metastatic neck nodes (rpN2b) and 3 (11.1%) showed bilateral nodal involvement (rpN2c). Six of the rpN+ patients (22.2%) had pathological evidence of nodes with extracapsular tumour spread.

Eleven patients had micrometastases, 14 had metastatic neck nodes up to 1 cm and only 2 had neck node metastases larger than 1 cm. In both cases of neck node metastases greater than 1 cm, the pathologic report pointed out that the size of the neck nodes was about 2 cm, and in one case it had necrosis. We reviewed the images of these two patients (a CT and a MRI corresponding to one patient with a hypopharyngeal crT4N0 tumour and one patient with an oropharyngeal crT2N0 tumour, respectively), and did not find any radiological evidence of neck disease.

Table II shows the percentage of patients with occult neck node metastases depending on the location of the primary tumour, local and regional extension of the primary tumour, neck management during the initial treatment and local extension of the recurrence. According to the results of uni-

variate analysis, the only variable significantly associated with the appearance of occult neck node metastases was the local extension of the tumour at the time of recurrence. None of the variables had significant prognostic influence when included in the multivariate analysis. Nevertheless, a higher frequency of occult neck node metastases was found in patients with locally advanced recurrences (rT3-4), and a lower frequency was found in those with glottic tumours. Information regarding HPV status was available for 17 of the 18 patients with oropharyngeal carcinoma. Only one patient was HPV positive, without showing evidence of occult metastasis in the neck dissection. The frequency of occult neck node metastasis in patients with HPV negative tumours was 18.8% (3/16).

Considering the appearance of occult neck node metastases as the dependent variable, the CRT method classified patients according to the initial tumour location and the extension of the recurrence. A total of four terminal nodes were obtained using this classification method (Fig 1). Due to the similar risk of occult neck node metastases between nodes 2 (rT3-4 glottic carcinoma) and 3 (rT1-2 non-glottic carcinoma), both nodes were grouped in one category. Table III shows the categories according to the risk of appearance of occult neck node metastases as defined by the CRT classification system.

The three patients with early glottic recurrences (rT1-2) who had occult neck node metastases were specifically reviewed. All three patients had recurrences with subglottic extension of the tumour (rT2). In two cases, the neck node metastases appeared in the anterior neck dissection, and not in the lateral neck dissection. In the third case, the occult neck node metastases appeared in the lateral selective neck dissection.

Survival was analysed according to the risk of having occult neck node metastases at neck dissection. Figure 2 shows adjusted survival curves after salvage surgery for patients without occult neck node metastases (rpN0, n = 138), and for patients with occult neck node metastases (rpN+ n = 27). Five-year adjusted survival was 71.1% (CI 95%: 62.9-79.3%) for rpN0 patients, and 38.1% (CI 95%: 18.4-57.8%) for rpN+ patients. Significant differences in survival were found according to the pathological state of the neck dissection (P = 0.0001).

Discussion

The management of nodal areas in patients without clinical or radiological evidence of cervical disease (crN0) treated with salvage surgery after local failure of the previous treatment with radiotherapy or chemoradiotherapy is a controversial topic. The incidence of occult neck node

Table II. Risk of occult neck node metastases in elective neck dissection according to different clinical variables.

		Univariate analysis		Multivariate analysis		
		rpN+	P	HR	CI 95%	P
Primary tumour location	Oral cavity (n = 14)	3 (21.4%)	0.088	1		
	Oropharynx (n = 18)	4 (22.2%)		0.94	0.16-5.41	0.946
	Hypopharynx (n = 7)	2 (28.6%)		1.16	0.13-10.12	0.891
	Supraglottis (n = 37)	10 (27.0%)		0.89	0.18-4.33	0.892
	Glottis (n = 89)	8 (9.0%)		0.23	0.04-1.28	0.095
Primary tumour local extension	T1-2 (n = 112)	14 (12.5%)	0.051	1		
	T3-4 (n = 53)	13 (24.5%)		1.23	0.40-3.82	0.711
Primary tumour regional extension	N0 (n = 131)	20 (15.3%)	0.455	1		
	N+ (n = 34)	7 (20.6%)		0.55	0.17-1.78	0.324
Recurrence local extension	rT1-2 (n = 82)	8 (9.8%)	0.023	1		
	rT3-4 (n = 83)	19 (22.9%)		2.47	0.90-6.80	0.079
Primary tumour neck management	Observation (n = 62)	6 (9.7%)	0.072	1		
	Radiotherapy (n = 103)	21 (20.4%)		0.78	0.18-3.78	0.739

metastases in elective neck dissection performed in these patients ranges between 0% and 25% in the different published series (Table IV). Variability in the percentage of occult neck node metastases may be attributed to the different types of patients included in each study. Some series evaluated patients with laryngeal tumours^{12 4 5 8 11-14 17}, including different proportions of patients with glottic

tumours, while in other series several head and neck locations were involved^{3 7 9 10 18 19}. Moreover, some series included patients with locally advanced tumours or recurrences^{4 10-12}, while others preferentially evaluated patients with more limited tumours^{5 7 8 18}.

As a result, conclusions by different authors are highly variable. A number of authors recommend performing elective neck dissection in crN0 patients when salvage surgery is carried out. Others only consider performing neck dissection in patients with locally advanced recurrent tumours, in patients with tumours localised in the supraglottis, or in patients with initial nodal involvement. Finally, based on the low incidence of occult neck node metastases and the acceptable results achieved with the policy of neck observation, a group of authors do not consider it necessary to perform elective neck dissection at the time of salvage surgery (Table IV).

One of the reasons to perform elective neck dissection in crN0 patients during salvage surgery after treatment with radiotherapy or chemoradiotherapy would be that the more aggressive biological behavior of the tumour involved in the recurrence is associated with an increased risk of occult neck node metastases. Additionally, as initial treatment with radiotherapy or chemoradiotherapy failed to eradicate the primary tumour, the persistence of subclinical disease at the cervical level could be possible. Moreover, in case of nodal recurrence, control options with a second salvage surgery at the cervical level are very limited^{20 21}.

The authors who advocate for a “wait and see” policy argue that due to the low incidence of occult neck node

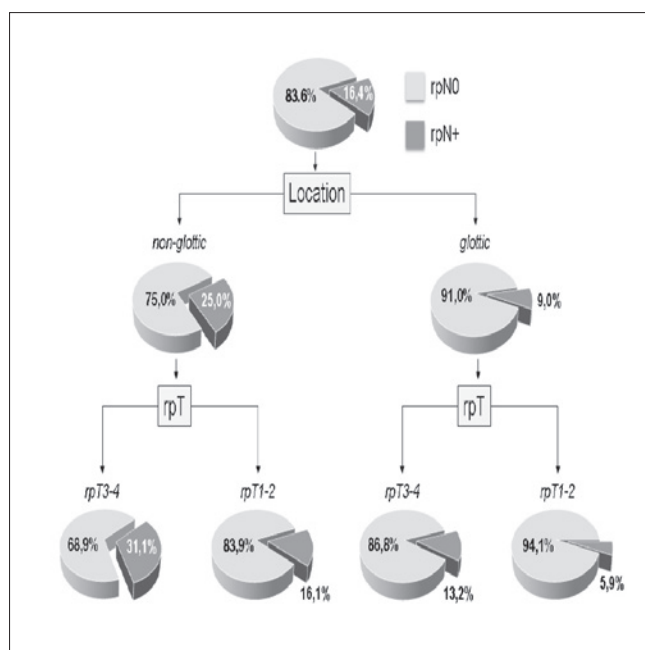
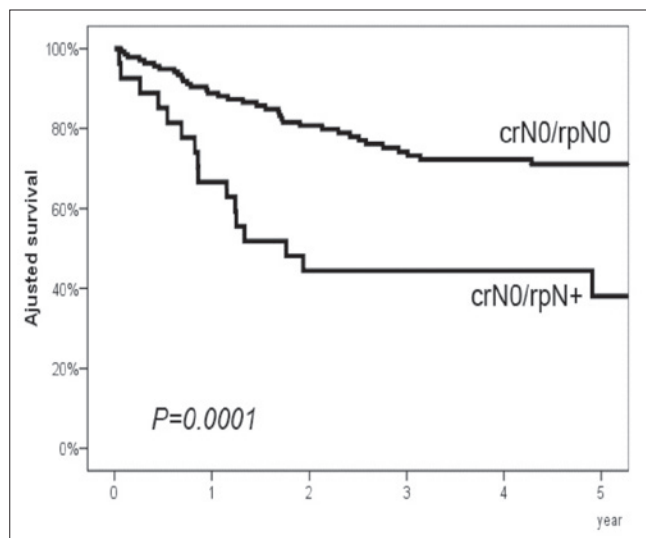
**Fig. 1.** Classification obtained with the classification and regression tree method.

Table III. Classification of patients according to the risk of occult neck node metastases in elective neck dissections.

Category		Number of patients	% Occult metastases
Low risk	Glottic tumours rT1-2	51	5.9%
Intermediate risk	Glottic tumours rT3-4 Non-glottic tumours rT1-2	69	14.5%
High risk	Non-glottic tumours rT3-4	45	31.1%

**Fig. 2.** Adjusted survival of patients with HNSCC local recurrence according to the presence of occult neck node metastases.

metastases, there is no evidence that the systematic addition of elective neck dissection increases regional control of the tumour or improves prognosis. In addition, some authors found that performing elective neck dissection involved an increase in postoperative complications^{8,9,12-14}. Sanabria et al.²² reviewed the results reported in the literature and concluded that the observation policy would be justified for patients with glottic tumours classified originally as early tumours (T1-T2), and also in recurrent early tumours (rT1-2). For patients with advanced laryngeal recurrences (rT3-4) and non-glottic tumours, an elective neck dissection should be considered.

Our study analysed a wide range of patients with head and neck tumours of different locations. They were treated with a protocol that included the systematic performance of elective neck dissection in crNO patients who are candidates for open salvage surgery. We reached conclusions similar to those of Sanabria et al.²². The recursive

partitioning analysis classified patients according to the risk of having neck node metastases, and three categories were defined. Patients with limited glottic recurrences (rT1-2) showed a relatively low risk of subclinical nodal involvement (5.9%), so that the observation policy for the neck would be justified. In case of recurrence with subglottic involvement, performing dissection of lymph nodes along the recurrent laryngeal nerves would be indicated. Patients with advanced glottic recurrences (rT3-4) or limited tumour recurrences located outside the glottis (rT1-2) showed an intermediate risk of nodal involvement (14.5%). Finally, in patients with advanced tumour recurrence with non-glottic location (rT3-4), the risk of occult neck node metastases was high (31.1%). Based on our results, we consider it justified to systematically perform elective neck dissection in patients whose risk of having lymph node involvement is intermediate or high.

In the majority of rpN+ cases, the tumour burden was low. Eleven patients had micrometastases, and 14 patients had metastatic nodes up to 1 cm. However, 2 patients had 2 cm neck nodes. We reviewed the radiological images carried out prior to the salvage surgery, and did not find any evidence of nodal neck disease. A progression of the tumour in the period between the radiologic study and the salvage surgery could justify the inconsistency between the image study and the pathologic report in those two patients.

One aspect to consider is the influence of radiation fields in the appearance of neck node metastases in case of recurrence. Radiotherapy causes loss of lymphoid tissue and its replacement by fibrous tissue^{23,24}. These changes may serve as a barrier for lymphatic dissemination in case of local recurrence in patients who were previously treated with radiotherapy. However, in a study performed by Soares et al.³ where the incidence of occult neck node metastases was assessed in patients who were treated with primary radiotherapy or chemoradiotherapy and had a local recurrence or a second primary tumour, the incidence and anatomic distribution of subclinical neck node metastases was comparable to what was reported in untreated NO necks. The authors concluded that previous treatment with radiotherapy did not change the anticipated pattern of neck node metastases in patients with local recurrence after primary treatment with radiotherapy. Similarly, Deganello et al.¹³ did not find significant differences between previous treatment with neck radiotherapy and the risk of occult neck node metastases in crNO patients treated with salvage surgery.

According to our results, the appearance of occult neck node metastases in neck dissection during salvage surgery was significantly associated with lower survival, as in patients with HNSCC and neck node metastases at initial treatment²⁵.

Table IV. Percentage of occult neck node metastases in crN0 patients and suggestions for performing elective neck dissection obtained from published studies.

Author (year)	Location	N	Treatment	% Occult metastases (rpN+/neck dissections)	Elective neck dissection
Wax (1999) ²	Larynx	34	RT	17% (6/34)	Yes
Solares (2005) ³	H&N	69	RT	25% (17/69)	Yes
Yao (2005) ⁵	Larynx	63	RT	12% (5/41)	Only rT3/4 and supraglottis
Temam (2005) ¹⁰	H&N	30	RT	3% (1/30)	Not necessary
Farrag (2006) ¹¹	Larynx	51	RT	12% (4/34)	Not necessary
Dagan (2010) ⁷	H&N	57	RT	10% (4/40)	Not necessary
Bohannon (2010) ¹²	Larynx	71	RT	8% (3/38)	Not necessary
Amit (2013) ⁴	Larynx	42	RT	19% (8/42)	Yes
Yirmibesoglu (2013) ⁹	H&N	44	RT	10% (3/30)	Not necessary
Lee (2013) ¹⁷	H&N	149	RT/Sur	8% (6/80)	Only initial N+ and early recurrence
Basheeth (2013) ⁸	Larynx	45	RT	8% (3/38)	Not necessary
Prendes (2014) ¹⁸	H&N (N+)	16	RT	40% (4/10)	Yes
Hilly (2013) ⁶	Larynx	87	RT	13% (6/48)	rT3-4
Deganello (2014) ¹³	Larynx	110	RT	0% (0/7)	Not necessary
Pezier (2014) ¹⁴	Larynx	28	RT	7% (2/28)	Not necessary
Koss (2014) ¹⁶	Larynx	68	RT	28% (19/68)	Yes

H&N: Head and neck; RT: Radiotherapy; Sur: Surgery

Only one of our patients with an oropharyngeal carcinoma treated with salvage surgery was HPV positive. We think that the low proportion of HPV positive oropharyngeal tumours in our study is a consequence of the low percentage of HPV positive patients in our geographical setting^{26,27}, coupled with the high control of the disease achieved with treatment in those HPV positive tumours. It would be interesting to investigate the frequency of occult neck node metastases in elective neck dissections in oropharyngeal patients in function of HPV status of the tumour.

The main limitation of our study is its retrospective nature and the wide period of time it covers. Although cervical management of patients with salvage therapy has not been substantially modified, progressive improvement of CT and MRI over the study period may have changed the classification of crN0 patients. We do not have experience about the efficiency of PET-CT in the assessment of crN0 patients who are candidates for salvage surgery. Currently¹⁸, F-FDG PET-CT has a fundamental role in the evaluation during follow-up of patients with a HNSCC, with a higher degree of accuracy in detecting recurrences of the disease than other imaging modalities^{28,29}. The results of a systematic review and a meta-analysis carried out by Gupta et al.³⁰ including 30 studies (1,525 patients) assessing the diagnostic performance of ¹⁸F-FDG PET and PET-CT in the assessment of response and surveillance for neck nodes in HNSCC patients, reported a high negative predictive value (94.5%) and a suboptimal positive

predictive value (52.1%). Most studies evaluating the predictive capacity of PET/PET-CT in the neck analyse the outcome obtained after completion of radical treatment. PET-CT has been shown to be an effective diagnostic tool for detecting occult cervical metastatic nodes in patients with negative neck palpation findings in the context of the initial assessment of patients with HNSCC^{31,32}. However, there are practically no data on the prognostic capacity in the detection of occult neck node metastasis of PET-CT in patients with local recurrence of the disease. Gilbert et al.³³ carried out a study examining the sensitivity and specificity of PET-CT in patients with a laryngeal carcinoma recurrence after radiotherapy treated with a total laryngectomy and neck dissections. The authors evaluated 8 patients crN0 who had PET-CT reads that were negative, three of whom had positive nodal disease in the elective neck dissection, giving a negative predictive value of the PET-CT of 62.5%. Larger studies are necessary to evaluate the efficiency of PET-CT in the detection of hidden cervical metastatic deposits in crN0 patients who are candidates for salvage surgery.

Conclusions

Based on our results, in patients without clinical or radiological evidence of lymph node involvement (crN0) we suggest to perform an elective neck dissection during salvage surgery in non-glottic rT1-T2 recurrences, and

in locally advanced glottic and non-glottic recurrences (rT3-T4). Due to the low incidence of occult neck node metastases in crN0 patients with early glottic recurrences (rT1-T2), elective neck dissection could be omitted in these cases.

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References

- 1 Yuen AP, Wei WI, Ho CM. *Results of surgical salvage for radiation failures of laryngeal carcinoma*. *Otolaryngol Head Neck Surg* 1995;112:405-9.
- 2 Wax MK, Touma BJ. *Management of the N0 neck during salvage laryngectomy*. *Laryngoscope* 1999;109:4-7.
- 3 Solares CA, Fritz MA, Esclamado RM. *Oncologic effectiveness of selective neck dissection in the N0 irradiated neck*. *Head Neck* 2005;27:415-20.
- 4 Amit M, Hilly O, Leider-Trejo L, et al. *The role of elective neck dissection in patients undergoing salvage laryngectomy*. *Head Neck* 2013;35:1392-6.
- 5 Yao M, Roebuck JC, Holsinger FC, et al. *Elective neck dissection during salvage laryngectomy*. *Am J Otolaryngol* 2005;26:388-92.
- 6 Hilly O, Gil Z, Goldhaber D, et al. *Elective neck dissection during salvage total laryngectomy - a beneficial prognostic effect in locally advanced recurrent tumours*. *Clin Otolaryngol* 2015;40:9-15.
- 7 Dagan R, Morris CG, Kirwan JM, et al. *Elective neck dissection during salvage surgery for locally recurrent head and neck squamous cell carcinoma after radiotherapy with elective nodal irradiation*. *Laryngoscope* 2010;120:945-52.
- 8 Basheeth N, O'Leary G, Sheahan P. *Elective neck dissection for N0 neck during salvage total laryngectomy: findings, complications, and oncological outcome*. *JAMA Otolaryngol Head Neck Surg* 2013;139:790-6.
- 9 Yirmibesoglu E, Fried D, Shores C, et al. *Incidence of sub-clinical nodal disease at the time of salvage surgery for locally recurrent head and neck cancer initially treated with definitive radiation therapy*. *Am J Clin Oncol* 2013;36:475-80.
- 10 Temam S, Koka V, Mamelle G, et al. *Treatment of the N0 neck during salvage surgery after radiotherapy of head and neck squamous cell carcinoma*. *Head Neck* 2005; 27:653-8.
- 11 Farrag TY, Lin FR, Cummings CW, et al. *Neck management in patients undergoing post-radiotherapy salvage laryngeal surgery for recurrent/persistent laryngeal cancer*. *Laryngoscope* 2006;116:1864-6.
- 12 Bohannon IA, Desmond RA, Clemons L, et al. *Management of the N0 neck in recurrent laryngeal squamous cell carcinoma*. *Laryngoscope* 2010;120:58-61.
- 13 Deganello A, Meccariello G, Bini B, et al. *Is elective neck dissection necessary in cases of laryngeal recurrence after previous radiotherapy for early glottic cancer?* *J Laryngol Otol* 2014;128:1089-94.
- 14 Pezier TF, Nixon IJ, Scotton W, et al. *Should elective neck dissection be routinely performed in patients undergoing salvage total laryngectomy?* *J Laryngol Otol* 2014;128:279-83.
- 15 León X, Orús C, Quer M. *Design, maintenance, and exploitation of an oncologic database for patients with malignant tumours of the head and neck*. *Acta Otorrinolaringol Esp* 2002;53:185-90.
- 16 Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. 7th ed. Chichester, England: Wiley-Blackwell; 2009.
- 17 Koss SL, Russell MD, Leem TH, et al. *Occult nodal disease in patients with failed laryngeal preservation undergoing surgical salvage*. *Laryngoscope* 2014;124:421-8.
- 18 Lee DJ, Kwon KH, Chung EJ, et al. *The role of elective neck dissection during salvage surgery in head and neck squamous cell carcinoma*. *Acta Otolaryngol* 2013;133:886-92.
- 19 Prendes BL, Aubin-Pouliot A, Egbert N, et al. *Elective lymphadenectomy during salvage for locally recurrent head and neck squamous cell carcinoma after radiation*. *Otolaryngol Head Neck Surg* 2014;151:462-7.
- 20 Deschamps DR, Spencer HJ, Kokoska MS, et al. *Implications of head and neck cancer treatment failure in the neck*. *Otolaryngol Head Neck Surg* 2010;142:722-7.
- 21 León X, Gañán L, Costey M, et al. *Isolated lymphatic recurrences in patients with head and neck carcinomas*. *Acta Otorrinolaringol Esp* 2003;54:710-7.
- 22 Sanabria A, Silver CE, Olsen KD, et al. *Is elective neck dissection indicated during salvage surgery for head and neck squamous cell carcinoma?* *Eur Arch Otorhinolaryngol* 2014;271:3111-9.
- 23 Burge JS. *Histological changes in cervical lymph nodes following clinical irradiation*. *Proc R Soc Med* 1985;68:77-9.
- 24 Jonsson K, Libshitz HI, Osborne BM. *Lymphangiographic changes after radiation therapy*. *AJR Am J Roentgenol* 1978;131:803-6.
- 25 Gourin CG, Conger BT, Porubsky ES, et al. *The effect of occult nodal metastases on survival and regional control in patients with head and neck squamous cell carcinoma*. *Laryngoscope* 2008;118:1191-4.
- 26 Cerezo L, López C, de la Torre A, et al. *Incidence of human papillomavirus-related oropharyngeal cancer and outcomes after chemoradiation in a population of heavy smokers*. *Head Neck* 2014;36:782-6.
- 27 Rodrigo JP, Heideman DA, García-Pedrero JM, et al. *Time trends in the prevalence of HPV in oropharyngeal squamous cell carcinomas in northern Spain (1990-2009)*. *Int J Cancer* 2014;134:487-92.
- 28 Kostakoglu L, Fardanesh R, Posner M, et al. *Early detection of recurrent disease by FDG-PET/CT leads to management changes in patients with squamous cell cancer of the head and neck*. *Oncologist* 2013;18:1108-17.

- ²⁹ Rangaswamy B, Fardanesh MR, Genden EM, et al. *Improvement in the detection of locoregional recurrence in head and neck malignancies: F-18 fluorodeoxyglucose-positron emission tomography / computed tomography compared to high resolution contrast-enhanced computed tomography and endoscopic examination.* Laryngoscope 2013;123:2664-9.
- ³⁰ Gupta T, Master Z, Kannan S, et al. *Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis.* Eur J Nucl Med Mol Imaging 2011;38:2083-95.
- ³¹ Ng SH, Yen TC, Chang JT, et al. *Prospective study of [18F] fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck.* J Clin Oncol 2006;20;24:4371-6.
- ³² Roh JL, Park JP, Kim JS, et al. *18F-fluorodeoxyglucose PET/CT in head and neck squamous cell carcinoma with negative neck palpation findings: a prospective study.* Radiology 2014;271:153-61.
- ³³ Gilbert MR, Branstetter BF, Kim S. *Utility of positron-emission tomography/computed tomography imaging in the management of the neck in recurrent laryngeal cancer.* Laryngoscope 2012;122:821-5.

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HEAD AND NECK

IFN- γ and other serum cytokines in head and neck squamous cell carcinomas

IFN- γ e altre citochine sieriche nei carcinomi squamocellulari della testa e del collo

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SUMMARY

Altered immune responses have been reported in head and neck cancer, and some of these responses have been associated with poor clinical outcomes. A multiple-array technology platform was used to simultaneously evaluate the levels of 25 cytokines. Pre-treatment serum levels were evaluated in 31 HNSCC patients and 6 healthy controls. The levels of 8 cytokines, specifically IL-1ra, IL-2, IL-5, IL-6, IL-8, IL-17, IFN- γ and IP-10, were significantly higher in patients than in controls. Among cancer patients we observed lower levels of IFN- γ and IL-7 in cases with nodal metastases compared to those with cN0 disease. We observed increases in the levels of some serum cytokines in HNSCC patients, as well as reductions in selected cytokines associated with regional progression. These findings provide an intriguing perspective on the development and validation of novel markers for follow-up evaluations and predictions of regional spreading in HNSCC patients.

KEY WORDS: Head and neck SCC • Nodal metastasis • Predictive factors • Cytokines • Inflammation • IFN- γ

RIASSUNTO

È noto che nelle neoplasie della testa e del collo vi siano delle alterazioni della risposta immune, ed alcune di tali alterazioni sono state associate ad un peggioramento prognostico. Abbiamo utilizzato una piattaforma con una tecnologia multi-array per valutare simultaneamente i valori di 25 citochine nel siero di 31 pazienti, affetti da carcinomi squamosi della testa e del collo prima del trattamento, e di 6 controlli sani. I livelli di 8 citochine, IL-1ra, IL-2, IL-5, IL-6, IL-8, IL-17, IFN- γ ed IP-10, sono risultati significativamente più elevati nei pazienti che nei controlli. Tra i pazienti i casi con metastasi linfonodali mostravano livelli significativamente inferiori di IFN- γ ed IL-7 rispetto ai casi cN0. Pertanto alcune citochine tendono ad essere più elevate nei soggetti affetti da carcinomi squamocellulari della testa e del collo, ma nel contesto di tale gruppo di pazienti si osserva un calo specifico di alcune citochine in caso di metastasi linfonodali. Tali dati aprono prospettive interessanti soprattutto ai fini di una miglior definizione del rischio di metastasi/recidive linfonodali con implicazioni sia in termini di impostazione terapeutica che di follow up.

PAROLE CHIAVE: Carcinomi squamosi della testa e collo • Metastasi linfonodali • Fattori predittivi • Citochine • Infiammazione • Interferon-gamma

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Introduction

Head and neck squamous cell carcinoma (HNSCC) represents approximately 3% of all malignant tumours in the United States ¹ and Europe ², but is much more prevalent in other parts of the world ³. The standard therapeutic approach, which includes surgery, irradiation and chemotherapy, either alone or in combination, has been somewhat modified over the last 30 years; however, the overall survival rate has not drastically improved ^{1,3}.

The persistently high rate of advanced lesions is among the potential reasons for the failure to improve the HNSCC survival rate. In general, screening attempts have been completely unsuccessful, such that for the larynx, the most frequently affected primary site in European patients ⁴, where less than 1% of SCC patients are asymptomatic at presentation. The definition of high-risk groups that should be submitted to screening would likely increase this rate. Oncogenic viruses, particularly Epstein-Barr and high-risk papillomavirus, have been shown to

play causative roles in subsets of nasopharyngeal⁵ and oropharyngeal⁶ cancers, respectively, and therefore might be a good starting point. Nevertheless, the most frequent site of origin for HNSCC are the oral cavity and larynx, for which the main proven risk factors remain cigarette smoking and alcohol consumption³; however, these factors do not define a sufficiently restricted population to monitor for effective prevention and/or screening.

Another issue in head and neck oncology is that the prognostic stratification is inadequate because patients who are affected by tumours with similar clinicopathological parameters and are undergoing the same treatment can differ widely in their prognoses. This is likely due to the extreme biological heterogeneity of HNSCCs, and contributes to the known controversies concerning therapeutic algorithms (on management of cN0 necks)⁷.

Many clinical and epidemiologic studies have suggested a strong association between inflammation, with its mediators, and cancer⁸⁻¹¹, including cancers of the head and neck¹²⁻¹⁴.

In the present study, we investigated the serum concentrations of various cytokines in patients with laryngeal and oral SCC, and compared these with the concentrations in healthy subjects, to identify alterations in inflammatory pathways associated with carcinogenesis.

We tested a panel of 26 cytokines that are important in the inflammatory response and immune system regulation and associated with different immune pathways, giving specific information, and in particular concerning Th2 and Th1 immune responses.

Cytokine levels were also correlated with tumour characteristics (e.g., site of origin and T and N classification) and oncologic outcomes to identify parameters that might supplement TNM and other information currently available to clinicians to assess prognoses, treatment responses and clinical behaviours (e.g., tendency to regional metastasis) of HNSCC patients.

Materials and methods

Patients

From February 2010 to March 2012, we enrolled 31 patients (5 women, 26 men; age range, 32-82 years; mean, 57 years) who were affected by primary, previously untreated and biopsy proven SCC arising from oral cavity or larynx, as evaluated by the multidisciplinary head and neck tumour board of the Policlinico Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.

Staging according to the TNM AJCC classification 7th edition, and treatment recommendation were defined, patients signed informed consent for their participation in

the present study, which had been previously approved by the ethical committee.

The circulating levels of interleukin-1b (IL-1b), interleukin-1 receptor antagonist (IL-1Ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, eotaxin, basic fibroblast growth factor (FGF-b), granulocyte colony-stimulating factor (G-CSF), interferon-gamma (IFN- γ), IFN- γ -inducible protein 10 (IP-10), human monocyte chemoattractant protein 1 (HuMCP-1), macrophage inflammatory proteins-1-alpha and 1-beta (MIP-1 α and 1 β), platelet-derived growth factor-BB (PDGF-BB), regulated upon activation, normal T-cell expressed secreted (RANTES), tumour necrosis factor-alpha (TNF- α) and vascular endothelial growth factor (VEGF) were investigated in sera collected before primary treatment. All SCC originated from the oral cavity (n = 16) and larynx (n = 15), which are the most frequent sites of HNSCC¹. All patients had a history of cigarette smoking.

Selection of primary treatment modality was always shared in the institutional multidisciplinary head and neck tumour board. All oral cavity cases were treated primarily by surgery. As for laryngeal SCCs, in our tumour board treatment choice is based mainly on cT, and on the patient's general condition and preference. Namely, we primarily irradiated cT1 and cT2 and we recommended primary surgery in cT4 cases; cT3 cases were discussed in the tumour board and underwent surgery or radiotherapy depending on the patient's general conditions and feasibility of function preservation surgery (supracricoid operations). Among patients who underwent primarily radiochemotherapy, there were also cT4 patients who refused the recommended total laryngectomy and preferred to try to keep their larynx, after having been informed about the lower survival rates reported in literature. Postoperative radiation (mostly associated with cisplatin) was administered for pN2-3 disease, extracapsular spread and adverse pathologic primary site features including pT4 disease, perineural invasion, involvement of surgical margins, or lymphovascular invasion.

The follow-up time was calculated from the treatment date (surgery or final session of chemo/radiotherapy). For controls, sera were collected from 6 healthy sex and age-matched volunteers who were current smokers with personal histories negative for malignancy, without recent trauma or surgery, and who were not pregnant. Personal data for cases and controls and clinical data for HNSCC patients are summarised in Table I. Peripheral venous blood was collected into Vacuette (Greiner bio-one, Kremsmünster, Austria) tubes and was immediately centrifuged at 4°C and 4000 rpm for 5 minutes. Serum samples were collected and multiple aliquots were stored

at -80°C until analysis, at which time the serum concentrations of cytokines were determined in a multiplex cytokine analysis.

Multiplex cytokine analysis

A Luminex xMAP system (Bio-Plex 200 System, Bio-Rad Laboratories, Hercules, CA, USA), which is a multiplex biometric enzyme-linked immunosorbent assay (ELISA)-based immunoassay that contains dyed microspheres conjugated to monoclonal antibodies specific for target proteins, was used according to the manufacturer's instructions. The cytokines evaluated in the panel (BioPlex Human Cytokine Assay; BioRad) were IL-1 β , IL1Ra, IL-2, IL-4, IL-5, IL-6, IL-7, CXCL8 (IL-8), IL-9, IL-10, IL-12 (p70), IL-13, IL-17, basic FGF, eotaxin, G-CSF, IFN- γ , IP-10, MCP-1, MIP-1a and β , PDGF-BB, RANTESTNF- α and VEGF.

The serum samples were diluted 1:4 and incubated with antibody-coupled beads. The resulting complexes were washed and incubated first with a biotinylated detection antibody and then with streptavidin-phycoerythrin prior to assessing the cytokine concentration titres. Concentrated human recombinant cytokines were provided by the vendor (BioRad, Inc.). Broad ranges of standards (1.95-32,000 pg/ml) were used to establish standard curves with which to maximise the sensitivity and dynamic range of the assay. Cytokine levels were determined on a Bio-Plex array reader, an automated flow-based microfluidics device that uses a dual-laser fluorescent detector with real-time digital signal processing for quantification. This instrument quantifies multiplex immunoassays in 96-well plates. The concentrations in pg/ml were calculated from standard curves with software provided by the manufacturer. A regression analysis was performed to derive an equation that was then used to predict the concentrations of cytokines in the serum samples.

Statistical analysis

Statistical analysis was performed with JMP software, release 7.0.1 (SAS Institute). The level was fixed at 0.05 for all statistical tests. Correlations between nominal variables were evaluated with a χ^2 test. Differences in the concentrations of different cytokines between controls (c) and patients (p) and between the cN0 and cN+ cases were evaluated with a t-test. Differences among tumours that originated in the two sites (oral cavity vs. larynx), controls and among different the cT and cN classifications were evaluated by ANOVA variance analysis, and pairs were then compared with the Tukey-Kramer test. For a more thorough evaluation of the variations in serum cytokine levels along with increasing tumour staging, we trans-

Table I. Characteristics of patients in the entire series according to the primary treatment group.

Characteristic	Patients (n = 31)		Controls (n = 6)	
Age				
Median	63		61	
Range	32-82		47-72	
Sex-no. (%)				
Male	26	(84%)	5	(83%)
Female	5	(16%)	1	(17%)
Smoking habits-no. (%)				
Less than 10 pack/years	10	(32%)	2	(33%)
More than 10 pack/years	21	(68%)	4	(67%)
Drinking habits-no. (%)				
Non drinker	12	(39%)	2	(33%)
1-4 glasses/day	13	(42%)	3	(50%)
More than 4 glasses a day	6	(19%)	1	(17%)
Follow up				
Median	8.3		-	
Range	0.2-21		-	
Site of primary-no. (%)				
Oral cavity	16	(52%)	-	
Larynx	15	(48%)	-	
Primary treatment-no. (%)				
Surgery	22	(71%)	-	
Radio \pm chemotherapy	9	(21%)	-	
TNM staging-no. (%)				
I	3	(10%)	-	
II	9	(29%)	-	
III	2	(6%)	-	
IVa	17	(55%)	-	
T stage-no.(%)				
T1	4	(13%)	-	
T2	12	(39%)	-	
T3	3	(9%)	-	
T4a	12	(39%)	-	
N stage-no.(%)				
N0	17	(55%)	-	
N1	3	(10%)	-	
N2a	2	(6%)	-	
N2b	4	(13%)	-	
N2c	5	(16%)	-	

formed the nominal cT and cN parameters to numerical variables (numeric T and N scores; cT4a = 4, cT4b = 5, cN2a = 2, cN2b = 3, cN2c = 4, cN3 = 5) and sought a linear fit by analysis of variance. The impact of different parameters on survival were evaluated by a Cox regres-

Table II. Mean values of cytokines in controls and cases (statistically significant differences are indicated with *).

Cytokine	Value in controls (mean±SD)	Value in cases (mean±SD)
IL-1b	3.3133333 ± 0.8841418	3.674 ± 0.8323154
IL-1ra*	174.90667 ± 17.770011	237.06833 ± 75.716824
IL-2*	1.715 ± 2.9156251	8.0387097 ± 7.2977836
IL-4	9.425 ± 2.0147332	11.432258 ± 2.3363158
IL-5*	3.4616667 ± 0.412864	4.4770968 ± 1.8866005
IL-6*	9.1083333 ± 1.1434232	14.095806 ± 4.3274864
IL-7	13.881667 ± 2.6957776	16.143548 ± 4.848343
IL-8*	32.186667 ± 5.5094489	40.000323 ± 10.059768
IL-9	33.548333 ± 18.8509	46.597097 ± 25.720585
IL-10	30.395 ± 33.645025	22.915161 ± 12.610672
IL-12	95.153333 ± 37.067161	132.97935 ± 84.327459
IL-13	12.19512,195 ± 3.6285024	14.570645 ± 5.7731684
IL-17*	190.29667 ± 61.275395	253.8671 ± 67.58494
Eotaxin	233.67167 ± 97.855583	243.08645 ± 112.18061
FGF-basic	47.305 ± 23.345764	55.560645 ± 27.172748
G-CSF	72.231667 ± 18.809514	75.645161 ± 16.2412
IFN-g*	311.015 ± 51.866943	376.45903 ± 75.010629
IP-10*	1488.3367 ± 510.41972	2502.8471 ± 1098.5081
Hu MCP-1(MCAF)	60.086667 ± 21.832594	45.274839 ± 16.429516
Hu MIP-1a	8.8483333 ± 2.2179217	9.0803226 ± 2.1559568
PDGF-bb	14614.73 ± 5313.271	17966.356 ± 4937.8699
MIP-1b	113.71333 ± 34.277828	118.45355 ± 30.917572
RANTES	9447.305 ± 850.45661	9032.6235 ± 1481.9593
TNF-alpha	39.131667 ± 7.2147	43.99129 ± 11.821503
VEGF	132.37667 ± 65.794253	203.30032 ± 175.79658

sion analysis (only univariate because of the low numbers of cases and recorded events).

Results

Statistically significant differences between controls and patients with regard to concentrations of the different cytokines are reported in Table II and schematically represented by box plots in Figure 1. The statistically significant differences observed among the two different tumour sites and controls are shown in Figure 2. Two cytokines were significantly overexpressed only in patients with specific SCC subsites, namely IL-6 in laryngeal SCC patients and IP-10 in oral cavity SCC patients.

We found no significant differences or correlations between the levels of various cytokines and the T classification, although a trend ($p = 0.0615$ in the variance analysis) towards a positive correlation between the IP-10 levels and numeric T scores was observed.

However, when we evaluated the association between cytokine levels and the N classification, a significant cor-

relation of lower levels of some with nodal involvement (IL-7, FGF-basic, IFN- γ , HuMIP-1a, see figure 3 on the right) and with the numeric N score were seen (IL-7, eotaxin, IFN- γ , see Figure 3 on the left).

In Cox univariate survival analysis, we observed that higher IFN- γ ($p = 0.0218$) and lower IL-1ra ($p = 0.0376$) levels were associated with longer disease-specific survival.

Discussion

We observed increases in the levels of several cytokines in sera from HNSCC patients compared to sera from controls. This observation confirms the well-known link between inflammation and cancer that has already been observed in head-and-neck oncology. This observation could be linked to the presence of the tumour and its interactions with the host^{8 15-18}, or could indicate an immunological predisposition to cancer development^{8 11 15}. In the former scenario, inflammatory mediators should be evaluated as tumour markers that could be employed in

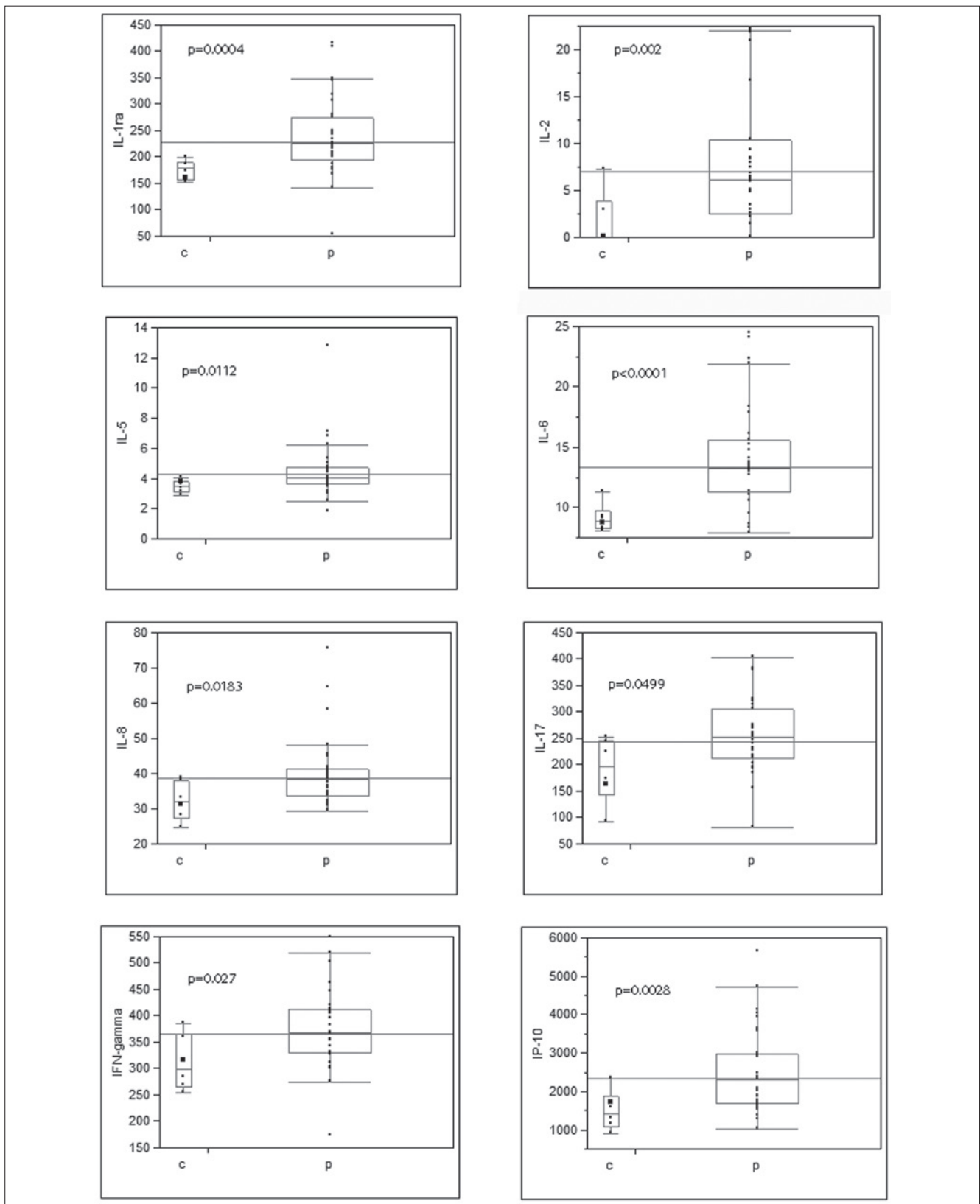


Fig. 1. Box plots of 8 cytokines (for which the levels were significantly higher in sera from patients (p), compared to controls (c). P-values were obtained with a two-sided t-test.

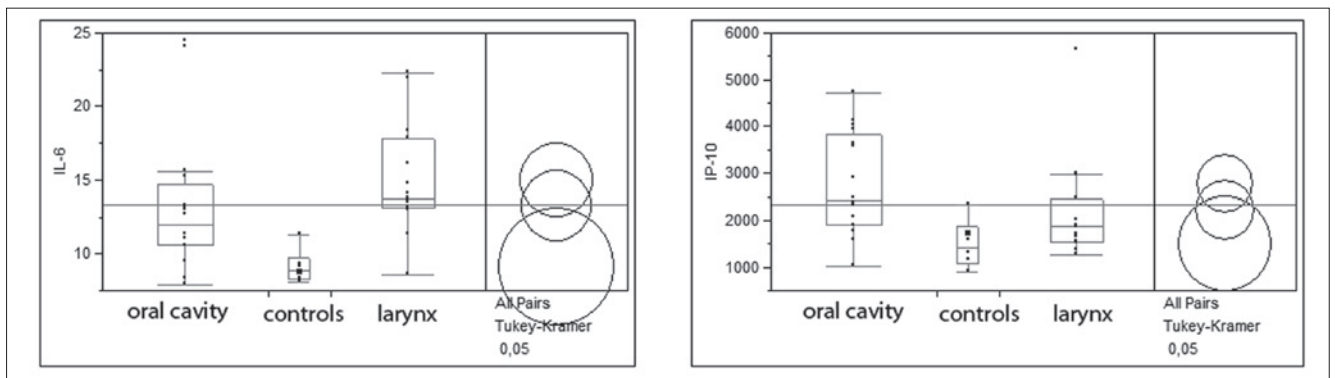


Fig. 2. When compared with controls, IL-6 serum levels were significantly higher in laryngeal but not in oral SCC patients; IP-10 levels were significantly higher only in oral SCC patients.

follow-up for early detection of recurrence; in the latter, certain immunological conditions might be risk factors for development of malignancy and could be taken into account when selecting subjects for screening.

Likely, both of these scenarios are true, and in our series, it was difficult to discriminate between the alterations that preceded and those that derived from cancer progression. In our patients, the cytokines with the most significant increases were IL-6 and IL-1Ra. Increased IL-6 levels have already been associated with HNSCC¹⁹⁻²¹, as well as with IL-8^{12,22}, another upregulated cytokine among our patients. IL-6 might contribute to cancer progression through STAT-3-mediated paracrine or autocrine proliferative stimulation and through additional inhibitory effects on anti-tumour Th1 immune responses^{23,24}. Nevertheless, in contrast to previous studies, in the present series, we failed to demonstrate any correlation between IL-6 itself and the disease stage²⁵ or prognosis¹⁹, although the limited number of patients and the short follow-up period might explain this result. Actually, in the present series, IL-6 was significantly increased only in laryngeal SCC patients, and the reasons for this observation remain to be clarified. We instead observed a correlation between increased levels of IL-1Ra and worse prognosis. IL-1Ra levels have been correlated with prognosis in Hodgkin lymphoma²⁶ and have been shown to be elevated in head and neck SCC tissues²⁷. IP-10 and its corresponding receptor CXCR3 have been shown to be involved in carcinogenesis²⁸ including malignant melanoma²⁹, ovarian carcinoma³⁰, multiple myeloma³¹, B-cell lymphoma³² and basal cell carcinoma³³. In our series, the increased levels of IP-10 in patients with oral SCC, which are usually bulkier than laryngeal SCC, and in those with higher T scores (even if not significant), could suggest that IP-10 levels are influenced by tumour volume.

The prognostic role of IL-1Ra deserves in-depth evaluation in larger perspective studies. Nevertheless, these results provide a perspective for the use of some cytokines as tumour markers in clinical practice, such as during follow-up of HNSCC patients, also on account of the clear lack of reliable serum follow-up markers, of which the SCC antigen is the most used, despite its known issues regarding sensitivity and specificity³⁴.

Immune responses in head and neck SCC patients are reportedly unbalanced towards the secretion of Th2 cytokines, which would prevent effective antitumour Th1 immune responses³⁵. In the present study, we observed the upregulation of both Th1 (IFN- γ , IL-2 and IP-10) and Th2 (IL-4, IL-6 and IL-10) cytokines in HNSCC patients compared to healthy subjects, and the above-cited imbalance become evident only with regional progression, which is, however, the main clinical factor that affects survival in these patients. In fact, IFN- γ , which is among the most important Th1 pathway cytokines, was clearly downregulated in cases with nodal involvement and such downregulation displayed a linear correlation with regional progression. IFN- γ was also the only serum cytokine that displayed a protective effect when evaluated relative to prognosis; its crucial role in HNSCC has already been described at both a molecular³⁶ and clinical level²². In addition to IFN- γ , other cytokines that did not have specific Th1 activity were significantly downregulated in cases with nodal involvement and/or showed linear correlations with numeric N scores in our series, and none of these differed significantly between the cases and controls (except IFN- γ). Among these downregulated cytokines, IL-7 was recently found to perform a relevant antitumour activity by inducing the expansion of tumour-specific CD4+ T cell effectors more efficiently than IL-2³⁷. The serum eotaxin levels undergo significant modifications after the induc-

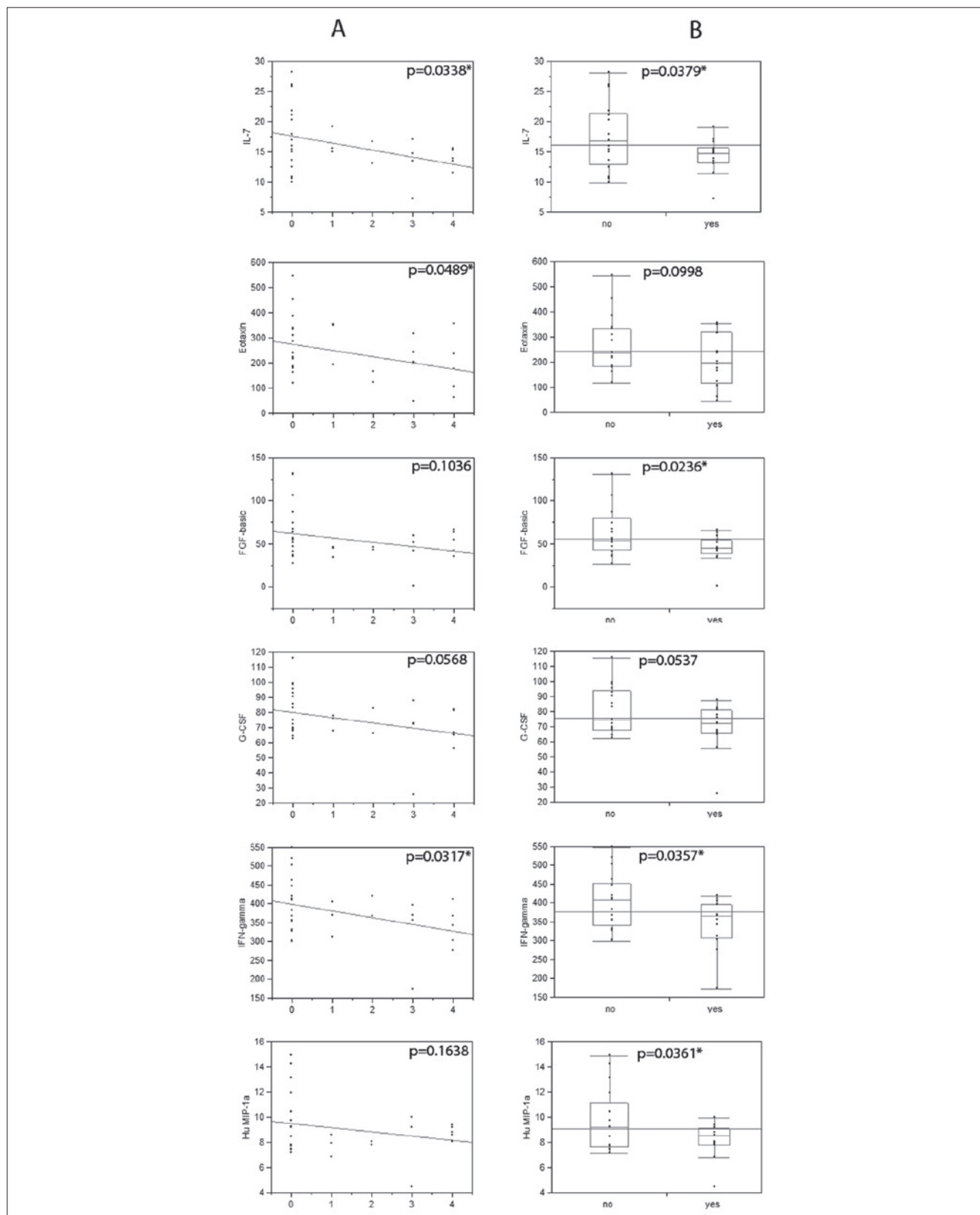


Fig. 3. Cytokine levels that correlated significantly with the numeric N score (on the left) and/or the nodal status (on the right). Statistical significance is indicated by asterisks.

tion of chemotherapy in head-and-neck cancer patients³⁸. Basic fibroblast growth factor expression was associated with good outcomes in patients with squamous cell carcinoma of the oesophagus³⁹.

These data might suggest that HNSCC development induces a non-specific immune response, along with increased serum levels of many cytokines, but tumour cells tend to overcome such responses by selectively down-regulating specific interleukins, thus promoting tumour progression, particularly lymphatic spreading. This phenomenon would be part of tumour-mediated immunosuppressive activity that, according to several authors, is associated with immune escape, rapid growth and frequent metastasis also observed in other cancers^{8 11 15}.

Conclusions

Regardless of the molecular/immunological basis of the findings of the present study, from a clinical point of view, the specific alterations associated with regional metastasis are very interesting for several reasons. The most immediate perspective is that downregulation of the above-cited cytokines, and IFN- γ in particular, could be used as risk markers of neck metastasis and could serve to modify the therapeutic recommendations by indicating, for example, elective neck treatment in cN0 cases and comprehensive neck dissection followed by adjuvant radiochemotherapy in pN+ cases. The prognostic role of IFN- γ could also facilitate prognostic assessments. Notwithstanding, further studies are necessary to confirm these findings on larger series and to determine the optimal cut-off value of serum IFN- γ for risk prediction in clinical practice.

Moreover, the suppression of IFN- γ and other cytokines, which we hypothesised to be tumour-dependent and to promote nodal metastasis, could be hindered pharmacologically in attempted immunotherapy for HNSCC, as previously proposed for other malignancies⁴⁰.

References

- Siegel RL, Miller KD, Jemal A. *Cancer statistics, 2015*. CA Cancer J Clin 2015;65:5-29.
- Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012*. Eur J Cancer 2013;49:1374-1403.
- Shah JP, Patel KJ. *Head and Neck Surgery and Oncology*. 3rd Edition: Mosby Ltd.; 2003.
- Ferlay J, Parkin DM, Steliarova-Foucher E. *Estimates of cancer incidence and mortality in Europe in 2008*. Eur J Cancer 2010;46:765-81.
- Licitra L, Bernier J, Cvitkovic E, et al. *Cancer of the nasopharynx*. Crit Rev Oncol Hematol 2003;45:199-213.
- Gillison ML, Koch WM, Capone RB, et al. *Evidence for a causal association between human papillomavirus and a subset of head and neck cancers*. J Natl Cancer Inst 2000;92:709-20.
- Almadori G, Bussu F, Paludetti G. *Should there be more molecular staging of head and neck cancer to improve the choice of treatments and thereby improve survival?* Curr Opin Otolaryngol Head Neck Surg 2008;16:117-26.
- Coussens LM, Werb Z. *Inflammation and cancer*. Nature 2002;420:860-7.
- Shacter E, Weitzman SA. *Chronic inflammation and cancer*. Oncology (Williston Park) 2002;16:217-26, 229.
- Hussain SP, Hofseth LJ, Harris CC. *Radical causes of cancer*. Nat Rev Cancer 2003;3:276-85.
- Dobrovolskaia MA, Kozlov SV. *Inflammation and cancer: when NF-kappaB amalgamates the perilous partnership*. Curr Cancer Drug Targets 2005;5:325-44.
- Chen Z, Malhotra PS, Thomas GR, et al. *Expression of pro-inflammatory and proangiogenic cytokines in patients with head and neck cancer*. Clin Cancer Res 1999;5:1369-79.
- Douglas WG, Tracy E, Tan D, et al. *Development of head and neck squamous cell carcinoma is associated with altered cytokine responsiveness*. Mol. Cancer Res 2004;2:585-93.
- Myers JN, Yasumura S, Suminami Y, et al. *Growth stimulation of human head and neck squamous cell carcinoma cell lines by interleukin 4*. Clin Cancer Res 1996;2:127-35.
- Lin WW, Karin M. *A cytokine-mediated link between innate immunity, inflammation, and cancer*. J Clin Invest 2007;117:1175-83.
- Balkwill F, Charles KA, Mantovani A. *Smoldering and polarized inflammation in the initiation and promotion of malignant disease*. Cancer Cell 2005;7:211-7.
- Ben-Baruch A. *Inflammation-associated immune suppression in cancer: the roles played by cytokines, chemokines and additional mediators*. Semin Cancer Biol 2006;16:38-52.
- Smyth MJ, Cretney E, Kershaw MH, et al. *Cytokines in cancer immunity and immunotherapy*. Immunol Rev 2004;202:275-93.
- Duffy SA, Taylor JM, Terrell JE, et al. *Interleukin-6 predicts recurrence and survival among head and neck cancer patients*. Cancer 2008;113:750-7.
- Teknos TN, Islam M, Arenberg DA, et al. *The effect of tetrathiomolybdate on cytokine expression, angiogenesis, and tumor growth in squamous cell carcinoma of the head and neck*. Arch Otolaryngol Head Neck Surg 2005;131:204-11.
- Riedel F, Zaiss I, Herzog D, et al. *Serum levels of interleukin-6 in patients with primary head and neck squamous cell carcinoma*. Anticancer Res 2005;25:2761-5.
- Woods KV, El-Naggar A, Clayman GL, et al. *Variable expression of cytokines in human head and neck squamous cell carcinoma cell lines and consistent expression in surgical specimens*. Cancer Res 1998;58:3132-41.
- Tanner J, Tosato G. *Impairment of natural killer functions by*

- interleukin 6 increases lymphoblastoid cell tumorigenicity in athymic mice.* J Clin Invest 1991;88:239-47.
- ²⁴ Sriuranpong V, Park JI, Amornphimoltham P, et al. *Epidermal growth factor receptor-independent constitutive activation of STAT3 in head and neck squamous cell carcinoma is mediated by the autocrine/paracrine stimulation of the interleukin 6/gp130 cytokine system.* Cancer Res 2003;63:2948-56.
- ²⁵ De Schutter H, Landuyt W, Verbeken E, et al. *The prognostic value of the hypoxia markers CA IX and GLUT 1 and the cytokines VEGF and IL 6 in head and neck squamous cell carcinoma treated by radiotherapy +/- chemotherapy.* BMC Cancer 2005;5:42.
- ²⁶ Casasnovas RO, Mounier N, Brice P, et al. *Plasma cytokine and soluble receptor signature predicts outcome of patients with classical Hodgkin's lymphoma: a study from the Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol 2007;25:1732-40.
- ²⁷ Westin U, Nystrom M, Ljungcrantz I, et al. *The presence of elafin, SLPI, IL1-RA and STNFalpha RI in head and neck squamous cell carcinomas and their relation to the degree of tumour differentiation.* Mediators Inflamm 2002;11:7-12.
- ²⁸ Neville LF, Mathiak G, Bagasra O. *The immunobiology of interferon-gamma inducible protein 10 kD (IP-10): a novel, pleiotropic member of the C-X-C chemokine superfamily.* Cytokine Growth Factor Rev 1997;8:207-19.
- ²⁹ Monteagudo C, Martin JM, Jorda E, et al. *CXCR3 chemokine receptor immunoreactivity in primary cutaneous malignant melanoma: correlation with clinicopathological prognostic factors.* J Clin Pathol 2007;60:596-9.
- ³⁰ Furuya M, Suyama T, Usui H, et al. *Up-regulation of CXC chemokines and their receptors: implications for proinflammatory microenvironments of ovarian carcinomas and endometriosis.* Hum Pathol 2007;38:1676-87.
- ³¹ Pellegrino A, Antonaci F, Russo F, et al. *CXCR3-binding chemokines in multiple myeloma.* Cancer Lett 2004;207:221-7.
- ³² Jones D, Benjamin RJ, Shahsafaei A, et al. *The chemokine receptor CXCR3 is expressed in a subset of B-cell lymphomas and is a marker of B-cell chronic lymphocytic leukemia.* Blood 2000;95:627-32.
- ³³ Lo BK, Yu M, Zloty D, et al. *CXCR3/ligands are significantly involved in the tumorigenesis of basal cell carcinomas.* Am J Pathol 2010;176:2435-46.
- ³⁴ Koch T, Eiffert H, Spindler MB. *Relevance of the new tumor marker SCC (squamous cell carcinoma antigen) for the diagnosis and follow-up control of squamous epithelial carcinoma of the head and neck.* HNO 1989;37:454-59.
- ³⁵ Sheu BC, Lin RH, Lien HC, et al. *Predominant Th2/Tc2 polarity of tumor-infiltrating lymphocytes in human cervical cancer.* J Immunol 2001;167:2972-8.
- ³⁶ Katayama A, Ogino T, Bandoh N, et al. *Expression of CXCR4 and its down-regulation by IFN-gamma in head and neck squamous cell carcinoma.* Clin. Cancer Res 2005;11:2937-46.
- ³⁷ Caserta S, Alessi P, Basso V, et al. *IL-7 is superior to IL-2 for ex vivo expansion of tumour-specific CD4(+) T cells.* Eur J Immunol 2010;40:470-9.
- ³⁸ Argiris A, Lee SC, Feinstein T, et al. *Serum biomarkers as potential predictors of antitumor activity of cetuximab-containing therapy for locally advanced head and neck cancer.* Oral Oncol 2011;47:961-6.
- ³⁹ Nakamura T, Ozawa S, Kitagawa Y, et al. *Expression of basic fibroblast growth factor is associated with a good outcome in patients with squamous cell carcinoma of the esophagus.* Oncol Rep 2005;14:617-23.
- ⁴⁰ Sgambato A, Cittadini A. *Inflammation and cancer: a multifaceted link.* Eur Rev Med Pharmacol Sci 2010;14:263-8.

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HEAD AND NECK

Long-term outcomes of alternating chemoradiotherapy in patients with advanced nasopharyngeal cancer: a single-centre experience over the last decade

Risultati a lungo termine di chemioradioterapia alternata in pazienti con carcinoma rinofaringeo in stadio avanzato: esperienza di un singolo centro nell'ultima decade

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SUMMARY

We assessed the long-term outcomes of alternating chemoradiotherapy (ACRT) using 5-fluorouracil and cisplatin (FP) in 25 patients with stage II or advanced nasopharyngeal cancer treated at our institution between April 1999 and April 2010. Median follow-up duration was 87 months (range 2-189). According to the 2009 TNM classification (UICC), six patients were in stage II, nine in stage III, and 10 in stage IV. Treatment completion, response and five-year survival rates were retrospectively assessed. ACRT was performed with a first course of chemotherapy administered followed by the initial round of radiotherapy (36 Gy). Then, a second course of chemotherapy with additional radiotherapy (20–30 Gy) was administered, followed by a final third course of chemotherapy. For chemotherapy, 5-fluorouracil (5-FU, 800 mg/m²/24 h) was intravenously administered for five days, and cisplatin (CDDP, 50 mg/m²/24 h) was administered on the last two days. Treatment completion rate was 96% (24 of 25 cases), and the response rate was 100% (CR: 24 cases and PR: 1 case). Additionally, the five-year overall survival rate was 89.3%. We have demonstrated that ACRT is an effective regimen to treat nasopharyngeal cancer, revealing higher treatment completion, response, and five-year overall survival rates compared with other combinatorial radiotherapy and chemotherapy treatment regimens.

KEY WORDS: Alternating chemoradiotherapy • Nasopharyngeal cancer • Cisplatin • 5-fluorouracil

RIASSUNTO

Abbiamo valutato gli outcome a lungo termine di chemioradioterapia alternata (ACRT) utilizzando 5-fluorouracile e cisplatino (FP) in 25 pazienti con carcinoma in stadio II o avanzato del rinofaringe trattati nel nostro istituto tra l'Aprile del 1999 e l'Aprile del 2010. La durata media del follow up è stata di 87 mesi (range 2-189). In accordo con il TNM del 2009 (UICC), sei pazienti erano in stadio II, nove in stadio III e dieci in stadio IV. Sono stati valutati retrospettivamente il completamento del trattamento, la risposta ed i tassi di sopravvivenza a 5 anni. ACRT è stata eseguita utilizzando un primo ciclo di chemioterapia seguito da radioterapia (36 Gy), quindi un secondo ciclo di chemioterapia seguito da radioterapia (20-30 Gy), quindi un terzo ciclo di chemioterapia. Per la chemioterapia è stato utilizzato 5-fluorouracile endovenoso (5-FU, 800 mg/m²/24 h) per cinque giorni e cisplatino (CDDP, 50 mg/m²/24 h) negli ultimi 2 giorni. Il tasso di completamento del trattamento è stato del 96% (24 casi su 25), quello di risposta del 100% (CR 24 casi, PR 1 caso). La sopravvivenza globale è stata dell'89,3%. Abbiamo dimostrato che ACRT è un regime efficace per il trattamento del carcinoma del rinofaringe, con un miglior tasso di completamento del trattamento, di risposta e di sopravvivenza a 5 anni se confrontato con altri protocolli di chemioradioterapia.

PAROLE CHIAVE: Chemioradioterapia alternata • Carcinoma del rinofaringe • 5-fluorouracile

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Introduction

Almost all nasopharyngeal cancers are poorly differentiated squamous cell carcinomas or undifferentiated carcinoma and are more sensitive to radiotherapy compared

with other head and neck cancers. Surgical treatment of nasopharyngeal cancer is difficult, and thus, various combination therapies of chemotherapy and radiotherapy are more viable management options. Specifically, adjuvant

or neo-adjuvant chemotherapy with radiotherapy, concurrent chemoradiotherapy and alternating chemoradiotherapy have been shown to improve survival outcomes of nasopharyngeal cancer patients¹⁻⁷. Since April 1999, our hospital has performed alternating chemoradiotherapy based on Fuwa's regimen¹ for stage II or higher nasopharyngeal cancer patients. In this study, we highlight the efficacy of alternating chemoradiotherapy in these patients focusing on the following outcomes: (1) treatment completion rates, (2) response rates, and (3) five-year survival rates.

Materials and methods

Patient criteria

This study was approved by the Institutional Review Board and Ethics Committee of the Fukushima Medical University (Fukushima, Japan). Patients with untreated nasopharyngeal cancer who met the following criteria were enrolled in this study: (1) diagnosed with squamous cell carcinoma, or undifferentiated carcinoma; (2) exhibited stage II or advanced nasopharyngeal cancer; (3) free of any organ abnormalities (renal function: creatinine clearance > 60 mL/min); and (4) provided written, informed consent.

There were no patients excluded from criteria above between April 1999 and April 2010 at Fukushima Medical University Hospital.

Patients

We examined 25 patients histologically confirmed as having stage II, III, or IV type nasopharyngeal cancer. These patients underwent ACRT between April 1999 and April 2010 at Fukushima Medical University Hospital and were included in this retrospective analysis. According to the 2009 TNM staging classification system, cancer stages of the patients were as follows: stage IIA (n = 2); stage IIB (n = 4); stage III (n = 9); stage IVA (n = 5); and stage IVB (n = 5). Patient characteristics are described in Table I. Nineteen patients were male, and six patients were female. The mean age was 46 years (range: 12-71 years) at the time of diagnosis of the primary tumour. The median observation period was 87 months (range: 2-189 months). Progression-free survival and OS rates were analysed with the Kaplan-Meier method. The time to event was calculated from the beginning of the treatment.

ACRT regimen

During ACRT, the first course of chemotherapy with FP was performed before the initial round of radiotherapy.

Table I. Characteristics of nasopharyngeal cancer.

Patient characteristics	Number of patients
Sex	
Male	19
Female	6
Performance status	
0	24
1	1
2	0
Stage	
II A	2
T2aN0:2	
II B	4
T2aN1:2 T2bN1:2	
III	9
T2aN2:1; T2bN2:5; T3N0:1; T3N1:1; T3N2:1	
IV A	5
T4N0:1 T4N1:3 T4N2:1	
IV B	5
T2bN3a:2; T2bN3b:1; T4N3a:2	
Histology	
WHO type I	3
WHO type II	12
WHO type III	10
Subsite	
Postero-superior wall	2
Lateral wall	23
Inferior wall	0
Follow up duration	
2-11 months	1
12-59 months	10
60-190 months	14

One course of initial chemotherapy consisted of continuous intravenous administration of 5-fluorouracil (5-FU) at a dose of 800 mg/m²/24 h for five days (days 1-5) and cisplatin (CDDP) at a dose of 50 mg/m²/24 h for two days (days 6-7). The drip infusion of fluid replacement was established at 4 L/day during CDDP administration. A minimum urine volume of 2 L/day was maintained for five days after CDDP administration. Steroids, palonosetron and aprepitant were used as antiemetics against CDDP. The second and third course of chemotherapies were performed 2-3 days after completion of the initial and additional rounds of radiotherapy (described below). Our regimen is described in Figure 1. When serum creatinine levels were above 1.5 mg/dL on the scheduled date of chemotherapy, chemotherapy was not performed. In

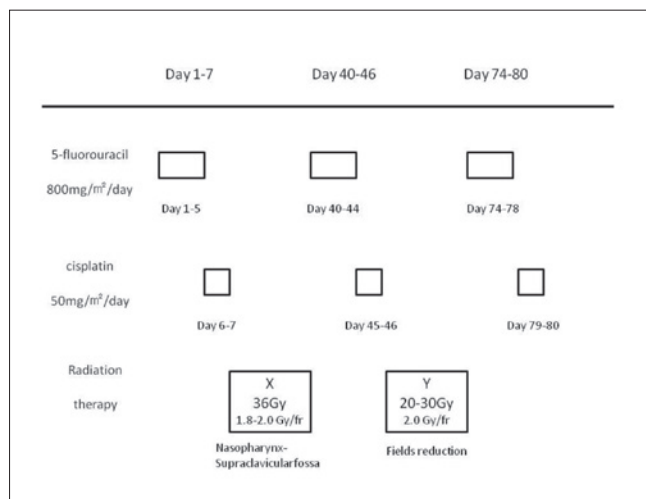


Fig. 1. Alternating chemoradiotherapy protocol. 5-FU, 5-fluorouracil, 800 mg/m²/day on days 1-5; CDDP, cisplatin, 50 mg/m²/day on days 6-7; Field X, large field (from the Nasopharynx to the supraclavicular fossa), 1.8-2.0 Gy, 5f/w, total tumour dose, 36Gy; Field Y, fields reduction, 2.0Gy, 5f/w, total tumour dose, 20-30Gy.

addition, when a WBC count below 3,000/mm² or a platelet count below 75,000/mm² was obtained, chemotherapy was postponed, and radiotherapy was performed instead. The initial radiation therapy was performed five times a week at an irradiation dosage of 1.8-2 Gy using a linear accelerator (6 mV photons) 4-5 days after completing chemotherapy. A 3D conformal shrinking field was used, and the radiation technique was provided along with the duration of the total course of treatments. A total 36 Gy was administered into the base of the skull and supraclavicular fossa. Additional radiation (20-30 Gy) was administered to a smaller area a week after the second course of chemotherapy.

Progression of the primary lesion in the nasopharynx was evaluated using CT, MRI and fibre-optic pharyngeal endoscopy. Metastasis to cervical lymph nodes was evaluated using CT, MRI and palpation. The evaluation of distant metastasis was performed using CT, liver ultrasonography, upper gastrointestinal tract endoscopy and bone scintigraphy. Since 2006, PET (positron emission tomography) CT, or PET-MRI has also been used to evaluate the extent of disease. Treatment completion, response and five-year survival rates of each ACRT-treated patient were calculated from medical records, and the results were compared to previously published data.

Results

Of the 25 patients, 24 (96%) underwent all three courses of chemotherapy and scheduled radiation doses; thus, there was a 96% treatment completion rate in our study. One

patient refused further treatment after it was determined there was a complete response (CR) after additional radiotherapy. In our study, the most common haematological side effect, at grade 3 toxicity or above, was neutropenia (three patients), and the most common non-haematological symptoms were nausea and mucositis (four patients). The toxicity profile is described in Table II, which was assessed before the third course of chemotherapy using Common Terminology Criteria for Adverse Events (CTCAE v. 4.0). Of note, there were no fatal toxicities due to ACRT, corroborating previous work². Distant metastases were revealed in five patients after ACRT. Of the five patients, one patient died, and four patients survived due to surgery, chemotherapy, or radiation therapy interventions. Local recurrences were revealed in the nasopharynx of five patients, and of these, four patients died, with one patient surviving following laser resection. Three patients received a neck dissection for cervical lymph node metastasis. In one patient, this metastasis persisted after the conclusion of ACRT, and the patient died of disease at seven months after neck dissection. In one patient, cervical lymph node metastasis was revealed six months after therapy, and the patient died of gastric cancer 24 months later. In the other patient, cervical lymph node metastasis was revealed 14 months after therapy, with the patient surviving for over eight years after receiving surgery for lung, liver and bone metastases. There were no cases requiring reduced dosages of chemotherapy drugs. Additionally, ACRT radiation exposure dynamics did not need to be modified, and percutaneous gastrostomy tubes were not placed before or during ACRT. The total doses of radiotherapy administered to each patient and their outcomes are described in Table III. Although dosage of radiotherapy in our ACRT regimen for nasopharyngeal cancer is lower than that of other chemoradiotherapy regimens, and the only patients who was treated with lower doses of radiotherapy did not tend to experience

Table II. Adverse effects during ACRT. Common terminology criteria for adverse events (CTCAE v. 4.0).

	Toxicity grade (number of patients)			
	1	2	3	4
Haematologic				
White blood cell	8	14	3	0
Neutrophil	9	13	3	0
Platelet	24	1	0	0
Non-haematologic				
Nausea	10	11	4	0
Mucositis	11	10	4	0
Renal dysfunction	23	2	0	0

ACRT = Alternating chemoradiotherapy

Table III. Total doses of radiotherapy administered to each patient and their outcomes.

Total doses (Gy)	Number of patients	Local recurrence	Neck metastasis	Clinical course
54.4	2	0	0	NED 2/2
56	1	0	0	NED
56.4	4	2	0	NED 1/4 DOD 2/4 DOOD 1
58.2	1	0	0	NED
58.4	1	0	0	NED
59.6	1	0	0	NED
60	2	0	0	NED 2/2
60.4	4	0	1	NED 4/4
61.2	1	1	0	DOD
62.4	1	0	1	DOOD
63	1	0	0	NED
66	1	0	0	Alive wD
66.4	4	2	1	NED 3/4 DOD 1/4
70	1	0	0	NED

NED = no evidence of disease; Alive wD = alive with disease; DOOD = died of other disease; DOD = died of primary disease.

local recurrence. Thus, in sum, the five-year progression-free survival (PFS) rate was 70%, and the five-year overall survival rate was 89.3% (Fig. 2).

Discussion

When an initial diagnosis of nasopharyngeal cancer is made, it typically lacks specific symptoms and is often in an advanced stage. Previous studies have shown that combined chemotherapy is better than radiotherapy alone for treatment of nasopharyngeal cancer³⁻⁷. For example, PFS and overall survival (OS) rates are significantly improved with concurrent chemoradiotherapy (CCRT) plus adjuvant therapy compared with RT alone. The three-year survival rate for RT patients was 47% compared with a 78% three-year survival rate for CCRT plus adjuvant therapy ($P = 0.005$), and three-year PFS was 24% versus 69%, respectively ($P < 0.001$). However, in these studies, the treatment period was longer (130 days), and the treatment completion rate was lower (55%) in patients treated via CCRT combined with adjuvant therapy²³. Other combinations of radiotherapy and chemotherapy have been used to treat nasopharyngeal cancer followed by an initial round of radiation. In particular, several methods are used including adjuvant chemotherapy^{8,9}, neo-adjuvant chemotherapy^{10,11}, ACRT^{17,12-14,20} and CCRT^{3,5,15-18}. It appears that the regimen used is different in each institution,

including the administration time of the individual drugs. In the present study, ACRT was performed with a treatment completion rate of 96% in our department. Previous ACRT treatment completion rates from other institutions were 80%, 70% and 76.1%^{13,14,20}, and CCRT completion rates were 63% and 66%^{3,17}. ACRT has been previously reported to result in fewer side effects compared to CCRT¹³. Therefore, we administered both a drug and radiation dose in our ACRT regimen that minimised side effects. Compared to the ACRT regimen outlined by Fuwa et al.¹³, additional radiation was reduced in our study if the patient had a CR after the second course of chemotherapy. At our institution, the total radiation dose ranged from 54.4 to 70 Gy (average: 60.7 Gy). Although the standard irradiation dose is 66-70 Gy in most regimens^{4,14}, 60 Gy was chosen for the curative irradiation dose based on previous studies of the synergistic interaction between chemotherapy and radiotherapy^{13,21}. As a result, the lower dosage of radiotherapy might have contributed to the higher treatment completion rate, and thus to the higher survival rates. Although the dosage of radiotherapy in our ACRT regimen for nasopharyngeal cancer is lower than that of other chemoradiotherapy regimens, the treatment completion rate, response rate and CR rate were all high, and the survival rate might have enough power to allow comparison with other studies.

Nasopharyngeal cancer is most common in East Asia, Japan included, and EBV is mentioned among the risk factors for nasopharyngeal cancer. Although the link between EBV infection and nasopharyngeal cancer is complex and not completely understood, the success of this low dose radia-

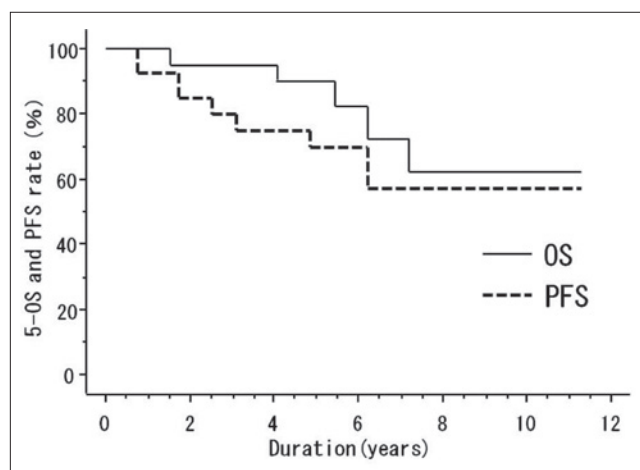


Fig. 2. 5-year overall survival (OS) and progression-free survival (PFS) of nasopharyngeal cancer patients who underwent alternating chemoradiotherapy in our institution by the Kaplan-Meier method. 5-year OS and PFS were 89.3% and 70%.

tion procedure might have been related to a factor specific to East Asian nasopharyngeal cancer. In addition, to improve ACRT treatment completion rate, the interval between radiation and chemotherapy was maintained in our study in order to control vital signs, symptoms, renal function, bone marrow activity and patient recovery. Similar to an original paper by Fuwa et al.¹³, when serum creatinine levels were above 1.5 mg/dL on the scheduled date of chemotherapy, chemotherapy was not performed. In addition, when a WBC count below 3,000/mm³ or platelet count below 75,000/mm³ was obtained, chemotherapy was postponed, and radiotherapy was performed instead. If necessary, at our institution, we waited three weeks to meet the inclusion criteria (WBC count > 3,000/mm³ and platelet count > 75,000/mm³) after the initial round of chemotherapy. We used G-CSF and consulted the internal medicine department to determine the next steps regarding the patient's administration of subsequent rounds of chemotherapy. Because it is important that all patients complete the third systemic course of chemotherapy, patients who refused this third course had a poor prognosis, as previously noted¹⁴.

In addition, when the WBC and platelet counts were respectively below 1,000/mm³ and 25,000/mm³ after chemotherapy, the dose of 5-FU and CDDP was decreased by 25% at the next administration of chemotherapy. Moreover, when serum creatinine levels temporarily exceeded 1.5 mg/dL, 5-FU and CDDP were decreased by 25%.

As mentioned, the CR rate in our study was 96%. A previous study highlighted an ACRT CR rate of 84%¹³, and other studies noted CCRT CR rates of 70% and 93%^{16,18}. With respect to the antitumour effects, ACRT is inferior to CCRT; however, in general, the CR rate is higher. This highlights the fact that completion of ACRT is extremely important. Moreover, the five-year survival rate was 89.3% in our study. Two previous studies showed that the three-year survival rate at institutions that performed neo-adjuvant chemotherapy was 58% and 59%, respectively^{10,11}. Additional studies highlighted the following survival rates with respective therapies: adjuvant chemotherapy, 59% (four-year survival rate)⁸ and 61% (five-year survival rate)⁹; CCRT, 72% and 70.3% (five-year survival rates)^{5,19}; and ACRT, 78.1%, 83%, and 78.04% (five-year survival rates)^{12,13,20}.

It has also been reported that a lower CDDP dose is more effective. This is because the treatment completion rate and survival rate over three years using a lower CDDP dose were both higher compared with treatment completion and survival rates using higher CDDP doses¹³. The extent to which the CDDP dosage can be reduced is unknown; however, ACRT demonstrates decreased invasiveness as compared with CCRT¹³. Moreover, for nasopharyngeal cancer,

a wider irradiation field is required during radiotherapy because of its progression pattern, and thus, mucositis is a concerning problem when radiotherapy alone is performed. Considering these characteristics of nasopharyngeal cancer, ACRT may be a useful method for treating nasopharyngeal cancer because a sufficient number of antitumour agents can be administered in combination with radiotherapy. Thus, mucositis can be decreased in the ACRT regimen as compared with CCRT¹⁵.

Prior to ACRT, we explained to patients the potential benefits in an attempt to increase willingness towards treatment and encourage full completion. There are several reports that a majority of individuals are not diagnosed with nasopharyngeal cancer until they are in stage IV¹³, and 40% of the cases in our department were also detected at stage IV. This is because nasopharyngeal cancer does not typically present with specific symptoms as stated earlier. However, it can be rapidly diagnosed in departments such as ours if nasal congestion and the ears are affected compared with presentation of symptoms such as headache and eye problems. Additionally, nasopharyngeal cancer is a rare form of head and neck cancer and is therefore not included as a differential diagnosis for many nonspecific symptoms. To address the issues of delayed diagnosis in the future, physicians should consider this type of cancer when patients present with persisting facial symptoms.

It is also important that a multidisciplinary approach (i.e., ACRT) is continuously employed in the treatment of distant metastasis after a neck dissection has been done to control such metastasis. Furthermore, the primary tumour recurrence rate is associated with poor prognosis, and thus, the choice of treatment is restricted due to anatomical reasons¹². Split course radiation has inferior treatment outcomes. However, ACRT is different from split course radiation therapy because of the subsequent course of chemotherapy. In addition, ACRT permits patients to take higher doses of antitumour agents compared with CCRT¹⁴.

Conclusions

In conclusion, we demonstrate that ACRT is an effective regimen to treat nasopharyngeal cancer, revealing higher treatment completion, response and five-year overall survival rates compared with other combinatorial radiotherapy and chemotherapy treatment regimens. Because our results are based on a clinical trial with only 25 patients, further study will be required to draw firm conclusions.

References

- ¹ Fuwa N, Ito Y, Kodaira T, et al. *Therapeutic results of alternating chemoradiotherapy for nasopharyngeal cancer using cisplatin and 5-fluorouracil: its usefulness and controversial points.* Jpn J Clin Oncol 2001;31:589-95.
- ² Rosenthal DI. *Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes.* J Support Oncol 2007;5:23-31.
- ³ Al-Sarraf M, LeBlanc M, Giri PG, et al. *Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099.* J Clin Oncol 1998;16:1310-7.
- ⁴ NCCN Guidelines Version 2. 2014 *Cancer of the Nasopharynx.* NCCN.org
- ⁵ Lin JC, Jan JS, Hsu CY, et al. *Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal cancer: positive effect on overall and progression-free survival.* J Clin Oncol 2003;21:631-7.
- ⁶ Marcial VA, Hanley JA, Chang C, et al. *Split-course radiation therapy of carcinoma of the nasopharynx: results of a national collaborative clinical trial of the Radiation Therapy Oncology Group.* Int J Radiat Oncol Biol Phys 1980;6:409-14.
- ⁷ Kawashima M, Fuwa N, Myojin M, et al. *A multi-institutional survey of the effectiveness of chemotherapy combined with radiotherapy for patients with nasopharyngeal carcinoma.* Jpn J Clin Oncol 2004;34:569-83.
- ⁸ Rossi A, Molinari R, Boracchi P, et al. *Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study.* J Clin Oncol 1988;6:1401-10.
- ⁹ Chi KH, Chang YC, Guo WY, et al. *A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients.* Int J Radiat Oncol Biol Phys 2002;52:1238-44.
- ¹⁰ Chua DT, Sham JS, Choy D, et al. *Preliminary report of the asian-oceanian clinical oncology association randomized trial comparing cisplatin and epirubicin followed by radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma.* Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 1998;83:2270-83.
- ¹¹ Chan AT, Teo PM, Leung TW, et al. *A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma.* Int J Radiat Oncol Biol Phys 1995;33:569-77.
- ¹² Goto Y, Kodaira T, Fuwa N, et al. *Alternating chemoradiotherapy in patients with nasopharyngeal cancer: prognostic factors and proposal for individualization of therapy.* J Radiat Res 2013;54:98-107.
- ¹³ Fuwa N, Shikama N, Hayashi N, et al. *Treatment results of alternating chemoradiotherapy for nasopharyngeal cancer using cisplatin and 5-fluorouracil - a phase II study.* Oral Oncol 2007;43:948-55.
- ¹⁴ Ueno T, Endo K, Kondo S, et al. *Factors affecting outcomes of alternating chemoradiotherapy for nasopharyngeal cancer.* Ann Otol Rhinol Laryngol 2014;123:509-16.
- ¹⁵ Lee AW, Lin JC, Ng WT. *Current management of nasopharyngeal cancer.* Semin Radiat Oncol 2012;22:233-44.
- ¹⁶ Bae WK, Hwang JE, Shim HJ, et al. *Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer.* Cancer Chemother Pharmacol 2010;65:589-95.
- ¹⁷ Lee AW, Tung SY, Chua DT, et al. *Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma.* J Natl Cancer Inst 2010;102:1188-98.
- ¹⁸ Xiao WW, Huang SM, Han F, et al. *Local control, survival, and late toxicities of locally advanced nasopharyngeal carcinoma treated by simultaneous modulated accelerated radiotherapy combined with cisplatin concurrent chemotherapy. Long-term results of a phase II study.* Cancer 2001;117:1874-83.
- ¹⁹ Chan AT, Leung SF, Ngan RK, et al. *Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma.* J Natl Cancer Inst 2005;97:536-9.
- ²⁰ Fuwa N, Kodaira T, Daimon T, et al. *The long-term outcomes of alternating chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multiinstitutional phase II study.* Cancer Med 2015;4:1186-95.
- ²¹ Fujii M, Tsukuda M, Satake B, et al. *Phase I/II trial of weekly docetaxel and concomitant radiotherapy for squamous cell carcinoma of the head and neck.* Int J Clin Oncol 2004;9:107-12.

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LARYNGOLOGY

The role of laryngectomy in locally advanced thyroid carcinoma. Review of 16 cases

Il ruolo della laringectomia nel carcinoma della tiroide localmente avanzato. Revisione di 16 casi

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SUMMARY

Locally advanced disease with larynx invasion is a challenge to the surgeon, but laryngectomy is almost never necessary in thyroid carcinoma. The aim of this study was to review the clinical outcomes of patients with locally advanced thyroid carcinoma invading the larynx who underwent laryngectomy. A case series of patients treated in a tertiary care hospital was reviewed. Data about the type of operation, method of reconstruction, complications and overall survival of 16 patients operated on between 2002 and 2015 with larynx invasion is presented. There were 10 females. The mean age was 63 ± 8.8 years. Besides total thyroidectomy and neck dissection, four patients underwent total pharyngolaryngectomy, 11 total laryngectomy and one hemi-laryngectomy. Reconstruction was made with regional flaps in 10 patients (7 pectoral/Bakamjian flaps and 3 gastric pull-through procedures) and a jejunum free flap in one patient. Two patients needed carotid artery reconstruction. Five tumours were classic (conventional) papillary carcinoma variants, while the others were aggressive histological varieties (insular, tall cell, sclerosing). The mean tumour size was 4.3 ± 1.6 cm. All tumours had lymphovascular invasion and 12 had positive lymph nodes. Concomitantly, oesophageal/hypopharyngeal invasion was present in 7 cases and invasion of carotid vessels in 2 cases. There were two postoperative deaths and two anastomotic leaks that were treated conservatively. The mean overall survival was 31 ± 33 months (median 27.6 months, range 0-120). Laryngectomy is an alternative surgical procedure to control selected cases of advanced thyroid carcinoma that offers good local control and long term survival.

KEY WORDS: Thyroid cancer • Laryngectomy • Surgery • Neck dissection

RIASSUNTO

Le malattie localmente avanzate con invasione della laringe sono una sfida per il chirurgo, tuttavia la laringectomia non si rende quasi mai necessaria nel carcinoma della tiroide. L'obiettivo di questo studio è stato quello di valutare gli outcomes clinici di quei pazienti sottoposti a laringectomia per carcinoma della tiroide localmente avanzato con invasione della laringe. Sono stati inclusi una serie di pazienti trattati in presidi ospedalieri di terzo livello. Pertanto sono stati raccolti i dati riguardo il tipo di intervento, la modalità di ricostruzione, le complicanze e la sopravvivenza di sedici pazienti operati tra il 2002 e il 2015. Tra questi, 10 erano donne; l'età media era di $63 \pm 8,8$ anni. Oltre alla tiroidectomia totale e alla dissezione del collo, quattro pazienti sono stati sottoposti a faringolaringectomia, undici a laringectomia, e uno ad emilaringectomia. La ricostruzione è stata effettuata con lembi regionali in dieci pazienti (7 lembi di pettorale e 3 procedure di pull-through gastrico) e lembo libero di digiuno in un paziente. Per due pazienti si è resa necessaria la ricostruzione dell'arteria carotide. Cinque tumori erano carcinomi papillari variante classica, gli altri erano varianti istologiche aggressive (insulare, sclerosante diffuso, a cellule alte). La dimensione media dei tumori era $4,3 \pm 1,6$ cm. Tutti i tumori presentavano un'invasione linfovascolare e dodici di essi avevano dato metastasi linfonodali. Sette casi presentavano una concomitante invasione ipofaringo-esofagea, mentre due casi presentavano invasione dei vasi carotidei. Ci sono state due morti postoperatorie e due deiscenze dell'anastomosi, trattate entrambe in maniera conservativa. La sopravvivenza media è stata di 31 ± 33 mesi (media pari a 27,6, range 0-120). La laringectomia è una procedura chirurgica per casi selezionati di carcinoma tiroideo, che offre un buon controllo locale e lunghi tempi di sopravvivenza.

PAROLE CHIAVE: Carcinoma tiroideo • Laringectomia • Dissezione del collo

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Introduction

Well-differentiated thyroid carcinoma has a good prognosis since patients have low risk malignancies. However, laryngo-tracheal invasion occurs in 7 to 13% of patients, and ¹²

most cases are asymptomatic. In the presence of intraluminal invasion, symptoms become evident and are related to vocal cord paralysis, airway obstruction, or tumour bleeding. In these cases, extended resections are required to control the disease, sometimes affecting quality of life.

The larynx is not invaded as frequently as the trachea or oesophagus, and its invasion is almost always associated with multivisceral spread. Fortunately, laryngectomy is seldom necessary in the treatment of locally advanced thyroid carcinoma (LATC) since even in the presence of locally advanced disease, it is possible to do a less invasive procedure without compromising long term results; this is why a radical resection is not easy to justify.

Locally advanced disease with laryngeal or cricoid invasion is a challenge to the surgeon, who must decide between partial resection, cricoid and tracheal resection, hemi-laryngectomy, or total laryngectomy, while almost always trying to solve an obstructive or bleeding complication. On the other hand, when complete resection is performed, local recurrence is infrequent³. With a less radical procedure, even when adding postoperative ¹³¹I therapy or radiotherapy the relapse is still frequent and persistent growing of an intraluminal mass, followed by vocal fold paralysis, airway obstruction, and death by asphyxiation or bleeding usually occurs. There are few case reports about laryngectomy in the treatment of LATC, and the existing reports are combined with isolated tracheal invasion which are less disruptive procedures. The objective of this study is to report the clinical outcomes of a series of patients with LATC invading the larynx who underwent total laryngectomy associated with thyroidec-tomy and neck dissection.

Materials and methods

This is a descriptive retrospective study approved by the ethics committees of the Hospital Pablo Tobon Uribe and the Head and Neck Service of the Universidad de Caldas, Colombia. All patients with a diagnosis of LATC who underwent partial or total laryngectomy with or without other organ resection (trachea, oesophagus, vessels) were identified at both centres. The data was collected from January 1, 2002 until January 31, 2015. Patients with isolated tracheal invasion identified pre- or intraoperatively were excluded from the analysis.

Patients were considered resectable if the surgeon considered that local and regional resection could be achieved to control the disease with free margins. If the tumour invaded the pre-vertebral fascia or the mediastinum great vessels, resection was not attempted. In cases of invasion of other adjacent organs (oesophageal/pharynx or jugular vein/carotid artery), a pre-operative evaluation with a multidisciplinary team was made to plan multivisceral resection. Pulmonary and/or bone metastasis were not a contraindication to resection. Patients with severe comorbidities with a high risk of intraoperative death defined

by anaesthesiologist (ASA 4-5) or poor functional status (Karnofsky index) were considered inoperable.

Before resection, fibre optic endoscopic evaluation was performed in all cases to assess the presence and location of luminal invasion, and when possible a tumour biopsy was taken. Imaging studies such as contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) helped to assess tumour extension before surgery.

Demographic, clinical, imaging, pathologic, treatment and prognostic variables were extracted from clinical records. The TNM staging system was used at the moment of diagnosis. Loco-regional and systemic recurrence was defined as present in those patients with imaging studies suggestive accompanied with pathologic evidence of carcinoma in the open or fine needle aspiration biopsy (FNAB). All margins were assessed by frozen section, and if positive margin resections were made. Patients were classified as incomplete (R1) or complete (R0), according to final pathology report. Follow-up time was calculated from the moment of surgery to the last clinical visit.

Decisions about diagnostic methods, treatment options and scheme of follow-up were defined by the attending surgeon. Follow-up included periodic imaging tests (ultrasound/CT or PET/CT) and serum markers measurement (TSH, thyroglobulin and anti- thyroglobulin antibodies). All patients were suppressed with high doses of levothyroxine.

Continuous variables are presented as mean and standard deviation and median-range. Categorical variables are shown as percentages. Overall and disease-free survival were calculated using the Kaplan–Meier method using the Stata 9.0 program (Stata Corp., Texas, USA).

Results

A total of 16 patients with LATC who underwent laryngectomy were identified from January 1, 2002 to January 31, 2015. Ten patients were female and six male, with a mean age of 63 ± 8.8 years. All patients had symptoms related with local invasion such as dysphonia, dysphagia, dyspnea, or haemoptysis at the first clinical evaluation. Three patients had a mass confined to a single thyroid lobe and 13 had disease in both lobes. Thirteen patients had concomitant cervical pathologic nodes confirmed by FNAB. All patients without previous surgery had a FNAB positive for papillary thyroid carcinoma in the gland. For cases with previous surgery, a revision of the final pathologic analysis that confirmed papillary carcinoma was done. Eleven patients had recurrent nerve paralysis at the first evaluation and none had had a previous tracheostomy. All patients underwent confirmation of laryngeal invasion

through fibre optic endoscopy before surgical treatment. Three had a biopsy taken during the exam that was positive for papillary carcinoma.

Ten patients had been operated on in other institutions in an attempt to perform thyroidectomy: six patients presented recurrence after total thyroidectomy and a shaving procedure associated with ^{131}I therapy; one also had previous course of radiotherapy and tracheal stent, and four patients had partial thyroidectomy with abortion of the procedure when operative findings indicated airway infiltration. Four patients had distant metastases when first seen and seven patients had concomitant invasion of the digestive tract (4 to the oesophagus and 3 to the pharynx). Patients were graded according to the TNM Staging system as stage IVa in 12 cases and stage IVc in the remaining.

Total or corresponding residual thyroidectomy with comprehensive neck dissection was performed in all cases. Four patients underwent total pharyngolaryngectomy, 11 total laryngectomy and in one case a hemi-laryngectomy was possible. Resection of adjacent structures and reconstruction is shown in Table I. The Bakamjian flap was used in 6 patients with previous radiotherapy only to cover skin defects after mucosal reconstruction and to allow reconstruction of tracheal stoma in cases of mediastinal retraction of the trachea, due to ease of its design and less operative time required. A pectoralis major myocutaneous flap was used when pharyngeal wall reconstruction was needed. The definitive pathological report showed classic (conventional) papillary carcinoma variant in five patients, follicular in two cases and the rest were aggressive histological varieties of papillary carcinoma, such as insular ($n = 2$), tall cell ($n = 3$), or sclerosing ($n = 4$). The mean tumour size was 4.3 ± 1.6 cm and all tumours had lymphovascular invasion. Positive lymph nodes were found in 12 patients. Three patients had positive microscopic margins.

Fifteen patients received a postoperative dose of 150 mCi (5550 MBq) of radioiodine ^{131}I and a complete course of radiotherapy, except the one who had undergone previous radiotherapy. Conventional radiotherapy technique was used for patients treated before 2010 and conformal 3D for those treated after 2010. A 45 Gy total dose in 1.8 Gy daily fractions were used and the field included the neck and superior mediastinum.

There were two postoperative deaths. The first was a female patient with gross invasion of common carotid artery who required a vessel graft. She developed a postoperative suture leakage that produced a carotid blowout at postoperative day 10, with a haemorrhagic shock that required carotid ligation with brain infarct and death at the ICU at postoperative day 15. The second, a 59-year-old female diagnosed with a gross mass invading the larynx, proximal trachea, oesophagus, left innominate vein and the common carotid artery, underwent total en-bloc thyroidectomy with pharyngolaryngectomy and neck dissection along with carotid resection with a graft, partial innominate vein resection reconstructed with a patch and gastric pull-up reconstruction. She developed a carotid graft thrombosis that required thrombectomy at postoperative day 4. She suffered a massive brain infarction and died on postoperative day 5.

There were three major complications; two were anastomotic leaks. One was healed with conservative management, wound care and nutrition and closed on day 23; the second was the patient who died due to carotid blowout. The third complication was a partial necrosis of the posterior wall of the trachea after total laryngectomy that required exploration and reconstruction of the stoma with a PTFE patch to replace the necrotic zone. The patient evolved properly and the patch was removed 12 weeks after surgery. During follow-up there was one local (stomal) recurrence, a regional recurrence was in two patients, so that additional neck dissection was performed. Four patients developed pulmonary metastasis treated with ^{131}I therapy with acceptable uptake. None of the patients was considered eligible to receive systemic therapy with tyrosine-kinase inhibitors due to absence of symptoms and lack of benefit to initiate this therapy in these specific cases.

The mean follow-up time was 43 ± 44 months (median 26, range 1-153). The mean overall survival was 31 ± 7 months (median 30.6 months, range 0-120). Excluding postoperative deaths, there were no other deaths at the moment of writing. Five-year overall survival was 80.1% (Fig. 1).

Discussion

The natural history of locally invasive thyroid carcinoma without adequate treatment is growth of intraluminal tu-

Table I. Extension of surgery and reconstruction procedures for patients with locally advanced thyroid cancer who underwent laryngectomy.

	Other structures resected				Reconstruction			Free flap	
	None	Pharynx	Oesophagus	Trachea	Large vessels	Primary	Regional flap		Gastric pull-through
Partial laryngectomy	0	0	0	0	0	1	0	0	0
Total laryngectomy	5	3	4	1	2	4	7	3	1

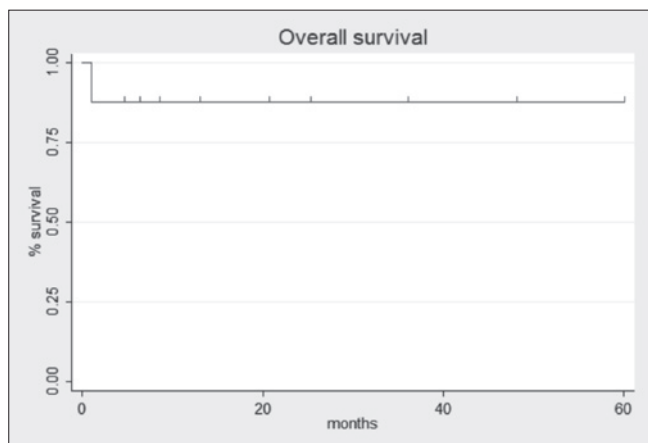


Fig. 1. Kaplan-Meier overall survival graph (months) in patients with locally advanced thyroid cancer who underwent laryngectomy (sticks over the survival line represents patients censored).

mour into the aerodigestive tract⁴. Many of these locally invasive tumours correspond to aggressive variants of papillary carcinoma or poorly differentiated thyroid carcinomas, which behaviour have been extensively reported in literature^{5,6}. Commonly, a paralysis of one or both vocal cords due to recurrent laryngeal nerve involvement is the first event followed by a progressive invasion of the cricoid, the trachea or the oesophagus and tumour erosion of the laryngeal cartilage with invasion of the larynx⁷. Still, there is no consensus in the pattern of invasion. Two routes have been proposed to explain laryngeal invasion: one by local direct invasion from the primary tumour and a second by a metastatic lymph node extension through extracapsular node spread⁸. The patients in this series showed local invasion through the laryngeal cartilage, usually associated with hypopharynx, oesophagus, or cricoid invasion, some of which were related to a bulky node with extracapsular spread, making it impossible to differentiate the pattern of invasion. One case treated initially with a shaving procedure, radiotherapy and endotracheal stent exhibited tumour growing through the tracheal lumen ascending to the cricoid and larynx and causing tumour bleeding and emergency airway obstruction. Additionally, vessel invasion was found in some cases needing vascular grafts, which describes the degree of local invasion. Similar to other reports, a history of voice changes, dysphagia, haemoptysis, dyspnoea and stridor was present, especially in patients with a bulky fixed tumour. This finding should alert the physician to inquire about more advanced disease⁹, to perform a fibre optic endoscopic evaluation and if possible, to obtain a tumour biopsy. We confirmed only three cases with endoluminal tumour biopsy, likely due to the potential risk of fatal bleeding. The imaging studies such as contrast-enhanced tomogra-

phy (CT) or magnetic resonance imaging (MRI) helped to clarify the luminal extent, and size of the tumour as well as to prepare the major resection, although in some cases the techniques were not able to identify the degree of invasion. Therefore, when CT or MRI shows cartilage gross spread, vocal cord or hypopharynx involvement, it must alert the surgeon to be prepared to make a major resection such as a total laryngectomy or pharyngolaryngectomy, keeping in mind that it should be discussed with the patient, while realising the goals of care and expectancies with regards to voice and swallowing preservation. Additionally, a deep discussion of potential complications such as fistula, bleeding, wound dehiscence, vascular outbreak, permanent tracheostomy, sepsis, or a fatal consequence as death should be conducted. Therefore, intervention of palliative care services to address goals of care, advanced directives and potential symptoms management should be taken in consideration prior to surgical intervention.

Laryngeal involvement in cases of thyroid carcinoma is rare, so that specific recommendations cannot be made and the treatment must be individualised. The largest series of laryngectomy in cases of LATC was published by Ballantyne in 1994³ with 32 patients (27 total laryngectomy and 5 pharyngolaryngectomies). He included patients with undifferentiated and anaplastic histology and medullary tumours, as well as patients with isolated tracheal or oesophageal invasion. He reported only one postoperative death and two carotid blowouts and 5 fistula that were treated conservatively. Nine patients developed locoregional recurrence during follow-up, and overall survival was around 75% at 5 years. Gaissert et al.¹⁰ reported on 82 patients, of which 75% corresponded to WDTC; 13 underwent total laryngectomy/laryngopharyngectomy, with a frequency of complete resection of 61%. 56% of these patients had a previous thyroidectomy, and 30% had received previous radiotherapy. The mean survival was 5.5 years with an overall survival of 38% at 5 years. Other authors have reported cases series with less than 10 patients¹¹⁻¹⁷ with similar results. In the cases reported, the decision of surgical treatment was made due to the large tumour volume with larynx or hypopharynx destruction that produced bleeding, dyspnoea, stridor, dysphagia and pain related to local invasion to soft tissues; in some cases as a consequence of a recurrent or persistent progressive invasion in spite of the treatments performed with no other alternative therapies. However, it is difficult to derive a more general conclusion from these studies due to inclusion of tumours of different histology, clinical stage and previous treatments. A recent consensus document from the American Head and Neck Society supports shave excision of tumours with partial thickness invasion of the oesophagus or larynx, but a composite tumour

excision (oesophagectomy, laryngectomy) for those with gross invasion, as reported in this study¹⁸.

The surgical possibilities includes shaving, partial laryngectomy and total laryngectomy¹⁹. Shaving procedures are not considered as a feasible alternative in cases of large tumours due to the risk of leaving viable tumour and late local recurrence. Most groups consider that shaving can only be offered when there is no gross invasion of the perichondrium. In cases of gross luminal invasion or extensive laryngeal invasion, partial or total laryngectomy is the ideal procedure²⁰, because it completely removes the tumour, relieves the obstruction and bleeding symptoms and avoids death by asphyxia. The decision of the type of operation is based on experience with surgical techniques of en-bloc resection, the patient's physical condition and the availability of other surgical teams such as vascular surgeons, thoracic surgeons and reconstructive surgeons, but the main factor is a high preoperative probability of complete resection of the tumour. Indications for the type of laryngectomy depend on location of the tumour, depth of invasion and extension of the tumour. Moritani²¹ reported on the feasibility of partial laryngectomy in 12 of 15 patients with intraluminal invasion, while Hartl et al., performed partial laryngectomy in 5 of 12 patients²². Laryngeal preserving surgery was possible in only one case herein. It is important to realise that we were dealing with very large tumours that commonly involve the larynx or even the pharynx circumferentially. Independent of the larynx subsites involved, if the thyroid tumour externally surpasses the limits of the larynx or pharynx, a total or extended procedure must be done in order to obtain free tridimensional margins, which is the principle of oncologic surgery. If the surgeon believes that R0 surgery is not possible to obtain, we do not recommend resection. Simultaneously, when local control is achieved, it is possible to offer systemic therapy with ¹³¹I for cases with distant metastasis.

In cases of recurrent disease after a thyroid invasive cancer previously treated with a conservative procedure, even with postoperative ¹³¹I therapy or a complete course of postoperative radiotherapy and the additional hostile field, en-bloc resection of the tumour and involved surrounding structures helps to obtain negative margins with consequent improvement in long-term local control^{16 23}. Retrospective studies in patients with laryngectomy have shown an increase in survival comparing with shaving procedures when the complete resection of the gross disease is completely achieved^{3 10}. Due to the brevity of follow-up, this series cannot document a major improvement in survival, but most patients had relief of obstructive or bleeding symptoms without evidence of local relapse. A 5-year overall survival larger than 80% is a promising number

that supports this type of aggressive procedure. Regarding vascular invasion, the two patients with large vessels resection died in the immediate postoperative period. There are few reports of successful resection and reconstruction of large vessels²⁴⁻²⁶. Due to these results, we recommend to make a preoperative plan in conjunction with vascular surgery in cases suspicious of vascular invasion to guarantee good oncologic resection and functional results.

The type of reconstruction was selected based on the extension of pharynx resection. For most patients, regional flaps were used due to the resection of pharyngeal mucosa that made primary closure impossible without stenosis or to cover a skin defect due to retraction of tissues after radiotherapy. Although the Bakamjian flap has been progressively replaced by other types of flaps, it is used due to the low bulk it provides and the less operative time to build it in comparison with free flaps. Circumferential reconstruction with stomach or jejunum was offered to patients with oesophageal invasion in which the surgeon suspected a high risk of fistula if a regional flap was used. In comparison with free flaps and gastric pull-through procedures, regional flaps have the advantage of less operative time and systemic impact and can be used in patients with comorbidities that make other procedures riskier.

Although only one partial laryngectomy was performed, it has been recommended that whenever possible, it should be attempted to preserve the quality of life related with voice preservation, without sacrificing oncologic principles²⁷. Only four patients with total laryngectomy were suitable to the provox system rehabilitation due to the type of reconstruction (gastric pull-through or jejunum flap), but it is recommended whenever possible²⁸.

Conclusions

Even if there is no high-level evidence due to low numbers of cases and heterogeneity of tumours and stages, partial or total laryngectomy and even pharyngolaryngectomy provides an alternative to control selected cases of WDTC with laryngeal or hypopharyngeal invasion, especially when a less radical procedure is not feasible. An exenteration procedure also seems to improve long-term local control. The surgeon should be prepared to suspect gross invasion and to manage it during the surgical intervention. The consequences of the surgical procedure should be discussed with the patient preoperatively.

References

- Shelton VK, Skolnik EM, Berlinger FG, et al. *Laryngotracheal invasion by thyroid-carcinoma*. Ann Otol Rhinol Laryngol 1982;91:363-9.

- 2 Chala A. *Abordaje del carcinoma de tiroides invasivo a traqueolaringe y grandes vasos*. Rev Colomb Cir 2002;17:10-21.
- 3 Ballantyne AJ. *Resections of the upper aerodigestive tract for locally invasive thyroid cancer*. Am J Surg 1994;168:636-9.
- 4 Kim AW, Maxhimer JB, Quiros RM, et al. *Surgical management of well-differentiated thyroid cancer locally invasive to the respiratory tract*. J Am Coll Surg 2005;201:619-27.
- 5 Akaiishi J, Sugino K, Kameyama K, et al. *Clinicopathologic features and outcomes in patients with diffuse sclerosing variant of papillary thyroid carcinoma*. World J Surg 2015;39:1728-35.
- 6 Okuyucu K, Alagoz E, Arslan N, et al. *Clinicopathologic features and prognostic factors of tall cell variant of papillary thyroid carcinoma: comparison with classic variant of papillary thyroid carcinoma*. Nucl Med Commun 2015;36:1021-5.
- 7 Segal K, Abraham A, Levy R, Schindel J. *Carcinomas of the thyroid gland invading larynx and trachea*. Clin Otolaryngol 1984;9:21-5.
- 8 Machens A, Hinze R, Lautenschlager C, et al. *Thyroid carcinoma invading the cervicovisceral axis: routes of invasion and clinical implications*. Surgery 2001;129:23-8.
- 9 Talpos GB. *Tracheal and laryngeal resections for differentiated thyroid cancer*. Am Surg 1999;65:754-9; discussion 759-60.
- 10 Gaissert HA, Honings J, Grillo HC, et al. *Segmental laryngotracheal and tracheal resection for invasive thyroid carcinoma*. Ann Thorac Surg 2007;83:1952-9.
- 11 Zbaren P, Nuyens M, Thoeny HC, et al. *Laryngeal involvement by differentiated thyroid carcinoma*. Am J Surg 2005;190:153-5.
- 12 Cody HS, 3rd, Shah JP. *Locally invasive, well-differentiated thyroid cancer. 22 years' experience at Memorial Sloan-Kettering Cancer Center*. Am J Surg 1981;142:480-3.
- 13 Omura K, Kanehira E, Kawakami K, et al. *Pharyngolaryngoesophagectomy for well-differentiated papillary thyroid carcinoma widely invading the upper aerodigestive tract*. Surgery 2002;132:885-8.
- 14 Mattavelli F, Bombardieri E, Collini P, et al. *Role of surgery in treatment of advanced differentiated thyroid carcinomas*. Acta Otorhinolaryngol Ital 2007;27:62-7.
- 15 Jeannon JP, Simo R, Wallwork B, et al. *Surgical management of advanced differentiated thyroid cancer - introducing the concept of wide field total thyroidectomy: how we do it*. Clin Otolaryngol 2009;34:161-4.
- 16 Kim KH, Sung MW, Chang KH, et al. *Therapeutic dilemmas in the management of thyroid cancer with laryngotracheal involvement*. Otolaryngol Head Neck Surg 2000;122:763-7.
- 17 Shadmehr MB, Farzanegan R, Zangi M, et al. *Thyroid cancers with laryngotracheal invasion*. Eur J Cardiothorac Surg 2012;41:635-40.
- 18 Shindo ML, Caruana SM, Kandil E, et al. *Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHSNS consensus statement*. Head Neck 2014;36:1379-90.
- 19 Price DL, Wong RJ, Randolph GW. *Invasive thyroid cancer: management of the trachea and esophagus*. Otolaryngol Clin North Am 2008;41:1155-68, ix-x.
- 20 Djalilian M, Beahrs OH, Devine KD, et al. *Intraluminal involvement of the larynx and trachea by thyroid cancer*. Am J Surg 1974;128:500-4.
- 21 Moritani S. *Surgical management of laryngeal invasion by papillary thyroid carcinoma: a retrospective analysis*. Thyroid 2015;25:528-33.
- 22 Hartl DM, Zago S, Leboulleux S, et al. *Resection margins and prognosis in locally invasive thyroid cancer*. Head Neck 2014;36:1034-8.
- 23 Brauckhoff M, Machens A, Thanh PN, et al. *Impact of extent of resection for thyroid cancer invading the aerodigestive tract on surgical morbidity, local recurrence, and cancer-specific survival*. Surgery 2010;148:1257-66.
- 24 Kobayashi S, Miyakawa M, Sugeno A, et al. *Reconstruction of the carotid artery using a temporary shunt during an operation for advanced thyroid carcinoma - a case report*. Jpn J Surg 1988;18:592-4.
- 25 Lee YS, Chung WY, Chang HS, et al. *Treatment of locally advanced thyroid cancer invading the great vessels using a Y-shaped graft bypass*. Interac Cardiovasc Thorac Surg 2010;10:1039-41.
- 26 Urabe Y, Kato S, Fujii M, et al. *[Surgical reconstruction of the common carotid artery by an ePTFE graft for invasive thyroid cancer: a case report]*. No Shinkei Geka 2003;31:1105-9.
- 27 Ozturk K, Akyildiz S, Makay O. *Partial laryngectomy with cricoid reconstruction: thyroid carcinoma invading the larynx*. Case Rep Otolaryngol 2014;2014:671902.
- 28 Gaissert HA, Honings J, Grillo HC, et al. *Segmental laryngotracheal and tracheal resection for invasive thyroid carcinoma*. Ann Thorac Surg 2007;83:1952-9.

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RHINOLOGY

Cyclamen europaeum improves the effect of oral antibiotics on exacerbations and recurrences of chronic rhinosinusitis: a real-life observational study (CHRONOS)

L'estratto di Cyclamen europaeum per via intranasale implementa l'effetto degli antibiotici orali nel trattamento delle riacutizzazioni delle rinosinusiti croniche: studio osservazionale in vivo (CHRONOS)

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SUMMARY

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nose and paranasal sinuses affecting 11% of the European population. *Cyclamen europaeum plant extract (CE)* has demonstrated efficacy in treating acute rhinosinusitis, but its role in CRS exacerbations remains unknown. In this real-life, prospective, epidemiological, observational study, a total of 317 patients with exacerbations of CRS without nasal polyps (CRSsNP) of moderate severity were treated using three different options: oral antibiotics, *CE* extract nasal spray, or the combination of oral antibiotic with *CE* extract. The main outcomes were the effect of treatment on sinonasal symptoms and endoscopic appearance after 6 weeks of therapy, and the number of recurrences of CRS exacerbations after 6 months of follow-up. On the top of oral antibiotics, *CE* extract significantly improved sinonasal symptoms and endoscopic findings and caused a 4-fold reduction of CRS recurrences. When administered in monotherapy, *CE* extract was at least as effective as antibiotic in monotherapy on relief of both symptoms and reduction of CRS recurrences. In patients with CRS exacerbation of moderate severity, *CE* extract nasal spray in monotherapy or added to standard antibiotic treatment significantly reduces sinonasal symptoms and CRS recurrences compared to antibiotics in monotherapy.

KEY WORDS: Antibiotics • Chronic rhinosinusitis • *Cyclamen europaeum* • Nasal endoscopic score • Observational study • Real life • Symptom score

RIASSUNTO

La rinosinusite cronica (CRS) è una malattia infiammatoria delle cavità naso-sinusalì che colpisce l'11% della popolazione europea. L'estratto vegetale di Cyclamen europaeum (CE) ha dimostrato efficacia nel trattamento della rinosinusite acuta, ma il suo ruolo nelle riacutizzazioni della CRS rimane sconosciuto. Il presente studio prospettico osservazionale epidemiologico in vivo ha coinvolto 317 pazienti con riacutizzazioni della CRS senza polipi nasali (CRSsNP) di moderata gravità trattati con tre diverse opzioni terapeutiche: antibiotici per os, spray nasale contenente estratto di CE, o la combinazione di antibiotici per via orale con estratto di CE. L'efficacia è stata valutata in base all'efficacia del trattamento sui sintomi sinusalì, all'aspetto endoscopico dopo 6 settimane di terapia, al numero di recidive di esacerbazione di CRS con un follow-up di 6 mesi. In combinazione con la terapia antibiotica orale, l'estratto di CE ha migliorato significativamente i sintomi sinusalì, i reperti endoscopici ed ha ridotto di 4 volte le recidive di CRS. Quando amministrato come monoterapia l'estratto di CE si è dimostrato almeno altrettanto efficace dell'antibiotico somministrato singolarmente sia riguardo al miglioramento dei sintomi che riguardo alla riduzione delle recidive CRS. Conclusioni: nei pazienti con riacutizzazione di CRS di moderata gravità, lo spray nasale a base di estratto di CE in monoterapia o in aggiunta al trattamento antibiotico standard riduce in modo significativo i sintomi sinusalì e le ricorrenze di CRS rispetto agli antibiotici singolarmente somministrati.

PAROLE CHIAVE: Terapia antibiotica • Rinosinusiti croniche • *Cyclamen europaeum*

Introduction

In recent decades, an increase in the prevalence of respiratory diseases, particularly inflammatory diseases of the nose and paranasal sinuses, has been observed¹⁻³. Chronic rhinosinusitis (CRS) is a complex condition that dramatically affects the patient's quality of life and has profound effects on health care expenditure⁴⁻⁶. Management of this disease continues to challenge both patients and physicians. According to the European Position Paper on Rhinosinusitis and Nasal Polyp (EP₃OS 2012)⁷, the prevalence of CRS is increasing annually, currently being one of the most common chronic diseases. For instance, the prevalence of CRS is 3.4% among Canadian men and 5.7% among women⁸, 6% in Belgium⁹ and reaching 9.6% in the Scottish population¹⁰. CRS has been reported as high as 10.9% in Europe¹¹ and 14% in the USA¹².

An exact definition of an acute exacerbation of CRS (AE-CR) is not available. Usually this condition is defined as a sudden worsening of baseline symptoms (or developing new symptoms) in a patient with an established CRS diagnosis. Triggers leading to CRS disease exacerbation are also not well characterised. Previous epidemiologic studies have focused on identification of risk factors for a diagnosis of CRS rather than on risk factors that lead to disease exacerbation. Empirical definition criteria that were used for AE-CR are at least one of the following: a prescription for systemic antibiotics, systemic corticosteroids, plans for a semi-urgent surgical intervention, emergency department or urgent care visit, or hospitalisation¹³. Patients are approximately twice as likely to present with AE-CR in winter season when viral infections are known to be prevalent compared with spring, summer, or fall. Age and sex does not significantly affect the seasonal pattern^{13,14}. According to the EP₃OS document, AE-CR should be treated as acute rhinosinusitis (ARS), i.e. with intranasal corticosteroids and antibiotics, depending on symptom severity⁷.

There is good evidence supporting the concept that inflammation, more than infection, is the dominant aetiological factor in CRS. Unlike ARS, pathogenic microorganisms play a much smaller role in the pathogenesis of CRS^{15,17}. However, based on the available evidence, oral antibacterial antibiotics (mainly in acute exacerbations) and prolonged macrolide antibiotics are considered therapeutic options in the treatment of CRS¹⁸. Although necessary to control AE-CR, both so-called "short" and "long-term" courses of antibiotic therapy may interfere with diversity and abundance of the paranasal sinuses microbial community and carry a risk of aggravation of dysbiosis that already exists in chronic inflammatory respiratory diseases like CRS^{19,20}.

The ineffectiveness of the standard antibiotic therapy and the increased number of resistant strains of causative pathogens^{21,22}, coupled with some doubts on the efficacy of corticosteroids in CRS without nasal polyps²³ and the inability to achieve a total control with surgery²⁴, indicate the need to develop new topical therapeutic modalities.

Cyclamen europaeum plant extract (CE) has been used since ancient times as a topical remedy, is devoid of undesirable systemic side effects and in general, is safer than systemically administered drugs. Like other topical remedies, *CE* might offer a reliable alternative to conventional therapeutic approaches. Sinuforte® is the extract of the fresh tubers of *Cyclamen europaeum* that belongs to the Primulaceae family. This extract comes from a botanical raw material, a natural extract with many compounds, the active substances being saponins. Tubers of *Cyclamen europaeum* are lyophilised, without adding any excipient, to obtain 50 mg of the lyophilised extract. A solvent (5 ml of water for injection) is provided for reconstitution of the lyophilised powder. Sinuforte® is administered to each nostril (2.6 mg once daily) for 8 days. Recent studies have confirmed the efficacy of *CE* in treating ARS^{25,26} but its role in AE-CR is still not known.

The objective of this study was to evaluate efficacy of *CE* extract in treatment of AE-CR either as a monotherapy or in combination with an oral antibiotic and to compare its efficacy with standard oral antibiotic therapy.

Materials and methods

Study population

From June 2011 to February 2012, we conducted a real-life, prospective, observational study aimed to examine the efficacy of three different medical treatment protocols in patients with AE-CR without polyps. The study was conducted at 16 clinical centres across the Russian Federation. The study protocol was approved by the Inter-institutional Ethics Committee of the Sechenov First Moscow State Medical University. All the patients signed written informed consent before entering the study. A total of 327 patients aged 18 to 60 years and diagnosed with acute exacerbation of CRSsNP of moderate severity were enrolled. According to EP₃OS 2012 criteria⁷, a diagnosis of CRS was supported by clinical history, nasal endoscopy and computed tomography (CT) or plain X-rays of the paranasal sinuses.

Inclusion criteria

To be enrolled in the study, patients had to fulfill the following criteria: established diagnosis of CRS (code J32.0-4 and J.32.8-9

according to ICD-10 Version:2010), significant acute aggravation of symptoms (or development of new sinusitis symptom/symptoms) in the last 10 days that forced the patient to see an ENT physician, presence of two or more CRS symptoms and total Visual Analogue Scale (VAS) score of > 3-7 at the time of entering the study, physician's decision for the need of specific therapy or escalation of the previous management.

Exclusion criteria included patients with CRS with nasal polyps, mild or severe CRSsNP according to VAS, absence of paranasal sinuses opacification on CT scans/plain X-rays, orbital or intracranial complications, the use of systemic or topical antibiotics or corticosteroid therapy during the previous month, severe intercurrent illnesses (immunocompetent diseases, severe endocrine, respiratory or metabolic diseases, etc.) and pregnancy. Patients with concomitant allergic rhinitis were also excluded.

Patients with mild AECR were not included because they did not need antibiotic therapy. Patients with severe forms of AECR (in whom systemic antibiotics were necessary to prevent complications and monotherapy with *CE* would not be sufficient) were likewise not included.

Ten patients were withdrawn at different stages of the study because they were unable to attend the next visit due to personal reasons; no patient withdrew from the study due to adverse effects or lack of treatment efficacy. Therefore, 317 patients completed the study and were suitable for statistical analysis.

Study design

Physicians in all centres had free choice to include patients in one of the three treatment protocols: patients in group 1 were treated with an oral antibiotic plus intranasal *CE* (Sinuforte® Nasal Spray, Hartington Pharmaceutical, Barcelona, Spain), group 2 with intranasal *CE* in monotherapy and group 3 with oral antibiotic alone. There were no strict recommendations for empirical antibiotic therapy, and participating physicians selected a first-line oral antibiotic according to their personal clinical experience and institutional guidelines. When used, *CE* was administered to each nostril (2.6 mg once daily) for 8 days. Patients were free to stop the prescribed therapy and to discontinue their participation in the study at any time.

After start of the treatment, all patients were followed-up for 6 months by regular examination by the responsible observer. Patients from Groups 1 and 3 received systemic antibacterial therapy and the physicians' choice and dosages completely followed standards of empirical antibiotic therapy presented in rhinosinusitis national guidelines. The most common antibiotics prescribed were amoxicillin (1.0, 3 times daily) and amoxicillin/clavulanate (1.0, 2 times daily)

followed by macrolides (clarithromycin 0.25, 2 times daily) and cephalosporins of the I-III generation. Routine antibiotic treatment was for 7 days (according to national guidelines) with some exclusions (for instance, azithromycin 0.5 once daily for 3 days, and moxifloxacin 0.4 once daily for 5 to 6 days). Physicians were encouraged to change the treatment protocol and to prescribe or change antibiotic when necessary. They were also free to use additional treatment options such as systemic or topical corticosteroids, topical antimicrobials, antral tap, sinus lavage, or Proetz replacement irrigations. Any change in the treatment protocol, use of additional therapeutic options and withdrawals were registered in case report forms. After the inclusion visit (T_0), patients were visited at day 3 (T_1), day 5 (T_2), and day 8/end of treatment (T_3) and after 6 weeks (T_4) of follow-up. After 6 months (T_5), patients were interviewed by a telephone call and asked about the number of episodes of AECR after discontinuation of treatment (Table I).

Outcomes

1. *Nasal symptoms.* Treatment efficacy was assessed at visits T_1 - T_4 . Assessment was based on the patient's subjective evaluation of the severity of the four main CRS symptoms (nasal obstruction, nasal discharge, facial pain/pressure, loss of smell or hyposmia) by VAS, (10 cm) as well as the composite evaluation of total nasal symptoms score (TNSS).
2. *Nasal endoscopic assessment.* Treatment efficacy was assessed at visits T_1 - T_4 . Semi-quantitative scores were recorded for middle meatal discharge and mucosal oedema. These results were evaluated using an endoscopic appearance score (EAS)^{27 28}. Discharge was scored after decongestion as follows: 0, no discharge; 1, moderate amount of mucous or purulent discharge; and 2, large amount of thick, purulent discharge. Mucosal oedema was scored before decongestion as follows: 0, absent; 1, moderate, and 2, severe.
3. *Patient's self-perception of treatment efficacy* was assessed at visits T_3 and T_4 . The patient's assessment was scored as excellent, good, well/moderate, no effect, or bad/worsening.

Statistical analysis

With the help of a medical statistician (SSS), the results were entered into a computerised database and processed using the statistical software package SPSS version 17.0 for Windows. For each group of patients, the data distribution was identified, the frequency and scores were described and 95% confidence intervals were defined. Median, mode, standard error of the mean and standard deviation of the average, the minimum and maximum (variability), the in-

Table I. Procedures performed during visits over the study duration.

Procedures	Days/Visits					
	Day 1	Day 3	Day 5	Day 8	6 weeks	6 months
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4: Primary endpoint	End of follow-up: Secondary endpoint
Sign informed consent	X	-	-	-	-	-
Filling CRF, collecting medical history: concomitant diseases, inclusion/exclusion criteria, previous therapies	X	-	-	-	-	-
Evaluation of symptoms severity (VAS)	X	X	X	X	X	-
General ENT examination	X	X	X	X	X	-
CT/plain X-rays of paranasal sinuses	X	-	-	-	-	-
Nasal endoscopy	X	X	X	X	X	-
Selecting treatment protocol	X	-	-	-	-	-
Checking patient adherence	-	X	X	X	-	-
Adverse events registration	-	X	X	X	-	-
Evaluation of treatment efficacy	-	X	X	X	X	-
Telephone interview	-	-	-	-	-	X

terquartile range values, ANOVA analysis of variance (Levene Statistic) and ANCOVA analysis of covariance across treatment groups and Wilcoxon signed-rank test were used to compare variables between the groups to determine statistical significance at various time points. Values were presented as mean ± standard deviation (SD). Changes within and between the groups were considered statistically significant when p values were < 0.05.

Results

A total of 317 patients with AECR (135 men and 182 women) aged from 18 to 60 years (mean 46.4 ± 5.0) were included in the study: CE plus antibiotic (group 1, N = 128), CE in monotherapy (group 2, N = 90) and antibiotic in monotherapy (group 3, N = 99). Baseline characteristics of patients are presented in Table II.

Assessment of symptoms

Total Nasal Symptom Score (TNSS). At baseline (T₀), TNSS was higher in group 1 than in group 2 (p < 0.01). Starting from day 3 (T₁) and at all consecutive time points, either oral antibiotic plus CE or CE in monotherapy induced a significantly (p < 0.001) higher resolution of TNSS compared to oral antibiotic alone. After 6 weeks (T₄) of treatment initiation, TNSS was significantly reduced from 8.80±0.29 at baseline to 0.78 ± 0.16 by antibiotic plus CE, from 7.93 ± 0.25 to 0.76 ± 0.12 by CE alone and from 8.23 ± 0.34 to 1.70 ± 0.22 by antibiotic alone) (Fig. 1).

Individual Nasal Symptom Score. At baseline (T₀), scores for nasal congestion, facial pain/pressure and hyposmia were similar in all treatment groups, while score for na-

sal discharge in group 1 was higher than in groups 2 and 3 (p = 0.001). Either oral antibiotic plus CE or CE in monotherapy induced a significantly (p < 0.001) higher resolution of nasal congestion and nasal discharge from day 5 (T₂) to week 6 (T₄) and from day 8 (T₃) to week 6 (T₄) than antibiotics in monotherapy (Fig. 2 a-d). All three treatment options improved hyposmia during the treatment period but with no significant differences between the groups. No significant difference was found between oral antibiotic plus CE and CE in monotherapy for all individual symptom improvements.

Nasal endoscopy assessment. At baseline (T₀), EAS for middle meatus discharge, but not for oedema, was significantly (p < 0.01) worse in group 1 than in groups 2 and

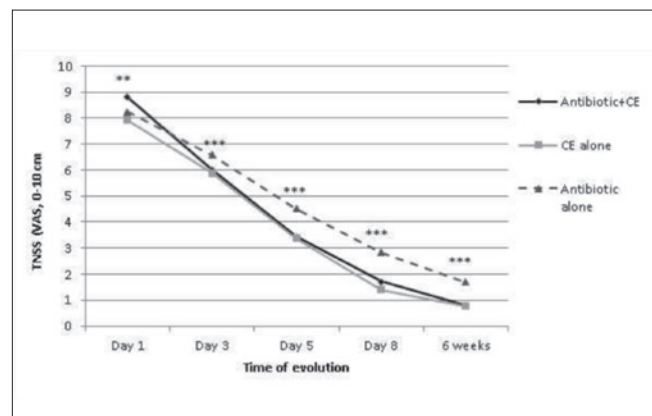


Fig. 1. Evolution of Total Nasal Symptom score (VAS) during AECR treatment. Comparison between groups (**, p < 0.01; ***, p < 0.001, between groups).

Table II. Baseline characteristics of patients receiving the three treatment protocols.

	Group 1 (antibiotic + CE)	Group 2 (CE in monotherapy)	Group 3 (antibiotic in monotherapy)	All patients
Patients, N (%)	128 (40.3%)	90 (28.4%)	99 (31.3%)	317 (100%)
Gender (female), N (%)	74 (57.8%)	53 (58.9%)	55 (55.6%)	182 (57.4%)
Age, years (mean±SD)	49.7 ± 4.7	47.3 ± 5.3	42.3 ± 4.9	46.4 ± 5.0
TNSS, VAS (mean±SD)	8.80 ± 0.29*	7.93 ± 0.25	8.23 ± 0.34	8.32 ± 0.29
EAS, middle meatus discharge (mean±SD)	2.35 ± 0.09	2.07 ± 0.10	2.11 ± 0.12	2,18 ± 0.1
EAS, middle meatus mucosal edema (mean±SD)	2.55 ± 0.07	2.49 ± 0.08	2.59 ± 0.11	2.54 ± 0.09

CE, *Cyclamen europaeum*; TNSS, Total Nasal Symptom Score; EAS, Endoscopic Assessment Score; SD, standard deviation; VAS, Visual Analogue Score; *, $p < 0.01$ vs. group 2.

3. Either oral antibiotic plus CE or CE in monotherapy induced a significant ($p < 0.001$) reduction of the middle meatus mucosal oedema from day 3 (T_1) to week 6 (T_4) (Fig. 3). Regarding the score for middle meatus discharge, there was no significant difference between groups at T_1 - T_3 visits, however, at visit T_4 the score in group 3 (oral antibiotic alone) was significantly ($p < 0.05$) higher than in group 2 (CE alone). No statistical difference was found between groups 1 and 2 at T_1 - T_4 visits.

Patient self-evaluation of treatment efficacy. After 8 days of active treatment (T_3), no patient in any group reported that they feel “worse/bad”; an absence of effect was revealed more frequently in group 3 (oral antibiotic alone)

and least in group 2 (CE) ($p = 0.013$). The number of “well/moderate” assessments was not significantly different between the three groups; “good effect” assessment in group 3 (oral antibiotic alone) was three times less frequent than in group 1 (oral antibiotic +CE) and group 2 (CE alone) ($p = 0.001$); the same number of “excellent” results according to patient assessment was recorded in all groups (Fig. 4a). Six weeks after (T_4), a “bad effect” was reported by a few patients in groups 2 and 3; “no effect” and “well/moderate” was observed in the same number of patients; a “good” effect was more often reported in group 1 than in group 2 ($p = 0.023$) and six times less frequently in group 3 ($p = 0.007$) (Fig. 4b).

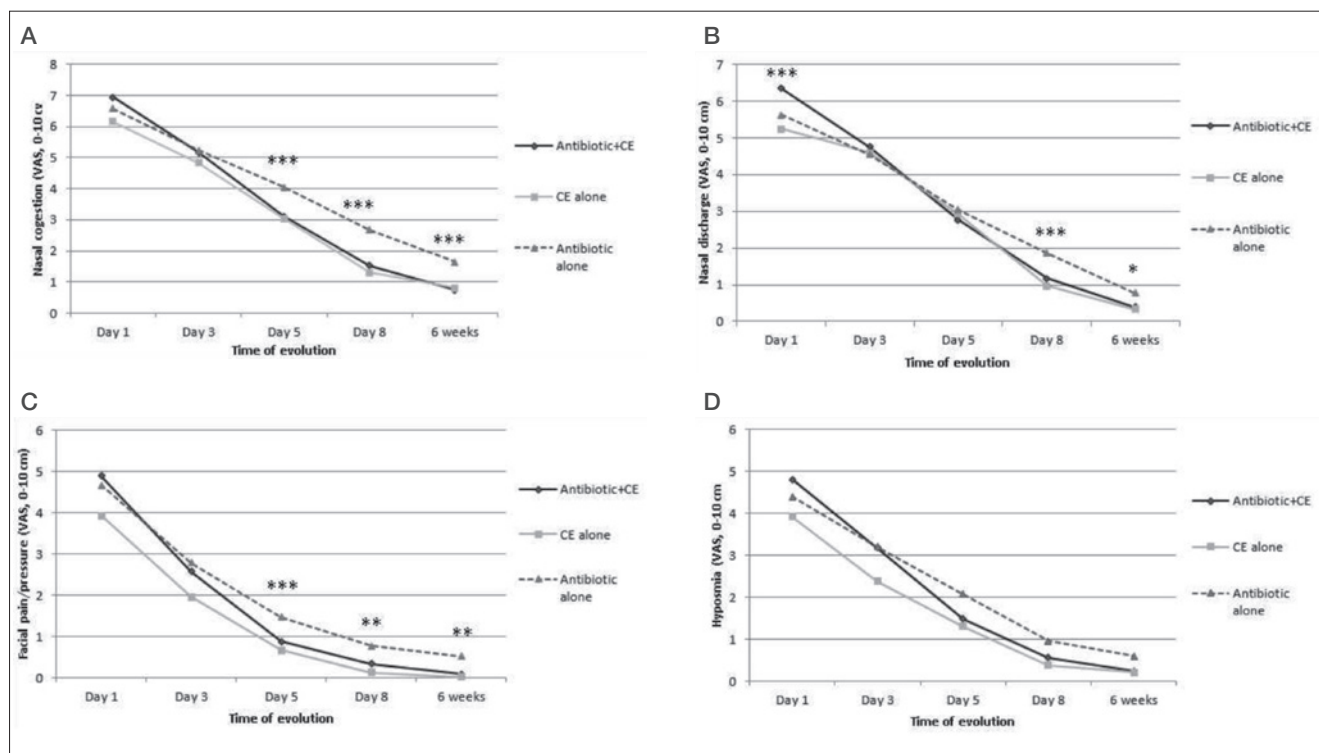


Fig. 2. Evolution of individual symptoms (VAS) during AECR treatment. Nasal congestion (A), nasal discharge (B), facial pain/pressure (C) and loss of smell/hyposmia (D). Comparison between groups (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

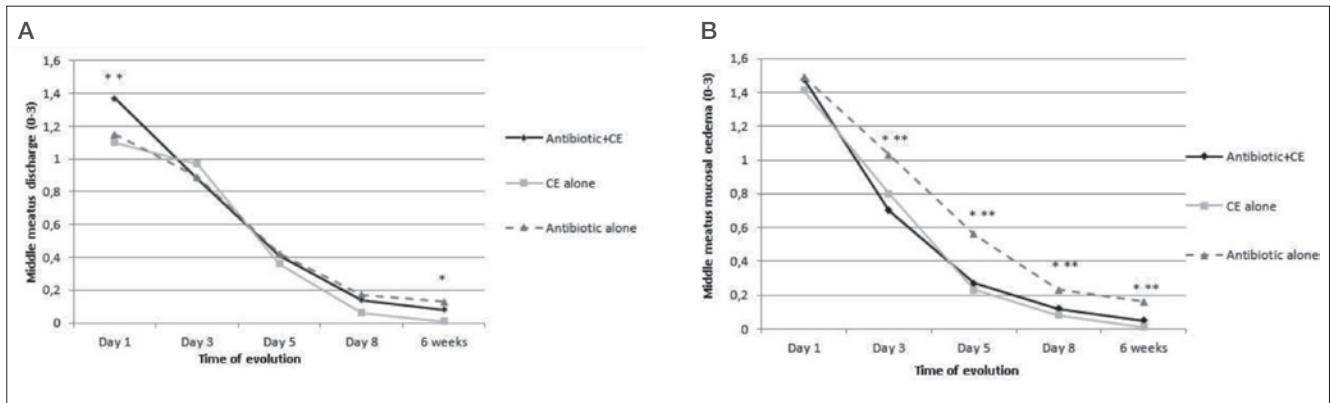


Fig. 3. Evolution of endoscopic appearance score (EAS) during AECR treatment. Middle meatus discharge (A) and mucosal oedema (B). Comparison between groups (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

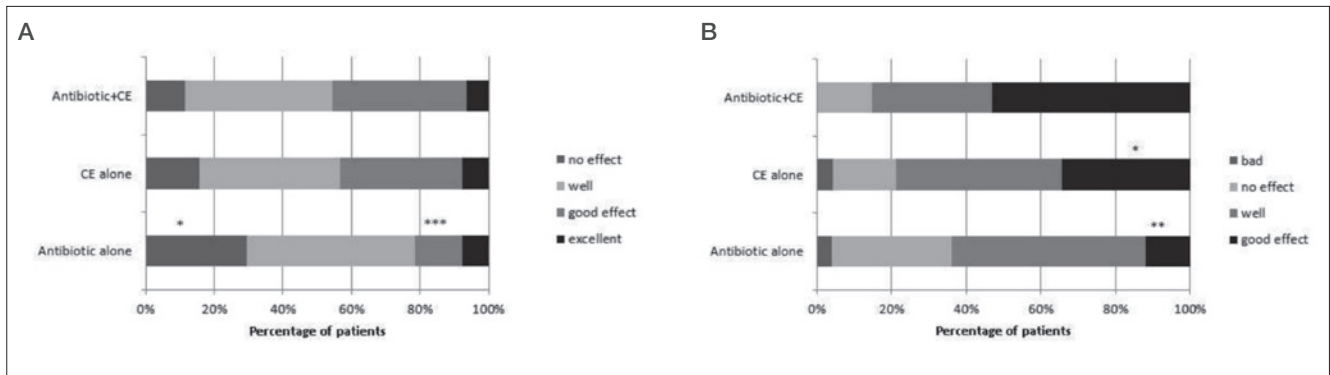


Fig. 4. Patients' self-perception of treatment efficacy: (A) after discontinuation of therapy (T3, 8 days) (*, $p < 0.01$ compared to group 1; ***, $p < 0.01$ vs. group 1). (B) short-term follow-up (T4, 6 weeks). (*, $p < 0.01$ vs. group 1; **, $p < 0.01$ vs. group 1).

Recurrence rate assessment

When interviewed by telephone 6 months (T_6) after the start of the therapy, patients treated with antibiotic and CE reported significantly less ($p < 0.01$) AECR than those treated with either CE or antibiotic in monotherapy (Fig. 5). Only 3.9% ($N = 5$) of patients treated with antibiotic plus CE reported exacerbations (4 patients with one episode and 1 patient with two episodes) compared to 23.3% ($N = 21$) of patients treated with CE alone (14 patients with one episode and 7 patients with two episodes) or 20.2% ($N = 20$) of patients treated with antibiotic alone (14 patients with one episode, 3 patients with 2 episodes, 2 patients with 3 episodes and 1 patient with 4 episodes).

Changes to therapeutic protocols

In group 1, the selected antibiotic was not replaced in any patient. In group 2, CE was supplemented with an antibiotic in 5.5% of patients. In group 3, the selected antibiotic was replaced due to lack of clinical efficacy with a

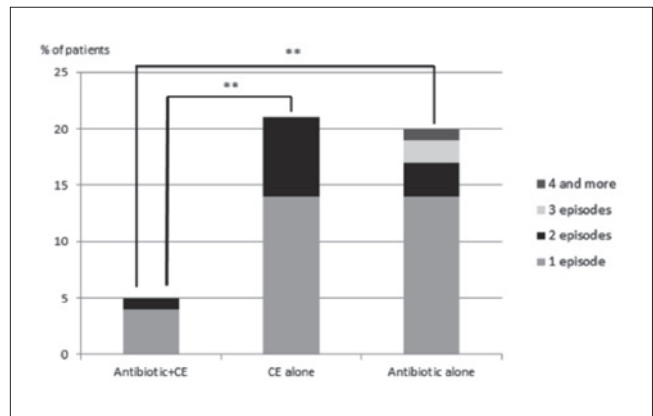


Fig. 5. Number of AECR during 6-month follow-up. Comparison between treatment.

second-line antibiotic in 5% of patients. In no case were systemic or topical corticosteroids added to initial therapy in any study group. Antral puncture and sinus lavage, as

adjunct to initial therapy, was performed after 3 or 5 days of therapy in 3.1% and 13.1% of patients from group 1 and group 3, respectively, but in no patients in group 2. Proetz nasal lavage, as adjunct to initial therapy, was conducted after 3 or 5 days in 2.3% of patients from group 1, 4.4% of patients from group 2 and 9.1% of patients from group 3. Therefore, in terms of the need for alternative therapeutic options, physician satisfaction with treatment efficacy was significantly ($p < 0.05$) higher in groups 1 and 2 (both with *CE* extract) than in group 3.

Adverse events. No severe adverse events were reported in this study. Only 7 patients (5 in group 1 and 2 in group 2) reported mild adverse effects (itching, sneezing, burning of the nose or throat irritation) after *CE* extract nasal spray, which did not require changes in the protocol or study withdrawal.

Discussion

While systemic antibiotics (for severe bacterial disease) and intranasal corticosteroids (for moderate to severe disease) remain a mainstay in treatment of ARS and AECR, several studies have been carried out in recent years to find alternative therapies to improve the symptoms and severity of rhinosinusitis. In particular, two randomised controlled studies assessed the efficacy of herbal compounds in treatment of ARS. One study showed that Pelargonium sidoides might be effective in alleviating symptoms of ARS in adults²⁹. The other randomised multicentre study assessed the efficacy of Myrtol in the treatment of ARS. The results showed a statistically significant difference in improvement of TNSS between active treatment and placebo. The need for antibiotic therapy after Myrtol was 23%, compared to 40% for placebo³⁰.

The tuber of *Cyclamen europaeum* (*Cyclamen purpurascens*), a member of the *Primulaceae* family, has been used in herbal medicine since ancient times as a topical remedy for a range of indications. An extract of the tuber has been used for sinusitis in the form of nasal spray. The chemical composition of *CE* has not been thoroughly studied. The most examined active components of *CE* are triterpenoid saponins that belong to the group of organic glycosides. The saponin fraction of *CE* stimulates nasoparanasal secretions. When delivered to the nasal cavity, *CE* with its saponin fraction causes irritation of the trigeminal nerve endings in the nasal mucosa through cholinergic pathways, leading to rapid and abundant discharge of inflammatory sinus exudates through the nose and subsequent decongestion lasting approximately 30 min³¹. Saponins also possess a direct osmotic effect and are able to stimulate mucociliary clearance by triggering mucus secretion³². Our previous study has shown that *CE* application increases microcirculation in the nasal mucosa and dilates blood vessels supplying the mucus glands^{33,34}.

Two recent randomised, double-blind, placebo-controlled trials, conducted in Europe²⁷ and the US²⁸, reported the improvement by *CE* of facial pain, endoscopic signs (middle meatus mucosal oedema and secretion), reduction of sinus opacification and increase of both investigator and patient treatment satisfaction in patients with ARS. These two studies with level of evidence Ib have confirmed *CE* is a suitable therapeutic option for ARS recommended by international guidelines (EP₃OS 2012)⁷. Few non-controlled, non-blinded studies have reported on the efficacy of *CE* in larger cohorts of patients with both ARS and CRS. When added to antibiotic treatment, *CE* therapy caused an increased reduction of ARS symptoms in adults compared to antibiotic alone^{32,35}.

Our real-life observational study is the first to show that *CE* alone or in combination with an oral antibiotic is significantly more effective in treating AECR than antibiotics alone in terms of relieving nasal symptoms (TNSS, nasal congestion, nasal discharge, and facial pain/pressure) as well as decreasing middle meatus mucosal oedema.

Furthermore, the combination of a course of oral antibiotic and *CE* showed the best results in terms of prevention of CRS recurrence after 6 months of follow-up. The number of AECR was 4 times less than in patients receiving oral antibiotic or *CE* in monotherapy. In addition, an increased number of AECR where physicians replaced a first-line antibiotic with a different one or used alternative treatment options due to insufficient efficacy of initial therapy was mainly observed in group 3 (antibiotic in monotherapy). These findings are in line with the results of previous observational study, which showed that adding *CE* to oral antibiotic increased the ARS success rate by 15% as well as *CE* on top of the combination of oral antibiotic plus topical corticosteroid, which increased the rate of clinical recovery by 24%³⁶.

Among the limitations of the present study, we may firstly highlight the lack of randomisation since allocation of a patient to the treatment group in this real-life observational investigation was based on the physician's choice. Worse initial TNSS in the group 1, as well as the higher initial middle meatus discharge score in this group might be explained by the physicians' intention to reserve combined therapy for patients with relatively more severe symptoms. Secondly, blinding was not used for either patients when receiving the treatment protocol and additional therapy or for physicians when grading endoscopic findings. Thirdly, patients were selected from the group of moderate severity probably discarding those with common cold exacerbations (mild) and those with bacterial rhinosinusitis (severe). All these factors could be theoretically a potential bias for both the physicians and patients. Moreover, like ARS, AECR is a self-limited disease and about 90% of cases improve spontaneously.

However, a multicentre (16 independent clinical centres around the Russian Federation) observational study was performed among three potential therapeutic protocols in a real-life design whose aim was to evaluate clinical outcomes for 6 weeks after treatment of AECR and recurrences during 6-month follow-up. The relatively short duration of oral antibiotic therapy (7 days) could be also considered a controversial issue in the study. Although longer courses are used to treat AECR in Western Europe and the US ⁷, the design of the study tried, however, to follow the recommendations endorsed in the Russian Federation, where one-week course of antibiotic therapy is recommended for treatment of ARS and AECR ³⁷.

Conclusions

The results of this observational study suggest that in AECR of moderate severity, both *CE* in monotherapy or added to oral antibiotics induces an increased symptom relief and prevents long-term CRS recurrences compared to antibiotics in monotherapy. Thus, intranasal *CE* may be considered as an alternative to standard antibiotic therapy in the treatment of non-complicated non-severe AECR and potentially help to reduce costs of disease ³⁶ as well as to reduce antibiotic abuse and the consequent increase in antibiotic resistance.

Acknowledgments

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References

- Bhattacharyya N. *Chronic rhinosinusitis: is the nose really involved?* Am J Rhinol 2001;15:169-73.
- Benninger MS, Ferguson BJ, Hadley JA, et al. *Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology.* Otolaryngol Head Neck Surg 2003;129:1-32.
- Meltzer EO, Hamilos DL, Hadley JA, et al. *Rhinosinusitis: establishing definitions for clinical research and patient care.* Otolaryngol Head Neck Surg 2004;131:1-62.
- Anand VK. *Epidemiology and economic impact of rhinosinusitis.* Ann Otol Rhinol Laryngol 2004;193:3-5.
- Lund VJ. *Impact of chronic rhinosinusitis on quality of life and health care expenditure.* Clin Allergy Immunol 2007;20:15-24.
- Alobid I, Guilemany JM, Mullol J. *The impact of chronic rhinosinusitis and nasal polyposis on quality of life.* Front Biosci 2009;1:269-76.
- Fokkens WJ, Lund VJ, Mullol J, et al. *European Position Paper on Rhinosinusitis and Nasal Polypos 2012.* Rhinol Suppl 2012;Mar 23:1-298.
- Chen Y, Dales R, Lin M. *The epidemiology of chronic rhinosinusitis in Canadians.* Laryngoscope 2003;113:1199-205.
- Gordts F, Clement PAR, Buisseret T. *Prevalence of sinusitis signs in a non-ENT population.* Otorhinolaryngology 1996;58:315-9.
- Ahsan SF, Jumans S, Nunez DA. *Chronic rhinosinusitis: a comparative study of disease occurrence in North of Scotland and Southern Caribbean otolaryngology outpatient clinics over a two month period.* Scott Med J 2004;49:130-3.
- Hastan D, Fokkens WJ, Bachert C, et al. *Chronic rhinosinusitis in Europe - an underestimated disease. A GA²LEN study.* Allergy 2011;66:1216-23.
- Kaliner MA, Osguthorpe JD, Fireman P, et al. *Sinusitis: Bench to bedside. Current findings, future directions.* J Allergy Clin Immunol 1997;99:829-48.
- Rank MA, Wollan P, Kita H, et al. *Acute exacerbations of chronic rhinosinusitis occur in a distinct seasonal pattern.* J Allergy Clin Immunol 2010;126:168-9.
- Brook I. *Bacteriology of chronic sinusitis and acute exacerbation of chronic sinusitis.* Arch Otolaryngol Head Neck Surg. 2006;132:1099-101.
- Brook I. *The role of bacteria in chronic rhinosinusitis.* Otolaryngol Clin North Am 2005;38:1171-92.
- Busaba NY, Siegel NS, Salman SD. *Microbiology of chronic ethmoid sinusitis: Is this a bacterial illness?* Am J Otolaryngol 2004;25:379-84.
- Kern RC, Conley DB, Walsh W, et al. *Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis.* Am J Rhinol 2008;22:549-59.
- Soler ZM, Oyer SL, Kern RC, et al. *Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations.* Int Forum Allergy Rhinol 2013;3:31-47.
- Boase S, Foreman A, Cleland E, et al. *The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection.* BMC Infect Dis 2013;13:210.
- Merkley MA, Bice TC, Grier A, et al. *The effect of antibiotics on the microbiome in acute exacerbations of chronic rhinosinusitis.* Int Forum Allergy Rhinol 2015;5:884-93.
- Legent F, Bordure P, Beauvillain C, Berche P. *A double-blind comparison of ciprofloxacin and amoxicillin/clavulanic acid in the treatment of chronic sinusitis.* Chemotherapy 1994;40:8-15.
- Namyslowski G, Misiolek M, Czecior E, et al. *Comparison of the efficacy and tolerability of amoxicillin/clavulanic acid 875 mg bid with cefuroxime 500 mg b.i.d. in the treatment of chronic and acute exacerbation of chronic sinusitis in adults.* J Chemother 2002;14:508-17.
- Parikh A, Scadding GK, Darby Y, et al. *Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray.* Rhinology 2001;39:75-9.
- Lund VJ. *Evidence-based surgery in chronic rhinosinusitis.* Acta Otolaryngol 2001;121:5-9.
- Pfaar O, Mullol J, Anders C, et al. *Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the man-*

- agement of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. *Rhinology* 2012;50:37-44.
- ²⁶ Ponikau JU, Hamilos DL, Barreto A, et al. *An exploratory trial of Cyclamen europaeum extract for acute rhinosinusitis*. *Laryngoscope* 2012;122:1887-92.
- ²⁷ Fokkens W, Lund V, Mullol J, and the European Position Paper on Rhinosinusitis and Nasal Polyps group. *EP₃OS 2007: European Position Paper on Rhinosinusitis and Nasal Polyps 2007. A summary for otorhinolaryngologists*. *Rhinology* 2007;45:97-101.
- ²⁸ Lund VJ, Mackay IS. *Staging in rhinosinusitis*. *Rhinology* 1993;31:183-4.
- ²⁹ Bachert C, Schapowal A, Funk P, et al. *Treatment of acute rhinosinusitis with the preparation from Pelargonium sidoides EPs 7630: a randomized, double-blind, placebo-controlled trial*. *Rhinology* 2009;47:51-8.
- ³⁰ Federspil P, Wulkow R, Zimmermann T. *Effects of standardized Myrtol in therapy of acute sinusitis – results of a double-blind, randomized multicenter study compared with placebo [in German]*. *Laryngorhinootologie* 1997;76:23-7.
- ³¹ Gedevanishvili MD, Gogitidze NM, Sigharulidze IS. *Reflex mechanisms of nasoparanasal secretion in the administration of Sinuforte [in Russian]*. *Vestn Otorinolaringol* 2007;(3):54I se.
- ³² Kryukov AI, Kunelskaya NL, Turovsky AB, et al. *New perspectives in non-invasive treatment of sinusitis [in Russian]*. *Vestn Otorinolaringol* 2007;2:33-7.
- ³³ Lopatin AS, Shempelev OA. *Influence of Sinuforte on nasal mucosa microcirculation [in Russian]*. *J Russian Rhinol* 2007;4:26-8.
- ³⁴ Piskunov SZ, Dolzhikov AA, Kalinkin AA. *Quantitative histological and histochemical study of the reaction of the nasal cavity and maxillary sinus glands to contact with Sinuforte [in Russian]*. *J Russian Rhinol* 2009;1:17-22.
- ³⁵ Rybak AA, Rybak AA, Matveeva TV, et al. *Effects of Sinuforte on quality of life in rhinosinusitis patients [in Russian]*. *Vestn Otorinolaringol* 2008;3:56-8.
- ³⁶ Mullol J, Crespo C, Carré C, et al. *Pharmacoeconomics of Cyclamen europaeum in the management of acute rhinosinusitis*. *Laryngoscope* 2013;123:2620-5.
- ³⁷ Angotoeva IB, Lopatin AS, Ekimenko YB. *How we treat acute rhinosinusitis in Russia? [in Russian]*. *J Russian Rhinol* 2007;1:23-6.

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OSAS

Modification of growth, immunologic and feeding parameters in children with OSAS after adenotonsillectomy

Modificazioni dei parametri di crescita, immunologici e alimentari in bambini con OSAS dopo adenotonsillectomia

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SUMMARY

Obstructive sleep apnoea syndrome can cause growth delay in children. Adeno-tonsillectomy can resolve the syndrome in most cases. The aim of our study is to examine modifications in clinical and laboratory growth and immunological parameters and food intake changes in OSAS children after surgery. Twenty-eight children with severe OSAS associated with adeno-tonsillar hypertrophy were submitted to paediatric evaluation to calculate auxologic parameters (weight, height, BMI and standard deviation scores), a blood draw to evaluate growth (GH; IGF-1) and immunological parameters (IgG; IgA; IgM) and a dietitian evaluation to calculate caloric intake before and after 3 months following adeno-tonsillectomy. Mean height and weight values in the study group were slightly inferior to same-age children mean according to the percentile values. After surgery, both height and BMI increased significantly at 3-months follow-up: mean height increased 2.93 cm ($p = 0.0001$); BMI values greatly increased by 0.72 kg/m² ($p = 0.009$). Standard deviation scores increased significantly for height ($p = 0.03$), weight ($p = 0.001$) and BMI ($p = 0.001$). These values significantly increased, despite almost unchanged caloric intake between the pre- and post-surgery period (90 ± 24 vs 91 ± 27 kcal/kg/day; $p > 0.05$). In all children, age-related GH values were normal and did not show any significant increase, while IGF-1 values significantly increased during the study period ($p = 0.01$). Regarding immunological parameters, only IgA levels decreased after surgery and maintained a value that was higher than normal (> 70 mg/dL). In conclusion, children affected by adenotonsillar hypertrophy and OSAS do not show significant growth delay, but they do experience a slowdown in growth rate. After adeno-tonsillectomy, the speed of growth soon increases, as weight and growth increase notwithstanding an unchanged food intake. Moreover, surgery does not cause reduction in the efficiency of the immune system.

KEY WORDS: Obstructive sleep apnoea syndrome • GH • IGF-1 • Adeno-tonsillectomy • Growing delay • Adenotonsillar hypertrophy

RIASSUNTO

La Sindrome delle apnee ostruttive del sonno può essere causa di ritardo nell'accrescimento in età pediatrica. Nella maggior parte dei casi l'intervento di adenotonsillectomia è in grado di risolvere la Sindrome apnoica. Obiettivo dello studio è verificare le modificazioni della crescita staturale e dei parametri ormonali di accrescimento e immunologici nonché dietetici in bambini affetti da OSAS dopo intervento di adenotonsillectomia. Sono stati pertanto esaminati ventotto bambini affetti da OSAS severa e ipertrofia adenotonsillare. Tali bambini sono stati sottoposti a valutazione pediatrica per studiare i parametri auxologici (peso, altezza, BMI e standard deviation score), ad un prelievo ematico per studiare i parametri ormonali di crescita (GH e IGF-1) e i parametri immunologici (IgG, IgM e IgA) ed infine ad una valutazione dietologica per calcolare l'introito calorico. Le stesse valutazioni sono state ripetute dopo tre mesi dall'intervento di adenotonsillectomia. Le altezze e i pesi medi del gruppo di studio nella fase iniziale risultavano leggermente inferiori rispetto alle medie dei percentili della stessa età. Al controllo a tre mesi dall'intervento invece sia il BMI che l'altezza mostravano un aumento significativo: l'altezza mostrava un incremento di 2,93 cm ($p = 0,0001$); il BMI era aumentato di 0,72 kg/m² ($p = 0,009$). Lo standard deviation score (SDS) risultava aumentato sia per il parametro altezza ($p = 0,03$), che per il peso ($p = 0,001$) che per il BMI ($p = 0,001$). Tutti questi incrementi si verificavano in assenza di una reale variazione di introito calorico tra il periodo pre e post-operatorio (90 ± 24 vs 91 ± 27 kcal/kg/die; $p > 0,05$). In tutti i bambini esaminati inoltre non sono emersi significativi incrementi dei valori del GH che risultavano normali anche prima dell'intervento mentre i valori dell'IGF-1 aumentavano significativamente durante il periodo di studio ($p = 0,01$). Per quanto riguarda invece i parametri immunologici, solo le IgA mostravano una riduzione peraltro non significativa nel post-operatorio, mantenendosi comunque su valori più alti della norma (> 70 mg/dL). Dal lavoro quindi emerge che i bambini affetti da OSAS e ipertrofia adenotonsillare non presentano un significativo ritardo di accrescimento ma sicuramente hanno un rallentamento nella crescita. Dopo l'intervento di adenotonsillectomia la velocità di crescita aumenta, in quanto vi è un incremento del peso e dell'altezza, nonostante non cambi l'introito calorico. Inoltre l'intervento di adenotonsillectomia non causa una reale riduzione di efficienza del sistema immunitario.

PAROLE CHIAVE: Sindrome delle apnee ostruttive del sonno • GH • IGF-1 • Adenotonsillectomia • Ritardo di crescita • Iperptrofia adenotonsillare

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Introduction

Obstructive sleep apnoea hypopnea syndrome (OSHAS) is characterised by recurring episodes of complete or partial upper airway collapse during sleep, resulting in snoring and apnoeas or hypopnoeas. Whereas apnoea is a complete cessation of airflow, hypopnea is characterised by a 70% reduction of airflow for ≥ 10 sec or any reduction in airflow that is associated with either an arousal from sleep or a $\geq 3\%$ arterial oxygen desaturation. In children, hypopnoeas are more common than apnoeas and absence of airflow is uncommon. OSHAS affects up to 2.5% of children and adolescents with snoring as its primary symptom, affecting up to 27% of individuals in this group.

In children, the reduction of airflow (RA) is often related to adeno-tonsillar hypertrophy (ATH) and is considered one of the most important factors in growth alteration¹.

Thus, it has been related to reduction of growth hormone (GH) secretion in these patients. GH is a peptide hormone synthesised and secreted by the pituitary gland and its primary function is to promote growth mostly through inducing synthesis of insulin-like growth factor type 1 (IGF-1 or somatomedin C). IGF-1 stimulates protein synthesis, above all in growth cartilages and muscles. Moreover, it promotes insulin-like effects on carbohydrate and lipid homeostasis². It circulates bound to at least 6 different binding proteins that regulate its bioavailability. From a clinical point of view, the most important is IGFBP-3, whose levels are regulated by both GH and IGF-1. Furthermore, IGF-1 levels, through an unclear mechanism, are modulated by food intake and greatly decrease in all malnutrition conditions³. GH secretion is pulsatile and is stimulated by GHRH and Ghrelin, while it is inhibited by SRIH, following alternating stages. Variable and episodic peaks, associated with consumption of proteic meals or physical activity, superimpose the fundamental pulsatility, while constant peaks occur during sleep stages 3 and 4, 1-4 hours after falling asleep⁴. Thus, sleep fragmentation associates with an abnormal GH secretion⁵. Indeed, GH secretion is suppressed in non-treated OSAS patients⁶. However, even if it is ascertained that adenotonsillectomy surgery resolves the symptoms along with growth problems in OSAS children⁷⁻¹⁰, its effect on the patients' immune system is not clear. While most authors report no significant reductions of serum levels of immunoglobulins¹¹, others have reported that such changes are able to influence immune status¹²⁻¹³. The purpose of the present study is to investigate changes in clinical and laboratory growth (GH and IGF-1), immunological (IgA, IgG and IgM) parameters and food intake in children with OSAS after adeno-tonsillar surgery.

Materials and methods

The study was performed between March and October 2012, at the Otorhinolaryngology Department of the University of Foggia, evaluating children affected by adenotonsillar hypertrophy with obstructive symptoms, apnoea and nocturnal respiratory problems. The patients underwent diagnostic exams included in the paediatric sleep respiratory problems protocol.

The protocol consisted in the following diagnostic procedures:

- Clinical history: symptoms were evaluated through questions made by the examiner regarding snoring, episodes of sleep apnoea (reported by parents), daily sleepiness, daily hyperactivity, concomitant lower airways pathologies, immune system or endocrine diseases.
- ENT general evaluation: facial morphologic evaluation (to exclude cranio-facial malformations) and oral cavity examination (evaluating teeth, uvulo-palatal morphology, tonsils and tongue base). Uvulo-palatal morphology was classified according to the Finkelstein classification, and tonsil hypertrophy using the tonsil grading score¹⁴.
- Anterior rhinoscopy and fibre endoscopy: to evaluate the presence of turbinate enlargement, adenoid hypertrophy, classified by Cassano score¹⁵ and associated sino-nasal pathologies (septal deviation, sinusitis, nasal polyposis, etc.).
- Nocturnal cardiorespiratory monitoring with Somnoscreen polysomnography (SOMNOmedics GmbH, Randersacker, Germany) for evaluation of the apnoea/hypopnoea index (AHI), baseline SpO₂, lowest SpO₂, number of desaturations < 90%, snoring and body positions.

The presence of severe OSAS (AHI > 10 at cardio-respiratory monitoring) associated with adeno-tonsillar hypertrophy was the main criterion for inclusion. Exclusion criteria were the presence of malformations of the upper airway, craniofacial anomalies, asthma, perennial allergies and chromosomal abnormality of trisomy 21 (Down's syndrome). Patients who met inclusion and exclusion criteria were enrolled in the study group and underwent the following exams:

- *Paediatric evaluation* to calculate auxologic parameters (weight, height, BMI). Weight was approximated to the closest half kilogram and was measured with a medical precision scale, while height was evaluated using the Harpenden stadiometer. Body mass index (BMI; kg/m²) was considered as a relative weight index. In prepubertal children, height and weight increases are expected, and thus the real weight, height and BMI increment was evaluated through standard deviation scores (SDS, z-scores) calculated according to standard national tables.

- *Blood draw* to evaluate the following growth and immunological parameters:

- GH;
- IGF-1;
- IgA;
- IgG;
- IgM.

For GH and IGF-1 dosage, a solid-phase, two-site chemiluminescent immunometric assay was used. A single polystyrene sphere is delivered into a special reaction test-tube that is used as a container for incubation, washing and signal development processes. Antibody anti-reagents were present on the spheres. An alkaline phosphatase (detection antibody) with two antibodies was used. After overnight incubation at room temperature, the reaction was terminated and the reaction mixture was separated. After incubation, the serum samples were aspirated and the spheres were washed twice with 7 ml of distilled water. The spheres were then evaluated for luminescence and the fluorescence intensity of the solution was measured with a fluorimeter. The amount of emitted light is directly proportional to the amount of linked alkaline phosphatase.

- Food diary, written by the dietitian to calculate caloric intake.

These assessments were repeated at 3 months from adenotonsillectomy surgery to evaluate changes in weight, growth, immunological status and associated haematological parameters. The Review Board of the Department of Otolaryngology approved the study protocol.

Parents of children in the study group gave informed consent to study participation and provided precise information about daytime and night-time symptoms.

The work was carried out in accordance with the code of Ethics of the Declaration of Helsinki for experiments involving humans.

Statistical analysis

Correlation between physical exam results and AHI were statistically evaluated by applying Pearson's correlation, Wilcoxon and logistic regression tests. To evaluate the rate of growth, body composition and IGF-1 levels during presurgical period and after three months a Friedman analysis was used. To evaluate the difference in values, a Wilcoxon signed-ranch test was used.

Regarding all tests, a $p < 0.05$ was considered significant. Statistical analyses were performed using SOFA Statistics 1.2.2 version software. Data treatment and graphs were obtained using LibreOffice 3.5.4 version productivity software (The Document Foundation) and LATEX. All software was launched in Linux Debian 6.0 "Squeeze".

Results

Twenty-eight children (15 boys and 13 girls) with an age between 48 and 108 months (mean 73.40 ± 18.47 months) fit the inclusion and exclusion criteria, and were therefore enrolled in the study.

Eighteen patients had a grade 4 adenoid hypertrophy (64.3%), while 10 had grade 3 (35.7%). According to the Tonsil Score, 20 children (71.4%) showed grade 4, while 8 children (28.6%) had grade 3.

Polysomnographic results classified all children as affected by severe OSHAS, with an AHI mean value of 16.2/h, mean basal saturation of 86% and $< 90\%$ desaturation of a mean of 8. Study group mean height before surgery was 116.81 cm, weight was 22.17 kg and BMI was 16.22 kg/m². Preoperative height and weight values in OSAS children were lower compared to mean percentile values of same-age children. The food diary showed a pre-surgical caloric intake of 90 ± 24 kcal/kg per day.

During the post-surgery period, both height and BMI increased significantly after 3-months follow-up: mean height increased by 2.93 cm, from 116.81 cm to 119.74 cm

Table I. Anthropometric parameters and standard deviation scores (SDS) at pre-operative and 3-month follow-up.

Anthropometric measurements		Values	SDS (Z-scores)
Height (cm)	Pre-operative	116.81 ± 11.41	0.24 ± 0.97
	Follow-up	119.74 ± 10.62	0.26 ± 1.01
		$p = 0.03$	$p = 0.03$
Weight (kg)	Pre-operative	22.17 ± 5.43	0.23 ± 1.32
	Follow-up	24.73 ± 6.17	0.42 ± 1.29
		$p = 0.0001$	$p = 0.001$
BMI (kg/m ²)	Pre-operative	16.22 ± 2.54	0.52 ± 1.90
	Follow-up	16.94 ± 1.98	0.61 ± 1.42
		$p = 0.009$	$p = 0.001$

($p = 0.0001$); BMI values greatly increased by 0.72 kg/m^2 ($p = 0.009$) from 16.22 to 16.94 kg/m^2 during the post-operative period. The standard deviation scores increased significantly for height ($p = 0.03$), weight ($p = 0.001$) and BMI ($p = 0.001$) (Table I).

Thus, those values greatly increased despite the almost unchanged caloric intake between pre- and post-surgery period (90 ± 24 vs $91 \pm 27 \text{ kcal/kg/day}$; $p > 0.05$).

In all children, age-related GH values were normal and did not show a significant increase (mean: 0.5 ng/ml), while IGF-1 values greatly increased during the study period (from 162.4 to 284.6 ng/ml ; $p = 0.01$) (Fig. 1).

Immunoglobulin levels were measured in all patients. IgG dosage results showed an initial mean value of 1005.87 mg/dL , with a statistically significant difference between males (mean: 967.24 mg/dL) and females (mean: 1061.35 mg/dL) ($p = 0.03$). After 3-months follow-up, mean values were 956.49 mg/dL .

IgA levels decreased during post-surgery period (106.64 mg/dL); however, they remained in a higher-than-normal range ($> 70 \text{ mg/dL}$). In this case, no statistically significant sex-related differences were found.

Pre-surgery IgM mean value was 102.42 mg/dL ; after 3 months, this value was almost the same (101.87 mg/dL). Sex-related differences were found; specifically, males showed a greater reduction than females, but none of the differences were statistically significant. The values were always higher than normal ($> 50 \text{ mg/dL}$) and substantial difference between pre- and post-surgery was never found (Fig. 2).

Discussion

Growth is divided in many phases as described to Bjork. The modifications of the general body end in the sexual maturation phase. Growth is related to many factors such as alimentation, hormones, physical activity and psycho-affective disorders. All of these factors have negative effects on GH secretion⁴.

In the recent years, there is increasing interest in respiratory disorders in children with growth alterations. Respiratory stimulus is one of the most important stimuli in both cranial and body growth. Much research has shown that adenotonsillar hypertrophy may be associated with a slowing or stopping of growth during paediatric age^{9,10,16}.

Growth deficit, which often affects OSAS children, is correlated with sleep disorders and GH secretion during growth. Many generic parameters are used to evaluate growth in children: weight and growth modifications, caloric intake, body mass index and height increase. Recently, other parameters GH secretion and IGF-1 have also been used to evaluate growth.

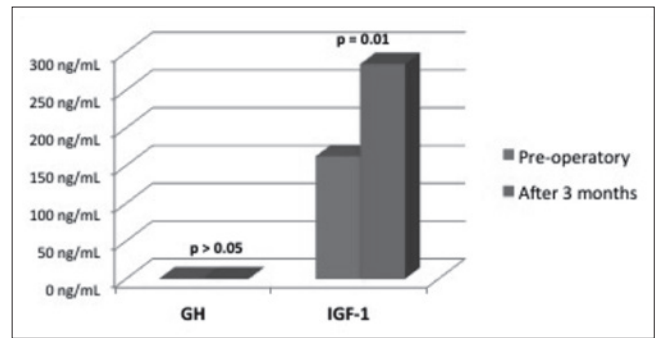


Fig. 1. Pre-operative and 3-month follow-up of GH and IGF-1 values (Wilcoxon's Test).

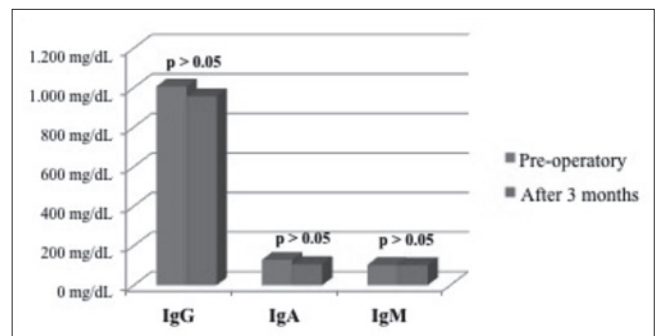


Fig. 2. Pre-operative and 3-months follow-up of immunoglobulins (Wilcoxon's Test).

In older children, Singer and Saenger evaluated a relationship between slow wave sleep phases and GH release. In order to study the negative influence exerted by OSAS on growth because of reduced GH secretion, the authors measured pre- and post-surgery GH levels in an achondroplastic child who had undergone tracheotomy for a severe respiratory sleep disorder. Before surgery, GH levels were very low, coincidentally with apnoea episodes and absence of slow wave sleep; surgery normalised both sleep parameters and GH sleep-related release. The study clearly showed that OSAS prevents GH production, leading to negative effects on growth⁶.

In the present paper, there was no evident delay in growth. The height of study children's was only slightly less than same-age children, just below the 3rd percentile.

Another way to express auxologic values is the Standard Deviation Score (SDS) adjusted according to age and sex⁴, and height increase measured by SDS can be a sign of a height increase.

Stradling also demonstrated a significant height-related SDS increase at six months after adeno-tonsillectomy surgery compared to a healthy control group. The study reported growth rates of 7.5 cm/year in the control group, compared

to 9.7 cm/year in treated children at 6 months from surgery. These results thus indicate a potential growth speed acceleration at 3-6 months after surgery ⁷.

Contrasting results were reported in another study by Bar et al. who found a non-significant height increase (SDS) compared to healthy patients at 18 months after surgery ⁹.

Weight is considered an important wellness parameter in children ¹⁶. Many studies have shown that weight increased in children undergoing adeno-tonsillectomy ⁷⁻¹⁰. Similarly, in the present paper, we found a significant weight increase at three months from surgery. During the pre-operative period, weight was approximately equal to that of same-age children; at the end of the follow-up period, weight increase was higher in treated patients, despite the unchanged caloric intake.

Marcus analysed caloric intake related to caloric expenditure and anthropometric measures in 14 prepubertal OSAS children before and after adeno-tonsillectomy. That study showed that nocturnal mean caloric expenditure decreased while weight-related SDS increased, despite the absence of significant caloric intake differences between the two periods. Even if the "Sleep Energy Expenditure" (SEE) decreased during sleep, a major reduction was observed during the REM stage. Moreover, children with higher SEE values had the lowest Z score values ($r = -0.62$; $p < 0.05$). Thus, the authors concluded that SEE reduction and weight gain improved thanks to surgery, believing that the basic mechanism could have been caused by increased energy expenditure due to increased respiratory work during sleep in OSAS children ¹⁷.

BMI is a widely used method to define the relationship between weight and height. In this study, we observed a substantial BMI increase at the end of the observation period. During the preoperative period, higher than normal BMI values can be explained by the similar weight and lower growth of OSAS children compared to healthy children ¹⁸.

This can be demonstrated by the weight/height index. BMI index and weight/height index substantially increase in treated children as shown in previous studies ¹⁹. BMI increase can be caused by fat mass increase compared to lean mass increase.

Serum IGF-1 values show minimal growth-related alterations during the prepubertal period ¹⁸. All examined children herein stayed in the prepubertal stage during the study period. Growth increase, especially weight gain after surgery, was followed by a significant serum IGF-1 concentration increase. This is in accordance with previous literature reports ^{7-9 17}.

IGF-1 is in close correlation with physiologic variations in GH secretion and is generally known as the most important mediator in GH promoting-growth activities ³, reflecting GH daily mean values ². It was also demonstrated that IG-

FBP-3 levels, the main GH-dependent IGF-1 transport protein, significantly relate with nocturnal GH secretion, even if this correlation is not as strong as that applied to IGF-1 ².

In the present paper, we noted substantial increases in serum IGF levels, which reflect same-age normal population values, as shown in other studies ^{9 19}.

Growth alteration in OSAS patients can correlate with abnormal nocturnal GH secretion caused by modifications in sleep patterns ⁴. In nutritional deficits such as protein malnutrition and nervous anorexia, IGF-1 and IGFBP-3 concentrations are noticeably decreased ²⁰. The markedly lower IGF-1 levels found in patients compared to mean values in healthy people can be due to lower GH levels.

The increases in growth rate and IGF-1 concentration seen during follow-up are important indicators of an increase in plasma concentrations of GH.

After surgery, clinical conditions appeared noticeably improved, as both parents and children themselves reported. Nocturnal awakenings, diurnal sleepiness or hyperactivity as well as edginess and focus capacity, are positively affected by therapy, allowing a better quality of life and a greater opportunity for the child to grow up in a healthy condition. However, removal of adeno-tonsillar lymphatic structures can influence the patient's immune status. In fact, the role of the Waldayer ring lymphoid tissue in the production of immunoglobulin and lymphocytes is well known.

In the literature, several papers report a reduction in serum levels of IgG, IgM and secreting IgA after tonsillectomy ²¹⁻²⁴. During the postoperative period, these values more or less quickly stabilised. According to other authors, Ig levels barely change ²⁵. Moreover, there are in vitro studies that show increases in Ig production after tonsillectomy, implying a stimulating effect on immunity ²⁶.

During the 1980s and 1990s, some studies suggested that serum and salivary Ig levels might be higher than expected by clinical signs ¹³ or increased risk of respiratory postoperative infections ¹², although other studies have not confirmed this ²⁷; this dispute is still ongoing.

In the present study, we determined pre- and post-operative Ig values in children affected by adeno-tonsillar hypertrophy, without other concurrent pathologies, and examined if changes in these levels could influence the respiratory tract immune system. First of all, mean levels were never lower than normal values. Moreover, infectious complications were not related to this during follow-up.

These complications can be pyogenic and recurrent infections in IgG deficit cases; in IgA reduction cases, increased risk of respiratory infections, otitis, allergies, autoimmune diseases and neoplasia can occur; finally, in cases with reduced IgM, there can be meningitis, septicaemia, recurrent otitis and respiratory tract infections ¹¹.

According to another study by Amoros Sebastia et al., who analysed data at one month and 4 months from surgery, IgG serum levels underwent a major reduction, showing a decrease after one month and partial restoration after 4 months. The most noticeable difference reported by our study, compared to literature data, is that this reduction was more prominent and recovery was less in patients who underwent only adenotomy, compared to those who had the adenoids and tonsils removed ($p < 0.1$). These data are contrary to the theory according which removal of the palatal tonsils, the main IgG producer, should give rise to such results¹¹. Thus, we conclude that tonsils do not appear very important in influencing serum IgG levels. Moreover, IgA serum levels experience a slight reduction during 4-months follow-up, and IgM serum levels do not show any significant changes. Hence, adeno-tonsillectomy surgery implies that IgG and IgA serum levels do decrease, but never below normal range, while IgM serum levels do not change after surgery, supporting the meager influence exerted by pharyngeal lymphoid tissue on Ig secretion²⁸.

Conclusions

Children affected by adeno-tonsillar hypertrophy and OSAS do not show significant growth delay, but do present a slowdown in growth rate. After adeno-tonsillectomy surgery, growth increased, as shown by increases in weight gain and growth after the three-months post-operative period, probably due to weight gain. These results suggest that GH levels and outcomes are greater after surgery and produce growth acceleration. Considering that OSAS complications are various, adeno-tonsillectomy should always be considered because of the possible evolution towards irreversible and sometimes cardiovascular pathologies. Surgery does not cause substantial reduction in the immune system and can be useful to reach the growth-weight optimum in OSAS children.

References

- Bower CM, Gungor A. *Pediatric obstructive sleep apnea syndrome*. Otolaryngol Clin North 2000;33:49-75.
- Blum WF, Albertsson-Wikland K, Rosberg S, et al. *Serum levels of insulin-like growth factor 1 (Igf-1) and Igf binding protein 3 reflect spontaneous growth hormone secretion*. J Clin Endocrinol Metab 1993;76:1610-6.
- Furlanetto RW. *Insulin-like growth factor measurements in the evaluation of growth hormone secretion*. Hor Res Paediatr 1990;33:25-30.
- Clayton P, Gill MS. *Normal growth and its endocrine control*. In: Brook CDG, Hindmarsh PC, Jacobs HS, eds. *Clinical Pediatric Endocrinology*. Fourth Edition. London, UK: Blackwell Science; 2001. p. 95-114.
- Cooper BG, White JE, Ashworth LA, et al. *Hormonal and metabolic profiles in subjects with obstructive sleep apnea syndrome and the acute effects of nasal continuous positive airway pressure (C-pap) treatment*. Sleep 1995;18:172-9.
- Singer LP, Saenger P. *Complications of pediatric obstructive sleep apnea*. Otolaryngol Clin North Am 1990;23:665-76.
- Stradling JR, Tomas G, Warley ARH, et al. *Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance, and symptoms in snoring children*. Lancet 1990;335:249-53.
- Williams EF, Woo P, Miller R, et al. *The effects of adenotonsillectomy on growth in young children*. Otolaryngol Head Neck Surg 1991;104:509-16.
- Bar A, Tarasiuk A, Segev Y, et al. *The effect of adenotonsillectomy on serum insulin-like growth factor and growth in children with obstructive sleep apnea syndrome*. J Pediatr 1999;135:76-80.
- Harding SM. *Complications and consequences of obstructive sleep apnea*. Curr Opin Pulm Med 2000;6:485-9.
- Redondo Ventura F, Guerrero Gilabert D, Reina Garcia P, et al. *Niveles sericos de inmunoglobulinas en pacientes adenoidectomizados. Un misterio sin resolver*. Acta Otorinolaring Esp 2000;51:403-6.
- Cantani A, Bellioni P, Salvinelli F, et al. *Serum immunoglobulins and secretory IgA deficiency in tonsillectomized children*. Ann Allergy 1986;57:413-6.
- Friday Jr GA, Paradise JL, Rabin BS, et al. *Serum immunoglobulin changes in relation to tonsil and adenoid surgery*. Ann Allergy 1992;69:225-30.
- Finkelstein Y, Talmi YP, Nachmani A, et al. *On the variability of velopharyngeal valve anatomy and function: a combined peroral and nasendoscopic study*. Plast Reconstr Surg 1992;89:631-9.
- Cassano P, Gelardi M, Cassano M, et al. *Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management*. Int J Ped Otorhinolaryngol 2003;67:1303-9.
- Chan J, Edman JC, Koltai PJ. *Obstructive sleep apnea in children*. American Family Physician 2004;69:1147-60.
- Marcus CL, Carroll JL, Koerner CB, et al. *Determinants of growth in children with the obstructive sleep apnea syndrome*. J Pediatr 1994;125:556-62.
- Juul A, Bang P, Hertel NT, et al. *Serum insulin-like growth factor-i in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index*. J Clin Endocrinol Metab 1994;78:744-52.
- Nieminen P, Lopponen T, Tolonen U, et al. *Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea*. Pediatrics 2002;109:e55.
- Palacio AC, Perez-Bravo F, Santos JL, et al. *Leptin levels and Igf-binding proteins in malnourished children: effect of weight gain*. Nutrition 2002;18:17-9.
- Childers NK, Powell WD, Tong G, et al. *Human salivary immunoglobulin and antigen specific antibody activity after tonsillectomy*. Oral Microbiol Immunol 2001;16:265-9.
- Jung KY, Lim HH, Choi G, et al. *Age-related changes of IgA immunocytes and serum and salivary IgA after tonsillectomy*. Acta Otolaryngol Suppl 1996;523:115-9.

- ²³ Kirstila V, Tenovuo J, Ruuskanen O, et al. *Longitudinal analysis of human salivary immunoglobulins, nonimmune antimicrobial agents, and microflora after tonsillectomy*. Clin Immunol Immunopathol 1996;80:110-5.
- ²⁴ Zielnik-Jurkiewicz B, Jurkiewicz D. *Implication of immunological abnormalities after adenotonsillotomy*. Int J Ped Otorhinolaryngol 2002;64:127-32.
- ²⁵ Paulussen C, Claes J, Claes G, et al. *Adenoids and tonsils, indications for surgery and immunological consequences of surgery*. Acta Otorhinolaryngol Belg 2000;54:403-8.
- ²⁶ Sainz M, Gutierrez F, Moreno PM, et al. *Changes in immunologic response in tonsillectomized children. Immunosuppression in recurrent tonsillitis*. Clin Otolaryngol Allied Sci 2007;17:376-9.
- ²⁷ Bock A, Popp W, Herkner KR. *Tonsillectomy and the immune system: a long-term follow up comparison between tonsillectomized and non-tonsillectomized children*. Eur Arch Otorhinolaryngol 1994;251:423-7.
- ²⁸ Amoros Sebastia LI, Ferrer Ramirez MJ, Lopez Molla C, et al. *Changes in immunoglobulin levels following adenoidectomy and tonsillectomy*. Acta Otorrinolaringol Esp 2004;55:404-8.

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AUDIOLOGY

Objective assessment of subjective tinnitus through contralateral suppression of otoacoustic emissions by white noise: effects of frequency, gender, tinnitus bilaterality and age

Valutazione oggettiva dell'acufene soggettivo attraverso la soppressione controlaterale delle otoemissioni acustiche effettuata con rumore bianco: effetti di genere ed età, di frequenza e bilateralità dell'acufene

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SUMMARY

Accumulating evidence seems to support an association between tinnitus and medial olivocochlear bundle (MOCB) dysfunction. Most studies use patient/control comparisons to support this correlation. The aim of this study was to investigate the hypothesis in a substantially different way and evaluate the roles of gender, age, frequency and tinnitus bilaterality as possible confounding factors. The population consisted of 78 normal hearing patients with chronic tinnitus, 28 normal hearing controls, 19 presbycusis tinnitus patients and 13 presbycusis controls (n = 276 ears). Mean suppression amplitudes of transient evoked otoacoustic emissions (TEOAEs) and distortion product OAEs (DPOAEs) by contralateral white noise (50 dB SPL) were computed. Mean suppression values < 1 dB SPL or < 2 dB SPL were validated as positive test results. Overall suppression (OS) values < 1 dB SPL were qualified as a diagnostic test of moderate positive predictive value for both DPOAEs and TEOAEs, while OS values < 2 dB SPL were found to be of large negative predictive value for DPOAEs and moderate for TEOAEs. Mean suppression values (for all frequencies, OS) are of higher diagnostic value than suppression values corresponding to either lower (1-2 kHz) or higher frequencies (2.8-4 kHz for TEOAEs and 2.8-6 kHz for DPOAEs). After excluding patients with unilateral tinnitus from the analysis, correlations were found to be stronger. Useful correlations were also attributed for all age groups < 61 years. In females, OAE suppression seems to have a stronger positive predictive value, while in males it seems to have a stronger negative predictive value. OAE-based assays of MOCB function as an objective diagnostic tool for subjective tinnitus might deserve further investigation. Tinnitus uni- or bi-laterality is a confounding factor, which probably confirms the observation that defective function of the MOCB usually applies to the contralateral ear as well. Gender is an additional confounding factor, while correlations can be verified for all age groups < 61 years old.

KEY WORDS: Tinnitus • Diagnosis • Specificity • Sensitivity • Contralateral suppression of otoacoustic emissions

RIASSUNTO

Evidenze sempre più numerose sembrano supportare l'esistenza di un'associazione tra acufene e disfunzione del fascio olivococleare mediale (FOCM). Svariati studi utilizzano il confronto paziente/controllo per sostenere questa correlazione. L'obiettivo di questo studio è stato quello di indagare la suddetta ipotesi in una maniera differente e valutare il ruolo del genere, dell'età, della frequenza e bi-lateralità dell'acufene come fattori confondenti. La popolazione comprendeva 78 pazienti normoudenti con acufene cronico, 28 controllo normoudenti, 19 pazienti presbiacusici con acufene e 13 presbiacusici di controllo (per un totale di 276 orecchie). È stato calcolato il valore medio di soppressione dell'ampiezza delle otoemissioni evocate da transienti (TEOAEs) e dei prodotti di distorsione (DPOAEs) utilizzando un rumore bianco controlaterale di 50 dB. Valori medi della soppressione inferiori a 1 dB SPL o 2 dB SPL sono stati validati come positivi. Valori di soppressione inferiori a 1 dB SPL, sia per le TEOAEs sia per le DPOAEs, sono stati considerati valori di moderato valore predittivo positivo, mentre valori di soppressione inferiori a 2 dB SPL sono stati considerati valori di alto valore predittivo negativo per le DPOAEs, e di moderato valore predittivo negativo per le TEOAEs. I valori di soppressione medi, ovvero per tutte le frequenze, sono di più alto valore diagnostico rispetto a quelli specifici per le basse frequenze (1-2 kHz) e per le alte frequenze (2,8-4 kHz per le TEOAEs e 2,8-6 kHz per le DPOAEs). Dopo aver escluso i pazienti con acufene monolaterale, le correlazioni effettuate si sono dimostrate più forti. Valide correlazioni sono state effettuate per tutti i gruppi di età inferiore a 61 anni. Inoltre, sembra che la soppressione per le TEOAEs abbia nelle donne un valore predittivo positivo maggiore, mentre nei maschi un valore predittivo negativo maggiore. Lo studio della funzionalità del fascio olivococleare mediale mediante otoemissioni, in qualità di test di valutazione oggettiva degli acufeni, meriterebbe ulteriori studi. La bi-lateralità dell'acufene è un fattore confondente, che conferma, probabilmente, la constatazione che la disfunzione del fascio olivococleare mediale riguarda solitamente anche l'orecchio controlaterale. Il sesso è un altro fattore confondente, mentre le varie correlazioni possono essere verificate in tutti i gruppi di età inferiori a 61 anni.

PAROLE CHIAVE: Acufene • Diagnosi • Sensibilità • Specificità • Soppressione controlaterale di otoemissioni

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Introduction

Tinnitus represents an important challenge for audiology and neurotology research in a number of ways. First, the underlying pathophysiology remains obscure. Patients reporting tinnitus have been found to exhibit defective medial olivocochlear bundle (MOCB) function, when assessed through contralateral suppression of otoacoustic emissions (OAEs) by acoustic stimuli in a number of studies¹⁻⁸. However, some researchers, who adopted substantially different methods of analysing and evaluating their results, have failed to establish a connection between MOCB dysfunction and tinnitus generation⁹⁻¹⁰. A review of the relevant literature¹¹ concluded that reduction of the neural efferent control of the cochlear amplifier seems to represent one of the possible pathophysiological abnormalities that may be related to tinnitus in normal hearing patients. Second, there is no objective examination that can measure or simply verify the existence of tinnitus. Diagnosis is based solely on the patient's report, thus raising reasonable doubts in cases where psychological issues, or any potential insurance, professional, or pension benefits are involved.

The aim of this study was to assess contralateral suppression of OAEs by acoustic stimulus as a potential tool for an objective investigation of tinnitus and investigate the roles of gender, age and tinnitus bi- or uni-laterality as possible confounding factors. Another aim of the study was to investigate any frequency-related differences that may reveal an association between high-frequency tinnitus and suppression malfunction at higher frequencies. Relevant implications regard both diagnostic and therapeutic assessment of tinnitus through focal or pharmacological manipulation of the olivocochlear system¹².

Materials and methods

The population of this study consisted of 110 right handed adults with chronic (more than 3 months) subjective tinnitus of high frequency and 28 controls ($n = 276$ ears), all with measurable transient evoked OAEs (TEOAEs) and/or distortion product OAEs (DPOAEs) in at least two frequencies. When no measurable OAEs were present no value was registered for the respective frequency/ies. The population included 78 normal hearing tinnitus patients (mean age \pm standard deviation; 46 ± 14 years, 45 females and 33 males), 28 normal hearing controls (aged 42 ± 13 , 15 females and 13 males), 19 presbycousic subjects with bilateral tinnitus (aged 60 ± 6 , 11 females and 8 males) and 13 presbycousic controls (aged 60 ± 6 , 7 females and 6 males). Tinnitus was lateralised to the right in 15, to the left in 26 and bilateral in 37 of normal hearing individuals. Cerebral dominance was considered as a potential confounding factor because of its

presumed role in the lateralisation of the contralateral suppression of OAEs¹³. Normal hearing was determined according to the ISO 7029 norm specified for subject's age. Patients with retrocochlear tumours, middle ear pathologies or possible inner ear diseases known to be associated with tinnitus, such as possible Ménière's disease, otosclerosis and sudden hearing loss were excluded from the study. None of the subjects included reported a medical history of traumatic brain injury, or psychological or mood disorders. Transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs) were obtained using an ILO v6 apparatus (Otodynamics Ltd.) in a sound-treated booth at first in the absence and later in the presence of contralateral suppression (white noise of 50 dB SL presented continuously through headphones). TEOAEs were obtained by linear click stimuli of 60 dB SPL at 5 frequencies (1, 1.4, 2, 2.8 and 4 kHz). DPOAEs were elicited by two tones of 65 and 55 dB SPL (L1 and L2 respectively) with $f2/f1$ ratio being set at 1.22 at 6 frequencies (1, 1.4, 2, 2.8, 4, 5 and 6 kHz). Both TEOAEs and DPOAEs were considered valid when emission amplitude exceeded the noise by at least 6 dB SPL. The suppressor stimulus was contralateral white noise of 50 dB SPL, delivered by an Amplaid A321 Twin Channel (Amplifon, Milan, Italy) diagnostic audiometer. Contralateral suppression was calculated by subtracting the value of OAEs with contralateral white noise from the value of OAEs without contralateral noise. The study was approved by the Institutional Review Board and informed consent was obtained by all participants.

Suppression testing and data collection/transcription was done by one researcher, who was blinded to the conduction, design and cut-off criteria of this study. DPOAEs enhancement was substituted by zero values to avoid computational problems. Given the fact that there are no set normative values for either TEOAE or DPOAE suppression, the association between patient-reported tinnitus and low overall suppression values was estimated for 2 different criteria (less than 2 and 1 dB SPL). The selection of these criteria was based on a previous work¹⁴. The potentially different implication of lower and higher frequency suppression amplitudes in the final results was investigated by comparing the results obtained for overall suppression (OS) values to those calculated separately for lower and higher frequencies. The confounding role of tinnitus bilaterality was evaluated by analysing the results for the subgroup of patients with either bilateral or no tinnitus.

Descriptive statistics, used to summarise the findings, were analysed with SPSS software version 21.0 (SPSS, Inc., Chicago, USA). Likelihood ratios, sensitivity, specificity and positive and negative predictive values were calculated for ears with/without tinnitus ($n = 276$). For 95% CIs on individ-

ual proportions (sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios), exact Clopper-Pearson confidence intervals were used. Statistical significance was attributed to two-sided $p < 0.05$.

Results

TEOAEs in at least two frequencies were recorded in all ears. The results on the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios for the six selected criteria used are summarised in Table I. Self-reporting of tinnitus was the “gold standard”. DPOAEs and TEOAEs did not seem to differ significantly as diagnostic tools. Mean suppression values (for all frequencies, OS) are of higher diagnostic value than suppression values corresponding to either lower (1-2 kHz) or higher frequencies (2.8-4 kHz for TEOAEs and 2.8-6 kHz for DPOAEs) (Table I).

Patients with unilateral tinnitus were excluded from the analysis presented in Table II. The diagnostic value of the test was therefore evaluated for patients with either bilateral tinnitus or no tinnitus. The results exhibited a trend toward better diagnostic potential than that calculated for the entire

study population (Tables I, II). The results obtained after dividing the study population into four age groups are shown in Table III. Similar results were recorded for age groups 20-35, 36-50 and 51-60 years, while patients older than 61 years had inconclusive data.

Results by gender are presented in Table IV. Significant differences were present. In females, contralateral suppression of both TEOAEs and DPOAEs could be characterised as an often useful diagnostic tool for the presence of the disease when mean suppression values were less than 1 dB SPL, while DPOAEs was demonstrated to serve as an often useful tool that may indicate the absence of disease when mean suppression values were more than 2 dB SPL. In males, however, suppression recordings for the selected cut-off values seemed to be of diagnostic value only in terms of ruling out the presence of tinnitus.

Discussion

An important drawback in clinical practice and research on tinnitus is the absence of an objective examination that may provide any indication of its presence. The lack of diagnostic tools and the mystery around its pathogenesis

Table I. Results obtained for the cut-off criteria used in this study.

Statistical test	Sensitivity	Specificity	PPV	NPV	Positive LR	Diagnostic value	Negative LR	Diagnostic value		
cut-off criterion	95% CI	95% CI	95% CI	95% CI	95% CI		95% CI			
OS	< 2 dB SPL	TEOAEs	87%	67%	77%	81%	2.69	Small	0.19	Moderate
		DPOAEs	81.05-92.25	58.45-75.65	69.71-82.84	72.45-88.4	2.07-3.49	0.12-0.29		
	< 1 dB SPL	DPOAEs	95%	64%	71%	93%	2.61	Small	0.08	Large
		TEOAEs	89.38-97.84	55.16-71.77	64.12-77.99	85.41-96.99	2.09-3.27	0.04-0.17		
		DPOAEs	75%	88%	87%	77%	6.09	Moderate	0.29	Small
		TEOAEs	45.35-61.78	84.56-95.45	79.61-93.88	54.05-68.64	3.35-10.75	0.43-0.61	0.51	Very small
LFS	< 2 dB SPL	TEOAEs	83%	63%	74%	75%	2.28	Small	0.26	Small
		DPOAEs	76.54-88.99	54.05-71.94	66.85-80.52	65.67-83.3	1.78-2.91	0.18-0.38		
	< 1 dB SPL	DPOAEs	89%	65%	71%	86%	2.55	Small	0.16	Moderate
		TEOAEs	82.72-94.03	56.21-72.96	63.77-78.12	77.84-92.21	2.01-3.23	0.10-0.27		
		DPOAEs	60%	87%	84%	65%	4.62	Small	0.46	Small
		TEOAEs	51%	90%	87%	60%	5.18	Moderate	0.54	Very small
HFS	< 2 dB SPL	TEOAEs	43.05-59.57	83.32-94.77	77.63-92.83	52.38-67.07	2.96-9.05	0.45-0.64		
		DPOAEs	60%	87%	84%	65%	4.62	Small	0.46	Small
	< 1 dB SPL	DPOAEs	50.99-67.75	79.89-92.44	75.32-90.57	57.67-72.67	2.87-7.44	0.38-0.57		
		TEOAEs	88%	51%	67%	78%	1.78	Very small	0.24	Small
		DPOAEs	80.88-92.60	41.62-59.98	59.27-73.50	67.80-86.94	1.47-2.16	0.15-0.39		
		DPOAEs	97%	50%	66%	94%	1.92	Very small	0.07	Large
< 1 dB SPL	TEOAEs	91.69-99.08	40.20-58.97	58.76-73.24	84.30-98.21	1.60-2.30	0.03-0.18			
	TEOAEs	49%	75%	69%	57%	1.96	Very small	0.68	Very small	
	DPOAEs	40.27-57.58	66.54-82.60	58.88-78.07	48.49-64.31	1.38-2.81	0.56-0.82			
	DPOAEs	78%	74%	75%	77%	2.99	Small	0.30	Small	
			69.41-85.07	65.11-81.56	66.17-82.19	68.40-84.53	2.18-4.11	0.21-0.43		

OS = mean suppression for all frequencies, LFS = mean suppression for lower frequencies (1-2 kHz), HFS = mean suppression for higher frequencies (2.8-4 kHz for TEOAEs and 2.8-6 kHz for DPOAEs), PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio.

Table II. Results obtained among patients with either bilateral or no tinnitus.

Statistical test			Sensitivity	Specificity	PPV	NPV	Positive LR	Diagnostic	Negative LR	Diagnostic	
cut-off criterion			95% CI	95% CI	95% CI	95% CI	95% CI	value	95% CI	value	
OS	< 2 dB SPL	TEOAEs	86%	69%	79%	78%	2.77	Small	0.21	Moderate	
		DPOAEs	77.84-91.61	58.02-78.69	70.35-85.58	67.28-87.11	1.99-3.85		0.13-0.33		
	< 1 dB SPL	DPOAEs	96%	65%	72%	94%	2.76	Small	0.07	Large	
		TEOAEs	89.35-98.82	55.02-74.64	63.57-80.04	85.62-98.37	2.10-3.63		0.02-0.17		
		DPOAEs	51%	95%	93%	59%	10.69	Large	0.52	Very small	
		TEOAEs	41.27-60.46	88.25-98.69	84.05-98.18	50.47-67.63	4.04-28.29		0.42-0.63		
LFS	< 2 dB SPL	DPOAEs	73%	90%	89%	75%	7.41	Moderate	0.30	Small	
		TEOAEs	63.54-81.59	81.67-95.27	80.41-94.92	66.04-83.00	3.94-13.93		0.21-0.41		
	< 1 dB SPL	TEOAEs	83%	67%	78%	75%	2.55	Small	0.25	Small	
		DPOAEs	74.78-89.47	56.30-77.35	68.98-84.62	63.30-84.01	1.85-3.52		0.16-0.39		
	< 1 dB SPL	DPOAEs	91%	69%	74%	89%	2.99	Small	0.13	Moderate	
		TEOAEs	83.58-96.17	59.18-78.51	65.26-82.09	79.80-95.22	2.19-4.08		0.06-0.25		
	< 1 dB SPL	TEOAEs	45%	94%	91%	56%	7.41	Moderate	0.59	Very small	
		DPOAEs	35.24-54.33	86.50-98.02	80.05-96.98	47.08-64.10	3.09-17.77		0.49-0.70		
	HFS	< 2 dB SPL	DPOAEs	62%	89%	88%	66%	5.83	Moderate	0.43	Small
			TEOAEs	51.61-71.21	80.85-95.04	77.59-94.12	56.67-74.65	3.09-11.02		0.33-0.55	
		< 1 dB SPL	TEOAEs	85%	51%	67%	74%	1.71	Very small	0.30	Small
			DPOAEs	76.01-91.17	39.40-61.76	57.92-75.12	60.34-84.46	1.36-2.17		0.18-0.50	
< 1 dB SPL		DPOAEs	98%	49%	67%	95%	1.90	Very small	0.05	Large	
		TEOAEs	91.47-99.70	37.23-60.31	57.48-75.01	83.08-99.39	1.53-2.37		0.01-0.20		
< 1 dB SPL	TEOAEs	47%	78%	72%	55%	2.14	Small	0.68	Very small		
	DPOAEs	36.78-57.29	67.54-86.44	59.24-82.40	45.66-64.41	1.35-3.38		0.55-0.85			
		DPOAEs	80%	76%	77%	79%	3.37	Small	0.26	Small	
			69.56-88.11	65.42-85.05	66.58-85.62	68.46-87.63	2.24-5.06		0.17-0.41		

OS = mean suppression for all frequencies, LFS = mean suppression for lower frequencies (1-2 kHz), HFS = mean suppression for higher frequencies (2.8-4 kHz for TEOAEs and 2.8-6 kHz for DPOAEs), LR = likelihood ratio.

are probably the reasons behind the lack of effective and aetiological treatment options. The involvement of the medial olivocochlear bundle (MOCB) in tinnitus generation has been hypothesised in the following concepts. A reduction in neural efferent control of the cochlear amplifier may result in an increase of its gain and enhancement of spontaneous activity in the auditory nerve or other plastic readjustments in the central auditory system¹⁵. Owing to the diffuse efferent innervation of outer hair cells (one fibre for 20-30 outer hair cells), efferent nerve fibres with reduced afferent input is shared with neighbouring outer hair cells partnering undamaged inner hair cells. As a result, those inner hair cells may receive defective efferent inhibition and thus create an area of hyperactivity in the basilar membrane that may be perceived as tinnitus¹⁶. Furthermore, the perceived tinnitus intensity and associated annoyance might be influenced by the efferent system through its connections with the reticular formation within the brainstem¹⁷. Furthermore, cochlear efferent innervation seems to be able to suppress the increased spontaneous firing rate in the inferior colliculus of a guinea pig model, where tinnitus was developed through acoustic trauma¹⁸.

Conduction of separate statistical analyses for lower and higher frequencies was based on the assumption that with patients reporting high frequency tinnitus, different results might arise for lower and higher frequency bands (Table I). However, this hypothesis was not confirmed. At high frequencies, the dysfunction of TEOAEs suppression seemed to lose its relationship with tinnitus. This may be partly due to the fact that recordings at high frequencies were absent in a large number of ears. On the other hand, DPOAEs suppression values lower than 2 dB SPL maintained a negative predictive value of 94%, which means that there was a high probability and that tinnitus was not present when DPOAEs suppression values were larger than 2 dB SPL at high frequencies (test negative). The absence of measurements in a large number of ears, which is also true for DPOAEs at high frequencies, is expected to have compromised the results of our analysis. At low frequencies, defective TEOAEs suppression (< 1 dB SPL) maintained its association with the presence of tinnitus, which may reflect the fact that TEOAEs actually render information that refers to outer hair cells (OHC) and MOCB functionality through the entire cochlea¹⁹⁻²². DPOAEs suppression values lower than 2 dB SPL

Table III. Results obtained for the cut-off criteria used in this study for patients according to age.

Statistical test	cut-off criterion		Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	Positive LR 95% CI	Diagnostic value	Negative LR 95%CI	Diagnostic value
20-35 years	< 2 dB SPL	TEOAEs	88%	70%	70%	88%	2.92	Small	0.18	Moderate
		DPOAEs	67.64-97.34	50.60-85.27	50.60-85.27	67.64-97.34	1.65-5.14	Small	0.06-0.53	
	< 1 dB SPL	TEOAEs	92%	60%	65%	90%	2.29	Small	0.14	Moderate
		DPOAEs	73-98.97	40.60-77.34	46.49-80.25	68.30-98.77	1.45-3.61	Large	0.43	Small
	< 1 dB SPL	TEOAEs	58%	97%	93%	74%	17.50	Large	0.27-0.7	
		DPOAEs	36.64-77.89	82.78-99.92	68.05-99.83	57.87-86.96	2.47-123.80	Large	0.22	Small
36-50 years	< 2 dB SPL	TEOAEs	79%	93%	90%	85%	11.88	Large	0.10-0.49	
		DPOAEs	57.85-92.87	77.93-99.18	69.62-98.83	68.10-94.89	3.06-46.02	Small	0.14	Moderate
	< 1 dB SPL	TEOAEs	93%	54%	77%	81%	2.02	Small	0.04-0.44	
		DPOAEs	79.61-98.43	32.82-74.45	62.69-87.97	54.35-95.95	1.29-3.15	Small	0.16	Moderate
	< 1 dB SPL	TEOAEs	89%	65%	79%	81%	2.58	Small	0.06-0.42	
		DPOAEs	75.20-97.06	44.33-82.79	63.96-89.96	58.09-94.55	1.51-4.43	Small	0.54	Very small
51-60 years	< 2 dB SPL	TEOAEs	53%	88%	88%	53%	4.20	Small	0.38-0.78	
		DPOAEs	36.13-68.49	67.64-97.34	67.64-97.34	36.13-68.49	1.40-12.60	Moderate	0.25	Small
	< 1 dB SPL	TEOAEs	77%	92%	94%	72%	9.62	Moderate	0.14-0.45	
		DPOAEs	60.67-88.87	73.97-99.02	79.19-99.23	53.25-86.25	2.52-36.74	Small	0.15	Moderate
	< 1 dB SPL	TEOAEs	88%	76%	78%	87%	3.67	Small	0.07-0.33	
		DPOAEs	76.56-95.65	62.36-86.51	65.27-87.71	74.26-95.17	2.27-5.96	Small	0	Large
> 61 years	< 2 dB SPL	TEOAEs	100%	68%	74%	100%	3.17	Small		
		DPOAEs	92.89-100	54.76-80.09	61.43-83.50		2.16-4.64	Moderate	0.40	Small
	< 1 dB SPL	TEOAEs	65%	87%	83%	72%	5.04	Moderate	0.27-0.59	
		DPOAEs	50.91-78.03	75.10-94.63	67.94-92.85	59.81-82.69	2.46-10.35	Moderate	0.27	Small
	< 1 dB SPL	TEOAEs	76%	89%	86%	81%	7.17	Moderate	0.17-0.45	
		DPOAEs	61.13-86.66	78.48-96.04	72.07-94.7	69.09-89.75	3.31-15.55	Very small	0.37	Small
> 61 years	< 2 dB SPL	TEOAEs	80%	53%	80%	53%	1.71	Very small	0.17-0.85	
		DPOAEs	63.06-91.56	26.59-78.73	63.06-91.56	26.59-78.73	0.97-3.02	Small	0.08	Large
	< 1 dB SPL	TEOAEs	95%	65%	61%	96%	2.69	Small	0.03-0.23	
		DPOAEs	75.13-99.87	46.49-80.25	42.19-78.15	78.05-99.89	1.69-4.29	Not applicable	0.66	Very small
< 1 dB SPL	TEOAEs	34%	100%	100%	39%	Not applicable	Not applicable	0.52-0.83		
	DPOAEs	19.13-52.21	78.20-100	73.54-100	24.04-56.61	2.04	Small	0.48	Small	
			47.65-84.12	40.99-86.66	54.87-90.64	34.02-78.18	1.01-4.10		0.26-0.90	

OS = mean suppression for all frequencies, PPV = positive predictive value, NPV = negative predictive value, LR = likelihood ratio, CI = confidence interval.

maintained a high negative predictive value. Mean suppression values (for all frequencies) were demonstrated to be of higher diagnostic value than suppression values corresponding to either lower or higher frequencies (Tables I, II).

Negative or positive associations were stronger among patients with either bilateral or no tinnitus than among patients with unilateral tinnitus (Table II). This probably confirms the observation that defective function of the medial olivocochlear bundle usually applies to the contralateral ear as well, with lateralisation of tinnitus in these cases possibly originating from central nervous system mechanisms^{4,8}. Functional magnetic resonance imaging studies have also demonstrated that brain hyperactivity in tinnitus patients may not be lateralised, despite the unilateral perception of the symptom²³. Mean suppression values (for all frequencies) were better predictors for the presence or

absence of tinnitus than suppression values corresponding to either lower or higher frequencies (Table I).

Patients with diverse age groups were included so as to investigate the applicability of the selected cut-off points in clinical practice. Regarding age, analysis of the results by age-group in Table III verified that age is not a trivial confounding factor, since age groups 20-35, 36-50 and 51-60 years seem to present similar results to each other and to the general population. Despite the subdivision of the population into smaller groups, the selected cut-off points consistently retained their predictive abilities, both regarding the high probability of a negative test result given the absence of tinnitus in case of OS < 2 dB SPL and regarding the high probability of a positive test result in the absence of tinnitus for OS < 1 dB SPL. With respect to the group of patients older than 61 years, the results were less clear, but this may

Table IV. Results obtained by gender.

Statistical test cut-off criterion			Sensitivity 95%CI	Specificity 95%CI	PPV 95%CI	NPV 95%CI	Positive LR 95%CI	Diagnostic value	Negative LR 95%CI	Diagnostic value
Female	OS < 2 dB SPL	TEOAEs	84%	67%	74%	79%	2.52	Small	0.24	Small
		DPOAEs	74.42-91.28	54.57-77.34	64.08-82.71	66.32-88.14	1.80-3.55		0.14-0.40	
	OS < 1 dB SPL	TEOAEs	93%	54%	66%	90%	2.05	Small	0.12	Moderate
		DPOAEs	85.12-97.80	42.83-65.69	56.20-74.96	77.34-96.53	1.60-2.63		0.05-0.29	
	OS < 2 dB SPL	TEOAEs	54%	94%	92%	64%	9.66	Moderate	0.49	Small
		DPOAEs	42.30-64.75	86.38-98.47	80.02-97.68	54.26-73.23	3.65-25.57		0.39-0.62	
Male	OS < 2 dB SPL	TEOAEs	74%	91%	89%	77%	7.97	Moderate	0.28	Small
		DPOAEs	63.21-83.58	81.71-96.16	79.06-95.56	67.11-85.53	3.89-16.32		0.19-0.42	
	OS < 1 dB SPL	TEOAEs	91%	69%	80%	85%	2.91	Small	0.13	Moderate
		DPOAEs	82.03-96.74	54.11-80.89	69.20-87.96	70.83-94.43	1.93-4.40		0.06-0.28	
	OS < 2 dB SPL	TEOAEs	95%	48%	64%	91%	1.83	Very small	0.11	Moderate
		DPOAEs	85.38-98.90	35.23-61.61	52.38-73.71	74.98-98.02	1.42-2.36		0.04-0.34	
OS < 1 dB SPL	TEOAEs	54%	86%	84%	58%	3.91	Small	0.54	Very small	
	DPOAEs	41.20-65.72	73.74-94.30	69.93-93.36	46.02-69.14	1.90-8.04		0.41-0.71		
			76%	84%	84%	75%	4.63	Small	0.29	Small
			63.26-85.78	71.20-92.23	71.67-92.38	62.71-85.54	2.51-8.56		0.18-0.46	

OS = mean suppression values for all frequencies, LR = likelihood ratio.

be partly attributed to the fact that in this group of patients OAEs may not be recorded in multiple frequencies, possibly due to a subclinical presbycusis, thus compromising statistical calculations.

An unexpected finding of this study was the difference between genders (Table IV). In females ($n = 78$), the association between objective findings and subjective tinnitus seem to refer mainly to the presence of disease, with DPOAEs only reaching the criteria of a useful correlation between the possible absence of tinnitus and the recording of negative results. In males ($n = 60$), however, powerful correlations were demonstrated only for the absence of the disease in patients with mean suppression values larger than 2 dB SPL. The limited number of patients included in each subpopulation may account for the differences in results. Emotional and attentional state, psychological disorders, hyperacusis or temporo-mandibular joint lesions are some additional known causes involved in the generation, development and perception of tinnitus²⁴⁻²⁷. The underlying mechanisms remain obscure and seem to regard both central and peripheral auditory pathway structures interacting with or projecting to multiple non-auditory central nervous system structures. The patients included in the study were questioned regarding medical history of psychological or mood disorders. The study did not include any further investigation, for example through suitable questionnaires. Patients were not queried regarding possible temporo-mandibular joint disorders or hyperacusis. These might be considered as limitations of this study. Further studies including larger populations divided into subgroups according to the aforementioned possible

tinnitus triggers may reveal additional information on the pathophysiology of tinnitus.

Conclusions

The results of this study appear to reinforce the hypothesis that defective MOCB function may play a crucial role in the pathogenesis of tinnitus in normal hearing patients. Mean suppression values were demonstrated to be potentially useful objective tools in prediction of the presence or absence of subjective tinnitus. Mean suppression values (for all frequencies) were demonstrated to have stronger associations with tinnitus presence/absence than suppression values referring to either lower or higher frequencies. Gender and tinnitus laterality appear to be important confounding factors that should be taken into consideration. The potential clinical implications of this observation seem to extend to a broad age range (20-60 years old) with young tinnitus patients (< 35 years old) exhibiting strong and clear associations, while older patients (> 61 years old) presented inconclusive results. OAEs suppression seems to be a useful tool that could provide insight into a subjective symptom of normal hearing subjects of diverse age groups.

References

- 1 Chéry-Croze S, Collet L, Morgon A. *Medial olivo-cochlear system and tinnitus*. Acta Otolaryngol 1993;113:285-90.
- 2 Attias J, Bresloff I, Furman V. *The influence of the efferent auditory system on otoacoustic emissions in noise induced tinnitus: clinical relevance*. Acta Otolaryngol 1996;116:534-9.

- ³ Ceranic BJ, Prasher DK, Raglan E, et al. *Tinnitus after head injury: evidence from otoacoustic emissions*. J Neurol Neurosurg Psychiatry 1998;65:523-9.
- ⁴ Fávero ML, Sanchez TG, Bento RF, et al. *Contralateral suppression of otoacoustic emission in patients with tinnitus*. Braz J Otorhinolaryngol 2006;72:223-6.
- ⁵ Fernandes Lda C, Santos TM. *Tinnitus and normal hearing: a study on the transient otoacoustic emissions suppression*. Braz J Otorhinolaryngol 2009;75:414-9.
- ⁶ Komis A, Maragkoudakis P, Gkoritsa E, et al. *The effect of tinnitus and presbycusis on contralateral suppression of otoacoustic emissions*. JHS 2014;4:9-20.
- ⁷ Lalaki P, Hatzopoulos S, Lorito G, et al. *A connection between the efferent auditory system and noise-induced tinnitus generation. Reduced contralateral suppression of TEOAEs in patients with noise-induced tinnitus*. Med Sci Monit 2011;17:MT56-62.
- ⁸ Riga M, Papadas T, Werner JA, et al. *A clinical study of the efferent auditory system in patients with normal hearing who have acute tinnitus*. Otol Neurotol 2007;28:185-90.
- ⁹ Geven LI, Wit HP, de Kleine E, et al. *Wavelet analysis demonstrates no abnormality in contralateral suppression of otoacoustic emissions in tinnitus patients*. Hear Res 2012;286:30-40.
- ¹⁰ Paglialonga A, Fiocchi S, Del Bo L, et al. *Quantitative analysis of cochlear active mechanisms in tinnitus subjects with normal hearing sensitivity: time-frequency analysis of transient evoked otoacoustic emissions and contralateral suppression*. Auris Nasus Larynx 2011;38:33-40.
- ¹¹ Riga M, Katotomichelakis M, Danielides V. *The potential role of the medial olivocochlear bundle in the generation of tinnitus: controversies and weaknesses in the existing clinical studies*. Otol Neurotol 2015;36:201-8.
- ¹² de Azevedo AA, Langguth B, de Oliveira PM, et al. *Tinnitus treatment with piribedil guided by electrocochleography and acoustic otoemissions*. Otol Neurotol 2009;30:676-80.
- ¹³ Bidelman GM, Bhagat SP. *Right-ear advantage drives the link between olivocochlear efferent 'antimasking' and speech-in-noise listening benefits*. Neuroreport 2015;26:483-7.
- ¹⁴ Riga M, Komis A, Maragkoudakis P, et al. *Objective assessment of subjective tinnitus through contralateral suppression of otoacoustic emissions by white noise; suggested cut-off points*. Int J Audiol 2016;55:775-81.
- ¹⁵ Weisz N, Hartmann T, Dohrmann K, et al. *High-frequency tinnitus without hearing loss does not mean absence of deaf-ferentation*. Hear Res 2006;222:108-14.
- ¹⁶ Chery-Croze S, Truy E, Morgon A. *Contralateral suppression of transiently evoked otoacoustic emissions and tinnitus*. Br J Audiol 1994;28:255-66.
- ¹⁷ Hazell JW, Jastreboff PJ. *Tinnitus I: Auditory mechanisms: a model for tinnitus and hearing impairment*. J Otolaryngol 1990;19:1-5.
- ¹⁸ Mulders WH, Seluakumaran K, Robertson D. *Efferent pathways modulate hyperactivity in inferior colliculus*. J Neurosci 2010;30:9578-87.
- ¹⁹ Probst R, Harris FP. *Transiently evoked and distortion product otoacoustic emissions. Comparison of results from normally hearing and hearing impaired human ears*. Arch Otolaryngol Head Neck Surg 1993;119:858-60.
- ²⁰ Wagner W, Plinkert PK. *The relation between audiology threshold and evoked otoacoustic emissions*. Eur Arch Otorhinolaryngol 1999;256:177-88.
- ²¹ Granjeiro RC, Kehrle HM, Bezerra RL, et al. *Transient and distortion product evoked oto-acoustic emissions in normal hearing patients with and without tinnitus*. Otolaryngol Head Neck Surg 2008;138:502-6.
- ²² Henry JA, Roberts LE, Caspary DM, et al. *Underlying mechanisms of tinnitus: review and clinical implications*. J Am Acad Audiol 2014;25:5-22.
- ²³ Shore SE, Roberts LE, Langguth B. *Maladaptive plasticity in tinnitus--triggers, mechanisms and treatment*. Nat Rev Neurol 2016;12:150-60.
- ²⁴ Salviati M, Bersani FS, Valeriani G, et al. *A brain centred view of psychiatric comorbidity in tinnitus: from otology to hodology*. Neural Plast 2014;2014:817852.
- ²⁵ Cianfrone G, Mazzei F, Salviati M, et al. *Tinnitus Holistic Simplified Classification (THoSC): a new assessment for subjective tinnitus, with diagnostic and therapeutic implications*. Ann Otol Rhinol Laryngol 2015;124:550-60.
- ²⁶ Eggermont JJ. *The auditory cortex and tinnitus - a review of animal and human studies*. Eur J Neurosci 2015;41:665-76.

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VESTIBOLOGY

Binocular cyclotorsion in superior vestibular neuritis

La ciclorsione binoculare nella neurite vestibolare superiore

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SUMMARY

Conjugated cyclotorsion of the eyes toward the affected side can commonly be observed in vestibular neuritis. The aim of this study was to assess the differences in cyclotorsion between the ipsi- and contralesional eye during selective involvement of the superior branch of the vestibular nerve. We studied binocular cyclotorsion through ocular fundus photographs in 10 patients affected by acute superior vestibular neuritis (SVN). Cyclotorsion was also studied in 20 normal subjects. All SVN patients showed an ipsilesional cyclovergence of the eyes. Normal subjects exhibited a constant mild exocyclovergence ($6.42 \pm 2.34^\circ$). In SVN patients, contralateral incyclotorsion ($8.4 \pm 8.14^\circ$) was lower and not normally distributed compared to ipsilateral eye exocyclotorsion ($17.9 \pm 4.36^\circ$) with no correlation between them. The interocular difference in cyclodeviation could be related to the starting physiological exocyclovergence, to different tonic effects on the extraocular muscles of the two eyes and to the different influence of spontaneous nystagmus on cyclodeviation in the two eyes. We recommend referring only to ipsilateral exocyclotorsion in the evaluation of utricular function during SVN and its subsequent compensation. Further studies are required to determine the binocular cyclotorsion in the case of other kinds of selective involvement of the vestibular nerve.

KEY WORDS: Vestibular neuritis • Cyclotorsion • Utricle • Eye movement

RIASSUNTO

La ciclorsione coniugata degli occhi verso il lato malato può comunemente essere osservata in corso di neurite vestibolare. Lo scopo di questo studio è stato quello di valutare le differenze nell'entità della ciclorsione tra l'occhio ipsi- e contra-lesionale in caso di un coinvolgimento selettivo della branca superiore del nervo vestibolare. Abbiamo studiato la ciclorsione binoculare ottenendo fotografie del fondo oculare in 10 pazienti affetti da neurite vestibolare superiore acuta (NVS). La ciclorsione è stata studiata anche in 20 soggetti normali. Tutti i pazienti con NVS hanno mostrato una ciclovergenza ipsilesionale degli occhi. I soggetti normali invece hanno mostrato una exociclovergenza lieve costante ($6,42 \pm 2,34^\circ$). Nei pazienti con NVS, l'inciclororsione controlaterale ($8,4 \pm 8,14^\circ$) era minore e non normalmente distribuita tra i soggetti rispetto alla exociclororsione dell'occhio ipsilaterale ($17,9 \pm 4,36^\circ$). Non è stata osservata correlazione significativa tra la ciclorsione dei due occhi. La differenza interoculare della ciclorsione potrebbe essere legato in parte alla presenza della exociclovergenza fisiologica, in parte ai diversi effetti tonici sui muscoli estrinseci dei due occhi, e infine alla diversa influenza del nistagmo spontaneo sulla ciclorsione dei due occhi. Alla luce di questo studio consigliamo di far riferimento solo alla exociclororsione ipsilaterale nella valutazione della funzione utricolare durante una NVS e del suo successivo compenso. Ulteriori studi sono necessari per determinare il comportamento della ciclorsione binoculare in caso di coinvolgimento selettivo delle altre componenti del nervo vestibolare.

PAROLE CHIAVE: Neurite vestibolare • Ciclororsione • Utricolo • Movimenti oculari

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Introduction

Ocular cyclotorsion is defined as a rotation of the eye around its visual axis. Cyclotorsion can refer to the position of a single eye (in- or exocyclotorsion or cyclodeviation) or even to the situation in both eyes (in- or exocyclovergence or dextro- or levocyclovergence). Cyclotorsion is absent when the vertical meridian traversing the centre of the cornea is parallel to a plumb line. In a state of incyclotorsion, the nasal end of the horizontal meridian is

lower than the temporal part: the optic disk is lower than the fovea. Conversely, the optic disk is higher in cases of exocyclotorsion ¹.

Torsional movements of the eyes are mainly determined by the inferior and superior oblique extraocular muscles. Cyclodeviations can be observed under those conditions that cause a functional imbalance between pairs of muscles inducing cyclotorsion, in the case of oblique axis astigmatism which is uncorrected or improperly correct-

ed² and even as a complication following ocular or orbital surgery³.

Different methods have been proposed to measure cyclotorsion (scotometry, double Maddox rod test, cyclodeviation of the retinal vascular arcades)^{3,4}, but fundus observation is considered to be the best method⁵.

Under normal conditions, cyclotorsion allows binocular single vision to be maintained when the head is tilted around the sagittal and/or transverse axis. This is guaranteed by a reflex of the extraocular muscles coming from activation of the vestibular receptors in response to the head motion. The torsional components of the vestibulo-ocular reflex (VOR) are mainly determined from activation of the ampullar receptors of the vertical semicircular canals and of the utricular macula⁶.

In the case of a sudden unilateral vestibular loss of function, a conjugated cyclotorsion of the eyes toward the affected side can be observed, together with alteration of vertical perception, skew deviation and head tilt of the eye-head postural reaction known as ocular tilt reaction (OTR), due to the acute vestibular asymmetry⁷. Except rare cases where an acute vestibular deficit is not followed by a lasting vestibular loss of function⁸, in vestibular neuritis the OTR may be long-lasting. While the altered perception of the subjective visual vertical⁹ represents an indirect sign of ocular cyclotorsion, and its improvement may depend on perceptual compensation due to neural plasticity following a vestibular deficit¹⁰, the evaluation of the ocular cyclotorsion can be used as a measure of long-term functional recovery after vestibular neuritis, depending directly on the utricular function¹¹.

Few studies have focused on binocular cyclotorsion following acute vestibular asymmetry. Most have been conducted on patients who underwent a vestibular neurectomy for intractable Ménière's disease, and concluded that there was no significant difference in degrees between the excyclodeviated and incyclodeviated eyes during the acute phase following a complete vestibular nerve surgical resection^{12,13}.

Even rarer are studies analysing the effect of acute vestibular asymmetry due to vestibular neuritis on binocular cyclotorsion^{11,14}, and to the best of our knowledge, there has been no publication discussing the possible different pathophysiological mechanisms acting on determination of cyclotorsion of the ipsi- and contralateral eye following acute vestibular loss.

As a consequence, it is not yet clear what is the best parameter to measure in the evaluation of cyclotorsion as a static utricular sign following a vestibular deficit, whether it is ipsilateral excyclotorsion, contralateral incyclotorsion, or the mean value of both.

Moreover, although it occurs more frequently in the region of the superior vestibular nerve (superior vestibular neuritis; SVN), vestibular neuritis could also affect the entire vestibular nerve (complete vestibular neuritis) or selectively only the inferior vestibular nerve (inferior vestibular neuritis)^{15,16}.

Due to the involvement of different vestibular receptors, we hypothesise that, as with spontaneous nystagmus (SN), these three conditions should be considered separately in the study of binocular cyclotorsion of vestibular origin.

The aim of this work was to establish if there was a different behaviour in terms of degree excursion between ipsilateral excyclotorsion and contralateral incyclotorsion in response to acute unilateral SVN. A pathophysiological explanation of our findings is given.

Materials and methods

This was an observational case-control study based on a clinical population of 10 patients suffering from SVN and recruited during the period from January 2012 to December 2014. The study was conducted at the Department of Otolaryngology of the University of Perugia (Italy). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all participants in the study.

All 10 patients received complete otoneurological, clinical and instrumental examination. Diagnosis of SVN was performed through meeting relevant criteria for vestibular neuritis proposed by Strupp and Brandt¹⁷. In particular, it was verified the presence of a pluripositional, unidirectional SN with well recognisable, dual horizontal and torsional components during its slow phase.

In order to verify the inferior vestibular nerve function, we recorded c-VEMPs (EPIC-Plus, LABAT, Italy) in all patients. We considered normal, symmetrical function when¹⁸:

1. the PIN1 complex had a well recognisable morphology (between 13 and 23 msec) with a stimulus consisting of a click of 120 dB SPL;
2. PIN1 amplitude was between 50 and 70 nV;
3. the asymmetry ratio (AR), i.e. the ratio between the amplitude difference between the two sides (A1 and A2) and their sum, $AR: (A1-A2) / (A1 + A2) \times 100$ where $A1 > A2$, was lower than 35%.

Patients with symptom onset longer than 3 days were excluded from the study. Those patients with a previous history of other otoneurological diseases were also excluded. MRI of the brain was conducted to exclude central lesions

of any kind. Exclusion criteria also included a history of pre-existing abnormalities of eye movements, a history of ocular or orbital surgery, abnormal fundoscopic examinations and refractive defects.

At the same time as diagnosis of SVN, binocular cyclotorsion was measured by obtaining fundus photographs in both eyes taken in the sitting position with the head upright during fixation on a central target (SPECTRALIS®, Heidelberg Engineering, Heidelberg, Germany). The cyclodeviation angle was given by measuring the angle formed by a horizontal line passing through the fovea and a line which connects the centre of the fovea with the centre of the optical disc (Fig. 1). The final values of cyclotorsion for each eye were given by the mean of the angle obtained in five consecutive photographs to limit the effect of the torsional dynamic component of spontaneous nystagmus on static cyclotorsion¹⁹.

Cyclotorsion was measured with the same technique, but with a unique fundus photograph in both eyes in a group of 20 healthy volunteers, matched for age and sex.

Statistical analysis

The main parameter of the investigation was the amount in degrees (°) of the cyclotorsion measured in both eyes and expressed as positive values regardless of the direction. Average values were expressed as mean ± SD.

The normality of the distribution of measured values in each data series was tested with the Shapiro-Wilk test,

while Levene’s test has been used to assess the homogeneity of variances among compared data sets. According to the results of the Shapiro-Wilk and Levene’s tests, parametric paired *t*-test and non-parametric Wilcoxon signed rank test were used to compare paired data, while parametric Student’s *t* test and non-parametric Mann–Whitney *U*-test was used for unpaired data.

The correlation between excyclotorsion of the ipsilesional eye and incyclotorsion of the contralesional eye was studied with the non-parametric Spearman Rank-Order Correlation Coefficient.

Differences with $p < 0.05$ were considered to be statistically significant.

Results

Control group

All subjects showed some degree of excyclotorsion in both eyes (excyclovergence). Mean excyclotorsion was $6.89 \pm 2.21^\circ$ in the right eye and $5.95 \pm 3.42^\circ$ in the left eye.

Values of excyclotorsion (degrees) were normally distributed for $p < 0.05$ in both the right eyes ($W = 0.90$; Shapiro-Wilk test), and the left eyes ($W = 0.954$; Shapiro-Wilk test). Variances of excyclotorsion (degrees) of the right and left eyes were homogeneous ($a = 0.76$; Levene’s test). There were no statistically significant differences in excyclotorsion between the right and left sides ($p < 0.05$; paired *t*-test). For this reason, the average value of the

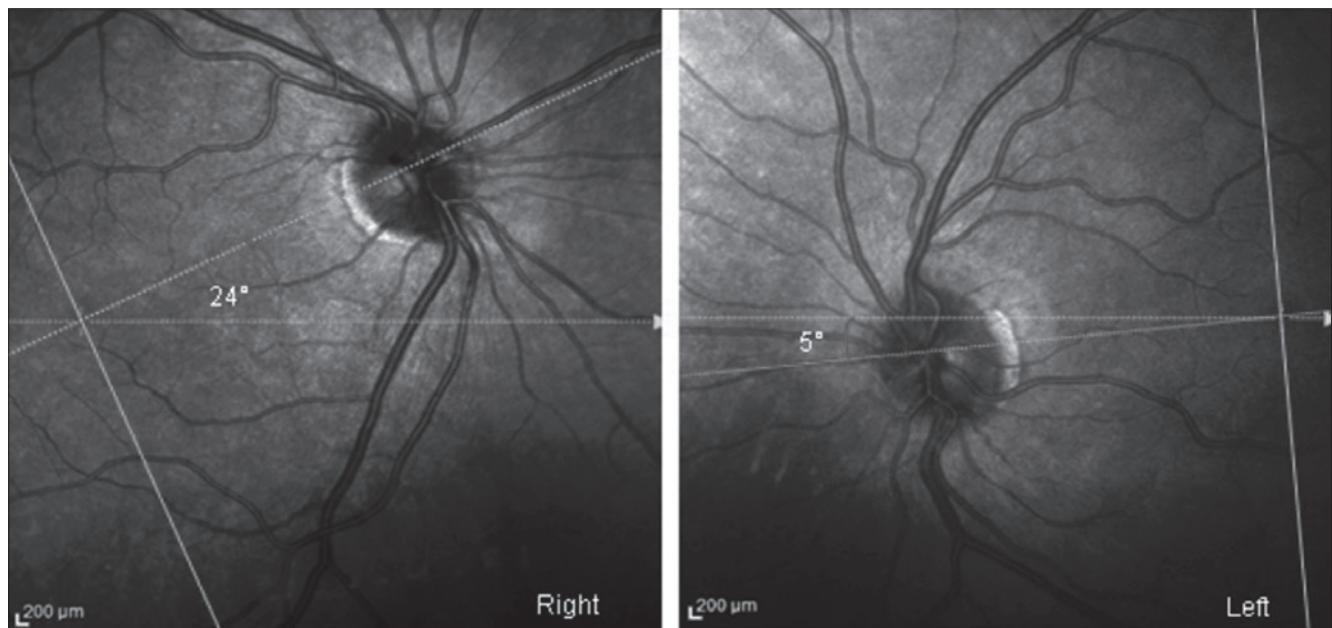


Fig. 1. Fundus photography in a patient with SVN (patient 6 from Table I) in the right eye. Excyclotorsion (right eye) and incyclotorsion (left eye) angles are shown.

Table I. Cyclodeviation (minus sign before incyclotorsion values indicates the changing of the side of the deviation) in both eyes in patients during acute SVN and statistical analysis (Mann–Whitney U-test).

Patient	Ipsilesional excyclotorsion repeated measures	Mean \pm SD	Contralesional incyclotorsion repeated measures	Mean \pm SD	p
1	21; 19; 20; 21; 20	20 \pm 0.84	-10; -3; -4; -1; -1	-4 \pm 3.70	0.000
2	16; 17; 18; 18; 16	17 \pm 1	-8; -6; -6; 1; -7	-5 \pm 3.56	0.000
3	21; 20; 20; 20; 22	21 \pm 0.89	-20; -21; -19; -17; -19	-19 \pm 1.48	0.000
4	15; 16; 15; 17; 16	16 \pm 0.84	-13; -11; -4; -10; -6	-9 \pm 3.70	0.000
5	9; 7; 8; 10; 10	9 \pm 1.3	-1; -7; -1; -2; -1	-2 \pm 3	0.000
6	24; 26; 25; 25; 24	25 \pm 0.84	-2; -5; 1; 1; 3	0 \pm 3.13	0.000
7	15; 16; 16; 17; 16	16 \pm 0.71	-3; -8; -2; 0; 2	-2 \pm 3.77	0.000
8	18; 18; 19; 19; 19	19 \pm 0.55	-20; -22; -22; -21; -20	-21 \pm 1	0.000
9	21; 22; 21; 21; 21	21 \pm 0.45	-21; -19; -20; -16; -20	-19 \pm 1.92	0.000
10	15; 14; 16; 14; 16	15 \pm 1	-2; -8; -4; 0; -2	3 \pm 3.03	0.000

mean excyclotorsion of the two eyes in each patient was calculated ($6.42 \pm 2.34^\circ$) with no significant difference between the mean values for the separate eyes and the average value of the mean excyclotorsion for the two eyes.

SVN patients

Ten patients (4 males and 6 females, mean age 42.8 ± 8.35 years) satisfied the inclusion criteria and were enrolled in the study.

Measurement of the five repeated photos of the ocular fundus of both eyes in each patient are reported in the Table I with the relative statistical analysis.

All patients, except patient 5 ($p = 0.028$; Student's *t* test), showed an excyclotorsion of the ipsilesional eye that was highly significantly greater compared to the normal range ($p = 0.000$; Student's *t* test), while all patients showed incyclotorsion of the contralesional eye significantly different compared to the normal cyclotorsion ($p = 0.000$; Student's *t* test).

In patient 5, the lower value of ipsilesional excyclotorsion can be explained supposing to start from a basal excyclotorsion of the lowest value of the normal range.

Mean ipsilesional excyclotorsion was $17.9 \pm 4.36^\circ$ with a normal distribution of the values at $p < 0.05$ ($W = 0.958$; Shapiro-Wilk test). Mean contralateral incyclotorsion was $8.4 \pm 8.14^\circ$ with a non-normal distribution of the values at $p < 0.05$ ($W = 0.816$; Shapiro-Wilk test).

Ipsilateral excyclotorsion was statistically significantly higher than the mean basal excyclotorsion in the control group ($U = 2.5$, $p < 0.05$; Mann–Whitney *U*-test).

To assess the significance of the variation of mean contralateral incyclotorsion from the normal basal excyclotorsion (in degrees), their negative values were used so as to include the change in cyclotorsion direction in the statistical analysis, and the difference was statistically

significant ($U = 0$, $p < 0.05$; Mann–Whitney *U*-test).

Variances between ipsilesional excyclotorsion and contralesional incyclotorsion were homogeneous ($\alpha = 1.78$, Levene's test). The amount in degrees of the ipsilesional excyclotorsion was significantly higher than the contralesional incyclotorsion (Z -value = -2.6 , $p < 0.05$; Wilcoxon signed rank test).

There was no significant correlation between the independent variable excyclotorsion and the independent variable incyclotorsion (Spearman Rank-Order Correlation Coefficient = 0.25 ; $p = 0.48$), with a non-linear relationship between them.

Discussion

Cyclovergence toward the affected side is consistently observed in unilateral vestibular loss. To the best of our knowledge, this is the first study in the literature focusing in detail on the differences between cyclotorsion of the ipsilesional and contralesional eye in vestibular neuritis, in particular, in the case of a lesion involving only the superior branch of the vestibular nerve.

Different physiological and pathological vestibular effects on the extraocular muscles should be considered in each eye.

Under static conditions, normal cyclotorsion is given by the synergic tonic action of the anterior semicircular canal (ASC), the posterior semicircular canal (PSC) and the medial part of the utricular macula (UM). The ASC activates the ipsilateral superior rectus muscle and the contralateral inferior oblique muscle. The PSC activates the contralateral inferior rectus muscle and the ipsilateral superior oblique muscle. The UM activates the ipsilateral superior rectus and superior oblique muscles and the contralateral inferior rectus and inferior oblique muscles (Fig. 2).

In the case of SVN, we observed the simultaneous ipsilateral loss of function of both the ASC and the UM⁶.

As a consequence of deafferentation of the ASC, together with the consequent prevalence of the contralateral PSC, under static conditions, this will result in hypotropia of the ipsilesional eye and incyclotorsion of the contralateral eye⁶. As a consequence of deafferentation of the medial part of the UM, together with the prevalence of the contralateral UM, under static conditions, this will result in hypotropia and abnormal excyclotorsion of the ipsilesional eye, and hypertropia and incyclotorsion of the contralesional eye⁶.

It can be seen that an abnormal excyclotorsion of the ipsilesional eye is attributable only to UM involvement, while incyclotorsion of the contralesional eye is attributable to involvement of both the UM and ASC (Fig. 2B).

From the results of these tonic components, a consistently higher contralesional incyclotorsion than ipsilateral abnormal excyclotorsion should be expected.

This was not confirmed from our results which showed a significantly lower contralesional incyclotorsion. This could be partially explained by the basal physiological excyclotorsion that should exert an additive effect on ipsilesional abnormal excyclotorsion and a subtractive effect on contralesional incyclotorsion.

Figure 2 shows the expected changes from the normal excyclovergence in binocular cyclotorsion due to the asymmetrical activation of vestibular receptors in the course of a SVN (Fig. 2B), but also of inferior vestibular neuritis (Fig. 2C) or total vestibular neuritis (Fig. 2D). This model is, however, only theoretical. In fact, in our case, if the difference in degrees between ipsilateral abnormal excyclotorsion and contralateral incyclotorsion due to the onset of SVN was due only to the physiological basal bilateral excyclotorsion, they should be linearly correlated. This correlation is, however, not verified statistically (Spearman Rank-Order Correlation Coefficient = 0.25; $p = 0.48$).

Therefore, an unpredictable external mechanism influencing the statistically significantly greater variability of the contralesional incyclotorsion than the ipsilesional abnormal excyclotorsion should be hypothesised. The reason for this may be explained in the potential effect of the biphasic ocular movement due to the concomitant SN on the tonic ocular torsional position.

The repetition in the single patient of the cyclotorsion measurement through five consecutive photos of both eyes showed a lesser dynamic effect of the SN in primary position on the ipsilesional excyclotorsion (low SD; Tab. I) than on the contralesional incyclotorsion (high SD; Tab. I).

In detail, SN can influence the value of cyclotorsion depending on during which of its phases, rapid or slow, the photograph is taken. The slow phase of the SN represents the compensatory phasic ocular movement that follows asymmetrical activation of the vestibular receptors in addition to its tonic effect. Otherwise, the rapid phase of the SN is anti-compensatory because it will tend to bring the eyes back to their initial position.

The contralesional incyclotorsion will be more pronounced as the fundus photograph is taken at the end of the slow phase of the SN. At this point, in fact, the eyes are found in their most extreme position toward the lesion side and the contralesional incyclotorsion will reach its peak value. On the other hand, if the fundus photograph is taken within the rapid phase of the SN, the anti-compensatory phasic excyclotorsion will be opposed to the tonic incyclotorsion and the latter will be reduced even up to its potential suppression (at the end of the rapid phase).

Furthermore, the repetition of five consecutive photographs in each eye in order to minimize the dynamic effect of the SN is insufficient in reducing the inter-individual variability of the contralesional incyclotorsion.

This may depend not only on possible differences in the tonic effect of the vestibular receptors involved, but also on the angular velocity of the SN. Theoretically, the faster the SN, the higher the probability that the fundus photograph will be taken during the rapid phase of the SN and the lower will be the contralesional incyclotorsion and vice versa. However, further studies are required to correlate the angular velocity with the degree of contralesional incyclotorsion.

Conclusions

Although the tonic oculomotor component following SVN should be more pronounced in the contralesional eye, measurement of incyclotorsion showed lower and more inconsistent values than ipsilateral abnormal excyclotorsion. For this reason, due to its more constant behaviour and because it is a direct consequence of utricular deafferentation, we suggest that only ipsilesional abnormal excyclotorsion should be used for direct clinical evaluation of utricular dysfunction and for its subsequent compensation in case of SVN.

Future studies should investigate binocular cyclotorsion in other topographic localisations of vestibular neuritis.

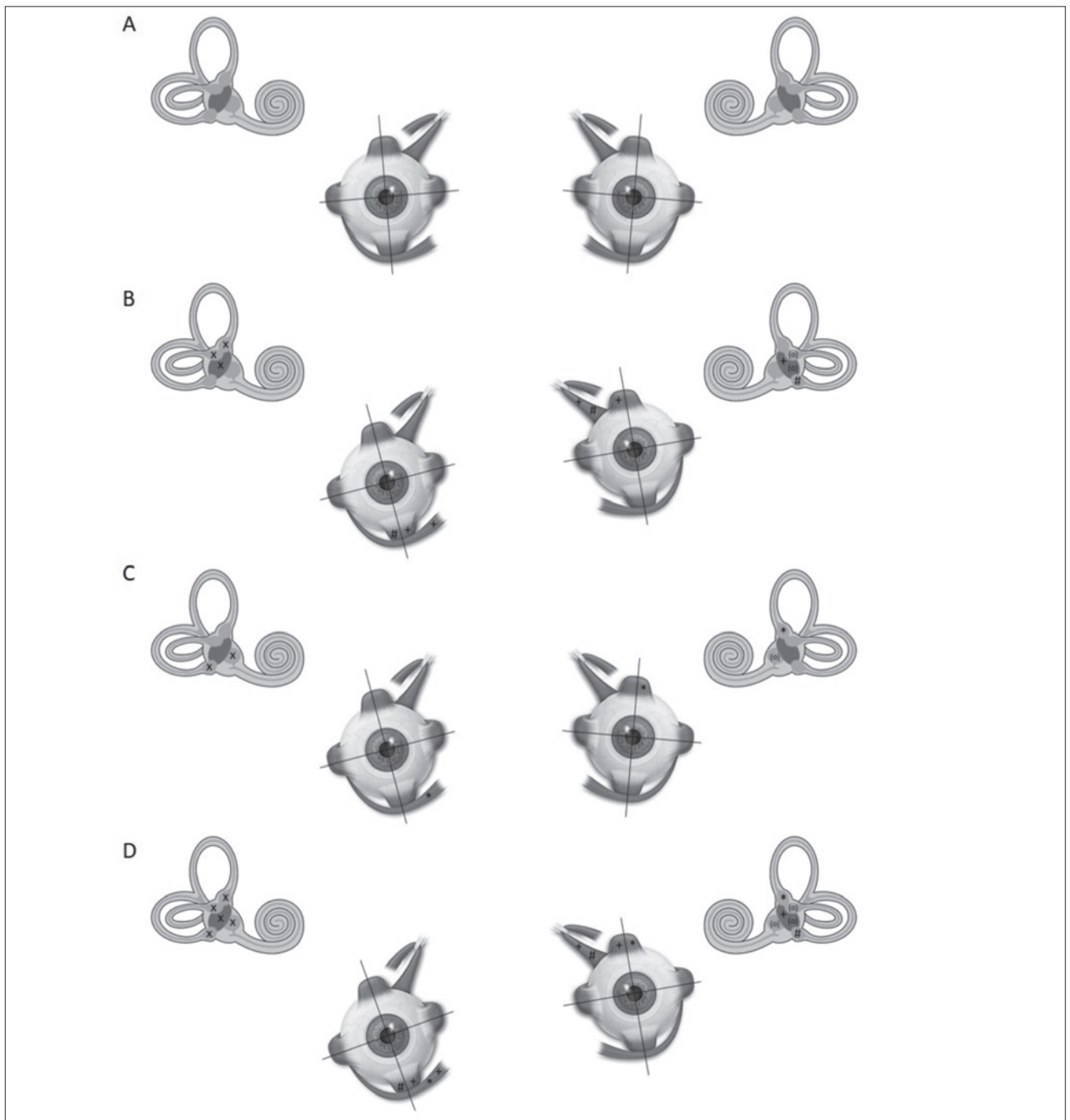


Fig. 2. Expected changes from the normal (**A**) in binocular cyclotorsion and vertical alignment due to the asymmetrical tonic activation of vestibular receptors. **B: Right superior vestibular neuritis (SVN).** Deafferentation (**x**) of the right anterior semicircular canal (ASC) and of the right utricular macula (UM). The left posterior semicircular canal (PSC) exerts a tonic effect (**#**) on the left superior oblique muscle (SOM; incyclotorsion) and of the right inferior rectus muscle (IRM; hypotropia). The left medial part of UM exerts a tonic effect (**+**) on the left SOM, on the left superior rectus muscle (SRM; hypertropia), on the right inferior oblique muscle (IOM, excyclotorsion) and on the right IRM. The result will be a right hypotropia with an abnormal excyclotorsion, a left hypertropia with an incyclotorsion lower than the contralateral excyclotorsion. **C: Right inferior vestibular neuritis (IVN).** Deafferentation (**x**) of the right PSC and of the right saccular macula (SM). The left ASC exerts a tonic effect (*****) on the left SRM and on the right IOM. The result will be an abnormal right excyclotorsion and a left hypertropia with a normal excyclotorsion. **D: Right total vestibular neuritis.** Deafferentation of all vestibular receptors (**x**). The tonic effect of the left PSC (**#**), of the left medial part of the UM (**+**) and of the left ASC (*****) is equivalent to the sum of the previous two situations. The result will be a right hypotropia with an abnormal excyclotorsion more pronounced than in SVN and IVN and a more pronounced left hypertropia than in SVN and IVN with an incyclotorsion comparable to that of SVN. The tonic effect (*****) of the left horizontal semicircular canal, of the left lateral part of the UM and of the SM is not reported given their null effect on SOB, IOM, SRM and IRM.

References

- ¹ Spielmann A. *Cyclotorsions*. J Fr Ophtalmol 2002;25:959-67.
- ² Toselli C, Miglior M. *Oftalmologia Clinica*. Bologna: Monduzzi Editore; 1979.
- ³ Lemos J, Eggenberger E. *Clinical utility and assessment of cyclodeviation*. Curr Opin Ophthalmol 2013;24:558-65.
- ⁴ Parsa CF, Kumar AB. *Cyclodeviation of the retinal vascular arcades: an accessory sign of ocular torsion*. Br J Ophthalmol 2013;97:126-9.
- ⁵ Seo JM, Kim K, Kim JH, et al. *Measurement of ocular torsion using digital fundus image*. Proceedings of the 26th Annual International Conference of the IEEE EMBS. San Francisco, CA, USA, September 1-5, 2004.
- ⁶ Marcelli V. *Vestibologia clinica. Casi clinici e test diagnostici*. Pavia: Selecta Editrice; 2013.
- ⁷ Halmagy GM, Gresty MA, Gibson WP. *Ocular tilt reaction with peripheral vestibular lesions*. Ann Neurol 1979;6:80-3.
- ⁸ Loader B, Linauer I, Korkesch S, et al. *A connection between neurovascular conflicts within the cerebellopontine angle and vestibular neuritis, a case controlled cohort study*. Acta Otorhinolaryngol Ital 2016;36:421-7.
- ⁹ Faralli M, Lapenna R, Mandalà M, et al. *The first attack of Ménière's Disease: a study through SVV perception. Clinical and pathogenetic implications*. J Vestib Res 2014;24:335-42.
- ¹⁰ Micarelli A, Chiaravallotti A, Schillaci O, et al. *Aspects of cerebral plasticity related to clinical features in acute vestibular neuritis: a "starting point" review from neuroimaging studies*. Acta Otorhinolaryngol Ital 2016;36:75-84.
- ¹¹ Strupp M, Arbusow V, Maag KP, et al. *Vestibular exercises improve central vestibulospinal compensation after vestibular neuritis*. Neurology 1998;51:838-44.
- ¹² Devèze A, Montava M, Lopez C, et al. *Vestibular compensation following vestibular neurectomy*. Eur Ann Otorhinolaryngol Head Neck Dis 2015;132:197-203.
- ¹³ Lopez C, Borel L, Magnan J, et al. *Torsional optokinetic nystagmus after unilateral vestibular loss: asymmetry and compensation*. Brain 2005;128:1511-24.
- ¹⁴ Kim HA, Hong JH, Lee H, et al. *Otolith dysfunction in vestibular neuritis: recovery pattern and a predictor of symptom recovery*. Neurology 2008;70:449-53.
- ¹⁵ Goebel JA, O'Mara W, Gianoli G. *Anatomic considerations in vestibular neuritis*. Otol Neurotol 2001;22:512-8.
- ¹⁶ Kim JS, Kim HJ. *Inferior vestibular neuritis*. J Neurol 2012;259:1553-60.
- ¹⁷ Strupp M, Brandt T. *Vestibular neuritis*. Semin Neurol 2009;29:509-19.
- ¹⁸ Welgampola MS, Colebatch JG. *Vestibulocollic reflexes: normal values and the effect of age*. Clin Neurophysiol 2001;112:1971-9.
- ¹⁹ Babić B. *Cyclotropia after unilateral vestibular damage*. Srp Arh Celok Lek 130 Suppl 2002; 1:1-7. [Article in Serbian].

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VESTIBOLOGY

Vertigo returning to the sitting position after the Semont manoeuvre. Is it a prognostic symptom?

La comparsa di vertigine al ritorno nella posizione seduta della manovra di Semont può essere considerata un fattore prognostico?

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SUMMARY

Benign paroxysmal positional vertigo (BPPV) is a frequent benign vestibular condition usually managed with particle repositioning manoeuvres, such as Semont manoeuvre (SM). Since few authors have described prognostic aspects of liberatory manoeuvres, the purpose of the present study was to investigate the possibility of considering vertigo in the final sitting position of the SM as a prognostic symptom in the outcome of posterior BPPV. One hundred and thirteen patients with diagnosis of unilateral posterior BPPV were taken into account in our retrospective cohort study: 41 men and 72 women, aged 22 to 85 years. All were submitted to one repositioning SM and afterwards controlled 3 to 5 days later by means of an additional Dix-Hallpike manoeuvre. The main outcomes investigated were the occurrence of Ny and vertigo in the different phases of the SM, as well as their characteristics in relation to outcome of the disease. Among all patients, 75 (66%) presented both orthotropic Ny and vertigo in the second SM position and 72% obtained a complete resolution of the disease after the liberatory manoeuvre. Contrarily, 17 subjects (15%) manifested vertigo in the final sitting position of the SM and among these, only 7 (41%) completely recovered from BPPV. According to our data, in case of sudden vertigo returning to the final sitting position of the SM, the failure rate of the liberatory manoeuvre was higher, even though not statistically significant: therefore, it can be considered as a negative prognostic factor of posterior BPPV after SM.

KEY WORDS: BPPV • Semont manoeuvre • Semont prognostic factors • BPPV outcomes • Positional vertigo

RIASSUNTO

La vertigine parossistica posizionale benigna (BPPV) è la patologia che più frequentemente colpisce il labirinto e si manifesta con crisi di vertigine parossistiche, ovvero intense e di breve durata. Poiché la BPPV, provocata da un disturbo meccanico dell'organo dell'equilibrio, è considerata una patologia ad andamento benigno, viene normalmente gestita con manovre di riposizionamento degli otoliti chiamate manovre liberatorie: tra queste vi è la manovra di Semont (SM). L'obiettivo del presente studio è indagare se vi sia la possibilità di considerare la vertigine che talvolta insorge al ritorno nella posizione seduta finale della SM come un fattore prognostico riguardo l'esito della manovra stessa e quindi la risoluzione della patologia. Sono stati presi in considerazione per questo studio retrospettivo 113 pazienti con diagnosi di BPPV unilaterale posteriore: 41 uomini e 72 donne, di età compresa tra 22 e 85 anni. Tutti sono stati sottoposti a una SM liberatoria e in seguito controllati dopo 3-5 giorni mediante una nuova manovra Dix-Hallpike diagnostica. Tra le diverse variabili indagate, il principale dato preso in considerazione è stato il verificarsi di nistagno (Ny) e/o vertigine nelle diverse posizioni della SM, nonché le loro caratteristiche in funzione dell'evoluzione della malattia. Tra tutti i campioni, 75 pazienti (66%) presentavano sia vertigine che Ny nella seconda posizione della SM ed il 72% di essi ha ottenuto una completa risoluzione della malattia dopo tale manovra liberatoria. Al contrario, 17 soggetti (15%) hanno manifestato esclusivamente vertigini al ritorno nella posizione seduta finale della SM e tra di essi solo 7 pazienti (41%) hanno ottenuto una completa remissione della BPPV. Secondo i dati in nostro possesso si può pertanto affermare che, in caso di insorgenza di vertigini nella posizione seduta finale della SM, il tasso di fallimento della manovra liberatoria è risultato molto più elevato, anche se non statisticamente significativo: tale risultato può essere considerato un fattore prognostico negativo nell'outcome della BPPV posteriore dopo SM.

PAROLE CHIAVE: BPPV • Manovra di Semont • Fattori prognostici della BPPV • Esiti di BPPV • Vertigine posizionale

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Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent vestibular disorder^{1,2} and is characterised by

recurrent acute vertigo episodes triggered by changes in head position in everyday activities, commonly when rolling over in bed, bending forward or tilting the head to

look upward. The disease was first described by Bárány in 1921 as a disorder of the otolithic organ and was afterwards named by Dix and Hallpike in 1952³. Canalithiasis is recognised as the most widely accepted theory in the pathogenesis of the disease: according to this theory, free-floating otoliths move along the concerned semicircular canal under the influence of gravity when changing the head position along the earth-vertical plane. These displacements induce a hydrodynamic endolymphatic flow which induces a deflection of the cupola, leading to the onset of acute vertigo and nystagmus (Ny) by changing the firing rate of the vestibular nerve^{4,5}.

A population-based study estimated that BPPV has a lifetime prevalence of 2.4% and accounts for 8% of individuals with moderate to severe dizziness or vertigo⁶.

In 60-90% of cases, BPPV affects the posterior semicircular canal; the lateral semicircular canal is only occasionally involved whereas the superior semicircular canal is rarely indicated as the cause of the disorder⁷.

Liberatory manoeuvres are nowadays considered the gold standard in the treatment of BPPV, inducing short term resolution of vertigo in more than 70% of cases and an overall success rate of 90% after carrying out four different manoeuvres^{8,9}. These manoeuvres are intended, employing stepwise changes in head position, to flush free-floating otolithic debris out of the most sensitive part of the inner ear to a less sensitive location, namely from the involved semicircular canal back to the utricle. In case of involvement of the posterior semicircular canal, Semont's (SM) and Epley's manoeuvres are considered the most effective therapeutic procedures^{10,11}, and nowadays the SM level of recommendation for treating BPPV is currently B⁸.

The main side effects after repositioning manoeuvres are the possible conversion from posterior to lateral semicircular canal BPPV and a postural persisting unsteadiness⁹. Immediate recurrence is rarely reported in literature, whereas long-term recurrence is described in about 50% of cases⁹.

A typical immediate manifestation during repositioning manoeuvres such as SM is the occurrence of an orthotropic Ny beating in the same direction of the one recorded just after reaching the primary position (the rapidly obtained side-lying position to the affected side after the head is turned 45° to the unaffected side). This sudden Ny is always associated with a paroxysmal vertigo and both come out as soon as the patient is forced by the physician to turn the head toward the healthy side (second position)².

The occurrence of this Ny several seconds to minutes after reaching the second SM position, which is also described performing the Epley canalith repositioning procedure, is defined "liberatory Ny" and is considered as a positive predicting factor for the effectiveness of the previously ex-

ecuted manoeuvre^{6,7,12-14}. In the absence of such orthotropic Ny soon after the second SM position, sometimes BPPV patients manifest an intense paroxysmal acute vertigo getting up to the final sitting position of the same manoeuvre, with the legs hanging off the edge of the examination table. The purpose of the present retrospective cohort study was to define whether the occurrence of acute vertigo returning to the final sitting position of SM could be considered a prognostic factor for the effectiveness of the liberatory manoeuvre itself.

Materials and methods

A cohort of 113 patients suffering from unilateral posterior semicircular canal BPPV were included in the present retrospective study after being investigated by our ENT tertiary referral centre at the University of Turin "Città della Salute" Hospital, over a three-year period (January 1st, 2014 - December 31st, 2016).

Posterior semicircular canal BPPV was diagnosed according to the American Academy of Otolaryngology Head and Neck Surgery Foundation guidelines¹⁵: (a) history of vertigo associated with changes in head position; (b) characteristic mixed torsional-vertical nystagmus, with the upper pole of the eye beating toward the affected ear and the vertical component beating toward the forehead (clockwise geotropic nystagmus in left ear forms and counterclockwise geotropic nystagmus in right ear forms from the examiner point of view). Ny detected with Frenzel's glasses (optical or video) or videonystagmography in the Dix-Hallpike maneuver (DHM) that increases and resolves within 1 minute; (c) paroxysmal vertigo associated with the elicited nystagmus; (d) latency period between the completion of the DHM and the onset of rotational vertigo and the objective nystagmus.

Exclusion criteria were diagnosis of either lateral or anterior semicircular canal canalithiasis, bilateral forms of BPPV, presence of other middle and inner ear pathologies, previous liberatory manoeuvres carried out to treat the same episode of disease and persistence of positional vertigo in the 3-5 days between the appropriate repositioning manoeuvre and outpatient control visit.

Furthermore, patients who did not present both characteristic Ny and vertigo in the primary position of SM were excluded, whereas patients suffering from recurrent BPPV were admitted to the study.

We decided to evaluate the following parameters of the disease: mean duration of the last BPPV episode since the onset of symptomatology, number of previous crisis and vertigo intensity by a visual-analogue- scale ranging from 0 to 10.

Ten minutes after a positive DHM, patients were submitted to liberatory SM as follows: the patient is seated in the upright position on an examination table with the legs hanging down, then the head is turned 45° toward the unaffected side and rapidly moved to the opposite side-lying position. The patient is held in this position until both vertigo and Ny disappear (approximately 30 seconds). Afterward the patient is suddenly turned 180° toward the unaffected side-lying position, without pausing in the sitting position and without changing the head position relative to the shoulder (therefore at the end of this movement the head is turned down); the present position is maintained, like before, until both vertigo and Ny disappear or, in the absence of any manifestation, for at least 2 minutes. Finally, the patient is gently raised up to the first seated position, eventually reporting the occurrence of either orthotropic Ny or vertigo.

All patients admitted to the study were afterwards controlled 3 to 5 days later in the outpatient and submitted again to a DHM; in case of positivity of the DHM, we evaluated the intensity of the reported vertigo and the relative Ny, comparing them to the baseline control.

Written informed consent to be routinely submitted to the tests was obtained by each of the enrolled subjects. The study was carried out according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards; nevertheless, in all cases we performed the common diagnostic and therapeutic procedures usually carried out to pursue the resolving BPPV.

Statistical analysis of the data was performed using SPSS software ver. 23 (Chicago, IL, USA). A Kolmogorov-Smirnov test was used to test the normality of the distribution among the different groups of patients enrolled in this study. Since the Kolmogorov-Smirnov test demonstrated a normal distribution among all the different groups of patients, the parametric test of Chi-square (for categorical variables) and Student's T test (for continuous variables) were used when appropriate. A level of significance of 0.05 was set for all tests.

Results

Among all the 113 patients suffering from posterior semicircular canal BPPV enrolled in the present study, 72 subjects (64%) were females and 41 subjects (36%) were males, while the mean age of the group resulted 62.6 ± 12 years (range 22-85). The right ear was affected in 70 cases (62%) whereas the left ear was involved in 43 patients (38%). A certain aetiology was identifiable in only 10 cases (9%) and among these trauma in 7 cases (6%) and vestibular neuritis in 3 patients (3%).

The BPPV episodes investigated presented an average duration of 41 ± 53 days since the occurrence of positional symptomatology and the mean value at the visual-analogue scale was 5 of 10 (range 1-9). The reported average number of similar previously experienced episodes was 2.2 (range 0 to 15), whereas 58 patients (51%) were observed during their first episode of vertigo.

Among all subjects, 75 patients (66%) presented both orthotropic Ny and vertigo in the second position of SM, 17 subjects (15%) manifested vertigo returning to the final SM sitting position and 21 patients (19%) demonstrated neither objective Ny nor vertigo in either the second or final SM sitting positions.

None of the patients reported vertigo getting up to the last sitting position after having had orthotropic Ny in both the first and in the second face down SM positions. Differently, in case of vertigo returning to the sitting position, we detected (47%) the development of Ny beating in the opposite direction respect to the one recorded in the primary SM position in 8 cases.

Age at diagnosis, duration of the BPPV episode since the onset of symptomatology, overall number of crisis and vertigo intensity did not differ significantly ($p > 0.05$) at the ANOVA test in relation to the occurrence of clinical signs such as orthotropic Ny or to the onset of subjective symptoms like vertigo during the SM (Table I). Similarly, even the gender of patients and evidence of a well-known cause for BPPV did not significantly conditioned the response to SM ($p > 0.05$ by Chi-Square test).

Performing the outpatient control visit at 3 to 5 days after the first SM by additional diagnostic DHM, 70 patients (62%) manifested a complete resolution of the disease, 24 subjects (21%) reported a stable persistence of symptomatology, with objective Ny and vertigo, and 19 patients (17%) demonstrated a moderate improvement of the disease, characterised by a less intense vertigo and evidence of a lower intensity of orthotropic Ny.

Similar to the previous results, age of the patients, duration of the BPPV episode since the onset of symptomatology, overall number of crisis and vertigo intensity did not differ significantly ($p > 0.05$) at the ANOVA test even in relation to the outcome of the disease 3 to 5 days after the SM (Table II), despite an evident shorter mean duration of the BPPV episode.

The prevalence of the final outcome of the liberatory manoeuvre, classified as complete resolution of BPPV, moderate improvement of the disease and stable persistence of disease, in relation to the clinical signs and symptoms after SM as reported in Table III. Differences at Chi-Square test were not significant ($p > 0.05$), although there was a higher probability of obtaining a complete resolution in

Table I. Age at diagnosis, last episode duration since the onset of symptomatology, overall number of crisis and vertigo intensity in relation to the clinical manifestations occurred performing SM due to posterior BPPV. Differences not significant by ANOVA test ($p > 0.05$).

	Age (a)	Last episode duration (b)	Overall number of crisis	Vertigo intensity (c)
No clinical manifestations (n = 21)	61 ± 14	45 ± 48	2.7 ± 2.8	4.8 ± 2.1
Both orthotropic Ny and vertigo in the second SM position (n = 75)	63 ± 11	43 ± 59	2.1 ± 2.1	5.1 ± 1.3
Vertigo returning to sitting position (n = 17)	62 ± 11	29 ± 27	1.9 ± 2.2	5.1 ± 1.7
p	> 0.05	> 0.05	> 0.05	> 0.05

a: age is expressed in years; b: last episode duration is expressed in days; c: vertigo intensity values are expressed out of 10 at the visual-analogue-scale.

Table II. Age at diagnosis, last episode duration since the onset of symptomatology, overall number of crisis and vertigo intensity in relation to the final outcome of a single SM performed due to posterior BPPV. Differences resulted not significant at the ANOVA test ($p > 0.05$).

	Age (a)	Last episode duration (b)	Overall number of crisis	Vertigo intensity (c)
Persistence of disease (n = 24)	65 ± 9	24 ± 26	2.2 ± 2.3	5.4 ± 1.2
Moderate improvement (n = 19)	62 ± 11	43 ± 34	3 ± 3.3	4.8 ± 1.6
Complete resolution (n = 70)	62 ± 14	46 ± 62	2 ± 1.9	5 ± 1.6
p	> 0.05	> 0.05	> 0.05	> 0.05

a: age values are expressed in years; b: last episode duration is expressed in days; c: vertigo intensity values are expressed out of 10 at the visual-analogue-scale.

Table III. Final outcome of a single SM due to posterior BPPV in relation to the clinical manifestations occurred performing the manoeuvre itself. Differences resulted not significant at Chi-Square test ($p > 0.05$).

	No clinical manifestations	Both orthotropic Ny and vertigo in the second SM position	Vertigo returning to sitting position
Persistence of disease (n = 24)	4 (17%)	14 (58%)	6 (25%)
Moderate improvement (n = 19)	7 (37%)	8 (42%)	4 (21%)
Complete resolution (n = 70)	10 (14%)	53 (76%)	7 (10%)

case of onset of both objective orthotropic Ny and vertigo during the second SM position; furthermore, among patients who reported an intense vertigo returning to final sitting SM position, there was a higher prevalence of stable persistence of disease 3 to 5 days after performing the manoeuvre, even though such difference was not significant ($p > 0.05$).

Discussion

Particle repositioning manoeuvres by Epley and Semont^{9 11} are nowadays considered the gold standard in BPPV therapy due to posterior semicircular canal canalithiasis, with a success rate after the first manoeuvre ranging from 50 to 90%^{7 8 12 16 17}.

A typical prompt reaction after liberatory manoeuvres is the sudden onset of an orthotropic Ny coupled with an objective vertigo, which comes out getting the second po-

sition of the SM, namely the stance with the head turned toward the unaffected ear.

This occurrence is commonly considered as a positive prognostic sign with respect to the efficacy of the manoeuvre itself^{7 8 12 14}, since it should confirm the exit of otoconial debris from the posterior semicircular canal to the utricle; on the other hand, the absence of such typical orthotropic Ny might suggest that the manoeuvre did not correctly displace the otoliths toward the utricle. In literature a 70% to 80% success rate of the SM is described in case of onset of an orthotropic Ny in the second position of the manoeuvre itself; contrarily, in the lack of any clinical objective signs, such value will drop to 50%^{7 9 14}.

In the absence of both orthotropic Ny and vertigo soon after the second position of the liberatory manoeuvre, we frequently observed the onset of vertigo which manifests as soon as the patient gets in the final sitting position of the SM; such objective vertigo was sometimes so intense

that the subject had to be strongly held by the examiner to avoid falling from the examination table. This aforementioned clinical manifestation has never been considered as a possible prognostic factor for the outcome of the liberatory manoeuvres.

In order to correlate the immediate events after SM with the outcome of the manoeuvre itself, in the present study it was decided to examine a group of patients affected by BPPV due to posterior canalithiasis and submitted to SM, the liberatory manoeuvre we use as first choice in our ENT department in these cases.

Our results demonstrated a complete resolution of vertigo in 62% of patients after the first SM; nevertheless, also taking into account subjects who reported a significant improvement of symptomatology, which is often considered sufficient to obtain a good quality of life while waiting for natural resolution of the disease, we have reached an overall 79% of positive results after the first treatment. The outcome of the SM was not correlated to gender, age of patients at diagnosis, overall number of crisis, or subjective vertigo intensity during the episodes¹⁸. Even the duration of the BPPV episode since the onset of symptomatology was not significantly different in relation with the outcome of the SM (persistence of disease, moderate improvement of disease and complete resolution).

Moreover, in concordance with previous studies^{7 8 12 16}, our data has highlighted the occurrence of both typical orthotropic Ny and vertigo in 66% of patients in the second position of the SM. Among the 38 patients who manifested neither orthotropic Ny nor vertigo in the second face down position of the SM, we observed the occurrence of an intense vertigo when returning to the final sitting position in 17 cases, namely 15% of the overall sample. Since the onset of vertigo induced by liberatory SM is considered probative of otoconial particle movements⁷, we can therefore suppose that SM led to otolith displacement in 81% of patients, although with different final outcomes.

According to our data, differences in the outcome did not result significantly correlate either with the presence or with the absence of any clinical manifestation in the second SM position, even if the rate of success was considerably higher in patients who manifested orthotropic Ny. Therefore, the present study supports our conviction that the onset of Ny during the second position of liberatory SM should not be interpreted as a certain positive prognostic factor for posterior canalithiasis, since even in the absence of orthotropic Ny we could not exclude in advance the probable resolution of the disease. For that reason, an outpatient vestibular control, including an additional DHM to check any persistence of BPPV after the

first SM, should be always afterward scheduled, whatever the outcome of the manoeuvre⁷.

Among all patients submitted to SM due to posterior BPPV, we reported a higher rate of complete resolution of the disease in case of occurrence of both orthotropic Ny and vertigo in the second SM position, as like as a higher persistence of disease was described in those subjects who manifested vertigo returning to the last sitting position. Therefore, the onset of such acute vertigo, evoked while getting up to the last sitting position soon after SM, could be considered as a negative prognostic sign in the outcome of posterior BPPV, highlighting a relatively higher failure rate of the liberatory manoeuvre.

The accurate examination of patients who experienced acute vertigo in the final sitting position of the SM allowed us to also detect a simultaneous Ny in 47% of cases; nevertheless, we cannot exclude that the aforementioned Ny could be evaluated every time at the end of the manoeuvre, although difficult to observe due to the intense postural imbalance evoked in these patients, which obliged us to firmly handle them to avoid any fall from the examination bed.

The direction of the Ny evoked in the last sitting position of the SM furthermore allows us to speculate about its genesis: since it has been reported to proceed in a direction opposite to the one evoked both by primary and secondary SM positions due to an ampullifugal movement of otoconia¹³, we can therefore suppose in this case that the otoliths displacement was directed toward the ampulla. As a result, the occurrence of this response to liberatory SM could demonstrate the persistence of otoconial debris within the semicircular canal, probably due to a more proximal position of such otoconia to the ampulla, leading to a protraction of the symptomatology and to a worse prognosis of the disease.

Conclusions

In conclusion, the possibility of identifying any prognostic criteria during or soon after the administration of a SM due to posterior BPPV might be useful to plan further controls or to suggest post-manoevure postural restrictions, even though they have been considered useless according to the AAO-HNS guidelines¹³. Our data, in agreement with the above-mentioned guidelines, suggest that the occurrence of an orthotropic Ny in the second SM position is a positive prognostic factor in the outcome of a posterior BPPV, although it cannot be considered as certainly probative of vertigo resolution. Contrarily, in case of vertigo returning to the final sitting SM position or otherwise in the absence of any clinical manifestations (Ny

and/or vertigo) after SM, the failure rate of the liberatory manoeuvre increases, so that these conditions can be considered as negative prognostic signs of posterior BPPV outcome.

References

- ¹ Hotson JR, Baloh RW. *Acute vestibular syndrome*. N Engl J Med 1998;339:680-5.
- ² Furman JM, Cass SP. *Benign paroxysmal positional vertigo*. N Engl J Med 1999;341:1590-6.
- ³ Dix MR, Hallpike CS. *The pathology, symptomatology and diagnosis of certain common disorders of the vestibular system*. Ann Otol Rhinol Laryngol 1952;61:987-1016.
- ⁴ Parnes LS, McClure JA. *Free-floating endolymph particles: a new operative finding during posterior semicircular canal occlusion*. Laryngoscope 1992;102:988-92.
- ⁵ Rajguru SM, Rabbitt RD. *Afferent responses during experimentally induced semicircular canalolithiasis*. J Neurophysiol 2007;97:2355-63.
- ⁶ von Brevern M, Radtke A, Lezius F, et al. *Epidemiology of benign paroxysmal positional vertigo: a population based study*. J Neurol Neurosurg Psychiatry 2007;78:710-5.
- ⁷ Soto-Varela A, Rossi-Izquierdo M, Santos-Pérez S. *Can we predict the efficacy of the semont maneuver in the treatment of benign paroxysmal positional vertigo of the posterior semicircular canal?* Otol Neurotol 2011;32:1008-11.
- ⁸ Mandalà M, Santoro GP, Asprella Libonati GA, et al. *Double-blind randomized trial on short-term efficacy of the Semont maneuver for the treatment of posterior canal benign paroxysmal position vertigo*. J Neurol 2012;259:882-5.
- ⁹ Zhang X, Qian X, Lu L, et al. *Effects of Semont maneuver on benign paroxysmal positional vertigo: a meta-analysis*. Acta Otorhinol 2017;137:63-70.
- ¹⁰ Semont A, Freyss G, Vitte E. *Curing the BPPV with a liberatory maneuver*. Adv Otorhinolaryngol 1988;42:290-3.
- ¹¹ Epley JM. *The canalith repositioning procedure: for treatment of benign paroxysmal positional vertigo*. Otolaryngol Head Neck Surg 1992;107:399-404.
- ¹² Oh HJ, Kim JS, Han BI, et al. *Predicting a successful treatment in posterior canal benign paroxysmal positional vertigo*. Neurology 2007;68:1219-22.
- ¹³ Toupet M, Ferrary E, Bozorg Grayeli A. *Effect of repositioning maneuver type and postmaneuver restrictions on vertigo and dizziness in benign positional paroxysmal vertigo*. ScientificWorldJournal 2012:162123.
- ¹⁴ Califano L, Capparuccia PG, Di Maria D, et al. *Treatment of benign paroxysmal positional vertigo of posterior semicircular canal by "Quick Liberatory Rotation Manoeuvre"*. Acta Otorhinolaryngol Ital 2003;23:161-7.
- ¹⁵ Bhattacharyya N, Baugh RF, Orvidas L, et al. *American Academy of Otolaryngology Head and Neck Surgery Foundation. Clinical practice guideline: benign paroxysmal positional vertigo*. Otolaryngol Head Neck Surg 2008;139:S47-81.
- ¹⁶ Chen Y, Zhuang J, Zhang L, et al. *Short-term efficacy of Semont maneuver for benign paroxysmal positional vertigo: a double-blind randomized trial*. Otol Neurotol 2012;33:1127-30.
- ¹⁷ Kahraman SS, Yildirim YS, Tugrul S, et al. *Repositioning intervals in the modified Epley's maneuver and their effect on benign paroxysmal positional vertigo treatment outcome*. Acta Otolaryngol 2017;137:490-4.
- ¹⁸ Babac S, Djeric D, Petrovic-Lazic M, et al. *Why do treatment failure and recurrences of benign paroxysmal positional vertigo occur?* Otolaryngol Neurotol 2014;35:1105-10.

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OTOLOGY

Acquisition of surgical skills for endoscopic ear and lateral skull base surgery: a staged training programme

L'acquisizione degli skills chirurgici nella chirurgia endoscopica dell'orecchio medio e del basicranio laterale: un programma di apprendimento a stadi

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SUMMARY

Endoscopic ear surgery is radically changing the treatment of several middle and inner ear pathology, but its learning presents well-known manual and technical difficulties. The aim of this paper is to present a training programme based on a modular model of increased difficulties. The experience from 2007 to 2016 at the University Hospital of Modena and University Hospital of Verona was reviewed and analysed for further considerations and to establish stages of training. The increasing experience of expert surgeons who deal with this kind of surgery represented the main guide to establish the steps and progression of training. In addition, the potential risk of damage of vascular structures or nerves represents fundamental criteria for progression toward higher levels. Some not-mandatory skills were also suggested for stage of difficulty. Five stages of training were deemed appropriate for progressive learning of endoscopic ear and lateral skull base surgery, ranging from simple middle and external ear procedures to surgery of inner ear and internal auditory canal. Mastering of each level is suggested before attempting procedures at a higher level, in particular for procedures involving lateral skull base. Standardisation and adoption of modular incremental training are expected to facilitate improvement of otolaryngologists and neurosurgeons starting with endoscopic middle ear and lateral skull base surgery. Adherence to such a programme during the growth phase may potentially decrease the rate of complications, making the training programme safer.

KEY WORDS: Transcanal approach • Endoscopic ear surgery • Training program • Inner ear surgery • Lateral skull base

RIASSUNTO

La chirurgia endoscopica dell'orecchio sta cambiando radicalmente il trattamento di molte patologie dell'orecchio medio e interno ma il suo apprendimento presenta difficoltà manuali e tecniche. Lo scopo di questo lavoro è presentare un programma basato su un modello di apprendimento con difficoltà crescente. L'esperienza accumulata nell'Ospedale Universitario di Modena e in quello di Verona dal 2007 al 2016 è stata analizzata accuratamente con lo scopo di definire un programma di training chirurgico. I vari skills chirurgici sono stati definiti dai chirurghi esperti in questo campo. Il potenziale rischio di lesione delle strutture vascolari e nervose gioca un ruolo molto importante nella chirurgia otologica e per questo rappresenta un criterio fondamentale utile nella definizione dei diversi livelli di apprendimento chirurgico. Sono stati identificati 5 livelli di competenza in questo programma di apprendimento che, partendo dagli step chirurgici dell'orecchio esterno e dell'orecchio medio, arriva agli approcci chirurgici dell'orecchio interno e del basicranio. L'acquisizione di competenze progressivamente crescenti richiede necessariamente autonomia e padronanza degli skills chirurgici precedenti. Sono state riportate e discusse in una tabella riassuntiva tutte le informazioni relative ai pazienti operati durante il periodo analizzato. I risultati fanno riferimento al tasso di complicanze relativo agli interventi chirurgici di miringoplastica, timpanoplastica e di stapedoplastica in particolare al deficit del facciale, alle lesioni della dura madre e alla perdita uditiva. La curva di apprendimento degli otorinolaringoiatri e dei neurochirurghi che approcciano alla chirurgia endoscopica potrebbe essere standardizzata e ben definita da questo programma a stadi che, presupponendo l'acquisizione di competenze progressivamente crescenti, potrebbe essere utile anche a ridurre il tasso di complicanze.

PAROLE CHIAVE: Approccio transcanalare • Chirurgia endoscopica dell'orecchio • Programma di apprendimento • Chirurgia dell'orecchio interno • Basicranio laterale

Introduction

Endoscopic instrumentation, techniques and knowledge have improved during the last few years, and we believe that, in the future, endoscopic surgical techniques will gain increasing importance in otologic surgery. From our 9-year experience in endoscopic ear surgery, we believe that most of the spaces considered to be of difficult accessibility with the microscopic technique can be easily visualised by endoscope-assisted surgery or by exclusive endoscopic approaches, and we feel that new anatomical and surgical concepts should be introduced for this.

A gradual introduction of endoscopic techniques to middle ear pathology treatment has taken place since the 1990s¹. Endoscopy was used primarily for the visualisation of hidden areas such as the posterior epitympanum during classic microscopic tympanoplasties². Gradually, it was also used in surgery to replace the microscope as the main tool during middle ear operations. Exclusive endoscopic tympanoplasty for cholesteatoma treatment was first described by Tarabichi et al.^{3,4}. The new concept of endoscopic ear surgery redirected the attention away from the less critical areas (i.e. mastoid) toward the tympanic cavity and its “hard-to-reach” extensions. The endoscopic technique was codified for a minimally invasive eradication of limited attic cholesteatoma preserving the ossicular chain wherever possible, with complete removal of the disease. From this, a clinical application of the transcanal endoscopic approach has allowed to extend the indication of this technique to the cholesteatoma of the whole tympanic cavity without mastoid involvement.

At present, the main application of endoscopic surgery is in the surgical treatment of middle ear pathology, but with the natural evolution of the technique, there have also been advantages in lateral skull base diseases⁵. During the experience of recent years, present authors progressively noticed that the inner ear and the entire temporal bone can also be accessed in an endoscopic assisted fashion or even by exclusive endoscopic transcanal approaches. For the first time, an exclusive endoscopic approach to the internal auditory canal (IAC) was described⁶ and used to remove a cochlear schwannoma involving internal auditory canal (IAC) in March 2012⁶. The operation used a direct transcochlear approach from lateral to medial and from external to internal auditory canal, without any external incision.

Despite the several advantages compared to microscope, endoscopic ear surgery presents some technical and manual skills that are objectively difficult to acquire. This is due to several factors: the necessity of adequate hand-eye

coordination; the very limited space of the surgical field; bleeding which prevents visualisation by obstructing the optic tip; some anatomical conditions (e.g. narrow external auditory canal (EAC)) which can limit the maneuvering of both optics and operative instruments.

In 2007 Snyderman et al. published an article that suggested a training program for acquisition of surgical skills in endonasal skull base surgery⁷. The authors standardised the training by suggesting a modular incremental training programme. Since endoscopic ear and lateral skull base surgery is a relatively new technique, a training program has not yet been established. The aim of this paper is to present a training programme based on modular model of increased difficulties, in a similar way of that already done for endoscopic skull base surgery.

Materials and methods

The experience from 2007 to 2016 (9 years) at the University Hospital of Modena and at the University Hospital of Verona was reviewed and a case series analysed for further considerations and to establish stages of training. The increasing experience of surgeons dealing with these types of surgeries represented the main guide to establish the steps and progression of training. In addition, the potential risk of damage to vascular structures and nerves represented a fundamental criteria for progression toward higher steps. The skills acquired by the authors before attempting that kind of surgery (e.g. microscopic ear surgery or endoscopic nasal surgery) were considered to establish their necessity before starting each level in endoscopic ear and lateral skull base surgery. Timeline and subjects of publications dealing with endoscopic ear surgery by our team were also reviewed and compared to confirm the progression throughout the stages. The stages were conceived and designed with the highest level of intrastage homogeneity of difficulty. Data from literature and data obtained from chart review of patients operated during the period analysed are also reported and discussed. In particular, the results were focused on complication rates to facial nerves, dura lesion and sensorineural hearing loss during myringoplasties, tympanoplasties and stapedoplasties.

Results

during the period of time selected, more than 500 endoscopic ear surgeries were performed at our institutions. Progression toward new procedures was made following a coronal plane from lateral to medial direction (Fig. 1). The beginning of the endoscopic ear surgery started with

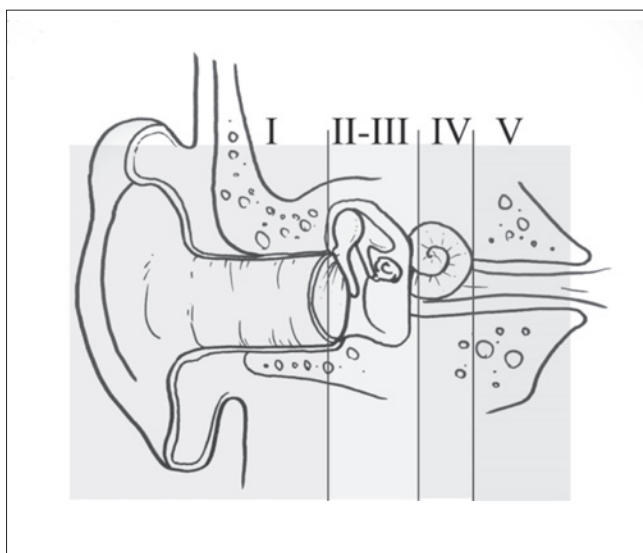


Fig. 1. Schematic drawing showing progression of training, in a coronal plane, from a lateral to a medial direction. Levels are indicated in roman numbers.

endoscopic-assisted procedures during microscopic tympanoplasties or myringoplasties^{2,8,9}. Next, the first exclusive endoscopic procedures for cholesteatoma treatment were performed^{10,11}. The endoscopy was gradually implemented for other procedures such as tympanic facial nerve decompressions, and to improve former results such as in ossicular chain preservation¹². With a sound experience acquired in middle ear surgery, and after a preliminary experience on cadavers, the first attempts to lateral skull base were then made, and the first cochlear schwannoma of the IAC was removed by an exclusive transcanal technique⁶. Then, more lateral skull base pathologies were treated by exclusive or combined techniques at our departments^{13,14}. Recently, the first case series of vestibular schwannomas of the IAC treated by an exclusive endoscopic technique (endoTTA) was published¹⁵. The

timeline of publications, reflecting the increasing experience of our team is reported in Table I.

As mentioned in the methods, a staging system for training was designed based on two factors, which represented a fundamental criteria for progression toward higher steps: the increasing experience of surgeons which had been dealing with that kind of surgery, and the potential risk of damage of vascular structures or nerves.

Five stages were provided, as reported in Table II. In each stage operations that have a homogeneous grade of difficulty and risks are reported. Possible risks associated with each operation are reported in Table III. The complementary skills were also suggested by our team (Table IV).

Complication rates OVER the years obtained by chart review of patients operated between 2009 and 2016 were analysed. Our data documented a very low rate of unfavourable events for endoscopic middle ear surgery (Table V).

Results were focused on three different types of complications: facial nerve palsies, dura lesions and sensorineural hearing loss. Chart review of patients treated reported only three transitory facial nerve injuries, seven cases of postoperative sensorineural hearing loss and no dura lesions.

Discussion

Each type of surgery requires an adequate training period to familiarise the surgeon with anatomy and develop manual skills¹⁶. Skull base surgery is universally considered a very challenging district for neurosurgeons, maxillofacial and otolaryngologists, due to its complex anatomy and the very important structures that crosses it or are in close relationships with it (jugular vein, carotid artery, cranial nerves). In 2007, Snyderman et al. published an article that described the acquisition of surgical skills for endonasal skull base surgery, proposing a training programme⁷. The programme provided five stages of progression from “basic” procedures to very complex operations performed by exclusive endonasal approaches, starting from sphenoid

Table I. Timeline of publication of new subjects dealing with endoscopic ear and lateral skull base surgery by our team.

2008	Endoscopic-assisted tympanoplastie ²
2009	Approaches to tensor fold area ⁸ , approaches to sinus tympani ⁹
2010	Exclusive Endoscopic “closed” tympanoplasties ¹⁰
2011	Exclusive Endoscopic “open” tympanoplasties ¹¹
2012	-
2013	Pilot lateral skull base procedure ¹³ ; first cochlear schwannoma treated by transpromontorial approach ⁶ ; benign neoplasms removal ²³
2014	Endoscopic cochlear implant procedure ²⁴ ; approach to geniculate ganglion ²¹ ; approach to petrous apex lesions ¹⁴
2015	Endoscopic cochlear implants in malformations ²⁵ ; pediatric tympanoplasties ²⁶
2016	Case series of exclusive transcanal transpromontorial approach to internal auditory canal to treat vestibular schwannomas ¹⁵ ; endoscopic stapes surgery ²⁷

Table II. Transcanal endoscopic middle ear and lateral skull base training program.

Middle ear	Level I
	Office based endoscopies for diagnosis Myringotomies with/without tympanic tube placement
	Level II
	Combined approaches (endoscope assisted microscopic surgeries) Office base tympanic perforation repair Myringoplasties Endoscopic explorative tympanotomies with/without ossiculoplasties
	Level III
	Tympanoplasties for cholesteatoma Stapedoplasties Facial nerve decompression Endoscopic assisted cochlear implants procedures Endoscopic resection of middle ear neoplasms (e.g. paragangliomas)
Inner ear and lateral skull base	Level IV
	Endoscopic ssovragenicular approaches Infracochlear approaches Transpromontorial approaches for inner ear disease
	Level V
	EndoTTA for IAC pathology

Table III. Structures at risk.

Level I
No relevant risks
Level II
Ossicular chain
Level III
Ossicular chain, facial nerve, labyrinth
Level IV
Facial nerve, labyrinth, Jugular bulb, carotid artery
Level V
Facial nerve, jugular bulb, carotid artery, lower cranial nerves, vessels of CPA (AICA), brainstem. Risk of post-operative CSF leak

noethmoidectomies (level I) to reach the highest level of difficulty (level V) which included treatment of aneurisms and highly vascularised tumours. The first levels (I and II) are those that are expected to be achieved within residency, then the program progresses in complexity.

Table IV. Complimentary expertise.

Level I
Endoscopic nasal surgery
Level II
Microscopic middle ear surgery
Level III
Microscopic middle ear surgery
Level IV
Microscopic transpetrous approaches
Level V
Acoustic neuroma surgery (retrosigmoid, translabyrinthine approaches)

Based on the substantial expertise of the authors, a staged training programme for acquisition of surgical skills for endoscopic middle ear and lateral skull base surgery is herein presented, strongly adhering to the same methods and principles used by Snyderman et al. As mentioned in the Results, the training programme described provides progression in a coronal plane, and with a lateral to medial direction, reflecting the complexity and presence of vital structures of the lateral skull base (Fig. 1).

Publications considered in Table I only deal specifically with surgery, and only those in which for the first time a new experience was described. Publications dealing exclusively with anatomy, physiologic issues, or reviews were excluded from this list. It can be noticed that they substantially reflected the progression proposed in Table II. The overall number of publications from 2007 to 2016 on the topic of endoscopic middle ear and lateral skull base by our team surpassed 40, and this is to testify the increasing interest by scientific community on that topic.

As reported in Table II, level I of the training programme presented includes office based explorations of EAC and tympanic membrane or tympanic tube placement. In fact, those basic procedures allow the surgeon to obtain the first impressions about depth of field, hand-eye coordination, magnification and surgical manoeuvring using the endoscope. The risks of severe complications in this kind of procedures are virtually absent. Prior expertise in endoscopic nasal surgery can be very helpful at this stage, although not mandatory, to acquire skills.

This step can be attempted very early, from the beginning of residency, during normal office evaluations or follow-up in the outpatient clinic. In addition, endoscopic ear de-waxing can be a good exercise at this level. When enough confidence is obtained, level II can be approached. In level II, the surgeon can start using the endoscope for more operative procedures, also attempting its use inside the

Table V. Complication rates in patients operated by EES between 2009 and 2016.

	2011	2012	2013	2014	2015	2016
Dura lesion	0	0	0	0	0	0
SNHL *	1	0	1	3	1	1
Facial palsy	1	0	0	1	0	1

* = hearing loss higher than 30 dB in at least one frequency.

tympanic cleft, for example in combined microscopic/endoscopic approaches². This can further improve manual skills, and also provide knowledge of instruments to operate inside the middle ear. Moreover, it allows surgeon to become familiarised with angled optics, which can be used to explore sinus tympani, tensor fold area, protympanic spaces, looking for cholesteatoma residuals^{8,9} during microscopic surgeries. Level II can also include myringoplasties or explorative tympanotomies, made by exclusive endoscopic approaches. In these operations, there is a potential risk of damage to the ossicular chain, and for this some experience must have been acquired at level I. In level II bleeding management is very important: in fact, due to the EAC skin incision and flap elevation, the surgeon will acquire the ability in bleeding control, and avoid dirtying the endoscopic tip. This is probably the most difficult skill to acquire in endoscopic ear and lateral skull base surgery, and in most cases it can discourage the surgeon in training. Bleeding control requires patience and good manual skills, but also knowledge in the positioning of the patient, cooperation with the anaesthesiologist in keeping blood pressure low and an appropriate technique

in raising the tympanomeatal flap, which could include also the use of hot blades. These factors are considered fundamental for progressing toward the next levels.

Level III provides exclusive approaches to treat typical pathologies of the middle ear (e.g. cholesteatoma), and more rare pathologies that could have risks of damage to the ossicular chain, facial nerve or labyrinth. Although it is very likely that adequate expertise is obtained by the surgeon in training after levels I and II, expertise in microscopic procedures is anyway advisable, because in case of problems during surgery or in particularly difficult procedures, a possible shift to the microscopic vision and bimanuality can be very helpful. Level III represents the final step for middle ear endoscopic surgery but similar considerations can be done with level IV, where lateral skull base procedures are attempted (Figs. 2, 3).

As already documented in former articles⁵, endoscopic approaches to lateral skull base are less invasive compared to classic microscopic procedures. Nonetheless, at this level the former experience in microscopic approaches can be very helpful in case of necessity, due to the fact that even more delicate structures will be manipulated (fa-

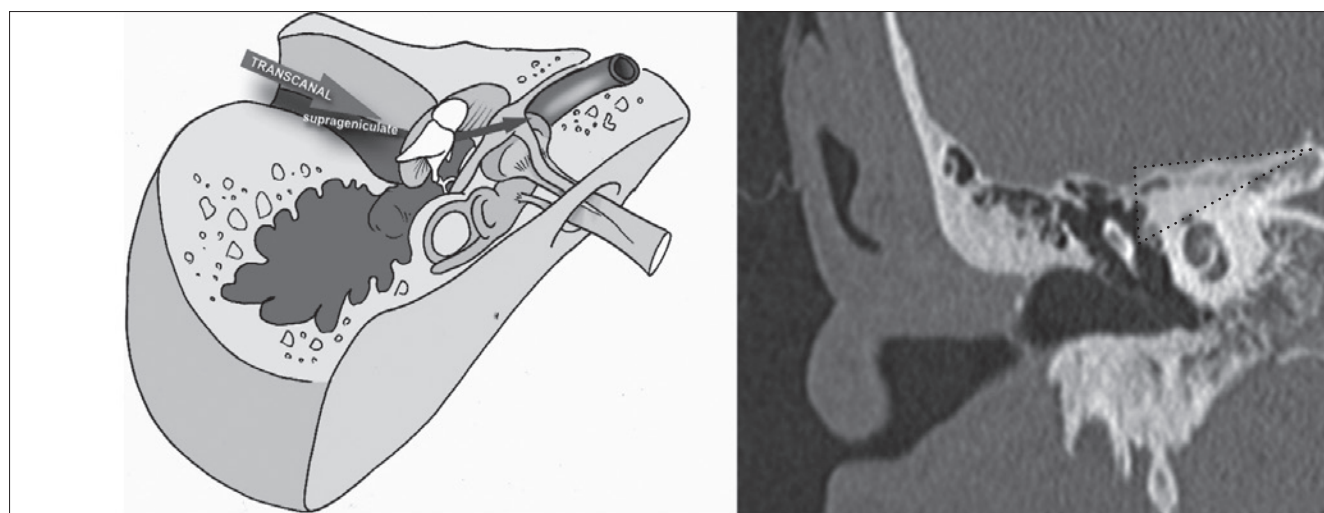


Fig. 2. The transcanal endoscopic suprageniculate approach: on the left the schematic drawing shows the surgical route from the external auditory canal to the suprageniculate fossa (black arrow); on the right, the CT scan in coronal view shows the working area and bony removal (dotted area) which may be performed under this approach between the middle cranial fossa and the facial nerve into the petrous apex over the cochlea (from Marchioni et al., 2013⁵, mod.).

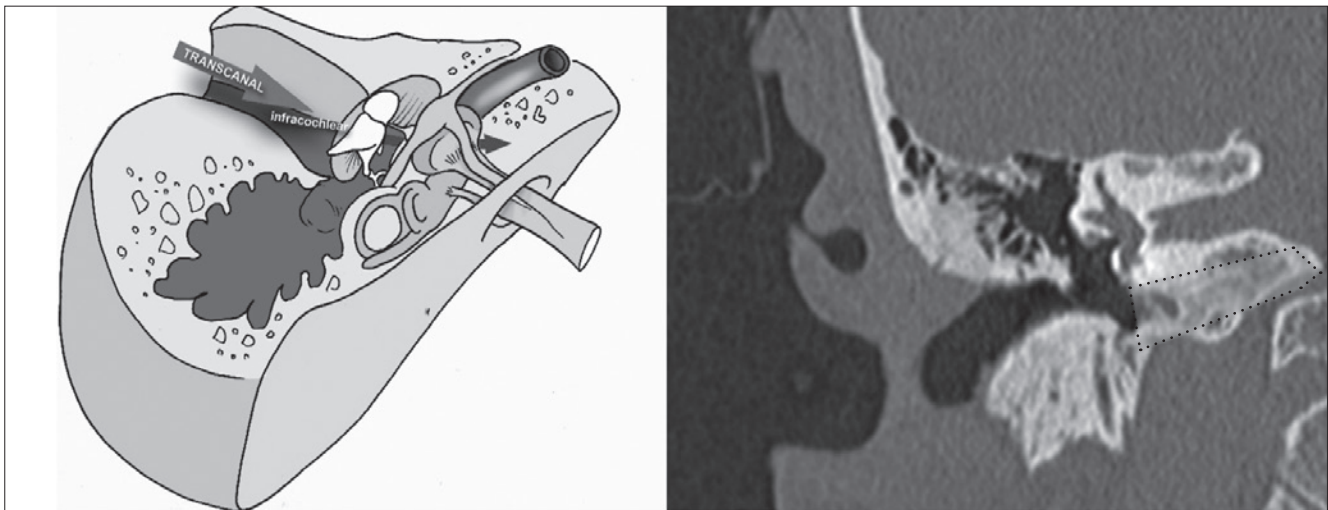


Fig. 3. The transcanal endoscopic infracochlear approach: on the left, the schematic drawing shows the surgical route from the external auditory canal to the infracochlear below the cochlea (black arrow); on the right, the CT Scan in coronal view shows the working area, and the bony removal (dotted area), which may be performed under this approach between the cochlea superiorly and the jugular bulb inferiorly in order to reach the petrous apex cells (from Marchioni et al., 2013⁵, mod.).

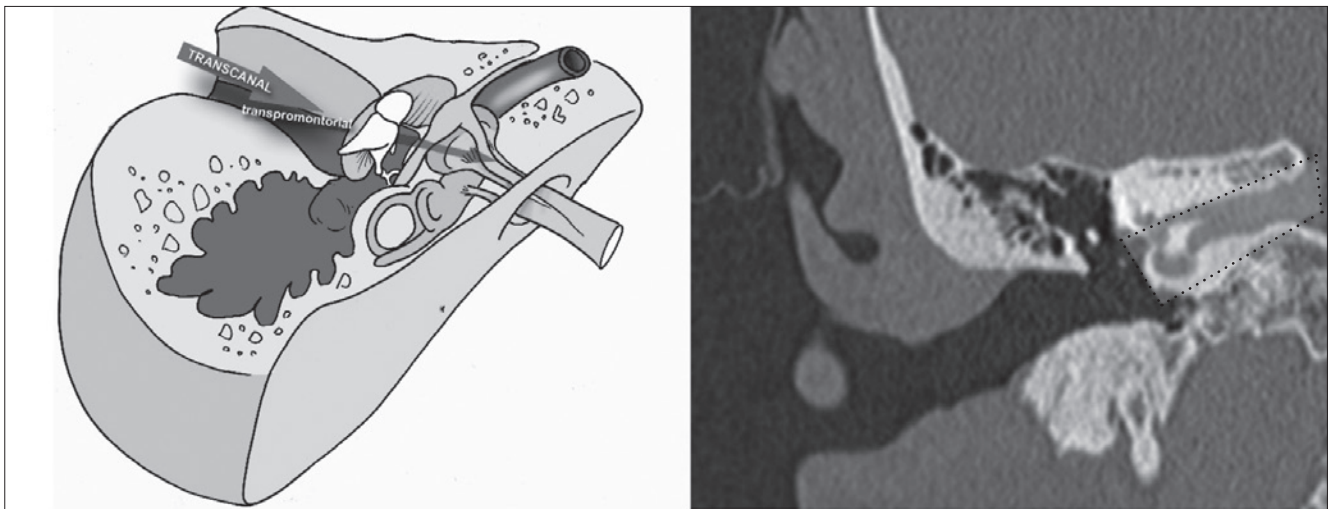


Fig. 4. The transcanal endoscopic transpromontorial approach: on the left, the schematic drawing shows the surgical route from the external auditory canal to the fundus of the IAC through the promontory (black arrow); on the right the CT Scan in coronal view shows the working area, and the bony removal (dotted area) which may be performed under this approach through the promontory, removing the cochlea and the vestibule, reaching the fundus of the IAC (from Marchioni et al., 2013⁵, mod.).

cial nerve, labyrinth, jugular bulb, carotid artery), and due to the risks of a possible damage.

In level V (Fig. 4), where the surgeon reaches the IAC and CPA, he/she must be aware not only of the complex anatomy of CPA with all the posterior fossa vascularisation and cranial nerves. Actually, it is also advisable to have former experience with CSF leak management and reconstruction procedures of lateral skull base to avoid post-operative complications related to it. Moreover,

strong expertise in dissecting the vestibular schwannoma can be helpful due to the fact that in exclusive endoscopic approaches it should be done by only one hand, as described in the endoscopic transcanal traspromontorial approach to IAC¹⁵.

Although the acquired skills suggested (Table IV) before attempting every level can be nowadays important, the authors do not consider them as mandatory. This is due to the fact that the evolution of middle ear and lateral skull

base is at present very difficult to predict, and will mostly depend on development of technologies¹⁷, instrumentation¹⁸⁻²⁰ and consequent evolution and modification of the technique. It is not unlikely that future generations will begin their expertise in this surgical field using directly and exclusively the endoscope, so for example the expertise in microsurgery could progressively become less necessary. Anyway, at present, the acquired skills mentioned will certainly increase the proficiency and safety in performing some operations, and may also very likely shorten the progression time.

Another very important point, as already underlined by Snyderman et al.⁷, is that although learning occurs mostly in the operating theatre, it is necessary that a sufficient amount of time be spent in the dissection laboratory. This should include both basic and advanced dissection courses, possibly focused on endoscopic middle ear and lateral skull base surgery, which are starting nowadays to be organised worldwide.

Actually, the long learning curve required to master endoscopic ear surgery urges the search for models to practice it. Many studies have demonstrated the validation of an animal model as a proper training model for this technique. In the experimental study reported by Anschuetz et al., the authors assessed the suitability of an ovine model for training in exclusive endoscopic surgery, assessing the time need for dissection and procedures. A significant improvement in all the surgical steps was demonstrated comparing mean surgical time required to perform them²⁸.

Simulators can also provide a challenging, safe and controlled environment to master the basic skills needed to perform endoscopic ear surgery. Several simulators for training of endoscopic techniques and procedures have been developed. Surgeons receiving simulator training show significant differences between first and last completion time with the dominant hand and average completion time for junior and senior residents suggesting construct validity. A 3-dimensional (3D) printed endoscopic ear surgery simulator may facilitate the development of surgical skills with high fidelity and low cost²⁹.

The simulator is considered useful for training eye-hand coordination for endoscopic surgery. However, the use of simulators in training hospitals is limited. This may be partly due to their high cost and extensive system requirements.

Neuronavigation systems can be applied in lateral skull base surgery to facilitate surgeons during training. Neuronavigation is very useful to obtain information during surgical procedures such as vascular details, cranial nerve positions and exact size and position of ENT tumours. Endoscopic approaches to the lateral skull base are the last

step during endoscopic ear surgery training program, so in particular for trainees, neuronavigation could help in situations with altered anatomy, such as revision cases, or in case of far advanced pathology that could alter completely anatomy.

Actually, as detailed in the results, complication rates in middle ear endoscopic surgery is very low. The surgery analysed was only that regarding middle ear procedures so as to obtain a significant number of patients. Although procedures included were relevant, complication rates were so low that eventually it was not possible to draw any meaningful timeline that could show improvement or worsening of surgeon performances.

As mentioned before, EES is a relatively new technique but results have been progressively reported in literature. Improvement of the technique lead to results that can be compared, at least in term of pathology eradication, to microscopic techniques. This was also reported by Presutti et al. whose literature review focused on outcomes obtained using endoscopic surgery for treatment of middle ear cholesteatoma. The authors analysed 515 patients treated exclusively with endoscope or with a combined procedure: the rates of recurrence and residual disease (9.3%) were similar than those obtained with microscopic approaches³⁰.

Even in the experience of our institution favourable results were obtained for endoscopic treatment of cholesteatoma at a mean follow-up of 5 years. In total 234 patients were treated: 144 underwent an exclusive endoscopic approach, whereas 100 were treated with a combined approach with mastoidectomy. Based on that analyses, 68% of patients treated were free from disease during postoperative follow-up visits; 12% were diagnosed a recurrence and 20% had residual disease³¹.

The experiences reported in authors' opinion demonstrate that training in EES is not associated with significant worsening of prognosis or complication rates, at least if a staged training programme is followed. In our institution, roughly 9 years were required to reach the IAC starting from basic procedures, which we would consider an adequate amount of time. Faster training could be potentially less safe, in particularly for mastering lateral skull base approaches.

In the authors' opinion, cooperation of otolaryngologists and neurosurgeons during the whole period of learning is strongly advisable. Otolaryngologists would particularly benefit from cooperation with neurosurgeons when attempting endoscopic lateral skull base procedures (levels IV and V). On the contrary, in the first level (from I to III) the neurosurgeon would strongly benefit from the otolaryngologist in understanding middle ear anatomy, landmarks and knowledge of middle ear surgery instru-

mentation. Standardisation and adoption of a modular incremental training are expected to facilitate the improvement of both otolaryngologists and neurosurgeons starting with endoscopic middle ear and lateral skull base surgery.

Conclusions

Five stages of training are deemed appropriate for progressive learning of endoscopic ear and lateral skull base surgery, from simple middle ear procedures to surgery of inner ear and IAC. Mastering of each level is suggested before attempting procedures at a higher level, in particular for procedures involving the inner ear and lateral skull base. Standardisation and adoption of a modular incremental training are expected to facilitate improvement of otolaryngologists and neurosurgeons starting these types of surgeries.

References

- 1 Thomassin JM, Korchia D, Doris JM. *Endoscopic guided otosurgery in the prevention of residual cholesteatomas*. Laryngoscope 1993;103:939-43.
- 2 Presutti L, Marchioni D, Mattioli F, et al. *Endoscopic management of acquired cholesteatoma: our experience*. J Otolaryngol Head Neck Surg 2008;37:481-7.
- 3 Tarabichi M, Nogueira JF, Marchioni D, et al. *Transcanal endoscopic management of cholesteatoma*. Otolaryngol Clin North Am 2013;46:107-30.
- 4 Marchioni D, Alicandri-Ciuffelli M, Rubini A, et al. *Endoscopic transcanal corridors to lateral skull base: first experiences*. Laryngoscope 2015;125:1-13.
- 5 Presutti L, Alicandri-Ciuffelli M, Cigarini E, et al. *Choclear schwannoma removed through the external auditory canal by a transcanal exclusive endoscopic technique*. Laryngoscope 2013;123:2862-7.
- 6 Snyderman C, Kassam A, Carrau R, et al. *Acquisition of surgical skills for endonasal skull base surgery: a training program*. Laryngoscope 2007;117:699-705.
- 7 Marchioni D, Mattioli F, Alicandri-Ciuffelli M, et al. *Endoscopic approach to tensor fold in patients with limited attic cholesteatoma*. Acta Otolaryngol 2008;25:1-9.
- 8 Marchioni D, Mattioli F, Alicandri-Ciuffelli M, et al. *Transcanal endoscopic approach to the sinus timpani: a clinical report*. Otol Neurotol 2009;30:758-65.
- 9 Marchioni D, Alicandri-Ciuffelli M, Molteni G, et al. *Endoscopic tympanoplasty in patients with attic retraction pockets*. Laryngoscope 2010;120:1847-55.
- 10 Marchioni D, Villari D, Alicandri-Ciuffelli M, et al. *Endoscopic open technique in patients with middle ear cholesteatoma*. Eur Arch Otorhinolaryngol 2011;268:1557-63.
- 11 Marchioni D, Alicandri-Ciuffelli M, Molteni G, et al. *Ossicular chain preservation after exclusive endoscopic transcanal tympanoplasty: preliminary experience*. Otol Neurotol 2011;3:626-31.
- 12 Presutti L, Nogueira JF, Alicandri-Ciuffelli M, et al. *Beyond the middle ear: endoscopic surgical anatomy and approaches to inner ear and lateral skull base*. Otolaryngol Clin North Am 2013;46:189-200.
- 13 Presutti L, Alicandri-Ciuffelli M, Gioacchini FM, et al. *Combined lateral microscopic/endoscopic approaches to petrous apex lesions: pilot clinical experiences*. Ann Otol Rhinol Laryngol 2014;123:550-9.
- 14 Marchioni D, Alicandri-Ciuffelli M, Rubini A, et al. *Exclusive endoscopic transcanal transpromontorial approach: a new perspective for internal auditory canal vestibular schwannoma treatment*. J Neurosurg 2017;126:98-105.
- 15 Pothier DD. *Introducing endoscopic ear surgery into practice*. Otolaryngol Clin North Am 2013;46:245-55.
- 16 Kakehata S, Watanabe T, Ito T, et al. *Extension of indications for transcanal endoscopic ear surgery using an ultrasonic bone curette for cholesteatomas*. Otol Neurotol 2014;35:101-7.
- 17 Khan MM, Parab SR. *Endoscopic cartilage tympanoplasty: a two-handed technique using an endoscope holder*. Laryngoscope 2016;126:1893-8.
- 18 Badr-El-Dine M, James AL, Panetti G, et al. *Instrumentation and technologies in endoscopic ear surgery*. Otolaryngol Clin North Am 2013;46:211-25.
- 19 Chan JY, Leung I, Navarro-Alarcon D, et al. *Foot-controlled robotic-enabled endoscope holder for endoscopic sinus surgery: a cadaveric feasibility study*. Laryngoscope 2016;126:566-9.
- 20 Marchioni D, Alicandri-Ciuffelli M, Piccinini A, et al. *Surgical anatomy of transcanal endoscopic approach to the tympanic facial nerve*. Laryngoscope 2011;121:1565-73.
- 21 Marchioni D, Alicandri-Ciuffelli M, Nogueira JF, et al. *From external to internal auditory canal: surgical anatomy by an exclusive endoscopic approach*. Eur Arch Otorhinolaryngol 2013;270:1267-75.
- 22 Marchioni D, Alicandri-Ciuffelli M, Gioacchini FM, et al. *Transcanal endoscopic treatment of middle ear benign neoplasms*. Eur Arch Otorhinolaryngol 2013;270:2997-3004.
- 23 Marchioni D, Grammatica A, Alicandri-Ciuffelli M, et al. *Endoscopic cochlear implant procedure*. Eur Arch Otorhinolaryngol 2014;271:959-66.
- 24 Marchioni D, Soloperto D, Guarnaccia MC, et al. *Endoscopic assisted cochlear implants in ear malformations*. Eur Arch Otorhinolaryngol 2015;272:2643-52.
- 25 Marchioni D, Soloperto D, Rubini A, et al. *Endoscopic exclusive transcanal approach to the tympanic cavity cholesteatoma in pediatric patients: our experience*. Int J Pediatr Otorhinolaryngol 2015;79:316-22.
- 26 Marchioni D, Soloperto D, Villari D, et al. *Stapes malformations: the contribute of the endoscopy for diagnosis and surgery*. Eur Arch Otorhinolaryngol 2016;273:1723-9.
- 27 Anschuetz L, Bonali M, Ghirelli M, et al. *An ovine model for*

exclusive endoscopic ear surgery. J Otolaryngol Head Neck Surg 2017;143:247-52.

²⁸ Barber SR, Kozin ED, Dedmon M, et al. *3D-printed pediatric endoscopic ear surgery simulator for surgical training.* Int J Pediatr Otorhinolaryngol 2016;90:113-8.

²⁹ Presutti L, Gioacchini FM, Alicandri-Ciufelli M, et al. *Re-*

sults of endoscopic middle ear surgery for cholesteatoma treatment: a systematic review. ACTA Otorhinolaryngol Ital 2014;34:153-7.

³⁰ Alicandri-Ciufelli M, Marchioni D, Kakehata S, et al. *Endoscopic management of attic cholesteatoma, long term results.* Otolaryngol Clin N Am 2016;49:1265-70.

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MAXILLO FACIAL AND PLASTIC SURGERY

Retrospective epidemiological study of mandibular rotational types in patients with orthodontical malocclusion

Studio retrospettivo epidemiologico delle tipologie rotazionali mandibolari in pazienti con malocclusione

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SUMMARY

The primary aim of this study was to illustrate the prevalence of facial skeletal discrepancy in an Italian sample. Another aim was to evaluate the effectiveness of the sagittal skeletal discrepancy classification in order to establish a morphologic pattern of growth useful for diagnosis and prediction of therapeutic results. The authors considered a sample of 732 patients (426 females and 306 males) aged between 6 and 17 years old. Cephalometric parameters were evaluated in order to establish a relationship between sagittal skeletal discrepancy and the classification of facial rotations (Lavergne and Petrovic). Facial types with neutral mandibular growth direction were the most prevalent, and were most observed in classes I and II; the latter was more represented than others in our sample. Facial types with posterior mandibular growth direction were the most prevalent in class III. Sagittal skeletal discrepancy classification is not able to establish a specific facial type or predict an individual responsiveness to treatment.

KEY WORDS: Malocclusion classification • Growth rotation • Rotational type

RIASSUNTO

L'obiettivo principale di questo studio è stato quello di definire la prevalenza delle asimmetrie cranio-facciali nella popolazione italiana. Obiettivo secondario è stato quello di valutare l'efficacia della classificazione delle asimmetrie scheletriche sul piano sagittale al fine di stabilire il pattern morfologico di crescita, utile per la diagnosi e la previsione dei risultati terapeutici. Gli autori hanno analizzato retrospettivamente 732 pazienti (426 donne, 306 maschi), di età compresi tra 6 e 17 anni. Sono stati quindi effettuati i vari tracciati cefalometrici per stabilire i rapporti scheletrico sagittali e la classificazione delle rotazioni facciali sec Lavergne e Petrovic. Le tipologie con la più alta prevalenza sono risultate essere quelle con una direzione neutrale di crescita mandibolare. Tali tipologie sono state quelle più frequentemente osservate sia in classe I sia in classe II (la classe malocclusiva maggiormente rappresentata). In classe III, invece, è stata osservata la più alta prevalenza di tipologie facciali con direzione posteriore di crescita mandibolare. In conclusione la classificazione delle asimmetrie craniofacciali non è in grado di stabilire una specifica tipologia rotazionale e predire la risposta individuale al trattamento.

PAROLE CHIAVE: *Classificazione delle malocclusioni • Tipologie rotazionali*

Acta Otorhinolaryngol Ital 2018;38:160-165

Introduction

The diagnosis of skeletal class in an orthodontic patient is in close relationship with its definition and classification. Many studies have emphasised that it is not possible to diagnose a skeletal class, thus establishing a correct treatment plan by taking a single cephalometric measurement into account. The evaluation of different angles and linear measurements based on several reference planes might be

more accurate, but that is certainly a more complex evaluation method and requires difficult to learn analytical reasoning. The use of a flow chart can lead to classification, and thus to a skeletal diagnosis that takes into account several variables. In this way, a diagnostic guide is easier to learn and has lower error rate. In our epidemiological study, we considered a flow chart based on Petrovic et al.^{1,2} to classify the facial type of 732 patients and compared our data with the results of previous studies based

on cephalometric measurements. The Strasbourg school system (Petrovic, Lavergne, Gasson and Stutzmann)^{3,4}, derived from the concepts of Hasund's facial floating norms⁵, combines patients into 11 rotational types and 33 rotational groups, if vertical dimension is taken into account. The facial growth rotational groups are predictors of potential growth and individual responsiveness to treatment.

The aim of this study was to evaluate relationships between classification of skeletal discrepancy based only on sagittal measures and classification of Facial Rotational types.

Materials and methods

A total of 732 (426 female and 306 Male) patients of the Orthodontics Department of Catholic University of Rome were enrolled in the study. We used the following inclusion criteria: age between 6 and 17 years old; absence of systemic diseases; absence of malformations; no previous orthodontic or orthopaedic treatment.

For each patient, the following cephalometric measurements were considered:

- SNA, angle between the nasion-sella line and nasion-point A line;
- SNB, angle between the nasion-sella line and nasion-point B line;
- ANB, angle between the nasion-point A line and nasion-point B line, values between 1 and 4 have been associated to the I skeletal class, the values > 4 to II class and values < 1 to the III class;
- ML/NSL, angle between the nasion-sella line and the mandibular plane (line passing through the gnathion tangent to the gonial angle);
- NL/NSL, angle between the nasion-sella line and the nasal line (anterior nasal spine to posterior nasal spine).

For calculation of rotational types, in addition to measurements performed on cephalometric tracings, the expected values of ML/NSL and NL/NSL were calculated by employing the following mathematical formulas:

- ML/NSL expected = $192 - 2(SNB)$;
- NL/NSL expected = $(ML / NSL) / 2 - 7$.

Using these angles, we calculated the values, through which it was possible to identify the rotational growth type of the patient on the diagram prepared by Petrovic¹². 11 rotational types can be distinguished and designated by trinomial label. In each label, the three successive symbols represent:

- growth rotation - P (posterior), R (neutral), A (anterior);
- potential difference in growth between the mandible and maxilla - 1 (no difference), 2 (greater potential growth for maxillary bone) or 3 (greater potential growth for the mandible);

• sagittal interjaw relationship - D (distal), N (normal), M (mesial).

Additionally, each rotational type is subdivided according to the vertical dimension (OB for open bite, N for normal bite, DB for deep bite) in 33 rotational groups.

Petrovic and Stutzmann^{6,7} classified the data relating to the index of tissue growth into 6 auxologic categories corresponding to a mitotic mandibular index progressively increasing from 1 to 6 and identified a connection between the 6 growth categories and specific rotational types (Table I).

Method error

The assessment of methodological error for the cephalometric measurements was performed on 40 cephalograms that were randomly selected from the total of the observations using Dahlberg's formula⁸. The error for all measurements was less than 1.

Results

The study included 732 patients (58% female) with a mean age of 9 years (Fig. 1). In this sample of orthodontic patients, skeletal class II, indicated by ANB angle value, was the most represented (52%), followed by class I (33%) and class III (15%) (Fig. 2).

Figure 3 shows the prevalence of rotational types in our sample, where the most represented is the R1N 4th category (20%), followed by R2D 3th category (17%), A1N (15%), P1N and A1D (13%).

We compared sagittal skeletal class, indicated by the value of ANB, to the facial rotational types.

The results were (Fig. 4):

- In skeletal class I the most frequent rotational type was R1N (35%) followed by A1N (27%) and P1N (22%). So these three types represented 84% of skeletal class I sub-group.

Table I. Relationship between growth category and rotational type.

Growth category (Growth potential)	Rotational type
1	P2D
2	A2D; P1N
3	R2D
4	R1N
5	A1D; A1N; P1M; R3M
6	A3M; P3M

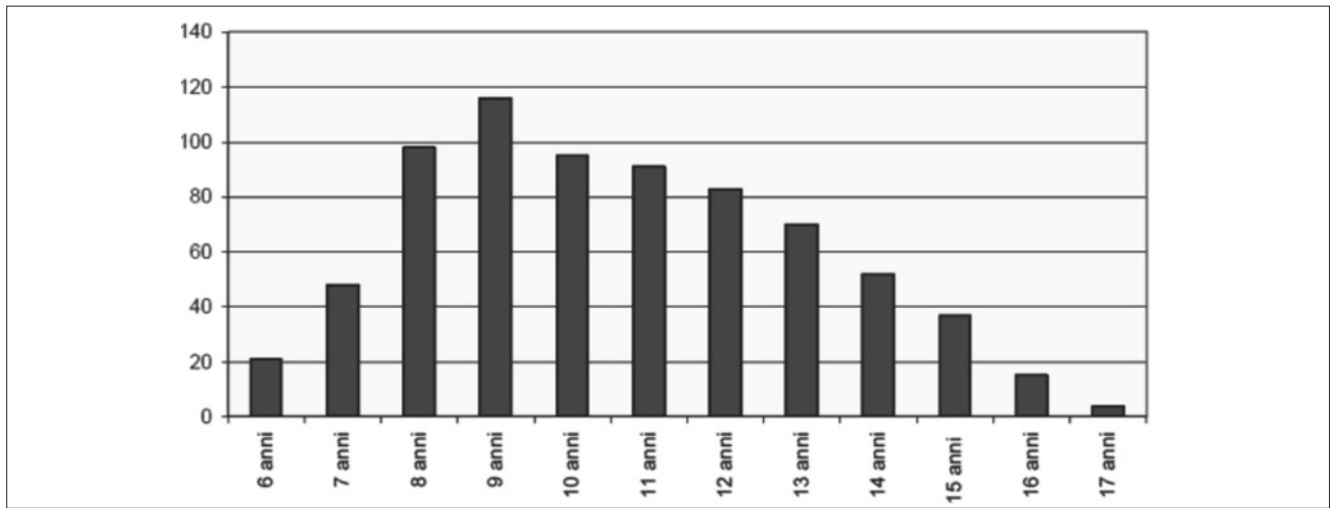


Fig. 1. Age distribution of the sample.

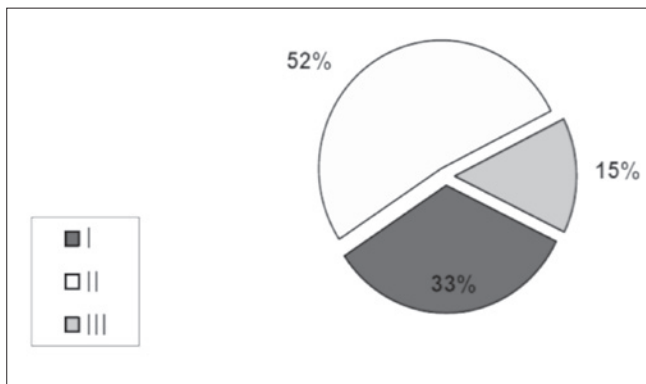


Fig. 2. Skeleton classes based on ANB calculation.

- In skeletal class II the most frequent rotational type was R2D (30%) followed by A1D (25%) and P2D (13%). These three types represented 68% of skeletal class II subgroup. Types A1N and R1N represented 21% of skeletal class II.
- In skeletal class III the most frequent rotational type was P1M (28%) followed by P1N (25%) and R3M (19%). These three types represented 72% skeletal class III subgroup. Types A1N and R1N represented 20% of skeletal class III.

Growth neutral rotation was seen in 40% of the sample, and the anterior rotation in 34% and the posterior rotation in 25.5%, and thus data are consistent with those reported

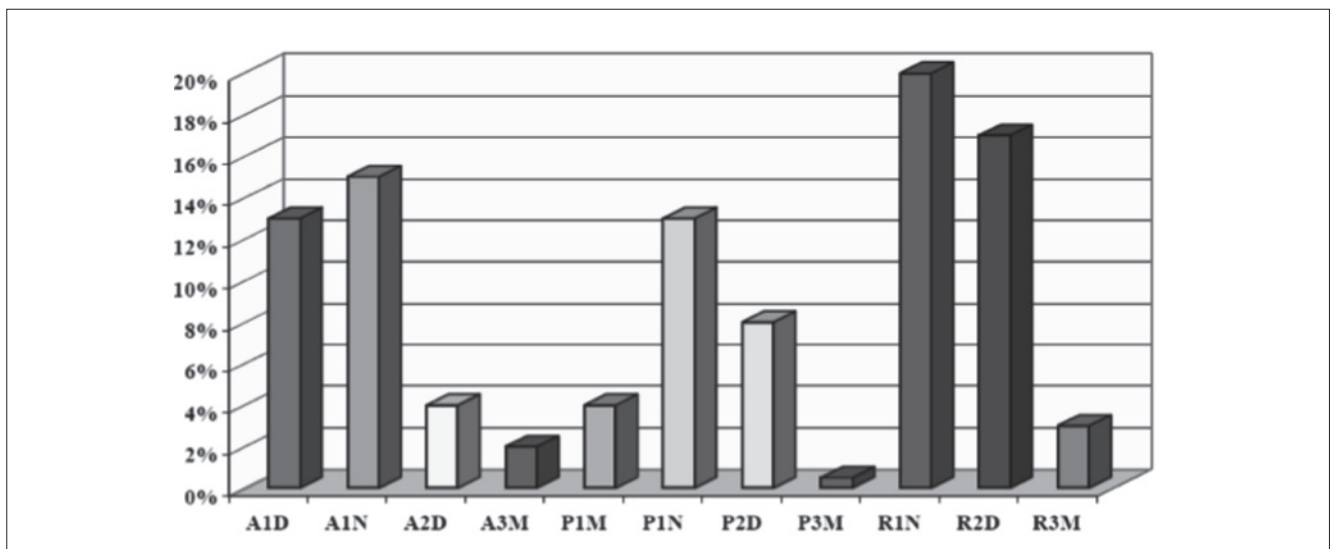


Fig. 3. Rotational types in the sample.

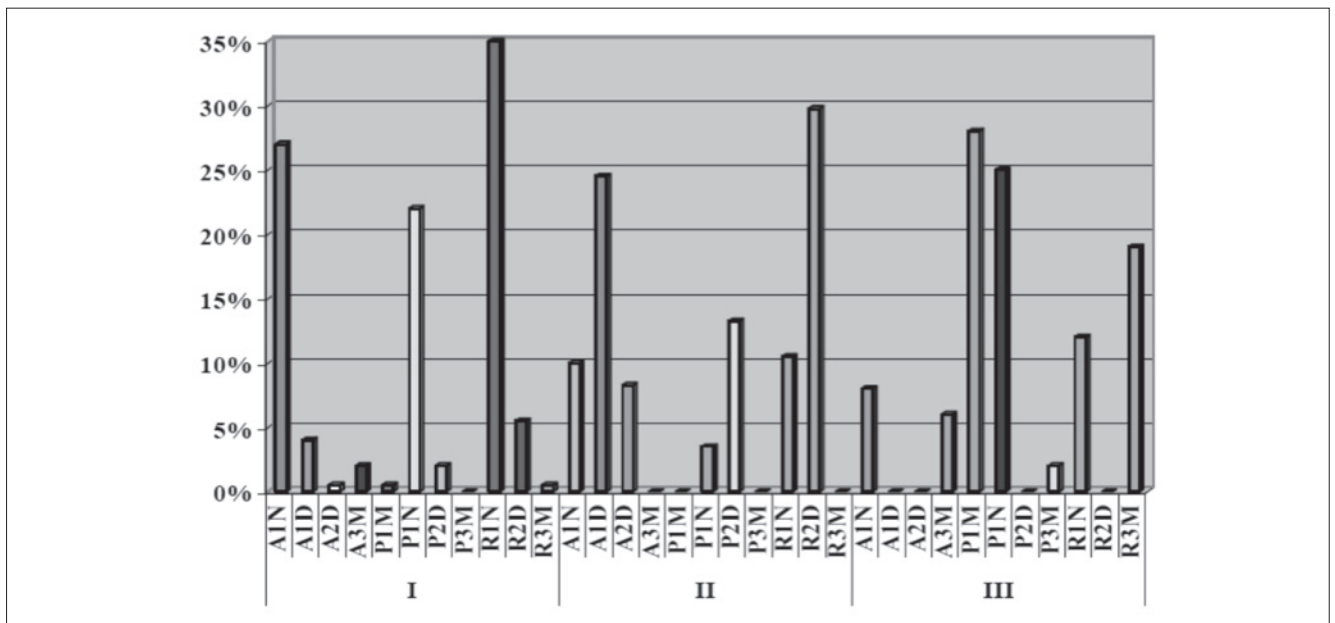


Fig. 4. Association between rotational types and skeleton classes.

by Lavergne and Petrovic (Neutral 39.5%, anterior 35%, posterior 25.5%).

About 75% of patients showed a neutral or anterior rotational type. This patient population was classified as high growth category and was mainly grouped into skeletal classes I and II.

Discussion

Each type of mandibular growth category may include multiple rotational types as shown in Table I: for example, the 5th category includes rotational types A1D, A1N, P1M and R3M.

The Strasburg's school linked cephalometric architectural changes with a mitotic cellular index of patients belonging to each type, anticipating Rabie's theory^{9,10} and showed that there is an individual variation in natural or induced by mechanical stimuli cellular proliferation.

Skeletal class I of our sample was almost completely represented by the types R1N cat.4, A1N cat.5 and P1N cat.2 (84%) where the growth of the jaws was harmonic and in position normal. It is interesting to note that 10% of skeletal class I was represented by R2D and A1D types. These rotational types have distal inter-maxillary relationships, but normal ANB values.

In skeletal class II, sample data showed that 22% was composed of cases with normal jaw relationship and high growth category (R1N and A1N) even though these rotational types belong most frequently to skeletal class I without differen-

tial growth of the jaws; 25% of skeletal class II was rotational type A1D where the mandible position is more posterior. Petrovic et al.³ in their studies of mitotic index showed that these patients had good potential growth. These findings are supported by several clinical studies¹¹⁻¹³. A further 30% had a rotational type R2D, in which there is a differential potential growth and a distal position of the jaw, but the vertical neutrality makes this subgroup able to favorably respond to the therapy, if it is properly planned and conducted. The remaining 25% was represented by rotational types in which growth is not favourable for a resolution of class II (Petrovic et al.^{3,11-13}). These findings are in agreement with the results of other studies that have evaluated the effect of orthodontic treatment on class II malocclusion.

O'Brien et al.¹⁴, in a randomised clinical trial (RCT) on the effectiveness of orthodontic treatment with Twin-Block appliance of class II malocclusion selected by presence of a minimum 7 mm overjet, reported that, although the Twinblock appliance appears to produce some skeletal changes, a substantial amount of this change was due to other factors. In conclusion, the author sustained that there is individual variation in growth that is not influenced by orthodontic "growth modification" treatment. Another study written by Tulloch et al.¹⁵ evaluated the increase in mandibular length and reported that 25% of the patients in control group had an additional growth of the mandible. Both RCTs, reported above, suggested that about 25% of the sample of class II malocclusion would have a significant increase of mandibular growth, and

this increase might depend for an individual variations in growth.

22% of the skeletal class II sample in our study was rotational type A1N and R1N. These patients would respond to the therapy with a greater increase of skeletal growth, because of normal growth and normal jaw relationship. Comparing this data with those of the above studies, we hypothesise that individual growth factors can be identified by calculation of rotational type.

In a recent systematic review, Cozza et al.¹⁶, analysed mandibular changes produced by functional appliances in class II malocclusion. They reported clinically significant supplementary elongation in total mandibular length for two-thirds of the sample in the treated group compared with untreated group. In our sample of class II malocclusion, 75% was represented by rotational types (A1N, R1N, A1D, R2D), which belong to categories responding favourably to treatment. These findings are comparable to those of Cozza et al.

In our study, 49% of skeletal class III subgroup (diagnosed by ANB angle) was represented by rotational types (P1M, R3M, P3M), which belong to high growth category (5 and 6). The 6% of the sample was A3M rotational type, 6th growth category, with mandibular growth in ante-rotation. The remaining sample was represented for 20% by rotational types A1N and R1N that usually belong to skeletal class I and for 25% by P1N, which belong to low growth category, although its verticality may cause therapeutic failures. A recent study by Cozza et al.¹⁷ evaluated the treatment and post-treatment effects of an orthopaedic protocol for class III malocclusion. Both treated group and control groups showed normal values of mandibular growth (respectively 3 mm and 6 mm) in about 20% of cases, hence both dental and skeletal therapeutic results could be achieved.

Conclusions

This study emphasises the need to classify skeletal classes in different ways than with ANB value. Rotational type classification leads to select more homogeneous groups that is able to reduce variability in the response to the same treatment protocol.

All studies reported above indicate the need to identify additional factors that can help to predict craniofacial growth. In fact, sagittal skeletal discrepancy classification is not able to establish a specific facial type or predict individual responsiveness to treatment.

This epidemiological study suggests that the rotational types that classify patients by several factors could be a reliable model of prediction facial growth. More clinical

studies are needed to confirm the efficacy of treatment protocols in patients selected by criteria indicative of growth patterns.

References

- Petrovic A, Lavergne J, Stutzmann J. *Diagnosis and treatment in orthodontics: principles and decision diagrams*. Orthod Fr 1987;58 Pt 2:517-42.
- Petrovic A. *Auxologic categorization and chronobiologic specification for the choices of appropriate orthodontic treatment-heritage paper*. Am J Orthod Dentofac Orthop 1994;105:192-205.
- Petrovic A, Lavergne J, Stutzmann J. *Tissue-level growth and responsiveness potential, growth rotation, and treatment decision (181-223)*. In: Vig PS, Ribbens KA. *Science and clinical judgement in orthodontics*. Monograph 19, Cranio-Facial Growth Series. Michigan, USA: Ann. Arbor, Center for Human Growth and Development, University of Michigan; 1986. p. 249.
- Petrovic A, Stutzmann J. *Further investigations into the functioning of the "comparator" of the servosystem (respective positions of the upper and lower dental arches) in the control of the condylar cartilage growth rate and of the lengthening of the jaw (255-291)*. In: *The biology of occlusal development*. Monograph 6, Cranio-Facial Growth Series. Michigan, USA: Ann. Arbor, Center for Human Growth and Development, University of Michigan; 1977. p. 331.
- Hasund A, Böe OE. *Floating norms as guidance for the position of the lower incisors*. Angle Orthod 1980;50:165-8.
- Petrovic A, Stutzmann J, Lavergne J. *Mechanisms of craniofacial growth and modus operandi of functional appliances: a cell-level and cybernetic approach to orthodontic decision making (13-73)*. Monograph 23, Cranio-Facial Growth Series. Michigan, USA: Ann. Arbor, Center for Human Growth and Development, University of Michigan; 1990. p. 232.
- Petrovic A, Stutzmann J. *The concept of the mandibular tissue-level growth potential and the responsiveness to a functional appliance (59-74)*. In: Graber Lee W. *Orthodontics: state of the art, essence of the science*. St Louis: CV Mosby; 1986. p. 421.
- Dahlberg G. *Statistical methods for medical and biological students*. New York, NY: Interscience Publications; 1940.
- Rabie AB, She TT, Harley VR. *Forward mandibular positioning up-regulates SOX9 and type II collagen expression in the glenoid fossa*. J Dent Res 2003;82:725-30.
- Rabie AB, Wong L, Hägg U. *Correlation of replicating cells and osteogenesis in the glenoid fossa during stepwise advancement*. Am J Orthod Dentofacial Orthop 2003;123:521-6.
- Petrovic A, Stutzmann J, Lavergne J, et al. *Is it possible to modulate the growth of the human mandible with a functional appliance? Bilt Udruz Orthodonata Jugosl* 1988;21:15-20.
- Petrovic A, Stutzmann J, Lavergne J. *Effect of the functional appliances on the mandibular condylar cartilage (38-52)*. In:

- Graber TM. *Physiologic principles of functional appliances*. St Louis: CV Mosby; 1985. p. 86.
- ¹³ Petrovic A, Stutzmann J, Lavergne J. *Mechanisms of cranio-facial growth and modus operandi of functional appliances: a cell-level and cybernetic approach to orthodontic decision making (13-73)*. Monograph 23, Cranio-Facial Growth Series. Michigan, USA: Ann. Arbor, Center for Human Growth and Development, University of Michigan; 1990. p. 232.
- ¹⁴ O'Brien KD, Wright J, Conboy F, et al. *Effectiveness of early orthodontic treatment with the Twin-block appliance: a multi-center, randomized controlled trial. Part 1: Dental and skeletal effects*. Am J Orthod Dentofacial Orthop 2003;124:234-43.
- ¹⁵ Tulloch JFC, Philips C, Proffit WR. *Benefit of early Class II treatment: Progress report of a two-phased randomized clinical trial*. Am J Orthod Dentofacial Orthop 1998;113:62-72.
- ¹⁶ Cozza P, Baccetti T, Franchi L, et al. *Mandibular changes produced by functional appliances in Class II malocclusion: A systematic review*. Am J Orthod Dentofacial Orthop 2006;129:599.
- ¹⁷ Cozza P, Baccetti T, Mucedero M, et al. *Treatment and post-treatment effects of facial mask combined with a bite-block appliance in Class III malocclusion*. Am J Orthod Dentofacial Orthop 2010;138:300-10.

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CASE SERIES AND REPORTS

Eagle's Syndrome, from clinical presentation to diagnosis and surgical treatment: a case report

Sindrome di Eagle: aspetti clinici, diagnostici e trattamento chirurgico

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SUMMARY

Eagle's syndrome is a condition associated with the elongation of the styloid process or calcification of the stylohyoid ligament, clinically characterised by throat and neck pain, radiating into the ear. In this report, we describe the case of a 60-year-old woman who presented with a severe unilateral trigeminal and glossopharyngeal neuralgia. The patient was subjected to conservative therapy for four months and did not report improvement of the symptoms. After several consultations with different physicians, a diagnosis was accomplished by radiological investigation (multidetector computer tomography with multi-planar reconstructions and 3D volumetric reconstructions). Surgical styloidectomy was performed, with subsequent sudden remission of symptoms. Eagle's syndrome represents a commonly unrecognised nosological entity, clinically characterised by non-specific cranio-facial pain. Differential diagnosis includes glossopharyngeal and trigeminal neuralgia, temporal arteritis, migraine, myofascial pain dysfunction and cervical arthritis. Eagle's syndrome should always be suspected, mostly in adult women when the pain is unilateral and not responsive to painkillers.

KEY WORDS: Eagle's syndrome • Elongation of the stylohyoid process • Oropharyngeal pain • Glossopharyngeal neuralgia

RIASSUNTO

La sindrome di Eagle è caratterizzata dall'allungamento del processo stilo-ioideo e/o dalla progressiva calcificazione del legamento stilo-ioideo. Il reperto è molto diffuso nella popolazione generale ma tale sindrome appare sintomatica solo in una piccola percentuale di casi. I sintomi sono rappresentati da: dolore ricorrente di tipo "trafittivo" riferito alla gola, regione antero-laterale del collo e orecchio, disfagia e sensazione di corpo estraneo in faringe. Riportiamo il caso clinico di una donna di 60 anni giunta alla nostra attenzione per dolore monolaterale sinistro, comparso da circa un mese, di tipo nevralgico, irradiato inizialmente solo lungo la branca mandibolare del nervo trigemino (nevralgia trigeminale) e successivamente alla regione laterocervicale omolaterale (nevralgia glossofaringea). La paziente era stata precedentemente valutata da numerosi specialisti e sottoposta per 4 mesi a terapia conservativa senza beneficio. La diagnosi è stata raggiunta mediante esami radiologici (Tomografia Computerizzata Multidetettore con ricostruzioni multiplanari e volumetriche 3D). È stata eseguita una stiloidectomia per via trans-cervicale, con successiva remissione dei sintomi. La sindrome di Eagle rappresenta un'entità nosologica comunemente misconosciuta, caratterizzata clinicamente da dolore cranio-facciale aspecifico. La diagnosi differenziale include la nevralgia del trigemino e glossofaringeo, l'arterite temporale, l'emicrania, il dolore miofasciale e l'artrosi cervicale. La sindrome di Eagle dovrebbe essere sempre sospettata, soprattutto nelle pazienti donne adulte e quando il dolore è unilaterale e non risponde agli antidolorifici.

PAROLE CHIAVE: Sindrome di Eagle • Processo stiloideo allungato • Dolore orofaringeo • Nevralgia del glossofaringeo

Acta Otorhinolaryngol Ital 2018;38:166-169

Introduction

Eagle's syndrome, defined by Eagle in 1949, is characterised by morphological abnormality/ossification of the styloid process¹. The average length of the styloid process is 20-30 mm in the adult Caucasians and 15.4-18.8 mm in the Asian population. An elongated styloid process is defined by being at least 30 mm long^{2,3}. The clinical picture is composed of recurrent throat and neck pain, radiating into the ear and dysphagia. Symptoms can be bilateral or, more frequently, unilateral. The incidence is 4-8 per 10,000 people^{1,4}.

The aetiology is not well defined and a number of theories have been suggested, such as congenital elongation due to the persistence of an embryonic cartilaginous outgrowth, calcification of the stylohyoid ligament and formation of bone tissue at the insertion of the ligament. This clinical picture might also be seen in patients after tonsillectomy⁵. We describe the case of a 60-year-old woman who presented with left neuralgic pain, lasting for about a month, localised in the throat and neck and radiating into the ear.

Case report

A 60-year-old woman presented with left neuralgic pain, lasting about a month, radiating at the first to the mandibular branch of the trigeminal nerve (trigeminal neuralgia) and later to the ipsilateral throat, tonsil, back of the tongue and ear (glossopharyngeal neuralgia).

An initial dental evaluation only showed a cavity on 38 so the dentist decided to extract the decayed tooth. However, despite the extraction, the pain still persisted and she decided to consult a gnathologist who prescribed painkillers. The patient was subjected for four months to conservative therapy consisting of 8% lidocaine spray on the oropharyngeal region corresponding to the tonsillar branches of the glossopharyngeal nerve, corticosteroids and NSAIDs *per os*. The patient, however, did not report improvement of symptoms, which worsened over time.

The patient described the pain as "stabbing" and not responding to painkillers. The sharp pain had the frequency of 10-20 episodes per hour and was less intense only in bed. It was exacerbated by yawning and crying. It was directed from the left side of the face towards the nose and throat, leaving a burning sensation, even after resolution. After several consultations with different physicians (physiotherapist, osteopath, neurologist, otolaryngologist), the patient was prescribed a more accurate radiologic investigation.

A panoramic X-Ray excluded osteo-dental alterations, and through CT scan expansive and osteolytic changes of the skull base were ruled out. Detailed MRI study of trigeminal ganglion was accomplished and no abnormalities were found. All these exams showed no pathological alterations on the oral cavity, oro-hypopharynx, larynx, soft tissues of the neck and temporal bones. However, radiologic attention was focused on the left stylo-mastoid process.

Multidetector computer tomography (MDTC) with multi-planar reconstructions (MPR) and 3D volumetric reconstructions (3D-VR) (Fig. 1) documented asymmetry of the stylo-hyoid process length, which was 27 mm from the right side and 30 mm from the left side. MDTC study of the bone allowed observing the extended length of the left stylohyoid process compared to the contralateral side (Fig. 2), allowing formulation of a hypothesis of Eagle's syndrome. Figure 3 shows shows the pre-operative comparison between sagittal views obtained by MDTC with 3D-VR and 2D-MPR.

As the symptoms intensified, the patient was urgently subjected to surgery: surgical resection of the left stylo-mastoid process, via a transcervical approach and under general anaesthesia was performed. Figures 4 and 5 show post-operative MDTC with 3D-VR and 2D-MPR, demonstrating a surgically amputated left styloid process.

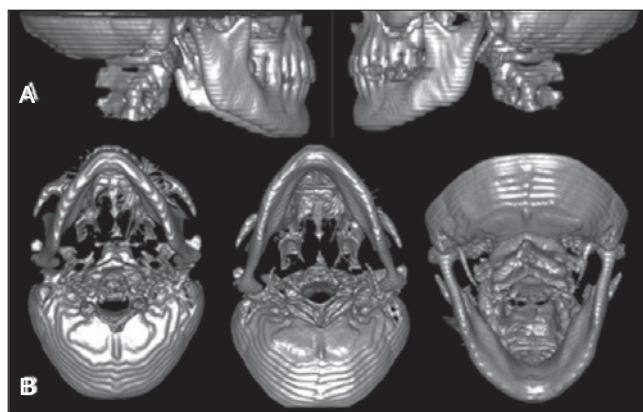


Fig. 1. Pre-operative 64-channel MDCT with multi-planar reconstructions (MPR) and 3D volumetric reconstructions (3D-VR) allowing to enhance the stylo-mastoid processes in the lateral (A) and craniocaudal (B) view.

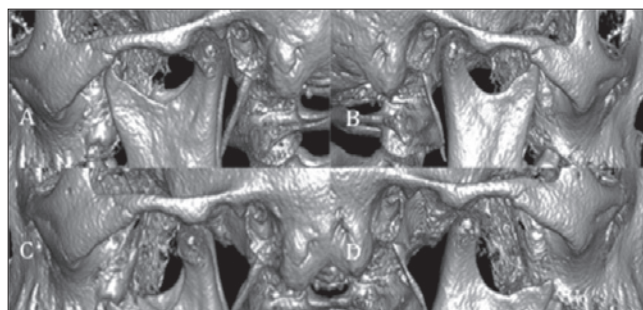


Fig. 2. pre-operative 64-channel MDCT with multi-planar reconstructions (MPR) and 3D volumetric reconstructions (3D-VR). Left- (A) and right-sided view (B) of the temporomandibular joint (closed mouth). Left- (C) and right-sided view (D) of the temporomandibular joint (open mouth).

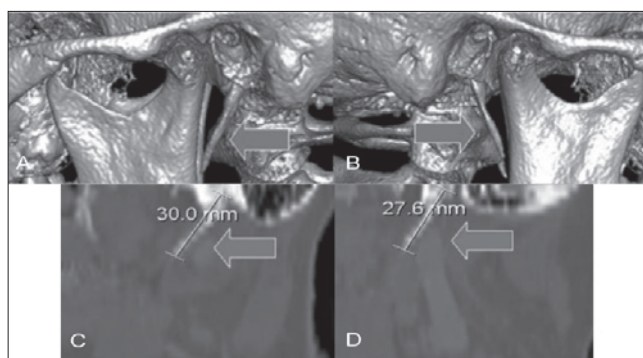


Fig. 3. Pre-operative comparison between MDCT with 3D VR sagittal views (A: left; B: right) and 2D MPR sagittal views (C: left; D: right).

After surgery the patient did not complain of any of the previously described symptoms, she did not need anti-inflammatory drugs and regained a normal quality of life.

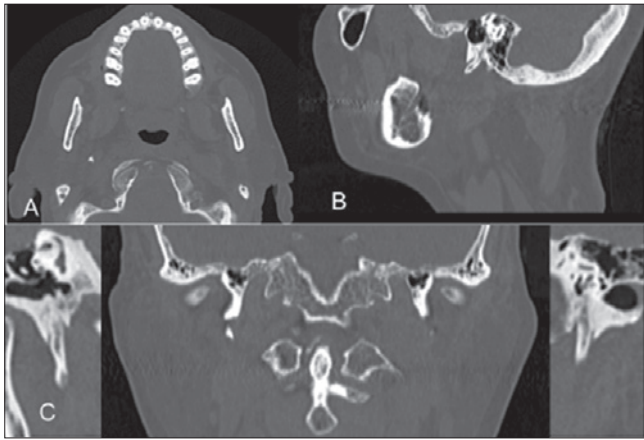


Fig. 4. Post-operative MDCT; A) axial view; B) sagittal view; C) coronal view showing comparison between normal right styloid process and surgically amputated left styloid process.

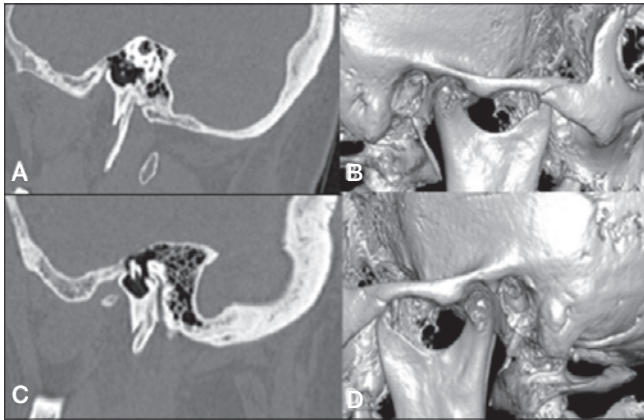


Fig. 5. Post-operative comparison between MDCT with 2D MPR sagittal views (A: right; C: left) and 3D VR sagittal views (B: right; D: left).

Discussion

Eagle's syndrome is related to the presence of an abnormally elongated styloid process with/without aberrant direction and/or ossificated styloid ligament. Cranio-facial pain resembles glossopharyngeal neuralgia and it is secondary to the irritation of the surrounding neurovascular and muscular anatomical structures (carotid artery, cranial nerves and muscles). It has been hypothesised that the pain deriving from the elongated styloid process may be due to compression of the glossopharyngeal nerve as it passes over the superior constrictor muscle. Rare cases of internal carotid artery compression/kinking have been described⁵. The styloid process may also compress the sympathetic nerve fibres, causing Horner syndrome⁶. The differential diagnosis should include glossopharyngeal and trigeminal neuralgia, temporal arteritis, migraine,

cluster headache, myofascial pain dysfunction syndrome, pain related to un-erupted third molars, cervical arthritis, tumours and ill-fitting or missing dentures^{7,8}.

The condition is more common in women and in patients older than 50 years. Mixed, non-specific symptoms, the absence of a clear aetiological link and the scant knowledge about this clinical entity often delay diagnosis, as described by our experience. Physical examination and clinical history are useful diagnostic tools. An elongated styloid process may be palpated during intraoral examination and may provoke the pain. Correct indication to radiological investigation, dedicated technology and experience are needed in order to reach a diagnosis. Although plain skull radiographs might be sufficient to reveal the anatomical abnormality, CT of the head/neck and especially 3D-CT scan is considered as the gold standard for visualisation of the anatomically complex styloid process, as it avoids the problems of obscured overlapping anatomy. Moreover, it underlines the styloid process angulation, which is crucial for the surrounding anatomical relationships. Some controversy exists in the literature as to how many patients with an elongated styloid apophysis, at radiologic examination, do not exhibit any clinical symptoms⁹. However, the surgical approach in patients with a diagnosis of Eagle's syndrome is quite conclusive: surgical styloidectomy has, in fact, a cure rate of 80%.

Conclusions

Eagle's syndrome should always be suspected when idiopathic unilateral pain occurs, especially in adult women and when the pain is not responsive to painkillers. In addition, the exacerbation of the pain by swallowing, yawning and crying, as in our patient, should help in diagnosis. Patients often seek assistance by many clinicians, which is related to the non-specificity of symptoms, with poor success. Multidisciplinary approach, early indication to radiological investigation, especially MDCT of the styloid process is advisable in such cases. The elongation of the styloid process is a relatively common condition, although not all the affected patients complain of symptoms. When occurring, the diagnostic workup may be critical, since throat and neck pain, mild dysphagia and foreign body sensation in the pharynx are misleading symptoms. Otolaryngologists, neurologists and dental surgeons should be aware of the existence and incidence of this clinical entity, which is associated with a critical decay in the quality of life.

References

- 1 Kawasaki M, Hatashima S, Matsuda T. *Non-surgical therapy for bilateral glossopharyngeal neuralgia caused by Eagle's*

- syndrome, diagnosed by three-dimensional computed tomography: a case report.* J Anesth 2012;26:918-21.
- ² Ceylan A, Köybaşıoğlu A, Çelenk F et al. *Surgical treatment of elongated styloid process: experience of 61 cases.* Skull Base 2008;18:289-95.
 - ³ Raina D, Gothi R, Rajan S. *Eagle syndrome.* Indian J Radiol Imaging 2009;19:107-8.
 - ⁴ Baddour HM, Mc Anear Jt, Tilson AB. *Eagles syndrome report of case.* J Oral Surg 1978; 36:486.
 - ⁵ Radak D, Tanaskovic S, Kecmanovic V, et al. *Bilateral Eagle syndrome with associated internal carotid artery kinking and significant stenosis.* Ann Vasc Surg 2016;34:15-8.
 - ⁶ Chang CA, Lin T, Fung K, et al. *Isolated Horner Syndrome from an elongated styloid process (Eagle syndrome).* J Neuroophthalmol 2015;35:387-9.
 - ⁷ Santos Tde S, Vajgel A, Camargo IB, et al. *Clinical-radiographic analysis of Eagle syndrome.* J Craniofac Surg 2014;25:1578-9.
 - ⁸ Costantinides F, Vidoni G, Tonni I, et al. *Orofacial pain induced by Eagle syndrome in an elderly patient with temporomandibular disorders - a case report.* Gerodontology 2016;33:428-31.
 - ⁹ Kent DT, Rath TJ, Snyderman C. *Conventional and 3-dimensional computerized tomography in Eagle's syndrome, glossopharyngeal neuralgia, and asymptomatic controls.* Otolaryngol Head Neck Surg 2015;153:41-7.

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CASE SERIES AND REPORTS

Transtracheal endoscopic-assisted resection of a rare inflammatory myofibroblastic tumour in adult trachea: a case report

Resezione transtracheale endoscopio-assistita di un raro tumore miofibroblastico infiammatorio della trachea di un paziente adulto: case report

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SUMMARY

Inflammatory myofibroblastic tumours (IMTs) are rare and clinically benign in childhood, and malignant in adults. The aetiology of IMTs is not clear, and recent studies report it as true neoplasm rather than a reactive or inflammatory lesion. IMTs can involve any part of the body, but are usually common in lungs. These are rarely seen in adults and tracheal involvement is also rare in both adults and children. We describe an 18-year-old woman who presented with respiratory difficulty to the emergency department. On clinical examination, the patient had complete absence of breath sounds on the right side of the chest. CT of the chest and virtual bronchoscopy revealed a polypoidal soft tissue mass lesion involving the carina with occlusion of right main bronchus. Endoscopic-assisted resection was performed under general anaesthesia and the final pathological diagnosis was tracheal IMT.

KEY WORDS: Strider • Inflammatory myofibroblastic tumour • Trachea • Bronchus • Spindle cell proliferation

RIASSUNTO

I tumori miofibroblastici infiammatori sono rari in età pediatrica, età nella quale sono clinicamente benigni; sono invece maligni in età adulta. L'eziologia non è chiara, recenti studi affermano che essi siano delle vere neoplasie piuttosto che delle lesioni reattive o infiammatorie. I tumori miofibroblastici infiammatori sono raramente riscontrati negli adulti e il coinvolgimento tracheale è raro sia nei bambini sia negli adulti. Noi descriviamo il caso di una paziente di sesso femminile di diciotto anni, che si è presentata al pronto soccorso per difficoltà respiratoria. All'esame clinico della paziente si evidenziava assenza dei suoni polmonari a destra, pertanto si eseguiva TC del torace e la broncoscopia virtuale rivelava una lesione polipoide soffice che coinvolgeva la carena occludendo completamente il bronco principale di destra. La resezione endoscopio-assistita è stata eseguita in anestesia generale e all'esame istopatologico definitivo la diagnosi è stata di tumore miofibroblastico infiammatorio.

PAROLE CHIAVE: Stridor • Tumore miofibroblastico infiammatorio • Trachea • Bronco • Proliferazione a cellule fusate

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Introduction

Inflammatory myofibroblastic tumours (IMT) are rare tumours, commonly seen in children less than 16 years of age and with frequency of 0.04-0.07% of all respiratory tract tumours¹⁻⁶. The World Health Organization defines it as a lesion consisting of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes and eosinophils^{1,2,5,6}. The aetiology of the disease is still not clear². Tracheal IMTs are rarely reported in adults

who are malignant and benign in children^{1,2}. In 1939, the first case of IMT was reported in the lungs⁴. A wide variety of names has been applied to IMTs which are mentioned in Table I^{1-4,6-8}. Because of its rarity, we report the case of 18-year-old woman with an IMT in the trachea.

Case report

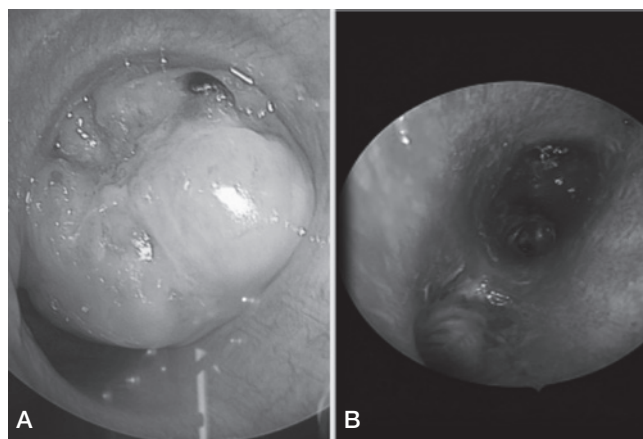
An 18-year-old woman reported to the emergency depart-

Table 1. Other names of inflammatory myofibroblastic tumour.

Inflammatory pseudotumour
Plasma cell granuloma (heart)
Inflammatory myofibrohistiocytic proliferation
Histiocytoma
Xanthoma
Fibro-xanthoma
Xanthogranuloma
Fibrous xanthoma
Xanthomatous pseudotumour
Plasma cell-histiocytoma complex (lung)
Plasmocytoma
Solitary mast cell granuloma
Inflammatory fibrosarcoma (bladder)

ment with difficulty in breathing since four months with insidious onset. The patient had significant loss of weight and there was no history of wheezes, chest pain, haemoptysis, or fever. On examination, the patient was thin with stable vitals and complete absence of breath sounds on right side of chest. Patient was subjected to CT of chest and neck and virtual bronchoscopy revealed a polypoidal soft tissue mass lesion involving the carina with occlusion of right main bronchus causing collapse of the right lung with crowding of right sided ribs and ipsilateral mediastinal shift (Fig. 1). The senior author (SA) performed rigid bronchoscopic examination under general anaesthesia to confirm the above findings and simultaneously the woman was admitted for surgery (Fig. 2 a).

Under jet ventilation general anaesthesia the supine position, anterior tracheotomy was performed and the trachea was transposed anteriorly by using 1-0 prolene suture. Through the tracheotomy a 4 mm 0° rigid endoscope was passed and the tumour mass removed with insulated instruments (Fig. 2 b). The tracheotomy opening was closed with 1-0 vicryl suture and the incision was closed in lay-

**Fig. 2.** (A) Endoscopic-assisted bronchoscopy showing the tracheal tumour occluding the right main bronchus. (B) After tumour removal.

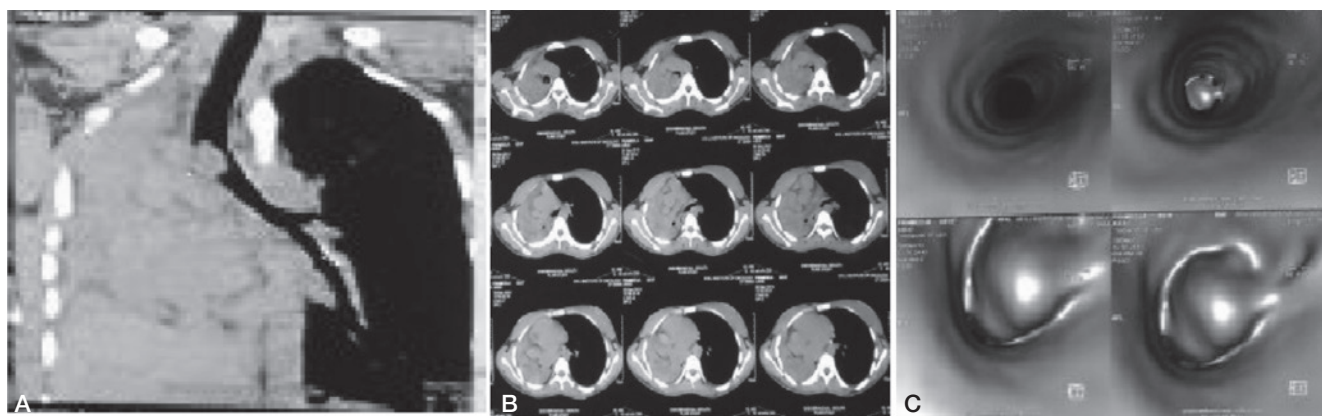
ers. The mass sent for histopathological examination, which was suggestive of inflammatory myofibroblastic tumour of the trachea (Fig. 4).

The patient was given tapering doses of corticosteroid postoperatively for 10 days and to date we are following the case without recurrence.

Discussion

IMTs are rare tumours, commonly seen in children less than 16 years of age and with a frequency of 0.04-0.07% among all the respiratory tract tumours¹⁻⁶. The World Health Organization defines it as a lesion consisting of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes and eosinophils^{1,2,5,6}. Adult IMTs occurring in the trachea are malignant^{1,2}.

A variety of names are applied for IMTs as mentioned in

**Fig. 1.** (A) and (B) CT of chest images. (C) Virtual bronchoscopy image showing a polypoidal mass obscuring the right main bronchus.

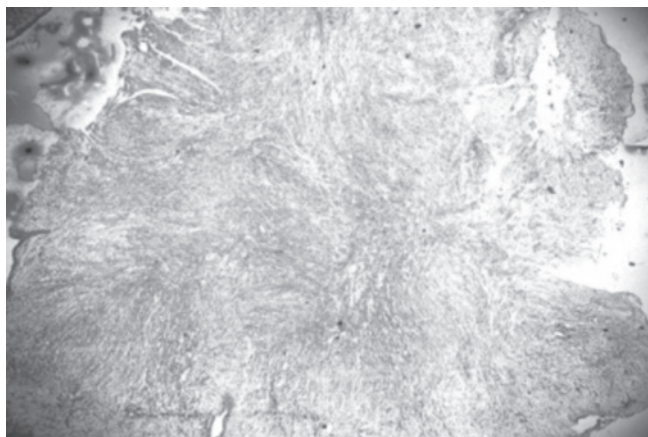


Fig. 3. Histopathological examination suggested inflammatory myofibroblastic tumour.

Table I^{1-4,6-8}. The aetiology of the disease is still not clear, but is probably the cause is an inflammatory reaction secondary to trauma, immune reaction, or infection^{2,4,6}. IMTs are most commonly seen in lungs, but can develop in any part of the body (Table II)^{1-6,8-11}. The symptoms of IMTs are usually nonspecific and depend on its location. Most respiratory tract IMTs are presented with dyspnoea, stridor, chronic cough, haemoptysis and pleuritic chest pain. Radiological evaluation with PA and left lateral chest radiograms, CT imaging and endoscopy (bronchoscopic) examination are the diagnostic methods for evaluation. The radiological evaluation gives the information about the tracheal lumen^{1,3,8}. IMTs are in the differential diagnosis with other tracheal tumours and tissue biopsy is needed for definitive diagnosis. Immunohistochemical study of IMTs is positive for vimentin, muscle-specific

Table II. Common sites for inflammatory myofibroblastic tumour.

Airway	Chest
Lung	Oesophagus
Nasal cavity	Heart
Nasopharynx	Breast
Larynx	GI
Trachea	Stomach
Head & Neck	Liver
Orbit	Spleen
Oesophagus	Pancreas
Thyroid	Kidney
Tonsil	Adrenal gland
Maxillary sinus	Retroperitoneum
Fourth ventricle	Diaphragm
Spinal cord meninges	Mesentery
Central nervous system	Genitourinary system
	Testis
	Bladder
	Uterus

Table III. Basic histologic patterns of inflammatory myofibroblastic tumour (Coffin et al.)

1. Myxoid/ Vascular pattern: Fasciitis-like appearance and loosely arranged plump spindle cells in an oedematous myxoid stroma with prominent vasculature. It has inflammatory infiltrate of more neutrophils, eosinophils and few plasma cells than the other two patterns.

2. Compact spindle cell pattern: Cellular proliferation of spindle cells with fascicular or storiform architecture in a collagenous stroma and typically show numerous plasma cells and lymphocytes mixed with spindle cells, but discrete lymphoid follicle and aggregates of plasma cells are common.

3. Fibromatosis-like pattern: Relatively hypocellular with elongated spindle cells in a densely collagenous background containing scattered lymphocytes, plasma cells and eosinophils.

actin, SMA and cytokeratin, which are characteristic for myofibroblasts^{1,3,4,13}.

Simple surgical excision of the tumour with a normal rim of tissue is the treatment of choice. However, endoscopic-assisted resection may be a choice of approach to remove the endoluminal tumours^{1-5,7,11,12,14}. CO₂ laser or electrocautery is also documented in the literature. Radiotherapy and chemotherapy are reserved for cases of recurrence^{1-4,11,12,14}.

Histologically, IMTs have variable cellular spindle cell proliferation in a myxoid to collagenous stroma with a prominent inflammatory infiltrate of plasma cells and lymphocytes with some eosinophils and neutrophils. Coffin et al. described three histologic patterns which are tabulated below (Table III)⁹. Salvatore et al. described three types depending on the predominant cell types⁷:

1. Organising pneumonia type with predominant fibroblast-like spindle cells;
2. Fibrous histiocytoma type;
3. Lymphoplasmacytic type. Death can occur by local recurrence and in cases with infiltration to mediastinal organs or rarely due to distant metastasis⁸.

Conclusions

IMT of the trachea are rare and pose a diagnostic dilemma. Most cases present with nonspecific symptoms. Radiological and endoscopic assessment are useful, but tissue biopsy is needed for definitive diagnosis. Simple surgical resection is the treatment of choice; RT and CT are reserved for unresectable cases. Death can occur in local recurrence and infiltration to mediastinal organs, and rarely to distant metastasis. The prognosis of patients who undergo radical resection is excellent.

Acknowledgments

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References

- ¹ Ozgül MA, Toru Ü, Acat M, et al. *A rare tumor of trachea: Inflammatory myofibroblastic tumor diagnosis and endoscopic treatment.* Respir Med Case Rep 2014;13:57-60.
- ² Oztuna F, Pehlivanlar M, Abul Y, et al. *Adult inflammatory myofibroblastic tumor of the trachea: case report and literature review.* Respir Care 2013;58:e72-6.
- ³ Boloursaz MR, Khalilzadeh S, Dezfoli AA, et al. *Inflammatory myofibroblastic tumor of the trachea.* Pediatr Surg Int 2011;27:895-7.
- ⁴ Zhang T, Yuan Y, Ren C, et al. *Recurrent inflammatory myofibroblastic tumor of the inguinal region: a case report and review of the literature.* Oncol Lett 2015;10:675-80.
- ⁵ Laursen BB, Pedersen U, Kjærgaard T. *Inflammatory myofibroblastic tumour of the trachea in a child with asthmatic symptoms.* Ann Otolaryngol Rhinol 2015;2:1053-4
- ⁶ Pecoraro Y, Diso D, Anile M, et al. *Primary inflammatory myofibroblastic tumor of the trachea.* Respirol Case Rep 2014;2:147-9.
- ⁷ Privitera S, Hwang DM, Darling GE. *Inflammatory myofibroblastic tumor of the left main stem bronchus.* J Thorac Oncol 2006;1:726-8.
- ⁸ Khodadad K, Hashemi N, Karimi S, et al. *Inflammatory myofibroblastic tumor of the lung: case series.* Tanaffos 2009;8:68-74.
- ⁹ Gleason BC, Hornick JL. *Inflammatory myofibroblastic tumours: where are we now?* J Clin Pathol 2008;61:428-37.
- ¹⁰ Jacob SV, Reith JD, Kojima AY, et al. *An unusual case of systemic inflammatory myofibroblastic tumor with successful treatment with ALK-inhibitor.* Case Rep Pathol 2014;2014:470340.
- ¹¹ Katara AN, Chandiramani VA, Dastur FD, et al. *Inflammatory pseudotumor of ascending colon presenting as PUO: a case report.* Indian J Surg 2004;66:234-6.
- ¹² Maturu VN, Bal A, Singh N. *Inflammatory myofibroblastic tumor of the lung in pregnancy mimicking carcinoid tumor.* Lung India 2016;33:82-4.
- ¹³ Kim HJ, Jong IN, Lee JS, et al. *Inflammatory myofibroblastic tumor of the thyroid gland: a brief case report.* Korean J Pathol 2014;48:319-22.
- ¹⁴ Johnson K, Notrica DM, Carpentieri D, et al. *Successful treatment of recurrent pediatric inflammatory myofibroblastic tumor in a single patient with a novel chemotherapeutic regimen containing celecoxib.* J Pediatr Hematol Oncol 2013;35:414-6.

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In Memoriam of Lorenzo Marcucci

(February 7, 1928 - January 21, 2018)

A few days before his 90th birthday, Lorenzo passed away. He was one of the last survivors of that generation of enthusiastic colleagues who contributed decisively to the success and progress of the Italian ENT Society. Lorenzo was from Tuscany and in Florence he began studying medicine, even though Parma was where he completed his professional training and the city that would become the most important for him. It was here that he completed his specialist ENT preparation at the school directed by Carlo Felice Porta. He remained for a long time at the Parma clinic, seeing patients and carrying out teaching and research that earned him, together with his human qualities, the esteem and friendship of all his colleagues, feelings that remained unchanged forever. He maintained this particularly deep fraternal bond throughout his life, especially with Piero Miani, and started collaborations that contributed much to the life and development of our Scientific Societies (particularly AOOI and SIO). Lorenzo preferred a clinical career over that of academia, and in 1965 transferred to Viterbo to become Head of the Neonatal ENT Division, a position he kept until his retirement in 1998.

Among his scientific contributions, I want to mention those related to bacterial infections in ENT, a subject that fascinated him for many years and which was the subject of his official SIO report at the 1986 National Congress, in addition to many communications at conferences on otorhinolaryngology and infectious diseases.

In truth, Lorenzo's main passion was his constructive contribution that for many years gave life to the development of our Scientific Societies. He always participated with constancy until a few years ago as a member of the AOOI Board of Directors, of which he held the Presidency from 1988 to 1990, and of SIO, which he directed in the 1994/1995. He was always full of useful advice dictated by his sense of equilibrium and immense common sense. His dedication to the ENT Societies (he was also Honorary Member of the Spanish ENT Society) was related in part to an admirable spirit of service, but also by the desire to see his colleagues and dear friends as often as possible.

One of the main characteristics of Lorenzo Marcucci was his sense of deep friendship, which was always reciprocated with affection because of his good spirit, availability and kindness. He was one of those few, very rare people who can confidently be defined as a friend of everyone.

In these last years he returned to Parma, to Rubbiano, near his daughter Federica, and, despite having been bedridden for a long time, his lively spirit and sense of humour remained unchanged. He was always a joy to speak with on the phone, remembering his friends and travels. For me, he was precious company that made the loss, in recent years, of many dear friends a bit more tolerable. Today, his loss makes me dwell even more on the sadness of loneliness.

Goodby dear Lorenzo, you have been a friend for the last 50 years who I will never forget.



Giorgio Sperati