ACTA Otorhinolaryngologica Italica

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

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

S.I.O.E.C.I.C.-F

PACINI EDITORE MEDICINA

Volume 39
February 2019

www.actaitalica.it

Otorhinolaryngologica Italica

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

What's new?

Single platform

New on-line submission

New web site

www.actaitalica.it

Available on Google Scholar

Cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, DOAJ, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

Journal Citation Reports:
Impact Factor 1.196

Editor-in-Chief: M. Ansarin

PACINI EDITORE MEDICINA

Acta Otorhinolaryngologica Italica

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

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

Publisher
Pacini Editore Srl
Via Gherardesca, 1 - 56121 Pisa, Italy
Tel. +39 050 313011 -Fax +39 050 3130300
info@pacinieditore.it - www.pacinimedicina.it

Acta Otorhinolaryngologica Italica is cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, DOAJ, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

Journal Citation Reports: Impact Factor 1.196
Acta Otorhinolaryngologica Italica is available on Google Scholar

S.I.O.E.C.I.C.-F

PACINI EDITORE MEDICINA

Volume 39
February 2019

www.actaitalica.it

Contents

Articles in open access, information for authors including editorial standards for the preparation of manuscripts and submission and Publisher's note available on-line: www.actaitalica.it

Editorial

Editoriale

Dear Authors and Colleagues,

We are pleased to announce that as of February 2019, *Acta Otorhinolaryngologica Italica* has a new website and platform, created in order to streamline the online submission and publication of new manuscripts.
The close collaboration and painstakingly meticulous dedication of the Editorial Board together with Pacini Editore and Archimede Informatica Società Cooperativa have enabled us to create a new system that overcomes the limitations of the previous system, and meets the need for a smooth and rapid way to publish new articles of current and upcoming scientific interest.
Furthermore, thanks to the introduction of the Crossref system, reference linking will be much easier for our associates. The associated DOI link will improve the visibility and citation of the articles, thereby enhancing the scientific prestige and exposure of *ACTA* and those who write for it.

Our compelling mission is, as ever, to promote scientific and clinical research in the field of otorhinolaryngology and head and neck surgery at an international level. It is our unwavering conviction that such an aim cannot be pursued without first and foremost empowering the means for scientific dissemination in keeping with the twenty-first century.
Our heartfelt thanks go to the Board of Directors of the Italian Otorhinolaryngology and Head and Neck Society, in particular to the president, Professor Claudio Vicini, whose supervision and unstinting support have been essential to the cause.
We sincerely hope that this upgrade may represent a suitable reward for your commitment and contribution to *Acta Otorhinolaryngologica Italica*.
Sincerely,

Mohssen Ansarin
Editor-in-Chief Acta Otorhinolaryngologica Italica

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:2-8; doi: 10.14639/0392-100X-2481

Review

Knowing the tumour microenvironment to optimise immunotherapy

Conoscere il microambiente tumorale per ottimizzare l'immunoterapia

M.C. MERLANO[1,2], A. ABBONA[2], N. DENARO[1], O. GARRONE[1,3]

[1] Medical Oncology Dept, S. Croce & Carle Teaching Hospital, Cuneo, Italy; [2] ARCO Foundation, Cuneo, Italy; [3] Breast Unit, Medical Oncology, S. Croce & Carle Teaching Hospital, Cuneo, Italy

SUMMARY

Effective immunotherapy requires thorough knowledge of the tumour microenvironment. Indeed, the interplay among the immune system, the tumour and treatment is conditioned by the composition of the tumour microenvironment. In addition, it must be taken into account that homeostasis of the tumour microenvironment is highly dynamic and changes rapidly in function of many factors, such as inflammation, hypoxia, tumour volume, all of which change over time, and the effect of treatments. All these elements interact with each other and with conditions related to the tumour (i.e. mutational load, rate of clonal and subclonal mutations) and to host (life style, diet, obesity, age). All these factors as well as their interplay, affect the response to immunotherapy. The target of this short review is to summarise some of the major aspects that impact the homeostasis of the tumour microenvironment and how its structure can drive treatment choice.

KEY WORDS: Immunotherapy • Tumour microenvironment • Treatment targets

RIASSUNTO

Una immunoterapia efficace richiede una profonda conoscenza del microambiente tumorale. Infatti l'interazione fra il sistema immune, il tumore e il trattamento è condizionata dalla composizione del microambiente. Inoltre si deve tenere in considerazione che l'equilibrio del microambiente è altamente dinamico e cambia rapidamente in funzione di molti fattori, come il livello di infiammazione, l'ipossia, il volume tumorale, tutti fattori che cambiano nel tempo, e gli effetti dei trattamenti. Tutti questi fattori interagiscono gli uni con gli altri e con condizioni correlate al tumore, (il carico mutazionale o la percentuale di mutazioni clonali o subclonali) o all'ospite (stili di vita, dieta, obesità, età). Tutti questi fattori, così come la loro interazione, influiscono sulla risposta all'immunoterapia. L'obiettivo di questa breve review è di riassumere alcuni dei principali aspetti che interferiscono con l'omeostasi del microambiente tumorale e come la sua struttura può guidare la scelta terapeutica.

PAROLE CHIAVE: *Immunoterapia • Microambiente tumorale • Bersagli della terapia*

Introduction

The main target of immunotherapy is the immune system. The effects against cancer are the consequence of immune system repolarisation from a tumour supportive phenotype towards a tumour suppressive one.

The increasing number of solid and haematologic tumours that benefit from the same immunotherapy agent supports the central role of the immune system [1]. However, the extent of the benefit changes widely among different tumours [2]. In addition, the same immune cells, such as T regulatory (Treg) cells or Tumour Associated Macrophages (TAM), may show different prognostic values according to the tumour site [3 4], attesting that other factors, apart from the cancer itself, influence homeostasis between the host and disease.

These aspects suggest that additional factors intervene in the simplistic view of a match involving two players: the immune system and the tumour.

First of all, the plasticity of both immune system and tumour impacts the way they interact with each other. Immune system changes according to age (e.g.: immune aging) [5], life styles (e.g.: diet, obesity) [6], presence of chronic infections (e.g.: CMV, HIV, HPV) and factors related to geographic origin (e.g.: microbioma, HLA polymorphisms) [6 7].

In turn, cancer tissue is well known for its instability. Tumour instability acts on the way it faces the immune system, for instance leading to different mutational load and mutational heterogeneity within the same tumour types [8 9]. Moreover, specific mutations interfere with the immune system in different ways: mutation of the transforming growth factor beta (TGFβ) receptor II (TGFβRII) gene

generating a non-functioning protein, causes the accumulation of TGFβ in the microenvironment, leading to the inhibition of the immune response and, eventually, to the immune exclusion [10]. Another example is the frequently observed disruption of the WNT–β-catenin axis, driving up-regulation of β-catenin that prevents the activation of the immune system through inhibition of recruitment of *Baft3* dendritic cells (DC) [11].

Secondly, the feature of both the immune system and the tumour characterise the field in which they interplay: the tumour microenvironment (TME).

It is clear that the TME reflects the plasticity of both the immune system and the tumour, although other aspects influence its plasticity: the pre-existing immune structure of the organ in which the cancer develops, or the specific anatomical aspects acquired by the tumour during its life, such as the degree of hypoxia and necrosis [12].

Therefore, the TME represents the crossroad of many different and frequently opposite signals that control the relationship between the host and the tumour.

Tackling the TME with therapeutic interventions that are able to change the equilibrium in favour of the host is a challenge of the near future.

The tumour microenvironment

A neoplastic mass is made up of tumour cells along with a large number of non-tumour cells and stroma, which represent the majority of tumour volume. All these components, including tumour cells, communicate continuously with each other through cell to cell contact and a complex network of cytokines, proteins and chemokines, whose balance push the match in favour of the immune system or the tumour, driving the action of the former and the reaction of the latter. Hence, any change in the TME may reflect changes of the balance between immune system and tumour. Many factors affect the homeostasis of the TME.

TME changes according to tumour volume

The TME changes according to tumour volume. For instance, NKG2D is an important activator receptor of all natural killer (NK) cells and most CD8+, CD4+, natural killer T (NKT) and γδT cells. MIC-A and MIC-B are two surface proteins similar to HLA and are expressed by cells under conditions of stress. They represent the NKG2D ligands (NKG2D-L). The binding of the receptor with MIC-A or MIC-B triggers the activation of immune cells and leads to an immune response.

Their up-regulation should be associated with a favourable outcome. Surprisingly, in human tumours, up-regulation of MIC-A/B plays a conflicting prognostic role.

To explain this paradox, it must be considered that the binding of NKG2D-L to the receptor induces not only cell activation, but also endocytosis and degradation of NKG2D. This explains why the receptor is markedly reduced in many infiltrating and circulating T cells [13]. Unfortunately, NKG2D-L can be shed into the TME. Soluble ligand and membrane bound ligand play an opposite role in immune response against the tumour: while membrane bound ligand facilitates attack by immune effector cells, soluble ligand blinds the immune cells that become unable to lyse target cells. A specific protease, "A disintegrin and metalloproteases-9" (ADAM-9) is the major NKG2D ligand sheddases. The amount of soluble ligand in the TME is function of tumour *"age"* (i.e. tumour volume and stage) [14].

A second example is the change of tumour interstitial pressure related to tumour volume. Gutmann et al., as far back as 1992, observed that interstitial fluid pressure (IFP) in head and neck cancer changes according to tumour volume [15]. The increased pressure reduces O_2 diffusion, increases hypoxia and reduces pH.

These effects directly hamper not only immune response, but also favour the accumulation of TAM M2 (highly immunosuppressive) and induction of cytokines, such as VEGF, TGFβ and galectin 1, into the TME. All these cytokines are highly immunosuppressive. In particular, Galectin 1 is able to skew the immune balance toward Th2 response, hindering Th1, Th17 and CD8+ cells, inhibiting activity of NK cells, polarising TAM toward the M2 phenotype, up-regulating Treg cells and inhibiting trans-endothelial migration of cytotoxic T lymphocytes (CTL) [16]. Therefore, a tumour at a more advanced stage expresses more efficient immune escape mechanisms.

TME changes according to the site of tumour origin

As reported above, some immune cells, such as Treg or TAM, have opposite prognostic role according to the site of tumour origin. However, site of origin drives other differences that are able to affect the TME. For instance, one is mutation of TGFβRII or its pathway. It may occur in up to 66% of head and neck cancers [17], but is present in only 27% of non- hypermutated colon cancers [18].

Plasticity of many immune cells favours dissimilarity among primary sites. Indeed, immune cells are genetically stable, but highly plastic. CD4+ T helper (Th) cells may be redirected from one lineage to another. Only terminally differentiated Th1 or Th2 cells cannot be switched to a different state, while Treg, Th17 and non-terminally differentiated Th1 and Th2 cells maintain their plasticity and can be reprogrammed [19]. Therefore, under the pressure of mutated homeostasis, Th1 can be converted in Treg or Treg can become Th17, and so on. Basically, the domi-

nant microenvironment drives the phenotype of immune cells. Also, TAM M1 or M2 polarisation depends on the TME: high levels of IFN-γ and TNF-α induce M1 polarisation (tumour suppressive), while IL-4, IL-10 and TGFβ drive M2 polarisation (tumour supporting) [20]. Many drugs have shown the capacity to reprogram the main regulatory immune cells, and much preliminary data have confirmed this finding in humans so far. For instance, toll-like receptor 9 agonists (αTLR9) reprogram TAM toward the M1 phenotype when administered intra-tumourally. In the clinic, the combination of αTLR9 with anti PD-1 has shown high activity and induction of the abscopal effect in non-injected lesions [21 22].

Myeloid derived suppressor cells (tumour supporting) can be induced to maturation toward DCs or TAMs (M1) by many agents, such as retinoic acid [23] or some chemotherapy agents such as gemcitabine [24].

Finally, Tregs can be selectively depleted using, for instance, low dose cyclophosphamide [25], or can be reprogrammed towards the Th1 phenotype targeting CCR8 or OX40 that can both avoid expansion of Tregs and the shift from Th1 to Treg [26 27].

TME changes due to cancer treatment

All anti-cancer treatments induce TME changes.

Many drugs interfere with the TME in different ways depending on their structure and/or mechanism of action. Chemotherapy can modulate immune cells depending on the drug and scheduling. Ghiringhelli et al. demonstrated that low dose cyclophosphamide selectively kills Treg cells, but not CD8+ cells or other CD3 lineages [25]. This selective effect might be due to the increased expression of pro-apoptotic molecules induced by the transcriptional factor Foxp3 that is mainly expressed by Treg. Foxp3 might contribute to the higher sensitivity to low-dose cyclophosphamide (reviewed in Sistigu et al. [28]). In addition to cyclophosphamide, many other drugs affect immune system. Bracci et al. reviewed this topic a few years ago [29]. Moreover, some chemotherapy agents are able to induce immunogenic cell death [30], a particular cell death leading to a potential increase of tumour immunogenicity that can induce strong changes in the TME and favour activity of the immune system.

Targeted therapies may alter TME as a consequence of their main activity. Cetuximab and bevacizumab serve as examples.

Cetuximab is a monoclonal antibody (mAb) targeting the EGFR expressed on the cell membrane and induces arrest of cell proliferation and migration. In addition, cetuximab is able to trigger antibody dependent cell cytotoxicity (ADCC) [31]. Activation of NK cells through the binding of Fc fragment of cetuximab to FcγRIII *(*CD16) induces release of cytotoxic granules by natural killer (NK) cells and release of pro-inflammatory cytokines, such as IFNγ and TNFα, which deeply impact the TME [32]. Furthermore, the link between the Fc fragment with FcγRI *(*CD 64) on DCs, leads to the priming of specific CD8+ clones targeting cells with high EGFR expression [33]. Indeed, the immune system can be activated not only by the presence of "non-self" antigens, but also by an excess of "self" antigens, such as the overexpression of EGFR on tumour cells.

Bevacizumab is a mAb directed against vascular endothelial growth factor (VEGF). Its activity results in remodeling of the vasculature and reactivation of the endothelial cells that favours trafficking and homing of T effector cells and oxygenation of hypoxic (immunosuppressive) areas. However, this effect is largely dose-dependent, since high dose bevacizumab, such as those routinely used for the treatment of most human cancers*,* induces the pruning of the microvasculature, reduces the homing of CTL and worsens hypoxia [34].

Immunotherapy directly interferes with the TME. Indeed, blocking the PD-1 – PD-L1 axis induces a number of major changes leading to the restoration of immune activity [35].

The immune checkpoint inhibitors may facilitate the homing of T effector cells preventing their contact with PD-L1 expressed on the endothelial cells or may hinder Treg cells.

Radiotherapy induces a number of immune effects both activating and immunosuppressive, such as up-regulation of MHC-I or up-regulation of chemokines recruiting effector cells, and of TGFβ or IL-10. These effects depend on total dose, dose per fraction and scheduling and require more investigation in humans.

TME drives resistance

Resistance to immunotherapy is largely due to the structure of the TME. Hedge et al. identified three different TMEs [36]. The "*inflamed*" tumours are characterised by infiltration of immune cells. These immune cells are inefficient because they are kept in check by immunosuppressive mechanisms. Inflamed tumours, such as many head and neck cancers, have a high chance to respond to immune checkpoint inhibitors. Immune cells localised at the margins of the tumour nests characterise the "*excluded*" tumours; this phenotype shows reduced response to ICIs. Finally, the "*desert*" tumours are characterised by lack of immune cells, both within the tumour and at its margins. These tumours usually do not respond to ICIs.

The mechanisms responsible of these diverse TME architectures are already known [37], and consequently the necessary approaches to counteract the resistance resulting

from them are known, at least in theory. Briefly, the immune resistance of inflamed tumours can be overcome by ICIs. The excluded tumours may benefit from drugs able to facilitate trafficking and homing of lymphocytes into the tumour nests, while immune desert tumours may take advantage by treatments that are able to improve the immunogenicity of cancer cells [38].

Tumour histotype does not necessarily correspond to one of these different TME but, rather, can coexist in any tumour type, probably with different ratios [36]. In addition, there is evidence that in human metastatic cancers, metastases may express any TME, regardless of the characteristics of the originating tumour and other metastatic sites [39]. Taken together, these observations can explain why the same immune checkpoint inhibitor reaches different activity in diverse tumour histotypes and within the same tumour.

Taking advantage of TME characteristics to achieve the best response

The knowledge of TME characteristics can allow for identification of the best treatment for each situation. For example, our group demonstrated in colon cancer patients treated with cetuximab and presenting with high basal ADCC activity, a significantly better overall survival compared to those treated with the same drug but expressing low basal ADCC [40]. We also analysed a series of patients treated with cetuximab and radiotherapy for locally advanced head and neck cancer not suitable for chemoradiation. In this population, high basal ADCC activity correlated with significantly better survival ($p = 0.033$) compared to low ADCC. On the contrary, ADCC did not correlate with better outcome in a control group treated with chemoradiation [41].

In addition, considering only patients with over expression of EGFR (+++) in which there is the highest probability of binding cetuximab and EGFR, the difference between high and low basal ADCC was stronger ($p = 0.024$) and patients in the group with high ADCC have 100% overall survival, compared to 49% in the low ADCC group at a maximum follow-up of 44 months [41].

It has also been observed that high mutational load predicts response to immunotherapy, while low mutational burden predicts response to chemotherapy. Indeed, in a randomised phase III study, Carbone et al. observed that tumours expressing high mutational load have a greater chance to achieve objective response and long benefit with nivolumab rather than with chemotherapy. On the contrary, tumours with low mutational burden correlate with an opposite attitude [42]. Interestingly, Riaz et al. observed that the mutational burden decreases during successful treatment with ICIs in patients with melanoma [43]. If this observation is extended to other tumours, it will pave the way to beneficial treatment with chemotherapy after prior immunotherapy. Actually, reports showing unexpected responses to single agent chemotherapy after immunotherapy already exist, at least, in lung cancer [44 45] and in head and neck cancer [46] and a similar observation was also reported at the 2018 ASCO meeting [47].

Selected promising agents targeting TME in clinical development in head and neck cancer

Anti PD-(L)1

PD-1 is a receptor expressed by immune cells following their activation and physiologically its role consists in limiting the immune response to avoid serious damage to the host tissues. Its ligand, PD-L1, is expressed in tumour cells and in stromal cells with regulatory functions, such as TAM and endothelial cells. Targeting PD-1 with mAb changes the TME from a Th2 phenotype (immunosuppressive) to Th1 phenotype (immunostimulatory) in a consistent proportion of lymphocyte infiltrated tumours. Treatment with anti PD-1 mAbs in patients with relapsed-metastatic head and neck cancer after failure of chemotherapy leads to a small but reproducible rate of long-term survivors [48 49].

Very recently, the KeyNote 048 study, comparing the anti PD-1 mAb pembrolizumab alone to the "extreme" regimen (cisplatin, fluorouracil and cetuximab) in patients never treated for recurrent disease, was presented at the 2018 ESMO meeting. Pembrolizumab showed a large and significant improvement in overall survival compared to extreme, with a strong reduction in adverse events, at least in patients with high expression of PD-L1 [50]. Many other randomised trials are in progress with agents targeting the PD-1/PD-L1 axis in relapsed/metastatic disease and in combination with radiotherapy with cetuximab and/or chemotherapy in locally advanced disease and results are awaited soon.

Toll-like receptor agonists

The Toll-like receptors (TLRs) are able to trigger the immune response when they recognise danger signals (alarmin, danger-associated molecular patterns – DAMPS – or pathogen-associated molecular patterns – PAMPS -).

SD101 is αTLR9 oligodeoxynucleotide. SD 101 induces a rapid IFN type I production, which, in turn, induces activation of NK, promotes CD8+ homing into the tumour and initiates an immune response while blocking immune suppression.

SD 101 was injected directly into tumour lesions of 22 patients with relapsed metastatic squamous cell carcinomas of the head and neck.

In combination with the anti PD-1 pembrolizumab, SD 101 induced reduction of tumour volume in injected and non-injected lesions (abscopal effect) in 6 patients (27%)

and stopped tumour progression in another 6 [51]. Further studies on SD 101 and other agonists of TLRs are in early clinical development.

STAT-3 inhibition

STAT-3 is a "double-edge sword" transcriptional factor that drives both pro-immune activities and suppressive immune activity. Its role depends on the level of activation: intermittent activation induces pro-immune activity, whilst continuous activation, such as in cancer, manages a number of immune suppressive activities including up-regulation of VEGF, TGF-β, IL-10 and down-regulation of HLA, IFN type I and II, CXCL10, CD80 and CD86.

AZD 9150 is an antisense oligonucleotide that is able to decrease STAT-3 expression in advanced clinical development in lymphoma and lung cancer [52].

Cohen recently reported preliminary results of AZD 9150 in combination with anti-PD-L1 in RM-HNC showing response rate higher than expected with the inhibition of the PD-1/PD-L1 axis and with no additional toxicity [53]. The approach looks highly promising.

Anti TGF-β

TGF-β is among the most immunosuppressive cytokines in cancer, whilst the physiological role of TGF-β is to preserve tissue homeostasis. Indeed, one of its main functions is to keep under control the cell proliferation. In cancer, TGF-β inhibits most effector cells, and contributes to maintaining an immunosuppressive TME as well as to drive epithelial-mesenchymal transition (EMT).

EMT is a phenotypical change of cancer cells that promotes invasion and metastatisation.

Increased level of TGF-β has been reported in the majority of HNC [54]. Therefore, it represents an interesting target of immunotherapy in this disease.

Preliminary results of a phase 1 study based on a fusion protein targeting both PD-L1 and TGF-β ("TGF-β trap") were presented during the 2018 ESMO meeting. With a very favourable toxic profile, TGF-β trap achieved a tumour burden reduction of 50 to 90% in 6 of 11 patients [55].

Anti NKG2A

HLA-E is a non-classical HLA class I molecule, which can be expressed in cancer cells. Around 80% of HNCs express HLA-E, which is the highest value among solid tumours together with renal cancer and melanoma. HLA-E binds to NKG2A, which is an inhibitory receptor expressed on NK cells and CD8+ cells, and induces a potent inhibitory signal. The prevention of the binding of HLA-E with NKG2A results in restoration of immune cytotoxicity, including ADCC. A monoclonal antibody (monalizumab) is currently under clinical investigation in combination with cetuximab in heavily pretreated RM-HNC. Preliminary results show responses in 27% of patients and this value is more than double of that expected with cetuximab alone. Moreover, overall survival of 10.3 months compares favourably to the extreme regimen (10.1 months in non-pretreated RM-HNC) and to the anti PD-1 monoclonal antibody pembrolizumab and nivolumab (around 8 months in similar patients) [56].

Conclusions

The key for successful treatment of cancer resides in the TME. The problem is its plasticity that leads to a continuous change over time and represents the result of an incredible number of crosstalks among host characteristics, cancer cells, immune cells and cancer therapies.

Therefore, the solution is to identify the characteristic of the TME in a specific patient at the time of treatment. Clearly, this is a very daunting challenge.

We already know many cards of the puzzle and can positively drive the outcome in many tumours, including some, such as metastatic melanoma, which were hopeless until a decade ago. This is largely due to the huge improvements in our ability to interfere with the TME thanks to the impressive development of immune oncology.

However, we need to further improve our knowledge focusing on the mechanisms driving TME plasticity. We have to enhance our skills to distinguish one specific clinical situation among many that we consider similar on the basis of histology, TNM, or stage.

Finally, it is also necessary to change the way used to design, conduct and analyse clinical trials.

In the tremendous heterogeneity of cancer, small phase II trials, designed to detect remarkable advantages in highly selected and strictly homogeneous patient populations, along with strong translational studies, might be more useful than classical large clinical trials at the present status of clinical research.

Conflict of interest statement

MCM received honoraria consultancies, speakers bureau from M.S.D., Merck Serono, Astra Zeneca and research fundings from Merck Serono, M.S.D. and for participation in conferences from B.M.S., Merck Serono and Novartis. AA, ND, OG. declare no conflict of interest.

References

1 Thallinger C, Fureder T, Preusser M, et al. *Review of cancer treatment with immune checkpoint inhibitors*. Wien Klin Wochenschr 2018;130:85-91.

2 https://www.*slideshare*.net/manojsci/merck-ascobriefingslides. slide n.9.

[3] Shang B, Liu Y, Jiang SJ, et al. *Prognostic value of tumor-infiltrating FoxP3+ regulatory T Cells in cancers: a systematic review and meta-analysis*. Sci Rep 2015;5:15179.

[4] Ruffell B, Coussens LM. *Macrophages and therapeutic resistance in cancer*. Cancer Cell 2015;27:462-72.

[5] Pawelec G. *Age and immunithy: what is "immunosenescence?* Exp Gerontol 2018;105:4-9.

[6] Zitvogel L, Pietrocola F, Kroemer G. *Nutrition, inflammation and cancer*. Nat Immunol 2017;18:843-50.

[7] Chowell D, Morris LGT, Grigg CM, et al. *Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy*. Science 2018;359:582-7.

[8] Rooney MS, Shkla SA, Wu CJ, et al. *Molecular and genetic properties of tumor associated with local immune cytolytic activity*. Cell 2015;160:48-61.

[9] McGranahan N, Furness AJS, Rosenthal R, et al. *Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade*. Science 2016;351:1463-9.

[10] Lin R-L, Zhao L-J. *Mechanistic basis and clinical relevance of the role of transforming growth factor-β in cancer*. Cancer Biol Med 2015;12:385-93.

[11] Pai SG, Carneiro BA, Mota JM, et al. *Wnt/beta-catenin pathway: modulating anticancer immune response*. J Hematol Oncol 2017;10:101.

[12] Le Q-T, Shi G, Cao H, et al. *Galectin-1: a link between tumor hypoxia and tumor immune privilege*. J Clin Oncol 2005;23:8932-41

[13] Groh V, Wu J, Yee C, et al. *Tumor-derived soluble MIC ligands impair expression of NKG2D and T-cell activation*. Nature 2002:419;734-8.

[14] Salih HR, Holdenrieder S, Steinle A. *Soluble NKG2D ligands: prevalence, release, and functional impact*. Front Biosci 2008;13:3448-56.

[15] Gutmann R. *Interstitial hypertension in head and neck cancer patients: correlation with tumor size*. Cancer Res 1993;52:1993-5.

[16] Rabinovich GA, Conejo-Garcia JR. *Shaping the immune landscape in cancer by galectin-driven regulatory pathways*. J Mol Biol 2016;428:3266-81.

[17] Lu S-T, Herrington H, Reh D et al. *Loss of transforming growth factor-β type II receptor promotes metastatic head-and-neck squamous cell carcinoma*. Genes Dev 2006;20:1331-42.

[18] *The Cancer Genome Atlas Network.* Nature 2012;487:330-7.

[19] Zhu J, Paul WE. *Heterogeneity and plasticity of T helper cells*. Cell Res 2010;20:4-12.

[20] Narendra BL, Reddy KE, Shantikumar S, et al. *Immune system: a double-edged sword in cancer*. Inflammation Res 2013;62:823-34.

[21] Ribas A, Medina T, Kummar S, et al. *SD-101 in combination with Pembrolizumab in advanced melanoma: results of a phase 1b, multicenter study*. Cancer Discov 2018; 8:1250-7.

[22] Wang D, Jiang W, Zhu F, et al. *Modulation of the tumor microenvironment by intratumoral administration of IMO-2125, a novel TLR9 agonist, for cancer immunotherapy*. Int J Oncol 2018;53:1193-203.

[23] Nefedova Y, Fishman M, Sherman S, et al. *Mechanism of all-trans retinoic acid effect on tumor-associated myeloid-derived suppressor cells*. Cancer Res 2007;67:11021-8.

[24] Eriksson E, Wenthe J, Irenaeseus S, et al. *Gemcitabine reduces MDSCs, tregs and TGFβ-1 while restoring the Teff/Treg ratio in patients with pancreatic cancer*. J Transl Med 2016;14:282.

[25] Ghiringhelli F, Menard C, Puig PE, et al. *Metronomic cyclophosphamide regimen selectively depletes CD4+ CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients*. Cancer Immunol Immunother 2007;56:641-8.

[26] Plitas G, Konopacki C, Wu K, et al. *Regulatory T cells exhibit distinct features in human breast cancer*. Immunity 2016;45:1122-34.

[27] Zhang X, Xiao X, Lan P, et al. *OX40 costimulation inhibits Foxp3 expression and Treg induction via BATF3-Dependent and independent mechanisms*. Cell Rep 2018;24:607-18.

[28] Sistigu A, Viaud S, Chaput N, et al. *Immunomodulatory effects of cyclophosphamide and implementations for vaccine design*. Sem Immunopathol 2011;33:369-83.

[29] Bracci L, Schiavoni G, Sistigu A, et al. *Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer*. Cell Death Differ 2014;21:15-25.

[30] Galluzzi L, Buqué A, Kepp O, et al. *Immunological effects of conventional chemotherapy and targeted anticancer agents*. Cancer Cell 2015;28:690-714.

[31] Monteverde M, Milano G, Strola G, et al. *The relevance of ADCC for EGFR targeting: A review of the literature and a clinically-applicable method os assessment in patients*. Crit Rev Oncol Hematol 2015;95:179-90.

[32] Wang W, Erbe AK, Hank JA, et al. *NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy*. Front Immunol 2015;6:368.

[33] Srivastava RM, Lee SC, Andrade Filho PA, et al. *Cetuximab-activated natural killer and dendritic cells collaborate to trigger tumor antigen-specific T-cell immunity in head and neck cancer patients*. Clin Cancer Res 2013;19:1858-72.

[34] Jain RK. *Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy*. Nat Med 2001;7:987-9.

[35] Sharpe AH, Pauken KE. *The diverse functions of the PD1 inhibitory pathway*. Nat Rev Immunol 2018;18:153-67.

[36] Hedge PS, Karanikas V, Evers S. *The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition*. Clin Cancer Res 2016;22:1865-74.

[37] Chen DS, Mellman I. *Elements of cancer immunity and the cancer-immune set point*. Nature 2017;541:321-30.

[38] Dammeijer F, Lau SP, van Eijck CHJ, et al. *Rationally combining immunotherapies to improve efficacy of immune checkpoint blockade in solid tumors*. Cytokine Growth Factor Rev 2017;36:5-15.

[39] Jimenez-Sanchez A, Memon D, Pourpe S, et al. *Heterogeneous tumor-immune microenvironments among differentially growing metastases in an ovarian cancer patient*. Cell 2017;170:927-38.

[40] Lo Nigro C, Ricci V, Vivenza D, et al. *Evaluation of antibody-dependent cell-mediated cytotoxicity activity and cetuximab in KRAS wild-type metastatic colorectal cancer patients*. World J Gastrointest Oncol 2016;15:222-30.

[41] Lattanzio L, Denaro N, Vivenza D, et al. *Elevated basal antibody-dependent cell-mediated cytotoxicity (ADCC) and high epidermal growth factor receptor (EGFR) expression predict favourable outcome in patients with locally advanced head and neck cancer treated with cetuximab and radiotherapy*. Cancer Immunol Immunother 2017;66:573-9.

[42] Carbone PD, Paz-Ares L, Creelan B, et al. *First-line Nivolumab in Stage IV or recurrent non-small-cell lung cancer*. N Engl J Med 2017;376:2415-26.

[43] Riaz N, Havel JJ, Makarov V, et al. *Tumor and microenvironment evolution during immunotherapy with nivolumab*. Cell 2017;171:934-49.e16.

[44] Schvartsman G, Peng SA, Bis G, et al. *Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer*. Lung Cancer 2017;112:90-5.

[45] Park SE, Lee SH, Ahn JS, et al. *Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer*. J Thor Oncol 2018;13:106-11.

[46] Denaro N, Merlano MC. *Unexpected response with palliative conventional therapy in head and neck squamous cell carcinoma after anti-programmed death-1 progression*. Head Neck 2019;41:E42-E47.

[47] Saleh K, Daste A, Martin N, et al. *Rsponse to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck*. J Clin Oncol 2018;36 (suppl):abstr 6015.

[48] Ferris RL, Blumenschein G Jr, Fayette J, et al. *Two-year update from checkmate 141: outcomes with nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck in the overall population and PD-L1 subgroups*. Radiation Oncol Biol Phys 2018;100:1317.

[49] Soulieres D, Cohen EEW, Le Tourneau C, et al. *Updated survival results of the KEYNOTE-040 study of pembrolizumab vs standard of care chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma*. Cancer Res 2018;78 (suppl):Abstr CT115.

[50] Burtness B. *First line pembrolizumab for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): interim results from the phase 3 keynote-048 Study*. Munich, ESMO 2018, Abstr 4832.

[51] Cohen EEW. *Phase 1b/2, open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naïve patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)*. Munich, ESMO 2018, Abstr. 3560.

[52] Hong D, Kuzrock R, Kin Y, et al. *AZD 9150, a next generation antisense oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer*. Sci Transl Med 2015;18:314ra185.

[53] Cohen EEW, Harrington KJ, Hong DS, et al. *A phase 1b/2 study (SCORES) of durvalumab (D) plus danvitarsen (DAN; AZD9150) or AZD5069 (CX2i) in advanced solid malignancies and recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC): updated results*. Munich, ESMO 2018, Abstr 4197.

[54] Pang X, Tang Y-L, Liang X-H. *Transforming growth factor-β signaling in head and neck squamous cell carcinoma: insights into cellular response"*. Oncology Lett 2018;16:4799-806.

[55] Cho BC, Daste A, Ravaud A, et al. *M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients (pts) with advanced SCCHN: results from a phase 1 cohort*. Munich, ESMO 2018, Abstr. 4263.

[56] Fayette J, Lefebvre G, Posner MR, et al. *Results of a phase II study evaluating monalizumab in combination with cetuximab in previously treated recurrent or metastatic squamous cell carcinomas of the head and neck (R/M SCCHN)*. Munich, ESMO 2018, Abstr. 1719.

Received and Accepted: January 2, 2019

How to cite this article: Merlano MC, Abbona A**,** Denaro N, et al. *Knowing the tumour microenvironment to optimise immunotherapy.* Acta Otorhinolaryngol Ital 2019;39:2-8. https://doi.org/10.14639/0392-100X-2481

Address for correspondence: Ornella Garrone, Breast Unit, Medical Oncology, S. Croce & Carle Teaching Hospital, via M. Coppino 26, 12100 Cuneo, Italy. E-mail: ornella.garrone@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:9-17; doi: 10.14639/0392-100X-1905

Head and neck

The evolving landscape of human papillomavirus-related oropharyngeal squamous cell carcinoma at a single institution in Northern Italy

Carcinoma squamocellulare HPV-correlato dell'ipofaringe: evoluzione epidemiologica in un singolo centro italiano

P. MORBINI[1, 2], P. ALBERIZZI[2], G. FERRARIO[2], G. CAPELLO[2], A. DE SILVESTRI[3], P. PEDRAZZOLI[4], C. TINELLI[3], M. BENAZZO[5]

[1] Department of Molecular Medicine, Pathology Unit, University of Pavia, Italy; [2] Pathology Unit, Foundation IRCCS Policlinico S. Matteo, Pavia, Italy; [3] Clinical Epidemiology and Biometrics Unit, Foundation IRCCS Policlinico S. Matteo, Pavia, Italy; [4] Department of Oncology, Foundation IRCCS Policlinico S. Matteo, Pavia, Italy; [5] Department of Otolaryngology, University of Pavia and Foundation IRCCS Policlinico S. Matteo, Italy

SUMMARY

The increasing incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) observed in several developed countries has not yet been documented in Italy. To investigate changes in the epidemiology of HPV-related OPSCC we reviewed the HPV status of cases evaluated at our centre in northern Italy before and after 2010. The results were correlated with patient age, sex, oropharyngeal subsite (classified as palatine tonsil, tongue base, palatine arch/palate/uvula, posterior oropharyngeal wall, and oropharynx not otherwise specified), AJCC tumour stage, risk factor exposure (smoke, alcohol), disease history (recurrence, metastasis, second tumours), outcome and survival. Positivity for p16 and HR HPV DNA was required to classify HPV-related OPSCC. HPV-related tonsillar OPSCC increased significantly after 2010, while a non-significant reduction of HPV-related extra-tonsillar OPSCC was observed. Non-keratinising morphology was strongly associated with HPV positivity. HPV16 was the most common genotype; the frequency of other high-risk genotype infections decreased after 2010. At multivariate analysis, HPV status showed a significant association with better outcome. We documented an increase of HPV-related OPSCC in our Italian population, synchronous with the increase observed in several Western countries, which in recent years reached a prevalence similar to that reported in central European countries. Our results indicate that HPV infection in head and neck oncology is relevant in Italy and needs to be considered for accurate patient stratification.

KEY WORDS: Human papillomavirus • Oropharyngeal cancer • Prevalence • Oncogenic • HPV infection

RIASSUNTO

L'incidenza dei carcinomi squamosi dell'orofaringe (OPSCC) correlati all'infezione da papillomavirus umano (HPV) risulta essere in aumento in numerosi Paesi industrializzati, ma questo dato non è ancora stata confermato in Italia. Con l'obiettivo di analizzare i mutamenti occorsi nell'epidemiologia degli OPSCC HPV-correlati sono stati rivisti e confrontati i risultati delle indagini di caratterizzazione di HPV eseguite sui casi di OPSCC diagnosticati presso un singolo centro nell'Italia settentrionale prima e dopo il 2010, correlando anche con età, sesso, sottosede anatomica (tonsilla palatina, base della lingua, pilastri palatini/palato/ugola, parete posteriore dell'orofaringe e orofaringe non ulteriormente precisata), stadiazione TNM, fattori di rischio (fumo, alcol), evoluzione (recidiva, metastasi, secondo tumore), esito, e durata della sopravvivenza. Si è osservato un significativo aumento, dopo il 2010, dei tumori tonsillari HPV-correlati, riconosciuti in base all'espressione di p16 e alla positività per DNA di genotipi ad alto rischio, in parallelo con una riduzione non significativa dei casi di tumore HPV-correlato ad origine extratonsillare. HPV16 è risultato il genotipo più comune; la frequenza delle infezioni sostenute da altri genotipi ad alto rischio ha mostrato una riduzione dopo il 2010. All'analisi multivariata, lo stato di HPV risultava associato con una miglior prognosi. Nel nostro centro abbiamo documentato un aumento dei casi di OPSCC HPV-correlato che coincide temporalmente con quanto osservato in numerosi paesi occidentali; la prevalenza registrata è simile a quella riportata in altre nazioni del centro Europa. I risultati indicano che l'infezione da HPV ha un ruolo in oncologia otorinolaringoiatrica nel nostro paese, e deve essere tenuta in considerazione per un corretto inquadramento clinico dei pazienti.

PAROLE CHIAVE: *Papillomavirus umano • Cancro orofaringeo • Prevalenza • Infezione da HPV*

Introduction

In 2007, the World Health Organization (WHO) recognised that high risk human papillomavirus (HR HPV) genotypes are responsible for the development of a subset of oropharyngeal (OP) squamous cell carcinomas (SCC), and of a smaller proportion of oral carcinomas [1]. This observation, associated with the evidence of sexual transmission of HPV oropharyngeal infection, younger patient age, different exposure to conventional risk factors [2], and in particular a more favourable prognosis [3], has stimulated extensive studies aimed at better defining the epidemiology of HPV-associated tumours.

At the same time, the worldwide analysis of cancer registry data [4] has provided evidence of increasing incidence rates of oropharyngeal cancer in several economically developed countries, especially among men < 60 years old, despite the concomitant declining incidence of tobacco-related oral cavity SCC. This trend, particularly relevant in North America and northern European countries, has strongly suggested a change in risk factors, supported by a series of individual studies and meta-analyses that documented a sharp increase in the prevalence of OPSCC attributable to oncogenic HPV infection over the last decades [5]. The most recent worldwide estimates for HPV-attributable OPSCC amount to 18-28% [5], but a recent large international study documented high variability among geographical areas [6]. In particular, the HPV-attributable fraction was lowest in southern Europe (7.6%) than in any other considered area (South America, central-eastern Europe, northern Europe, eastern Asia, central America, western Europe) in samples collected over a long time interval (1990-2012). Moreover, only part of the published single-population studies employed methods that discriminate oncogenic from incidental HPV infection, further impairing data comparison. Similarly, the projections on the increase of HPV-related OPSCC in the United States population over the next decade can not be reliably applied to other populations [7]. OPSCC HPV status is expected to impact patient treatment choices: retrospective and prospective data show that HPV-related OPSCC is associated with better prognosis, in particular in patients with locoregionally advanced diseases, and several de-intensified treatment trials are currently undergoing evaluation [8 9].

At variance with other Western countries, national cancer registries in Italy are lacking, and the coverage by local registries is heterogeneous in terms of geographical distribution and recorded tumour types (http://www.registri-tumori.it/cms/en). Neither nationwide data on oral and oropharyngeal SCC prevalence nor data on the prevalence of HPV infection in the oral cavity and in oral and oropharyngeal cancers are available. According to the Cancer Incidence in Five Continents Registry, a moderate parallel reduction of both oral and oropharyngeal cancer incidence has occurred in Italy over the last [3] decades [4]. A recent meta-analysis reporting OPSCC prevalence and HPV involvement in 29 countries suggested that HPV-related OPSCC in southern Europe are less frequent than in northern Europe and America [10]. Small single-centre studies suggest a lower but nonetheless increasing prevalence of HPV-related OPSCC: two studies published by the same institution in Milan with a 6-year interval reported a prevalence increasing from 17% [11] to 50% [12]; furthermore, two recent studies reported that HPV infection was responsible of 32% and 39.8% of in two consecutive series collected in different Roman institutions between 2009-2011 and 2010-2014 [13 14].

The head and neck tumour board at the Foundation IRCCS Policlinico San Matteo and University of Pavia has been investigating HPV infection in retrospective and prospective tumour series since 2003 [15 16]. In the present study, we reviewed all previously collected data in order to assess changes occurred in the epidemiology of OPSCC with respect to HPV infection in the population referring to our centre over the last two decades.

Materials and methods

Patient series and data collection

We retrospectively analysed the charts of the Pathology Unit to collect SCC cases occurring at any oropharyngeal subsite since 1992, when the digital archive of the Unit was started. For each patient, the following data were retrieved, when available: age, gender, anatomical tumour site (classified as palatine tonsil, tongue base, palatine arch/palate/uvula, posterior oropharyngeal wall and oropharynx not otherwise specified), tumour stage according to the American Joint Committee on Cancer (AJCC) staging system [17], risk factor exposure (smoke, alcohol), disease history (recurrence, metastasis, second tumours in the area), outcome, disease-free survival, overall survival, and HPV testing methods and results. The histological slides of all cases tested for HPV were also reviewed to record the presence of tumour cell keratinisation. HPV analysis was performed in compliance with relevant laws and institutional guidelines, and in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all patients at the time of testing. The study protocols were approved by the Institutional Ethical Review Board.

HPV testing

To define OPSCC HPV status we applied a validated diagnostic algorithm [16], slightly modified with respect to those previously published [18 19], which includes p16 immunostaining, HR HPV DNA in situ hybridisation (ISH) and HPV genotyping. Positivity for p16 and HR HPV DNA (by ISH and/or PCR) was required to classify HPV-related OPSCC. All tests were performed according to recently described protocols [16]. Cases that at chart review had ambiguous results or only partial testing were completed according to the algorithm employing the most recent test version. In particular, cases with positive p16 immunostaining that resulted negative for HR-HPV or positive for non-HPV16 HR genotypes underwent specific amplification of the E6 gene of HPV16 [16].

For immunohistochemical detection of p16, the CINtec® Histology Kit (Roche MTM Laboratories AG, Heidelberg, Germany) was used according to the manufacturer's instructions on a Ventana BenchmarkTX automated stainer (Ventana Medical Systems Inc., Tucson, AZ). Samples of high grade cervical intraepithelial lesions were used as positive controls. Strong and diffuse nuclear and cytoplasmic staining in > 70% of tumour cells was considered as positive according to previous studies [3 14]. HPV DNA ISH was performed with the INFORM-HPV III family 16 probe using the ISH I View Blue Plus Detection Kit according to the manufacturer's instructions, on a Ventana BenchmarkTX automated stainer. Any definitive (diffuse or dot-like) nuclear staining in tumour cells was considered positive. Cases were classified in a binary manner as either positive or negative. DNA extraction and HPV typing were performed according to previously reported protocols, using the INNO-LiPA HPV genotyping assay version Extra and Extra II (Fujirebio Europe, Ghent, Belgium). The Extra version of the assay allows the simultaneous and separate detection of 18 HR (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82), 7 low risk (LR) (6, 11, 40, 43, 44, 54 and 70), and 2 unclassified HPV types (69/71 and 74). Hybridisation patterns were analysed with the specific scanner Line reader and Analysis Software (LiRAS) for LiPA HPV and the results were confirmed by two independent readers. For HPV16 E6 PCR the DNA was amplified using a primer pair (3': CCATGCATGATTACAGCTGG; 5': GAACAGCAATACAACAAACCG) that amplifies a 201bp fragment within the E6 gene of HPV16 [16]. Amplification parameters were 94°C 10', followed by 95°C 30", 60°C 15", 72°C 30" for 35 cycles, and 72°C 5' final extension. Amplified products were analysed by electrophoresis on 2% agarose gel. SiHA cells containing a known number of HPV16 DNA copies and blank reagents were used as positive and negative controls in each PCR run, respectively.

Statistical analysis

The Shapiro-Wilk test was used to test the normal distribution of quantitative variables: if quantitative variables were normally distributed, the mean value and standard deviation (SD) were reported; otherwise results were expressed as median and interquartile range (IQR). Qualitative variables were summarised as counts and percentages. Comparisons among categorical data were analysed by chi square or Fisher's exact test, as appropriate. Univariate and multivariate (including factors significantly associated with survival at univariate analysis) Cox models were fitted to study overall survival (OS) and disease-free survival (DFS); the results were expressed as hazard ratio (HR) with their 95% confidence interval (CI). As a sensitivity analysis a competing risk model was also fitted. To avoid bias due to missing loco-regional recurrence (LRR) data, a multiple imputation model for missing data was fitted taking into account gender, age, survival, HPV, T stage, M1, surgical treatment, keratinising tumour phenotype. A total of 10 datasets were created and used as a sensitivity analysis. All tests are two-sided, a p-value < 0.05 was considered as significant. All analyses were performed with STATa 14.1 (StataCorps, College Station, USA).

Results

Approach to HPV testing

For the study purposes, OPSCC patients were divided in 2 groups according to the time of diagnosis, before and after 2010. There were 175 newly diagnosed OPSCC before 2010, and 81 between 2010 and November 2015. HPV status had been determined in 124 patients, 53 (30.2%) before 2010 and 71 (87.6%) after. Reasons for HPV testing of OPSCC diagnosed before 2010 were patient enrolment in study protocols [15], or the occurrence of a new oropharyngeal primary tumour after 2010; since 2010, the diagnostic evaluation of OPSCC approved by the institutional tumour board included the assessment of HPV status in all new cases. Referrals from other centres that provided HPV testing and/or patients with advanced disease with no therapeutic indication account for the untested cases after 2010. Age, sex, stage and risk factor distribution in tested and untested patient groups is detailed in Table I. The patient first-line treatment included surgery, chemotherapy and radiotherapy with different modalities according to the evolving standards of care over the period included in the study. The two populations significantly differed for a higher proportion of moderate/heavy drinkers ($p = 0.033$) and tumour recurrences ($p = 0.03$) in the untested population after 2010. In this group, we also observed a significantly ($p < 0.000$) shorter DFS, consequent

to the exclusion of the most advanced cases from HPV testing. The anatomical distribution of tumours was similar in tested and untested cases (Table II); before 2010, tonsillar SCC were tested more frequently (p = 0.02) than tumours occurring at other oropharyngeal subsites, while after 2010 no selection took place based on tumour site within the oropharynx.

HPV-associated OPSCC epidemiology

Evidence of transcriptionally active HR HPV infection was found in 47 cases (37.9%). HPV-related OPSCC became more frequent after 2010 (32, 45% vs 15, 28.3%), but the difference did not reach significance (p = 0.06). Comparing tumours involving at least one tonsillar subsite (palatine tonsil and base of tongue) with those only involving extra-tonsillar subsites, respectively, 44.7% and 14.2% were positive (p = 0.003). In tonsillar SCC, the proportion of HPV-related cases increased significantly after 2010 (31.7% before, 54.5% after, p = 0.03), while a modest non-significant reduction of HPV-related extra-tonsillar tumours was observed (16.6% vs 12.5%). Considering the difficulty of a precise clinical definition of tumour origin, especially in advanced cases, the morphological characters of tumours were also taken into account. Non-keratinising tumour phenotype was strongly associated with HPV positive status in the overall series (p < 0,0001): 58.8% of non-keratinising tumours were HPV-positive, compared to 12.5% of those showing cell maturation and keratinisation. Among non-keratinising tumours, 50% were HPV-related before 2010, and 63.6% after (ns), vs 10.6% and 14.8% of keratinising tumours (ns). Previous palatine tonsillectomy was reported by 12 patients. Five had an HPV-associated OPSCC, involving in all cases the lingual tonsil and showing the non-keratinising phenotype.

HPV infection distribution and features

Overall, 87 (70.1%) cases were positive for HPV DNA. The proportion of DNA-positive cases did not significantly increase over time (69.8% before 2010 and 71.8% after). HR HPV DNA was found in 56.3% of cases before 2010, and 60.3% after (ns). Beside OPSCC with evidence of oncogenic viral activity (i.e. p16 expression), HR HPV DNA was observed in 25 of the 77 (32.4%) p16-negative tumours, suggesting passenger infection. The proportion of HPV-unrelated tumours hosting passenger

Table I. Comparison of clinical features of HPV-investigated and not investigated OPSCC patient groups.

Group	Sex	Age (years)	Stage[a]				Surgery	Smoke[a]	Alcohol[a]	Recurrence[a]		DSD[a]	FU[a] (months)
	M/F	Mean ± SD	0-1	2	3	4	T/N	Y/N[b]	Y/N[c]	Y/N	DFS (months)	Y/N	
1992-2010	142/33	59.5 ± 9.6	9	25	37	69	49/45	24/27	32/10	63/18	57.8 ± 50.4	49/91	69.7 ± 54.1
Tested	45/8	59.9 ± 10.2	4	13	15	21	20/20	14/15	12/7	22/3	60.1 ± 52.7	24/24	74.8 ± 58.1
Untested	97/25	58.1 ± 10.72	5	12	22	48	29/25	10/12	20/3	41/15	54.2 ± 45.2	25/67	60 ± 44.3
p	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns	Ns			
2011-2015	65/16	63.5 ± 10.4	6	6	19	48	32/33	48/22	36/25	15/44	23.9 ± 14.4	17/60	22.0 ± 14.4
Tested	56/15	63.8 ± 10.3	5	6	16	43	25/25	42/21	29/25	11/42	25.2 ± 14.6	17/53	22.1 ± 14.7
Untested	9/1	61.5 ± 11.7	1	0	3	5	7/8	6/1	7/0	4/2	12.5 ± 4.5	0/7	20.7 ± 12.6
p	Ns	Ns	Ns	Ns	Ns	0.033	0.031	0.000	Ns	Ns			

a: data not available for the complete case series; b: never smoker or former smoker (any number) quitting more than 5 years before cancer diagnosis; c: clinical or laboratory evidence of alcoholism; M: male; F: female; SD: standard deviation; Y: yes; N: no; DFS: disease-free survival; DSD: disease-specific death; FU: follow-up; Ns: not significant.

Table II. Comparison of oropharyngeal subsite involvement in tested and untested OPSCC patients.

Group	Palatine tonsil[a]	Base of tongue[a]	Palatine arch[a]	Posterior wall[a]	NOS
1992-2010	74	74	37	2	8
Tested - n (%)	30 (40.5)	13 (17.5)	11 (29.7)	2 (100)	4 (50)
p[b]	0.02	Ns	Ns	Ns	Ns
2010-2015	30	45	27	1	4
Tested - n (%)	29 (96.6)	37 (82.2)	26 (96.2)	1 (100)	3 (75)
p[b]	Ns	Ns	Ns	Ns	Ns
Total	104	109	64	3	12
Tested - n (%)	59 (56.7)	50 (45.8)	37 (57.8)	3 (100)	7 (18.5)
p[b]	0.03	Ns	Ns	Ns	Ns

a: more than one subsite could be involved in the same patient; b: compared with all other sites combined; NOS: not otherwise specified; Ns: not significant.

HR HPV DNA was 30.1% before 2010 and 11.2% after (p = 0.01). Analysing the correlation between HPV infection and anatomical subsite, HPV infection rate was not different in tonsillar and extratonsillar tumours (71.1 and 70%), however, HR genotypes, independently of their oncogenic activity, were significantly more common at tonsillar (63.9 vs 25%, p = 0.002), and LR at extratonsillar sites (19.5 vs 45%, p = 0.01); furthermore, the non-keratinising phenotype was significantly associated with any (82.3 vs 51.1%, p = 0.002) and HR HPV infection (70.5 vs 41%, p = 0.001), while no difference was observed for LR HPV infections (19.1 vs 25%).

HPV16 was the most common genotype, being present in 55 cases (63.2% of the 87 cases positive for HPV DNA, and 77.4% of the 71 cases positive for HR genotypes) (Table III). It was identified in 85% of 47 oncogenic and in 62.5% of 24 passenger HR HPV infections. The proportion of HR infections sustained by HPV16 was significantly higher after 2010 (36 of 40 HR HPV DNA-positive cases, 90%), while in the previous period 12 of 31 (38.7%) HR HPV DNA-positive cases were negative for HPV16 and showed different single or multiple HR genotypes (p = 0.008). The proportion of oncogenic and passenger HR infections due to HPV16 was not significantly different before and after 2010. Of the 7 oncogenic infections negative for HPV16, before 2010 one was positive for HPV52, one for HPV31 and 2 for uncharacterised genotypes (considered to be HR for positive p16 and ISH results); after 2010, one was positive for HPV35, one for HPV51 and 52, and the last case was positive for uncharacterised genotypes. Coinfections with more than one HR genotype were observed in 7 oncogenic and 3 passenger infections before 2010, and in 6 oncogenic infections after. HPV52 was present in 11 cases, HPV31, 35 and 56 in 4 cases each, HPV51 in 3, HPV45 in 2, and HPV18, 33, 39 and 59 in 1 case each. Coinfection with low and intermediate risk genotypes were also observed. The overall number of HR non-HPV16 individual infections was 25 in 17 patients before 2010 (one case confected by 5 HR genotypes and 3 cases by 3), and 11 in 8 patients after (2 cases coinfected by 2 genotypes, beside HPV16). Non HPV16 HR genotypes, either isolated or associated with HPV16, were significantly more frequent before 2010 than after (p = 0.002), and in passenger than in oncogenic infections (15 of 24 vs 11 of 47, p = 0.001). The number of passenger infections involving non-16 HR genotypes was significantly higher before 2010 than after (87.5%, vs 12,5, p < 0.001), while 36.3% and 21.8% of oncogenic infections had non-16 genotypes in the two periods (ns), respectively.

Clinical and prognostic correlations

Age, sex, proportion of cases treated with surgery and AJCC stage distribution was similar in HPV-related and unrelated tumours in the overall series and two time periods. Tobacco smoke and alcohol consumption were significantly less frequent in HPV-related cases (p = 0.002 and 0.007, respectively) in the overall series (Table IV). Complete response to therapy was more frequent in HPV-positive patients in the whole series (p = 0.001) (Table V) and in the most recent cohort (p = 0.002). In patients with complete response, LRR was significantly less frequent in HPV-related cases in both cohorts, while distant metastases were rare and not significantly different; DFS was significantly longer in HPV-positive patients only in cases diagnosed in the 2001-2010 period (p = 0.03). Disease-specific deaths were significantly more frequent in HPV-negative patients in both cohorts (p = 0.001 and 0.01).

Cox proportional hazard analysis showed that OS was significantly associated with LRR (p < 0.001), T stage ≥ 2 (p = 0.004), M1 (p < 0.001), HPV status (p < 0.001) and keratinising tumour phenotype (p = 0.02). At multi-

Table III. HR HPV genotype distribution.

Genotype distribution	HPV DNA+ (n = 87)	HR HPV DNA+ (n = 71)	Oncogenic infection (n = 47)	Passenger infection (n = 24)
HPV 16+ (n = 55)	63.2%	77.4%	85.1% (40)	62.5% (15)
Before 2010 (n = 19)	51.3% (19/37)	61.2% (19/31)	73.3% (11/15)	50% (8/16)
After 2010 (n = 36)	72% (36/50)	90% (36/40)	90.6% (29/32)	87.5% (7/8)
p	Ns	0.008	Ns	Ns
HR non-16 infections (n = 26)	29.8%	36.6%	23.4% (11)	62.5% (15)
Before 2010 (n = 18)	48.6% (18/37)	58% (18/31)	36.3% (4/15)	87.5% (14/16)
After 2010 (n = 8)	16% (8/50)	20% (8/40)	21.8% (7/32)	12.5% (1/8)
p	0.002	0.002	ns	< 0.001
HR coinfections (n = 16)	18.3%	22.5%	19.1% (9)	29.1% (7)
Before 2010 (n = 10)	27% (10/37)	32.2% (10/31)	20% (3/15)	66.6% (7/16)
After 2010 (n = 6)	12% (6/50)	15% (6/40)	18.7% (6/32)	0 (0/8)
p	Ns	Ns	Ns	0.05

Ns: not significant.

variate analysis, HPV status (p = 0.001), together with T stage ≥ 2 (p = 0.009) and M1 (p = 0.001), showed a significant association with OS. The sensitivity analysis on 10 imputed datasets showed similar results: HPV status (HR: 0.37, 95%CI: 0.16-0.87, p = 0.022) was significantly associated with mortality reduction, LRR and M1 with an increase (HR: 2.94, 95% CI: 1.25-6.96, p = 0.015 and HR: 4.39, 95% CI: 1.55-12.30, p = 0.005 respectively). Considering the 9 deaths for other causes as a competing risk, HPV, M1 and LRR were still associated with mortality in the same way. DFS was associated with HPV status (p = 0.001), smoking (p = 0.04) and keratinising tumour phenotype (p = 0.01), but only HPV status remained significant at multivariate analysis (p = 0.01) (Fig. 1). The sensitivity analysis on 10 imputed datasets showed similar results: HPV (HR: 0.17, 95% CI: 0.06-0.46, p < 0.001) was significantly associated with DFS.

Discussion

Several studies and meta-analyses have documented the increase of HPV-related OPSCC incidence over the last decades; Finland, United Kingdom, United States and Sweden are the most affected countries [10]. Our experience, although limited to a single institution in Northern Italy, similarly showed an increase in the proportion of OPSCC that could be attributed to HPV infection from 28.3% in the period 1992-2010, to 45% in 2011-2015. To our knowledge, this is the first report of an increase in HPV-related OPSCC case number in an Italian population over the same time interval as the increase observed in other Western countries. Recent single-centre retrospective studies from central European countries with low-to-intermediate prevalence of HPV-related OPSCC reported comparable rates of HPV-related OPSCC (40-50%) in the most recent cohorts, with a similar increasing trend [20 21]. HPV-related OPSCCs rates in our series, on the other hand, are higher than those registered in other southern European countries [6], and provide evidence that the role of HPV infection in head and neck oncology is relevant in Italy and needs to be considered for accurate patient stratification.

Thanks to a better definition of the criteria used to classify HPV-associated tumours [22], emerging evidence in comparative studies shows that the geographic distribution of OPSCC and of their HPV attributable fraction, as well as the prevalence of non-oncogenic HPV infections, are highly heterogeneous [6 10]. The impact of different tobacco and alcohol exposure has been proposed as a causative factor, although 10-30% of HPV-related OPSCC occur in heavy smokers and/or drinkers [23], as was the case in our cohort. As far as Italy is concerned, previous single-centre reports, including ours, suggest an higher prevalence in northern (40-50%) than in central and northeastern Italy (29-40%) [11-16 24]. Differences in HPV-related OPSCC prevalence within a single country have been reported elsewhere [25], and, although heterogeneous testing algorithms are powerful confounders, it is not unexpected that the geographical and ethnic complexity of the Italian population [26] be reflected in a highly heterogeneous distribution of HPV infection and HPV-related cancers.

The cohort of HPV-related OPSCC in our series shared only some of the clinical features that have been associated with this subgroup of tumours. Patients with HPV-related OPSCC were more likely than those with HPV-unrelated cancers to be never or former smokers and non-drinkers,

Table IV. Comparison of clinical features and risk factor exposure in HPV-related and unrelated OPSCC patients.

Group	Sex	Age (years)	Stage[a]				Surgery	Smoke[a]	Alcohol[a]
	M/F	Mean ± SD	0-1	T/N	3	4	T/N	Y/N[b]	Y/N
1992-2010	45/8	58.1 ± 10.7	4	13	15	21	20/18	28/6	23/12
HPV +	10/5	56.7 ± 10.7	2	3	4	6	8/6	4/4	5/3
HPV -	35/3	58.6 ± 10.8	2	10	11	15	12/12	24/2	18/9
p	0.03	Ns	Ns				Ns	0.01	Ns
2010-2015	56/15	63.8 ± 10	6	6	16	43	22/25	41/21	29/25
HPV +	27/5	63.7 ± 10	1	3	8	20	11/14	15/13	8/17
HPV -	29/10	63.9 ± 10	5	3	8	23	10/11	26/8	21/8
p	Ns	Ns	Ns				Ns	0.06	0.006
Total	101/23	61.4 ± 10.8	10	19	31	63	44/43	69/27	52/37
HPV +	37/10	61.5 ± 11.1	3	6	12	25	19/20	19/17	13/20
HPV -	64/13	61.3 ± 10.6	7	13	19	38	22/23	50/10	39/17
p	Ns	Ns	Ns				Ns	0.002	0.007

a: data not available for the complete case series; b: never smoker or former smoker quitting more than 5 years before cancer diagnosis; M: male; F: female; SD: standard deviation; Y: yes; N: no; Ns: not significant.

Table V. Comparison of outcomes in HPV-related and unrelated OPSCC patients.

Group	CR[a]	LRR[a]	DR[a]	DFS[a]	DSD[a]
	Y/N	Y/N	Y/N	Median (IQR)	Y/N
1992-2010	40/9	19/21	5/35	34 (12-65)	25/24
HPV +	14/1	2/12	0/14	65.5 (60-90)	2/13
HPV -	26/8	17/9	5/21	24 (8-60)	23/11
p	Ns	0.003	Ns	0.001	0.001
OR (95% CI)	4.3 (0.4-101)	0.08 (0.01-0.5)	0 (0-2.1)		0.07 (0.009-0.4)
2010-2015	54/17	9/45	2/52	17 (8-36)	17/53
HPV +	30/2	2/28	2/28	21.5 (12-38)	3/29
HPV -	24/15	7/17	0/24	15 (7-27)	14/24
p	0.002	0.06	Ns	Ns	0.01
OR (95% CI)	9.3 (1.7-66)	0.17 (0.2-1.08)			0.17 (0.03-0.7)
Total	94/26	28/66	7/96	22 (10-42.5)	42/77
HPV +	44/3	4/40	2/41	30.5 (13-54)	5/42
HPV -	50/23	24/26	5/45	16 (8-42)	37/35
p	0.001	< 0.001	Ns	0.018	< 0.001
OR (95% CI)	6.7 (1.7-30.4)	0,1 (0.02-0.3)	0.4 (0.05-2.7)		0.11 (0.03-0.3)

CR: complete response; LRR: loco-regional recurrence; DR: distant recurrence; DFS: disease-free survival; DSD: disease-specific death; Y: yes; N: no; IQR: interquartile range; Ns: not significant; OR: odds ratio; CI: confidence interval; a: data available only for subsets of cases.

although over half were current smokers. Age distribution was the same in the two groups. This observation can be explained with the persistently high prevalence of active smokers in our population even among young people, although sexual habits could also have an influence. AJCC stage distribution did not differ in HPV-related and unrelated OPSCC. Despite that, HPV status was strongly associated with complete response to therapy and reduced LRR and DSD risk, and was a strong predictor of both DFS and OS, in accordance with previous reports [4]. Prognosis was also influenced by T but not N stage. Recently, the 8th edition of the AJCC classification updated N status in HPV-related OPSCC, reflecting the common observation that the previous classification did not accurately reflect prognosis in HPV-related OPSCC [27].

Evidence suggests that HPV-associated OPSCC develop as a consequence of HPV infection of tonsillar epithelium [28], but the diagnostic and predictive utility of this topographic association is not clear yet. Our experience indicates that a precise identification of the anatomical origin of the tumour within the oropharynx can be difficult at imaging and clinical evaluation, in particular for tumours that involve more than one oropharyngeal subsite, and that a non-keratinising tumour phenotype is more

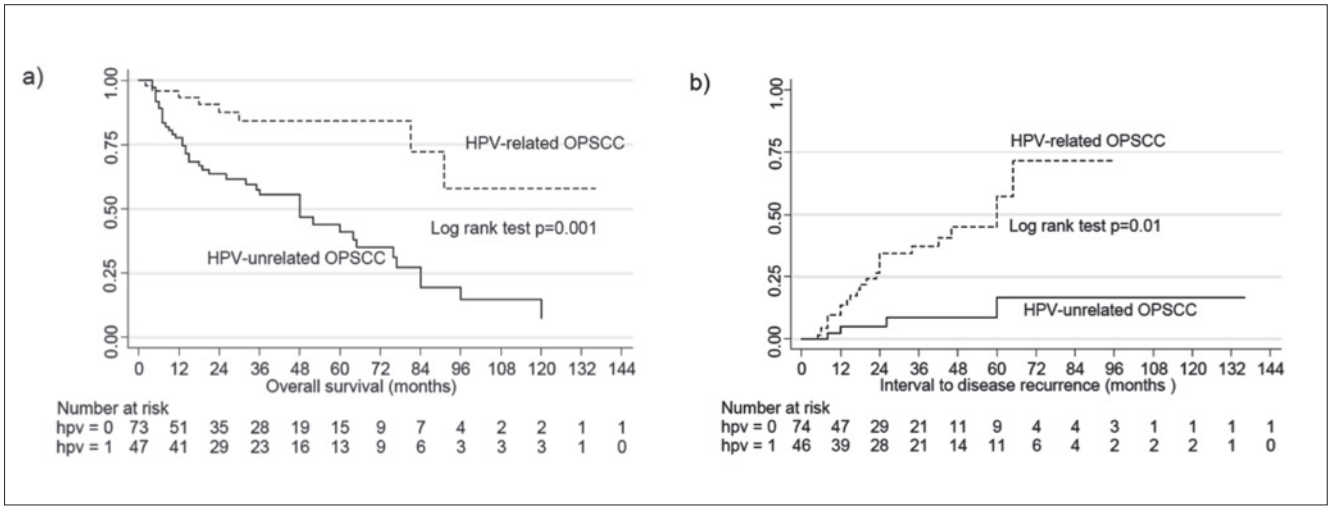


Fig. 1. Overall survival and time to recurrence for HPV-related and unrelated OPSCC patients.

strongly associated with HPV-related oncogenesis than its anatomical location. Garnaes et al. [29] recently combined imaging and pathological parameters to classify tumour origin in a registry-derived OPSCC series form eastern Denmark, documenting a 2.7% yearly increase of tonsillar-based tumours in the years 2000-2010, which was explained with an increase of HPV-related cases (from 68% in 2000 to 82% in 2010). In our series, we similarly found a significant increase of HPV-related cases after 2010 among tumours with anatomical involvement of the tonsils, although defined by different criteria and also including palatine tonsils; this increase was associated with an increase of non-keratinising OPSCC. It is important to notice, however, that HPV status was the only significant prognostic predictor in multivariate analysis, while neither tumour topography nor morphology impacted the risk of recurrence or patient survival. The latter should not be used to pre-select cases to submit to HPV testing, but rather all OPSCC should be tested to provide patients with adequate care. From a pathogenic point of view, the relationship between HPV infection and squamous cell keratinisation remains a matter of study. The occurrence of typical keratinising OPSCC hosting oncogenic HPV infection observed in our and other series [30] suggests that either HPV oncogenesis is not restricted to crypt epithelium and may as well involve the tonsillar surface, or that transformed crypt cells can undergo keratinisation (a phenomenon observed in ageing crypts).

In a present study, we confirmed in OPSCC, 70% of which were positive for HPV DNA, our previous observation of a high prevalence of HPV infection in tumour and oral cell samples of HNSCC patients [15]. The rate of HPV-DNA positive cases did not change over time, and is at least partially related to the high sensitivity of SPF10-LiPA amplification and genotyping platform. However, we observed that after 2010 oncogenic infections became more frequent and passenger HR infections, mostly sustained by HR-HPV non-16 genotypes, were less common. We have no explanation for this epidemiological shift, considering that the methods of analysis were the same in the entire cohort and that tests on the older samples were repeated to confirm the original results. It is clear that the distribution of HPV genotypes within a population is influenced by several factors, including evolving sexual behaviours, migratory trends, and more recently vaccination campaigns, and thus changes over time [31 32]. The lack of recent epidemiological data on the evolution of HPV infection distribution in Italy, and on sexual attitudes of the study cohorts impairs an explanation of this trend. Although the majority of oncogenic infections could be attributed to HPV16, as widely reported, isolated non-HPV-16 oncogenic infections were responsible for 15% of OPSCC. A recent large international study reported a similar proportion (12%) of non-HPV16 HR infections detected with SPF10LiPA in OPSCC [6]; in a comprehensive meta-analysis, their prevalence varied between 0.1% and 1.6% in OPSCC series from different geographical regions [10]; in both studies, however, the oncogenic role of non-HPV16 HR infections was not specified. The full extent of the involvement of these genotypes in OPSCC neoplastic transformation is still unclear. These observations support the use of broad-spectrum genotyping tests, and of more than one DNA-based test to reduce the risk of false negative results.

Our study clearly suffers of several limitations, in particular the lack of information on how OPSCC prevalence has changed in our geographical area in the considered time interval. The impact of therapy on patient outcomes could not be fully evaluated because of the remarkable changes occurred in treatments offered to patients over the time covered by the study. Finally, the retrospective quality of the study prevented a complete analysis of risk factor exposure, including sexual behaviours, which would have proven useful to explain the high prevalence of HR passenger infections.

Conclusions

The results of the present single centre experience highlight the urge for extensive national registries to map the geographic distribution and time evolution of tumours associated with actionable risk factors, and for the collaboration of the scientific societies involved. In particular, the evaluation of the impact that HPV vaccination will have on the epidemiology of oropharyngeal cancer in the younger generations will require more accurate monitoring and classification of these cancers and their correlation with exposure data.

Acknowledgements

This work was supported by grants RC08017800/12, RC08053903/12 and RF-2011-02351315 from the Italian Health Ministry to the IRCCS Policlinico San Matteo Foundation, Pavia, G11961 from Associazione Italiana per la Ricerca sul Cancro (AIRC).

Conflict of interest statement

None declared.

References

1 International Agency for Research on Cancer (IARC). *Monographs on the evaluation of carcinogenic risks to humans, in human papillomaviruses*. Lyon, France: World Health Organization; 2007.

2 Gillison ML, D'Souza G, Westra W, et al. *Distinct risk factor profiles for human papillomavirus type 16-positive and human papil-*

lomavirus type 16- negative head and neck cancers. J Natl Cancer Inst 2008;100:407-20.

3 Ang KK, Harris J, Wheeler R, et al. *Human papillomavirus and survival of patients with oropharyngeal cancer*. N Engl J Med 2010;363:24-35.

4 Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. *Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers*. J Clin Oncol 2013;31:4550-9.

5 Gillison M, Chaturvedi AK, Anderson WF, et al. *Epidemiology of human-papillomavirus-positive head and neck carcinoma*. J Clin Oncol 2015;33:3235-42.

6 Castellsagué X, Alemany L, Quer M, et al. *HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients*. J Natl Cancer Inst 2016;108:djv403.

7 Chaturvedi AK, Engels EA, Pfeiffer RM, et al. *Human papillomavirus and rising oropharyngeal cancer incidence in the United States*. J Clin Oncol 2011;29:4294-301.

8 Psyrri A, Rampias T, Vermorken JB. *The current and future impact of human papillomavirus on treatment of squamous cell carcinoma of the head and neck*. Ann Oncol 2014;25:2101-15.

9 Bhatia A, Burtness B. *Human papillomavirus-associated oropharyngeal cancer: defining risk groups and clinical trials*. J Clin Oncol 2015;33:3243-50.

10 Ndiaye C, Mena M, Alemany L, et al. *HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis*. Lancet Oncol 2014;15:1319-31. Erratum in: Lancet Oncol 2015;16:e262.

11 Licitra L, Perrone F, Bossi P, et al. *High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma*. J Clin Oncol 2006;24:5630-6.

12 Granata R, Miceli R, Orlandi E, et al. *Tumor stage, human papillomavirus and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study*. Ann Oncol 2012;23:1832-7.

13 Bussu F, Sali M, Gallus R, et al. *Human papillomavirus (HPV) infection in squamous cell carcinomas arising from the oropharynx: detection of HPV DNA and p16 immunohistochemistry as diagnostic and prognostic indicators - a pilot study*. Int J Radiat Oncol Biol Phys 2014;89:1115-20.

14 Donà MG, Spriano G, Pichi B, et al. *Human papillomavirus infection and p16 overexpression in oropharyngeal squamous cell carcinoma: a case series from 2010 to 2014*. Future Microbiol 2015;10:1283-91.

15 Morbini P, Dal Bello B, Alberizzi P, et al. *Oral HPV infection and persistence in patients with head and neck cancer*. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:474-8.

16 Morbini P, Alberizzi P, Tinelli C, et al. *Identification of transcriptionally active HPV infection in formalin-fixed, paraffin-embedded biopsies of oropharyngeal carcinoma*. Hum Pathol 2015;46:681-9.

17 Edge SB, Byrd DR, Compton CC, et al. *AJCC cancer staging manual*. Seventh Edition. NY: Springer; 2010.

18 Smeets SJ, Hesselink AT, Speel EJ, et al. *A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen*. Int J Cancer 2007;121:2465-72.

19 Thavaraj S, Stokes A, Guerra E, et al. *Evaluation of human papillomavirus testing for squamous cell carcinoma of the tonsil in clinical practice*. J Clin Pathol 2011;64:308-12.

20 Grisar K, Dok R, Schoenaers J, et al. *Differences in human papillomavirus-positive and -negative head and neck cancers in Belgium: an 8-year retrospective, comparative study*. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;12:456-60.

21 Melchers LJ, Mastik MF, Samaniego Cameron B, et al. *Detection of HPV-associated oropharyngeal tumours in a 16-year cohort: more than meets the eye*. Br J Cancer 2015;112:1349-57.

22 Westra WH. *Detection of human papillomavirus (HPV) in clinical samples: evolving methods and strategies for the accurate determination of HPV status of head and neck carcinomas*. Oral Oncol 2014;50:771-9.

23 Smith EM, Rubenstein LM, Haugen TH, et al. *Complex etiology underlies risk and survival in head and neck cancer human papillomavirus, tobacco, and alcohol: a case for multifactor disease*. J Oncol 2012:571862.

24 Baboci L, Holzinger D, Boscolo-Rizzo P, et al. *Low prevalence of HPV-driven head and neck squamous cell carcinoma in North-East Italy*. Papillomavirus Res 2016;2:133-40.

25 Quabius ES, Haag J, Kühnel A, et al. *Geographical and anatomical influences on human papillomavirus prevalence diversity in head and neck squamous cell carcinoma in Germany*. Int J Oncol 2015;46:414-22.

26 Capocasa M, Anagnostou P, Bachis V, et al. *Linguistic, geographic and genetic isolation: a collaborative study of Italian populations*. J Anthropol Sci 2014;92:201-31.

27 O'Sullivan B, Lydiatt WM, Haughey BH, et al. *HPV-mediated (p16+) oropharyngeal cancer*. In: *AJCC cancer staging manual.* Eighth Edition. NY: Springer; 2017.

28 Kim SH, Koo BS, Kang S, et al. *HPV integration begins in the tonsillar crypt and leads to the alteration of p16, EGFR and c-myc during tumor formation*. Int J Cancer 2007;120:1418-25.

29 Garnaes E, Kiss K, Andersen L, et al. *Increasing incidence of base of tongue cancers from 2000 to 2010 due to HPV: the largest demographic study of 210 Danish patients*. Br J Cancer 2015;113:131-4.

30 Cai C, Chernock RD, Pittman ME, et al. *Keratinizing-type squamous cell carcinoma of the oropharynx: p16 overexpression is associated with positive high-risk HPV status and improved survival*. Am J Surg Pathol 2014;38:809-15.

31 Dal Bello B, Spinillo A, Alberizzi P, et al. *Time trends of human papillomavirus type distribution in italian women with cervical intraepithelial neoplasia (CIN)*. Gynecol Oncol 2009;115:262-6.

32 Bosch FX, Burchell AN, Schiffman M, et al. *Epidemiology and natural history of human papillomavirus infections and type specific implications in cervical neoplasia*. Vaccine 2008;26(Suppl 10):K1-16.

Received: August 16, 2017 - Accepted: November 27, 2017

How to cite this article: Morbini P, Alberizzi P, Ferrario G, et al. *The evolving landscape of human papillomavirus-related oropharyngeal squamous cell carcinoma at a single institution in Northern Italy.* Acta Otorhinolaryngol Ital 2019;39:9-17. https://doi.org/10.14639/0392-100X-1905

Address for correspondence: Patrizia Morbini, Department of Molecular Medicine, Unit of Pathology, via Forlanini 16, 27100 Pavia, Italy. Tel. +39 0382 501240. E-mail: patrizia.morbini@unipv.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:18-21; doi: 10.14639/0392-100X-1720

LARYNGOLOGY

Suture lateralisation plus arytenoid cartilage release for treating bilateral vocal fold immobility with mechanical fixation

Lateralizzazione mediante sutura e rilascio aritenoideo per il trattamento dell'immobilità cordale bilaterale con fissazione meccanica

W.-F. SU[1], M.-C. LAN[1], S.-C. LIU[2]

[1] Department of Otolaryngology Head and Neck Surgery, Taipei Tzu Chi Hospital, Buddist Tzu Chi Medical Foundation, New Taipei City, Taiwan, School of Medicine, Tzu Chi University, Hualien; [2] Department of Otolaryngology Head and Neck Surgery, Tri-service General Hospital, National Defense Medical Center Taipei, Taiwan, Republic of China

SUMMARY

A suture lateralisation (SL) instead of an endolaryngeal tissue ablation procedure under endoscopy has been utilised to treat bilateral vocal fold immobility (BVFI) since 1980. However, mechanical fixation (MF) of the cricoarytenoid joint (CAJ) has continually challenged the effectiveness of glottic dilatation both in the SL procedure and the tissue ablation procedure. From 2007 to 2015, a total of 38 patients with BVFI underwent 40 exo-endolaryngeal suture lateralisation (exoeSL) procedures and three were diagnosed with MF in our hospital. For these MF, we introduced an external approach method to release the CAJ followed by a similar exoeSL procedure. The CAJ release procedure enabled the preservation of the endolaryngeal mucous membrane (ELM) and consequently spared the use of laser surgery. All three CAJ release procedures led to decannulations (one patient) or improvement of dyspnoea (two patients). The difference between the exoeSL and the endo-exolaryngeal suture lateralisation (endoeSL) procedure is discussed based on their effectiveness in MF management.

KEY WORDS: Suture lateralisation • Bilateral vocal fold immobility • Cricoarytenoid joint fixation • Arytenoidectomy • Arytenoid cartilage release

RIASSUNTO

La lateralizzazione mediante sutura al posto dell'ablazione di tessuto endolaringeo per via endoscopica è una procedura utilizzata per trattare la paralisi cordale bilaterale fin dal 1980. Tuttavia, la fissazione meccanica dell'articolazione cricoaritenoidea ha continuamente contrastato l'efficacia della dilatazione glottica, sia nella procedura di lateralizzazione mediante sutura che nell' exeresi di tessuto endolaringeo. Dal 2007 al 2015, un totale di 38 pazienti con paralisi cordale bilaterale sono stati sottoposti a 40 lateralizzazioni mediante sutura eso-endolaringea (exoeSL) e 3 di questi pazienti hanno avuto diagnosi di fissità meccanica nel nostro ospedale. Abbiamo introdotto un approccio esterno per rilasciare la giunzione cricoaritenoidea seguito da una procedura exoeSL simile. Questa procedura di rilascio della giunzione cricoaritenoidea ha permesso la preservazione della mucosa endolaringea, risparmiando quindi l'utilizzo della chirurgia laser. Tutte e tre le procedure di rilascio della giunzione cricoaritenoidea hanno portato a decannulazione (1 paziente) o a un miglioramento della dispnea (2 pazienti). La differenza tra la lateralizzazione exoeSL e endo esolaringea saranno quindi discusse in base all' efficacia nel trattamento della fissità meccanica.

PAROLE CHIAVE: *Sutura di lateralizzazione • Paralisi cordale bilaterale • Fissità dell' articolazione cricoaritenoidea • Aritenoidectomia • Rilascio cartilagine aritenoidea*

Introduction

A number of so-called minimally invasive operations carried out with endoscopy have been proposed for treating BVFI [1-4]. They have been generally categorised into two groups. The first is an irreversible endolaryngeal tissue ablation procedure [1 2] using a laser beam. The second is an ELM preservation procedure using an SL procedure with specially designed instruments to achieve endoeSL [2 3] or without it to perform an exoeSL procedure [4-8].

BVFI is a term used to describe vocal cords that are restricted secondary to neuropathy, muscular disorders, or MF. MF has continually challenged more or less the all aforementioned interventions on their principles. The tension on the vocal fold from the MF seems to work against the effectiveness of the SL procedure. As for this, in the setting

of the endoeSL procedure, while Rovo et al. [3] released the MF using an endolaryngeal scythe, Lichenberger et al [9] and Castellanos et al. [10] treated it using laser arytenoidectomy. In the setting of the exoeSL procedure, we have also introduced an external approach method to release the MF and retain the integrity of the ELM. With this major refinement of surgical technique in the cricoarytenoid joint (CAJ) mobility, the indications of exoeSL can be extended from neurological vocal immobility to MF. Moreover, exoeSL and endoeSL procedure will be discussed in terms of their effectiveness in MF management.

Materials and methods

From 2007 to 2015, a total of 38 patients with BVFI due to various causes underwent 40 exoeSL procedures, with five being diagnosed with MF, two patients postoperatively and three preoperatively. Consequently, a total of three MFs (two females and one male aged from 52 to 66 with mean 57) with two MFs due to previous laser surgeries and one MF due to intubations were treated with CAJ release and the SL procedure.

Evaluation of respiratory function

To objectively evaluate the improvement of respiratory function, pulmonary function test with flow-volume loop was performed before and 2 months after the operation. The ratio of maximal mid-expiratory flow to maximal mid-inspiratory flow, termed the mid-vital capacity flow ratio, was used to represent the severity of BVFI-related variable extrathoracic airway obstruction [11].

Evaluation of phonatory performance

An early and a late postoperative voice assessment were performed 2 and 9 months, respectively, after the operation using a perceptual rating scale for voice quality in two patients. The voice quality in terms of loudness, breathness and hoarseness was rated as (-); no change, (+); mildly, (++); moderately and (+++); severely deteriorated voice.

Evaluation of swallowing function

Swallowing function was evaluated subjectively. Subjects with clinical aspiration or history of cerebral stroke were excluded from this surgery, regardless of a preexisting tracheostomy tube or not. Swallowing function was simply rated as tolerable or intolerable aspiration based on clinic symptoms.

Technique description

The surgeons' real know-how lies in the method of achieving vocal fold lateralisation without any endolaryngeal soft tissue and the associated ELM loss. The first step is an open surgery for arytenoid cartilage release, which proceeds as follows. (1) A horizontal incision is made at the level of the lower edge of the thyroid cartilage, extending 5 cm laterally from the midline on the lateralisation side and 0.5 cm on the other side. (2) Strap muscles and the inferior constrictor muscle are divided to expose the oblique line and posterior edge of the thyroid lamina. (3) The inferior constrictor muscle and its inner lining; pyriform sinus mucosa (Fig. 1 red line) are dissected from the thyroid cartilage (Fig. 1) in a lateral-to-posteromedial direction until the muscular process can be palpated. (4) The CAJ is identified and the arytenoid cartilage (arrow in Fig. 2) is completely separated from the cricoid cartilage (arrow head in Fig. 2). (5) The depth of the paraglottic wound space (Fig. 1 red dotted line) is then measured from the posterior edge of the thyroid lamina to the deepest end of the space (Fig. 1 "B"). (6) A mark as a reference for the injection needle entrance is then made on the thyroid lamina, which should be at least 2 mm anterior to the deepest end of the space and measured as "L" in the Fig. 1. This needle entrance and its stitch canal in

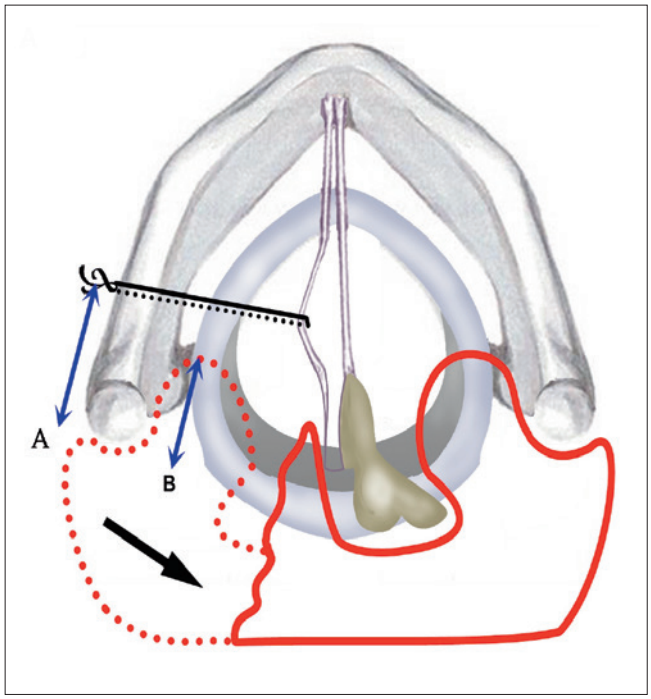


Fig. 1. The scheme illustrates the surgical method with arytenoid cartilage release through the paraglottic space plus suture lateralisation procedure. The surgical wound in the paraglottic space (red dotted line) was created after the pyriform sinus mucosa (red line) had been peeled off from the thyroid lamina laterally and the paraglottic space medially. Note the suture canal is outside the wound space. A: the distance from the entrance of the injection needle on the thyroid lamina to the posterior margin of the thyroid lamina. B: the distance from the deepest wound bed in the paraglottic space to the posterior margin of the thyroid lamina.

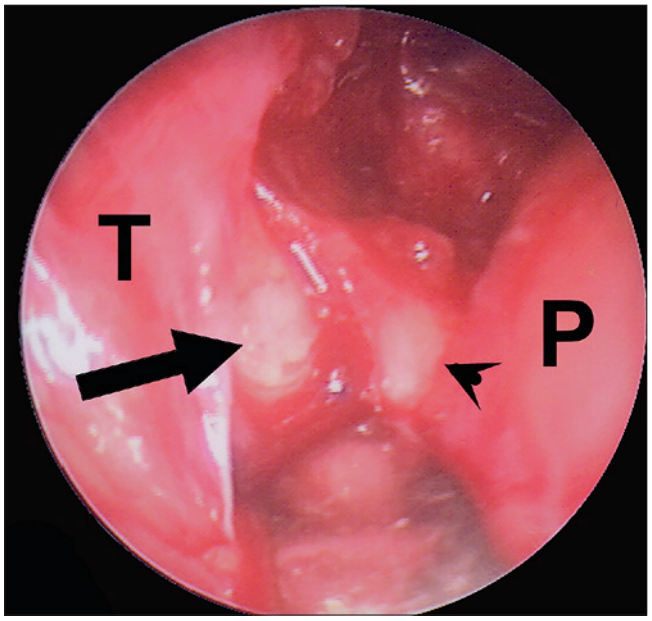


Fig. 2. The CAJ cavity is opened. The black arrow indicates the arytenoid cartilage and the arrow head indicates the cricoid cartilage. P: the pyriform sinus mucosa. T: the thyroid lamina.

the paraglottic soft tissue will be outside the wound space, avoiding the infection from the glottic lumen.

The second step is an exoeSL procedure after the larynx is exposed microscopically using a 0° telescopy. This was well described in our previous publication [4]. This study has been approved by the institutional review board.

Results

Respiration

All three arytenoid release procedures obtained decannulations (one patient) (Fig. 3) or improved dyspnoea (two patients). The mean mid-vital capacity flow ratio was 3.54 and 4.33 before the operation and was reduced to 0.89 and 1.33, respectively, after the operations in two completed flow-volume loop examinations.

Phonation

In the early postoperative voice assessment, two non-tracheostomised patients obtained moderately deteriorated voice (++) because of large glottal gaps. In the late postoperative voice assessment, two patients obtained mildly changed voice quality (+) because of ventricular compensation.

Evaluation of swallowing function

All three subjects had temporally mild or even no aspiration for a few days after the operation, but it disappeared spontaneously. The mean follow-up time was 17.1 months (range 13 to 21 months).

Discussion

The external approach to the CAJ was proposed to medialise the vocal fold in 1978 by Ishiki et al. [12]. On the contrary, Woodman et al. [13] lateralised the vocal fold through the same approach in 1946, which was modified by Shetty et al. [14] in 1998. They sutured on the vocal ligament and the thyroarytenoid muscle through the paraglottic space and fixed them posteriorly on the inferior horn or horizontally to the posterior edge of the thyroid lamina, respectively. The suture on the vocal ligament through the narrow paraglottic space appeared to be difficult. We performed the exoeSL through the thyroid lamina instead of the narrow paraglottic space to simplify the surgical access to the vocal fold if the CAJ is mobile, as in previous publications [2-8]. However, if the CAJ is fixed, this makes the endoscopic vocal fold lateralisation procedures more challenging. Thus, we released the arytenoid cartilage from the CAJ using the external approach at first and then the exoeSL procedure was used. Compared with the other exoeSL or endoeSL procedures, this arytenoid release procedure can keep the ELM intact and spare the use of laser surgery. All three MFs had a completely mobile CAJ from this circumferential arytenoid release procedure and subsequent decannulations (one patient) or improvement in dyspnoea (two patients). Compared to the endoscopic arytenoid lateropexy proposed by Rovo et al. [3], the endolaryngeal scythe could only have separated the anterior aspect of the CAJ, which was unable to completely resolve

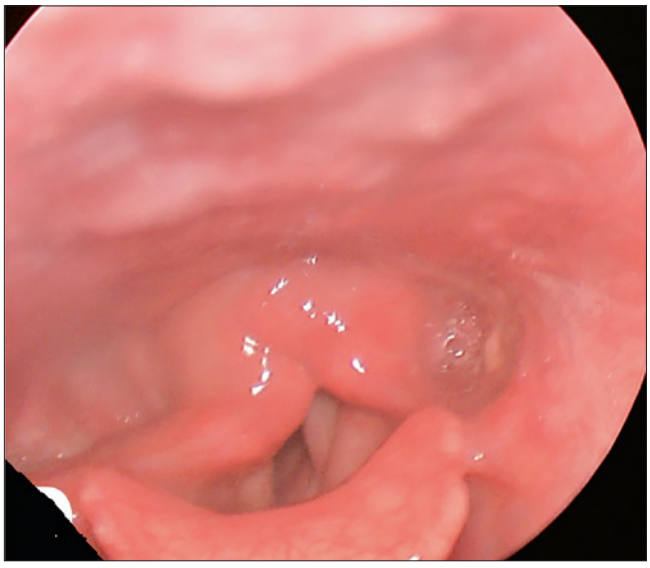


Fig. 3. Endoscopy shows the glottic lumen one year after the operation.

the MF arising from the rheumatoid arthritis or irradiation [3]. In patients with grade I or II isolated posterior glottal stenosis (PGS), the endoscopic arytenoid lateropexy might be highly recommended because of the expectation of future vocal mobility. However, in patients with PGS grade III or IV, surgical release itself may further produce joint capsule scarring. Not only will the future vocal movement be unpredictable, but also the mobility of the CAJ enhanced by the scythe will be queried. Similarly, the postcricoid mucosal advancement flap proposed by Castellanos et al. [10] was only appropriate in grade II PGS because the laser arytenoidectomy they used to treat the grade III and IV PGS was still unable to maintain the integrity of the ELM, as proposed by Litchenberger et al. [2 9]. In addition, revisions were usually required for granulation tissue formation after laser surgeries [3 15]. The disadvantages of this arytenoid release procedure include insufficient ventricular compensation for the voice due to the excessive glottic enlargement, compared with the simple SL procedure without arytenoid release [4]. Compared to the tissue ablation procedure (laser arytenoidectomy), the functional outcomes including the respiratory, phonatory and swallowing functions varied with the magnitude of tissue ablation and tissue regrowth. On the other hand, an intact ELM coupled with a tension-free suture loop might warrant the consistent effectiveness in the respiratory function. However, ventricular compensation longer than 9 months might be required for the breathing voice. As for swallowing function, the coordination of tongue-pharyngolaryngeal complex still play a major role in the aspiration after operation, especially in elderly patients.

Conclusions

With this major refinement of surgical technique in CAJ mobility, not only can the exoeSL procedure extend its indications to MF, but it also poses a better chance of avoiding granulation tissue formation due to laser surgery. Therefore, exoeSL with arytenoid cartilage release appears to be a viable or even essential option in some patients with severe MFs and merits further investigation and advocacy in the future. Nevertheless, patient selection should depend on various factors, including degree of upper airway obstruction, voice demands and quality of life priorities.

Conflict of interest statement

None declared.

References

1 Dennis DP, Kashima H. *Carbon dioxide laser posterior cordectomy for treatment of bilateral vocal cord paralysis*. Ann Otol Rhinol Laryngol 1989;98:930-4.

2 Lichtenberger G. *Reversible lateralization of the paralyzed vocal cord without tracheostomy*. Ann Otol Rhinol Laryngol 2002;111:21-6.

3 Rovò L, Madani S, Sztanò B, et al. *A new thread guide instrument for endoscopic arytenoid lateropexy*. Laryngoscope 2010;120:2002-7.

4 Su WF, Liu SC, Tang WS, et al. *Suture lateralization in patients with bilateral vocal cord paralysis*. J Voice 2014;28:644-51.

5 Songu M, Aslan H, Denizoglu I, et al. *Vocal and ventricular fold lateralization using crossing sutures with the thyroplasty window technique for bilateral vocal fold immobility: long-term results*. Acta Otolaryngol 2013;133:1201-6.

6 Ejnell H, Mansson I, Hallen O, et al. *A simple operation for bilateral vocal cord paralysis*. Laryngoscope 1984;94:954-8.

7 Katilmiş H, Oztürkcan S, Başoğlu S, et al. *New technique for the treatment of bilateral vocal cord paralysis: vocal and ventricular fold lateralization using crossing sutures with thyroplasty technique*. Acta Otolaryngol 2011;131:303-9.

8 Ezzat WF, Shehata M, Kamal I. *Adjustable laterofixation of the vocal fold in bilateral vocal fold paralysis*. Laryngoscope 2010;120:731-3.

9 Lichtenberger G. *Comparison of endoscopic glottis-dilating operations*. Eur Arch Otorhinolaryngol 2003;260:57-61.

10 Atallah I, Manjunath MK, Omari AA, et al. *Reconstructive transoral laser microsurgery for posterior glottic web with stenosis*. Laryngoscope 2017;127:685-90.

11 Kirchner FR. *Endoscopic lateralization of the vocal cords in abductor paralysis of the larynx*. Laryngoscope 1979;89:1779-83.

12 Isshiki N, Tanabe M, Sawada M. *Arytenoid adduction for unilateral vocal cord paralysis*. Arch Otolaryngol 1978;104:555-8.

13 Woodman, D. *A modification of the extralaryngeaI approach to arytenoidectomy for bilateral vocal cord palsy*. Arch Otolaryngol 1946;43:63-5.

14 Shetty SC, Prasad D. *Woodman's operation for bilateral vocal cords paralysis- Our experience*. Indian J Otolaryngol Head Neck Surg 1998;50:241-5.

15 Bottero S, Peradotto F, Roma R, et al. *Laryngotracheal reconstruction in glottic-subglottic stenosis associated with DiGeorge syndrome in a four and a half-month-old infant*. Acta Otorhinolaryngol Ital 2015;35:53-7.

Received: April 19, 2017 - Accepted: October 31, 2017

How to cite this article: Su W-F, Lan M-C, Liu S-C. *Suture lateralisation plus arytenoid cartilage release for treating bilateral vocal fold immobility with mechanical fixation.* Acta Otorhinolaryngol Ital 2019;39:18-21. https://doi.org/10.14639/0392-100X-1720

Address for correspondence: Wan-Fu Su, Department of Otolaryngology-Head and Neck Surgery, Buddist Tzu Chi General Hospital, Taipei Branch, 289, Jianguo Rd., Xindian Dist., New Taipei City 23142, Taiwan, R.O.C. E-mail: wfs19582001@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:22-27; doi: 10.14639/0392-100X-1882

Rhinology

Update on the pathophysiology and treatment of rhinogenic headache: focus on the ibuprofen/pseudoephedrine combination

Aggiornamento sulla fisiopatologia e sul trattamento della cefalea rinogena: focus sull'utilizzo combinato di ibuprofene e pseudoefedrina

A. CHIARUGI[1], A. CAMAIONI[2]

[1] Department of Health Sciences, Section of Clinical Pharmacology and Oncology, University of Florence, Italy; [2] Ear, Nose and Throat Department, San Giovanni Addolorata Hospital, Rome, Italy

SUMMARY

Rhinogenic headache is frequently encountered in clinical practice. Treatment of this condition should be based on a proper evaluation of its underlying pathophysiology. Fixed-dose combinations of two or more active agents, and specifically the combination of ibuprofen plus pseudoephedrine, have been shown to be more efficacious than either monotherapy. At present, an ibuprofen/pseudoephedrine fixed-dose combination is available as an over-the-counter drug. This paper reviews in detail the pathophysiology of rhinogenic headache and discusses the rationale for treatment of this condition with a fixed-dose ibuprofen/pseudoephedrine combination.

KEY WORDS: Combination therapy • Ibuprofen • Pathophysiology • Pseudoephedrine • Rhinogenic headache

RIASSUNTO

La cefalea rinogena è frequente nella pratica clinica. Il trattamento di questa patologia dovrebbe essere basato su un'appropriata valutazione della sottostante fisiopatologia. La combinazione di due o più farmaci, ed in particolare ibuprofene e pseudoefedrina, a dosaggi fissi si è dimostrata più efficace delle monoterapie. Al momento la combinazione ibuprofene/pseudoefedrina a dosaggio fisso è commercializzata quale farmaco da banco. Questo lavoro si focalizza sulla revisione in dettaglio della fisiopatologia della cefalea rinogenica e discute il razionale del trattamento mediante la combinazione ibuprofene/pseudoefedrina.

PAROLE CHIAVE: *Terapia combinata • Ibuprofene • Fisiopatologia • Pseudoefedrina • Cefalea rinogenica*

Introduction

Rhinogenic headache represents a major health issue that is frequently encountered in clinical practice [1]. The results of a worldwide survey in 2007 showed that rhinogenic headache is among the most common complaints among those seeking medical care. In addition to general practitioners, otolaryngologists see a large number of patients with rhinogenic headache [2]. Most patients with this condition are males aged 10-30 years [2-5].

Rhinogenic headaches have their primary pathophysiology centred in the nose, with headache and/or facial pain as a result of complex neurohumoral reflexes. The most common rhinogenic headache is that associated with acute rhinosinusitis [4 6]. Most cases of rhinogenic headache are caused by viral infections (up to 98%), and only 2% are complicated by bacterial sinusitis [1 7]. However, primary care physicians often treat sinusitis as an acute bacterial infection, prescribing antibiotic therapy and hence contributing to the onset of resistance [1]. In addition, rhinogenic headache is frequently misdiagnosed as other conditions such as migraine [2].

Therefore, it is important to identify and appropriately manage this common condition [1]. Treatment should be based on a proper evaluation of the underlying pathophysiology. Fixed-dose combinations of two or more active agents, and specifically the combination of ibuprofen plus pseudoephedrine, have been shown to be more efficacious than either monotherapy. At present, an ibuprofen/pseudoephedrine fixed-dose combination is available as an over-the-counter product [8].

This paper reviews in detail the pathophysiology of rhinogenic headache and discusses the rationale for treatment of this condition with a fixed-dose ibuprofen/pseudoephedrine combination.

Pathophysiology and clinical features of rhinogenic headache

The paranasal sinuses are lined with pseudostratified columnar epithelium, and under physiological conditions, the sinuses are normally sterile. Their function depends on regular transport of the mucus layer into a common area, the osteomeatal complex, in the middle meatus of the nasal cavity. This area is the focal point of sinus drainage; from the nasal cavity, the mucus then drains into the oropharynx [1]. Acute rhinosinusitis begins as a viral infection of the nose leading to inflammation of the sinuses. Inflammation leads to mucosal oedema, osteomeatal complex obstruction and development of negative atmospheric pressure within the sinuses cavities and decreasing partial pressure of oxygen. Excessive mucus production, with or without transudation of plasma, also occurs. Collectively, these events result in malfunction or complete cessation of movement of the cilia in the sinuses, leading to stasis of the mucus. Inevitably, this creates an environment that promotes the growth of pathogenic organisms [1]. In addition, specific anatomic variations, smoking, immunodeficiency disease, allergic rhinitis and exposure to increasing levels of humidity or irritants promote decreased ciliary function, sinus obstruction and superinfection [1 9].

Mucosal inflammation represents the central pathophysiological mechanism underlying most of the specific and interrelated factors that contribute to congestion, such as increased venous engorgement, increased nasal secretions and tissue swelling/oedema [10]. Inflammation diminishes the physical size of the nasal passages by inducing vasodilatation and increasing blood flow as well as vascular permeability. The result is engorgement of the nasal venous sinusoids, swelling of the anterior and inferior turbinates and obstruction of nasal airflow. Ultimately, this engorgement leads to nasal congestion [10].

Given the contribution of inflammation, it is not surprising that the levels of inflammatory cytokines (interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF)-α) in patients with acute rhinosinusitis are significantly increased in nasal lavage fluid compared with healthy controls [10-12]. Kinin levels are markedly increased in nasal secretions of patients with acute viral rhinosinusitis: these polypeptides act on blood vessels to cause vascular leakage and/or engorgement, and also stimulate afferent nerve fibres leading to hyperresponsiveness of the mucosa [13 14]. In addition, acute rhinosinusitis is associated with increased infiltration of inflammatory cells, including neutrophils and T cells, in the nasal epithelium and lamina propria [10].

Sterile inflammation (so-called neurogenic inflammation) may result from neurologic responses involving a wide range of neurotransmitter systems [10]. In particular, the nasal mucosa has sensory, parasympathetic and sympathetic nerves. Sensation to the nasal cavity is provided primarily via the maxillary and ophthalmic branches of the trigeminal nerve. Parasympathetic innervation controls nasal secretions and mucus gland production; moreover, it increases blood flow to the nasal cavity by release of NO. On the other hand, sympathetic innervation decreases the blood flow to the nasal cavity and nasal mucosa. In the presence of mucosal inflammation, parasympathetic and sympathetic tone is dysfunctional, and therefore changes in both glandular and vascular function in the nose occur.

The hypothesis of polymodal receptors in the nasal mucosa suggests that different heat, chemical and mechanical irritants (such as pressure on the mucosa) may cause antidromic release of neuropeptides including substance P and calcitonin gene-related peptide [15] from the peripheral terminals of nociceptive sensory nerve fibres [10], as well as vasoactive neuro-gasotransmitters (noradrenalin, acetylcholine, NO, adenosine) involving sympathetic and parasympathetic terminals. This leads to neurogenic inflammation and peripheral neural sensitisation, which bring about a complex cascade of neurohumoral signalling that is mainly sustained by reflex mechanisms [10]. Specifically, the perivascular release of the above-mentioned powerful vasodilators causes increased vessel permeability, plasma extravasation and tissue oedema, which further activate afferent trigeminal sensory fibres and, in turn, continuous antidromic release of vasoactive and inflammatory molecules. Inevitably, this leads to a vicious cycle of neurogenic inflammation that sustains rhinorrhoea, nasal congestion, sinus pain and upper respiratory symptoms [6 10 16]. With regard to rhinogenic headache, it is now known that this originates both by classic mechanisms of painful stimuli converging at the level of the trigeminal nucleus (the trigeminocervical complex) and activation of the parasympathetic loop, which plays a crucial role not only in sustaining mucosa vasodilation but also in intracranial spreading of neurogenic inflammation. Specifically, painful stimuli reaching the trigeminal nucleus activate direct signalling to the superior salivatory nucleus, which sends preganglionic parasympathetic fibres to the sphenopalatine ganglion. Postganglionic fibres close the reflex arch by sending fibres traveling together with the trigeminal fibres and innervating not only the nasal and sinus mucosa but also intracranial structures, such as the meninges and pial vessel. Hence, parasympathetic activation caused by sustained nasal mucosa inflammation triggers perivascular release of vasodilating compounds at the meninges and cerebral vessels, which activates and then sensitizes the terminals of trigeminal nociceptors with development of rhinogenic headache [17 18].

Rhinogenic headache and facial pain develop simultaneously with the onset or exacerbation of rhinosinusitis and usually resolve after remission or successful treatment of acute rhinosinusitis [2]. Sudden onset of two or more symptoms, including nasal discharge/rhinorrhoea, nasal blockage or congestion, facial pain/pressure/frontal headache and disorder of olfaction, of less than 10 days duration, is considered to be caused by a virus (common cold) [1 9]. Treatment should be initiated immediately for patients with rhinogenic headache [2].

Treatment optimisation for rhinogenic headache

Given the particular pathophysiology of rhinogenic headache, optimal therapy should induce prompt resolution of oedema/mucosa compression, suppression of inflammation, safe analgesia and stimulation of the central nervous system (CNS) within specific hypothalamic and brainstem nuclei to restore neurovegetative homeostasis [1].

Current treatments for rhinogenic headache include decongestants, anticholinergics, anti-histamine, corticosteroids, analgesics and anti-bacterial agents [1]. The different therapies used in this setting are sustained by different levels of evidence. Given that each of the above-mentioned drugs acts only against a subset of symptoms, fixed-dose combinations of two or more active ingredients are frequently used in clinical practice [19].

Analgesics, and especially ibuprofen, have a major role in the treatment of rhinogenic headache [16]. In this regard, it is worth remembering that the updated guidelines (2015) of the AAO-HNS (American Academy of Otorhinolaryngology - Head and Neck Surgery) for treatment of acute rhinosinusitis give a recommendation to analgesic for relief of both viral and bacterial ARS (Acute RhinoSinusitis) symptoms [20].

The main mechanism of action of ibuprofen is non-selective, reversible inhibition of cyclooxygenase enzymes COX-1 and COX-2. COX-1 and COX-2 catalyse the first step in the synthesis of proinflammatory prostanoids from arachidonic acid. These prostanoids enhance oedema formation, increase vascular permeability and promote leukocyte infiltration; they also reduce the threshold of nociceptor sensory neurons to stimulation. Ibuprofen exerts its anti-inflammatory and analgesic effects mostly by inhibiting the formation of these prostanoids [21]. Moreover, ibuprofen has inhibitory effects on polymorphonuclear leukocyte migration and function [22 23]. It also inhibits the release and biological effects of kinins and inflammatory mediators such as TNF-α and IL1, which are involved in the recruitment of neutrophils, thus exerting an immunoregulatory effect [24]. In addition, ibuprofen is reported to scavenge reactive oxygen and nitrogen species and to inhibit NO synthesis [21].

Ibuprofen has an excellent safety/tolerability profile even after multiple doses; the frequency of gastrointestinal adverse events is comparable with placebo [25]. In patients with cold and flu symptoms enrolled in a large study (n = 2815), ibuprofen was as well tolerated as paracetamol and much better tolerated than aspirin [26]. In a clinical trial on 80 patients with naturally acquired upper respiratory tract infections, ibuprofen 400 mg three times daily significantly reduced the severity of headache-associated symptoms, earache, muscle/joint pain, and sneezing, and also reduced body temperature [27].

Oral decongestants are another commonly used class of medications for the treatment of rhinogenic headache [1]. They are prescribed usually on a short-term basis to provide fast-acting relief. Oral decongestants have a weaker effect on nasal obstruction than topical intranasal decongestants; however, they do not cause a rebound phenomenon. After oral administration, the effect of nasal decongestion occurs within 30 minutes and persists for up to 6 hours. Decongestants contain sympathomimetic agents, which mimic the actions of norepinephrine. Pseudoephedrine mainly exerts its vasoconstrictive effects by promoting noradrenaline release, thereby behaving as an indirect vasoconstrictor. It has indirect agonist activity, particularly on peripheral α1 and cardiac β receptors through displacement of noradrenaline from the vesicle pool. Displaced norepinephrine is then released from the sympathetic prejunctional nerve terminal and subsequently binds to post-junctional α-adrenergic receptors on nasal venous sinusoids, thereby producing vasoconstriction, plasma extravasation and mucosal congestion [28].

Pseudoephedrine at the low dose used in over-the-counter medicines may cause nasal decongestion with minimal cardiac effects [29]. Small, but statistically significant increases in pulse and systolic blood pressure occurred after supramaximal doses of pseudoephedrine (120 mg and 180 mg). Conversely, pseudoephedrine at 60 mg is the optimal, single adult dose leading to prompt, maximal nasal decongestion without cardiovascular or other unwanted effects [30].

Role of the fixed-dose combination of ibuprofen and pseudoephedrine in clinical practice

According to the available evidence, a fixed-dose combination of ibuprofen and pseudoephedrine may be particu-

larly effective in the treatment of rhinogenic headache [31]. It combines two molecules with complementary mechanisms of action, namely reduction of pain and inflammation with ibuprofen and decrease of nasal oedema, mucous production and congestion with pseudoephedrine. Moreover, pseudoephedrine reduces compression on nociceptive terminals, thus boosting the analgesic effects of ibuprofen. Lastly, pseudoephedrine can help restore neurovegetative homeostasis. Indeed, by enhancing the sympathetic tone, it counteracts hyperactivation of the parasympathetic component that sustains vasodilation and neurogenic inflammation.

The clinical evidence supports effective management of the nasal and paranasal congestion syndrome with the ibuprofen/pseudoephedrine combination. Specifically, in a randomised study, 58 patients were assigned to receive pseudoephedrine 60 mg alone, pseudoephedrine 60 mg plus ibuprofen 200 mg, or placebo, four times daily for 4.5 days beginning 30 h after intranasal inoculation of rhinovirus under double-blind conditions [31]. The frequencies of infection, colds and viral shedding did not differ significantly between groups. Total symptom scores were significantly reduced by 59% by pseudoephedrine plus ibuprofen and 48% by pseudoephedrine alone, compared with placebo. Cumulative nasal scores and systemic scores were significantly reduced in patients receiving pseudoephedrine plus ibuprofen compared with those assigned to placebo, whereas pseudoephedrine alone was not better than placebo in reducing nasal congestion. Combination therapy was well tolerated, with an incidence of adverse events comparable to placebo (Table I).

In a recent study, data from an anonymous survey among 1770 pharmacy customers purchasing a product containing 200 mg ibuprofen plus 30 mg pseudoephedrine for treatment of common cold symptoms were reviewed [8]. Scores of symptoms responsive to ibuprofen (headache, pharyngeal pain, joint pain and fever), responsive to pseudoephedrine (congested nose, congested sinus and runny nose), and considered non-specific (sneezing, fatigue, dry cough, cough with expectoration) were analysed. After the first intake, the greatest improvement in a specific symptom (+ 63% vs baseline) was reported for headache, which was also the most bothersome symptom. Nasal and sinus congestion improved by more than 50% (Table II). More than 50% of participants reported symptom relief within 30 min (Fig. 1). The duration of overall symptom relief was reported to be up to 6 h in 54.4% and up to 12 h in 22.6% of patients. Statistical analysis showed that two tablets for the first dose were more effective than one. More than 95% of participants rated global tolerability as excellent or good.

Conclusions

Rhinogenic headache is frequently encountered in clinical practice. Given the particular pathophysiology of this condition, optimal therapy should target multiple pathogenic events and lead to resolution of oedema/mucosa compression and inflammation, as well as promote analgesia and CNS stimulation within specific hypothalamic and brainstem nuclei to restore neurovegetative homeostasis.

Table I. Adverse events with the ibuprofen/pseudoephedrine combination. Pseudoephedrine only and placebo, as reported by Sperber et al. [31].

		Number (percent) of patients					
	Number of patients	Any adverse event	Light-headedness	Difficulty Sleeping	Lethargy	Indigestion	Other
Pseudoephedrine plus ibuprofen	23	6 (26)	2 (9)*	1 (4)§	0	0	4 (17)§^
Pseudoephedrine alone	23	4 (17)	2 (9)*	0	1 (4)	1 (4)	0
Placebo	10	2 (20)	0	1 (10)	1 (10)	0	0

** Sum of all pseudoephedrine recipients (4/46) was not significantly different from placebo (0/10); § One patient reported difficulty sleeping and dry mouth; ^ One patient reported dry mouth, feeling hyper, feeling more awake, flushed face and increased heart rate. Increased pulse rate was not documented in this patient.*

Table II. Scores for typical ibuprofen-responsive symptoms at baseline and after intake of the first dose of the combination 200 mg ibuprofen plus 30 mg pseudoefedrine (irrespective of taking 1 or 2 tablets) as well as intra-individual change after firts intake.

Score	Baseline	After first intake	Reduction	% Reduction
TIRS	4.62 ± 2.19	1.87 ± 1.69	2.75 ± 1.89	60.0 ± 33.2
TPRS	4.89± 2.33	2.50 ± 1.74	2.39 ± 1.93	46.3 ± 64.6
NSS	3.33 ± 2.03	1.81 ±1.58	1.52 ± 1.53	45.4 ± 41.0
TSS	4.22 ± 1.65	2.02 ± 1.42	2.20 ± 1.41	52.8 ± 29.7

TIRS, typical ibuprofen-responsive symptoms consisting of headache, pharyngeal pain, joint pain and fever; TPRS, typical pseudoephedrine-responsive symptoms consisting of congested nose, congested sinus and runny nose; NSS, non-specific-symptoms consisting of sneezing, fatigue, dry cough, cough with expectoration; TSS < total symptoms consisting of all 11 symptoms. Data are means ± SD on a scale of 0 (smallest extent) to 10 (greatest extent) or % change (reproduced from Klimek et al., 2017 [8]).

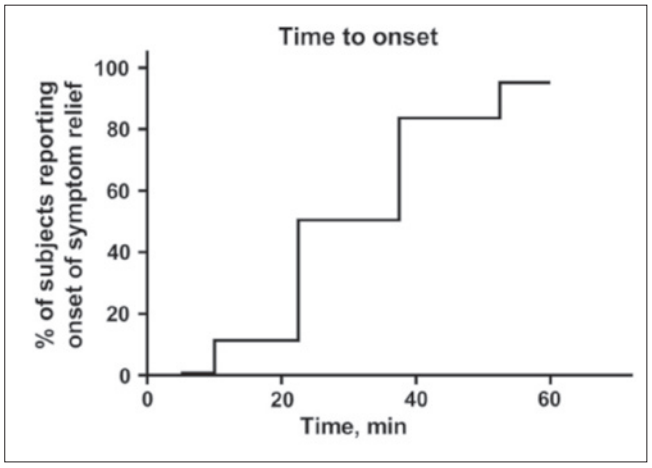


Fig. 1. Time to onset of action after ingestion of the first dose. Data are shown as cumulative % of survey participants reporting onset of symptom relief after ingestion of a combination of 200 mg ibuprofen plus 30 mg pseudoephedrine at a given time point (reproduced from Klimek et al., 2017 [8]).

Due to their mechanism of action, ibuprofen and pseudoephedrine may represent a suitable therapeutic strategy for the treatment of rhinogenic headache. In particular, ibuprofen reduces pain and inflammation, and pseudoephedrine contributes to decrease nasal oedema, congestion and neurovegetative dysregulation. Although current clinical evidence is still limited, the effects of the combination are significant with regard to clinical and safety/tolerability aspects. The fixed-dose combination of ibuprofen and pseudoephedrine has potential to have a major role in clinical practice for the management of rhinogenic headache.

Acknowledgements

Editorial assistance for the preparation of this paper was provided by Luca Giacomelli, PhD, on behalf of EDRA; this assistance was unconditionally supported by Angelini.

Conflict of interest statement

None declared.

References

1. Masood A, Moumoulidis I, Panesar J. *Acute rhinosinusitis in adults: an update on current management*. Postgrad Med J 2007;83:402-8.
2. Patel ZM, Setzen M, Poetker DM, et al. *Evaluation and management of "sinus headache" in the otolaryngology practice*. Otolaryngol Clin North Am 2014;47:269-87.
3. Kaur A, Singh A. *Clinical study of headache in relation to sinusitis and its management*. J Med Life 2013;6:389-94.
4. De Corso E, Kar M, Cantone E, et al. *Facial pain: sinus or not?* Acta Otorhinolaryngol Ital 2018;38:485-96.
5. Hu S, Helman S, Filip P, et al. *The role of the otolaryngologist in the evaluation and management of headaches*. Am J Otolaryngol 2019;40:115-20.
6. Mark E, Schereiber CP. *What do we know about rhinogenic headache? The otolaryngologist's challenge.* Otolaryngol Clin N Am 2014;47:255-64.
7. Sande MA, Gwaltney JM. *Acute community-acquired bacterial sinusitis: continuing challenges and current management*. Clin Infect Dis 2004;39(Suppl 3):S151-8.
8. Klimek L, Schumacher H, Schütt T, et al. *Factors associated with efficacy of an ibuprofen/pseudoephedrine combination drug in pharmacy customers with common cold symptoms*. Int J Clin Pract 2017;71.
9. Anselmo-Lima WT, Sakano E. *Rhinosinusisitis: evidence and experience. A summary*. Braz J Otorhinolaryngol 2015;81S1-49.
10. Naclerio RM, Bachert C, Baraniuk JN. *Pathophysiology of nasal congestion*. Int J Gen Med 2010;3:47-57.
11. Repka-Ramirez S, Naranch K, Park YJ, et al. *Cytokines in nasal lavage fluids from acute sinusitis, allergic rhinitis and chronic fatigue syndrome subjects*. Allergy Asthma Proc 2002;23:185-90.
12. Bachert C, van Kempen MJ, Hopken K, et al. *Elevated levels of myeloperoxidase, pro-inflammatory cytokines and chemokines in naturally acquired upper respiratory tract infections*. Eur Arch Otorhinolaryngol 2001;258:406-12.
13. Renné T, Schuh K, Muller-Esterl W. *Local bradykinin formation is controlled by glycosaminoglycans*. J Immunol 2005;175:3377-85.
14. Sarin S, Undem B, Sanico A, et al. *The role of the nervous system in rhinitis*. J Allergy Clin Immunol 2006;118:999-1016.
15. Stammberger H, Wolf G. *Headaches and sinus disease: the endoscopic approach*. Ann Otol Rhinol Laryngol Suppl 1988;134:3-23.
16. Eccles R. *Understanding the symptoms of the common cold and influenza*. Lancet Infect Dis 2005;5:718-25.
17. Cauchi M, Robertson NP. *CGRP and migraine*. J Neurol 2016;263:192-4.
18. Casale TB, Romero FA, Spierings EL, et al. *Intranasal noninhaled carbon dioxide for the symptomatic treatment of seasonal allergic rhinitis*. J Allergy Clin Immunol 2008;121:105-9.
19. Kale P. *Pharmacokinetics and bioavailability of single dose ibuprofen and pseudoephedrine alone or in combination: a randomized three-period, cross-over trial in healthy Indian volunteers*. Front Pharmacol 2014;5:98.
20. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. *Clinical practice guideline (update): adult sinusitis*. Otolaryngol Head Neck Surg 2015;152(Suppl 2):S1-S39.
21. Mazaleuskaya LL, Theken KN, Gong L, et al. *PharmGKB summary: ibuprofen pathways*. Pharmacogenet Genomics 2015;25:96-106.
22. Nielsen VG, Webster RO. *Inhibition of human polymorphonuclear leukocyte functions by ibuprofen*. Immunopharmacology 1987;13:61-71.
23. Maderazo EG, Breaux SP, Woronick CL. *Inhibition of human polymorphonuclear leukocyte cell responses by ibuprofen*. J Pharm Sci 1984;73:1403-6.
24. Eccles R. *Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu*. J Clin Pharm Ther 2006;31:309-19.
25. Kellstein DE, Waksman JA, Furey SA, et al. *The safety profile of nonprescription ibuprofen in multiple-dose use: a meta-analysis*. J Clin Pharmacol 1999;39:520-32.

[26] Moore N, Le Parc JM, van Ganse E, et al. *Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain*. Int J Clin Pract 2002;56:732-4.

[27] Winther B, Mygind N. *The therapeutic effectiveness of ibuprofen on the symptoms of naturally acquired common colds*. Am J Rhinol 2001;15:239-42.

[28] Johnson DA, Hricik JG. *The pharmacology of alpha-adrenergic decongestants*. Pharmacotherapy 1993;13:110-5S.

[29] Eccles R. *Substitution of phenylephrine for pseudoephedrine as a nasal decongestant. An illogical way to control methamphetamine abuse.* Br J Clin Pharmacol 2006;63:10-4.

[30] Empey DW, Young GA, Letley E, et al. *Dose-response study of the nasal decongestant and cardiovascular effects of pseudoephedrine*. Br J Clin Pharmacol 1980;9:351-8.

[31] Sperber SJ, Sorrentino JV, Riker DK, et al. *Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds*. Bull N Y Acad Med 1989;65:145-60.

Received: July 22, 2017- Accepted: November 23, 2017

How to cite this article: Chiarugi A, Camaioni A. *Update on the pathophysiology and treatment of rhinogenic headache: focus on the ibuprofen/pseudoephedrine combination.* Acta Otorhinolaryngol Ital 2019;39:22-27. https://doi.org/10.14639/0392-100X-1882

Address for correspondence: Angelo Camaioni, Ear, Nose and Throat Department, San Giovanni Addolorata Hospital, Rome, Italy. Tel. +39 06 77055553. Fax +39 06 77055553. E-mail: camaioniangelo@libero.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:28-39; doi: 10.14639/0392-100X-2313

Rhinology

Surgical management of inverted papilloma involving the frontal sinus: a practical algorithm for treatment planning

Approccio chirurgico al papilloma invertito interessante il seno frontale: un algoritmo pratico per la pianificazione del trattamento

G. PIETROBON[1], A. KARLIGKIOTIS[1, 2], M. TURRI-ZANONI[1, 2], E. FAZIO[1], P. BATTAGLIA[1, 2], M. BIGNAMI[1, 2], P. CASTELNUOVO[1, 2]

[1] Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, Varese, Italy; [2] Head and Neck Surgery & Forensic Dissection Research center (HNS&FDRc), Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

SUMMARY

Inverted papilloma of the frontal sinus is a challenging disease. Given its rarity, only small case series are present in the literature. The objectives of the present study are to review our experience in the surgical management of inverted papillomas involving the frontal sinus and to propose a practical algorithm for selecting the most appropriate approach. Data on patients affected by inverted papilloma involving the frontal sinus and surgically treated between 2002 and 2016 were collected. The type of involvement of frontal sinus and extent of surgery performed (endoscopic endonasal, external or combined approaches) were analysed. A brief review of consistent literature was also carried out. Forty-seven consecutive patients were treated using an exclusive endoscopic endonasal approach (EEA) in 18 cases, while a combined endonasal with external osteoplastic approach was required in 29 cases. Most patients (29/47, 62%) had been treated previously, mainly by an endoscopic approach. A single intraoperative complication occurred (1/47, 2%), i.e. cerebrospinal fluid (CSF) leak, that was successfully repaired intraoperatively without any consequences. Recurrences were observed in only 2/47 cases (4%) after a mean follow-up of 43 months (range, 12-137). The management of inverted papilloma involving the frontal sinus requires great expertise and the surgical technique should be tailored to the site of attachment of the tumour, its extension and the anatomical conformation of each frontal sinus. The encouraging results obtained in this case series support the use of this practical treatment algorithm.

KEY WORDS: Inverted papilloma • Frontal sinus • Endoscopic sinus surgery • Osteoplastic flap • Orbital transposition

RIASSUNTO

Il papilloma invertito del seno frontale è una patologia di non facile gestione. Data la sua rarità, in letteratura si possono ritrovare solo casistiche di dimensioni ridotte. Gli obiettivi del presente studio sono, da un lato, il presentare la nostra esperienza nella gestione chirurgica del papilloma invertito interessante il seno frontale e, dall'altro, il proporre un algoritmo pratico per la selezione del miglior approccio. Sono stati raccolti i dati dei pazienti affetti da papilloma invertito del seno frontale e trattati chirurgicamente dal 2002 al 2016. Sono stati analizzati il tipo di coinvolgimento del seno frontale e l'invasività della procedura chirurgica (endoscopica endonasale, esterna o combinata). È stata, inoltre, condotta una breve revisione della letteratura al riguardo. Complessivamente la casistica è risultata composta da 47 pazienti, di cui 18 trattati con approccio puramente endoscopico endonasale, mentre i restanti 29 con approccio combinato endoscopico con lembo osteoplastico frontale. La maggior parte dei pazienti era stata trattata precedentemente presso altri centri (29/47, 62%), prevalentemente tramite un approccio endoscopico endonasale. È stata riscontrata una singola complicanza intraoperatoria (1/47, 2%), rappresentata da una fistola rinoliquorale, immediatamente riparata e scevra di successive sequele. Sono state individuate due recidive di malattia (2/47, 4%) dopo un follow up medio di 43 mesi (range 12-137). La gestione del papilloma invertito interessante il seno frontale richiede una valida esperienza e la tecnica chirurgica deve essere adeguata al sito d'attacco del tumore, alla sua estensione e alla conformazione dei seni frontali. I risultati incoraggianti ottenuti nella nostra casistica supportano l'utilizzo di questo algoritmo pratico di trattamento.

PAROLE CHIAVE: *Papilloma invertito • Seno frontale • Chirurgia endoscopica nasosinusale • Lembo osteoplastico frontale • Trasposizione orbitaria*

Introduction

Inverted papilloma is the most common epithelial benign tumour of the nose and paranasal sinuses, accounting for approximately 0.5 to 4% of all sinonasal neoplasms [1]. It arises from the Schneiderian mucosa and grows into the underlining stroma with a typical endophytic pattern. Though considered a benign lesion, this tumour is characterised by a well-known tendency to relapse in case of incomplete removal [2] and by a variable association with squamous cell carcinoma, either synchronous or metachronous [1 3 4]. These features, along with frequently associated bony alterations (erosion or osteosis), make inverted papilloma an unpleasant lesion, which needs to be approached carefully and excised thoroughly.

The frontal sinus is an anatomically challenging region, both functionally and aesthetically: its anterior wall gives shape to the forehead, while its posterior wall encloses the frontal lobes, i.e. the ventral edge of the anterior cranial fossa. Inverted papilloma involving the frontal sinus represents only 2.5% of all cases [5] and has been traditionally managed through external transcranial approaches [3]. Nowadays, the endoscopic endonasal technique is considered the gold standard approach for the treatment of sinonasal Schneiderian papillomas [6], without the common post-surgical complications of the external approaches, let alone reduced discomfort for patients and time of hospitalisation [7]. However, endoscopic access to the frontal sinus can still be challenging because of its anatomy and unfavourable position, requiring curved instrumentation and the necessity to control any of its recesses when dealing with either benign or malignant tumours.

To date, there is still debate about the best technique to address inverted papillomas in this site and no definitive guidelines exist. The aims of this study are to share our experience in the management of inverted papilloma arising from or extending into the frontal sinus, and to propose a practical algorithm for the surgical management of these lesions. The different surgical procedures available and their specific indications are also discussed and reviewed along with the small amount of data present in the literature.

Materials and methods

Study design

A retrospective review of a single institutional database on inverted papillomas arising from or extending to the frontal sinus, treated surgically between July 2002 and December 2016, was performed. Approval was obtained from the Insubria Board of Ethics. The following data were collected: sex, age at intervention, side involved, symptoms at presentation, previous treatments, origin and extension of disease, type of surgery, early and late complications, histology, time of follow-up and recurrence. Inclusion in the study required a minimum follow-up of 12 months.

Pre-operative work-up

A plain CT scan and/or a contrast-enhanced MRI were obtained in all cases. All patients were also submitted to endoscopic endonasal evaluation to identify intranasal extension of the lesion. A biopsy under local anaesthesia was always performed after imaging evaluation to confirm diagnosis and assess for possible coexistence of carcinomatous foci.

Surgical strategies

All surgical procedures were performed under general anaesthesia. The entity of dissection was modulated in relation to the site and extent of the lesion defined by preoperative imaging and intraoperative findings. Informed consent about the possibility of intraoperatively switching from an endoscopic to a combined endoscopic-transcranial approach was obtained in all patients, especially for those with massive frontal sinus and/or supraorbital cell involvement. When present, the naso-ethmoidal and maxillary sinus component of the inverted papillomas were treated according to the three different types of endoscopic procedures (Types 1, 2, 3), which have been extensively described in a previous publication (Table I) [8]. An endoscopic frontal sinusotomy (type I, IIA, IIB, or III) according to Draf [9] was performed in all cases.

Whenever a mucosal involvement inside a supraorbital

Table I. Summary of surgical steps in the 3 types of endoscopic procedures [8].

Type of endoscopic procedure	Surgical steps
1	Anterior and posterior ethmoidectomy, sphenoidotomy, large middle antrostomy, partial or complete middle turbinectomy, frontal sinusotomy (type I, IIA, IIB, or III according to Draf's classification [9] in relation to the extent of disease)
2	Anterior and posterior ethmoidectomy, sphenoidotomy, medial maxillectomy, partial or complete middle turbinectomy, frontal sinusotomy (type I, IIA, IIB, or III according to Draf's classification [9] in relation to the extent of the disease) (± naso-lacrimal duct section)
3	Anterior and posterior ethmoidectomy, sphenoidotomy, endonasal Denker operation with naso-lacrimal duct section, complete inferior and middle turbinectomy, frontal sinusotomy (type I, IIA, IIB, or III according to Draf's classification [9] in relation to the extent of disease)

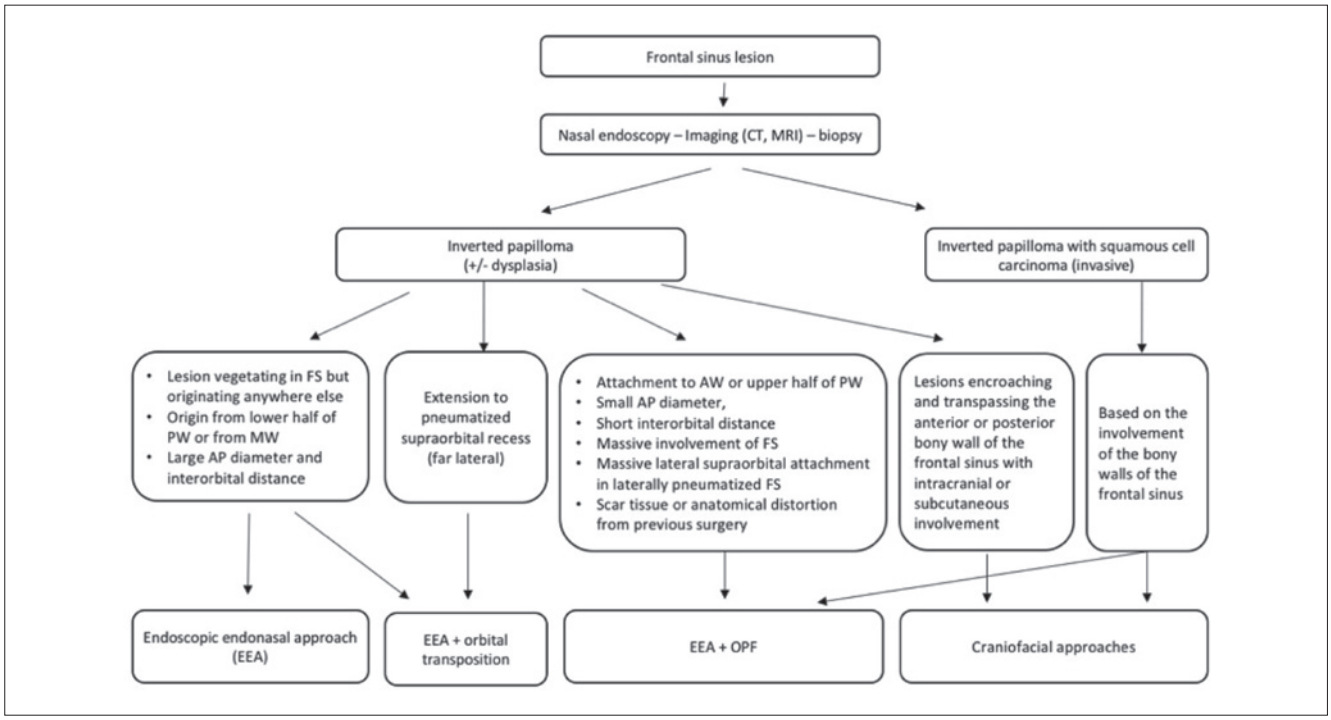


Fig. 1. Practical algorithm used to plan surgical resection of frontal sinus inverted papilloma. AP: anteroposterior; FS: frontal sinus; PW: posterior wall; MW: medial wall; AW: anterior wall; OPF: osteoplastic flap; EEA: endoscopic endonasal approach.

cell extending far laterally over the orbital roof was identified, resection was performed, or anyway attempted as first step, using an endoscopic endonasal orbital transposition approach [10], which has become common practice in the last decade. In case of massive involvement of the frontal sinus, particularly when highly pneumatised, an osteoplastic flap (OPF) using a bicoronal approach was planned. Inverted papillomas encroaching and possibly crossing the anterior or posterior bony wall of the frontal sinus, with intracranial extension or subcutaneous involvement, or inverted papillomas associated with squamous cell carcinoma, should be treated using traditional transcranial approaches (Riedel's technique and its modifications or classic craniofacial resection) [11 12]. The practical algorithm used to plan the surgical resection is summarised in Figure 1. Frozen sections were extensively used intraoperatively to ensure a free-margins resection. Based on the radiological and surgical findings, all tumours were staged according to the system of Krouse [13].

Follow-up

Patients were followed after surgery with serial endoscopic endonasal evaluations. Irrigations with saline solution (twice daily) were recommended for at least 1 month. Post-operative contrast-enhanced MRI scans were performed at 6 months after surgery and thereafter in the presence of scar tissue obscuring the visualisation of the site of origin of the lesion (every 6 months for the first 2 years and then once a year for the following 3 years). Postoperative MRI evaluation was scheduled in case of clinical or endoscopic suspect of local recurrence.

Results

Patient population

Forty-seven patients fulfilled the inclusion criteria and were included in the study. There were 34 males and 13 females (M:F = 2.5:1). Age at surgery ranged from 26 to 78 years (mean 57 years). Frontal sinus was the site of origin of the tumour in 16 cases; the remaining patients had the frontal sinus involved as extension from the anterior ethmoid (27 cases, including frontal recess in 2 cases) and posterior ethmoid (4 cases). Bilateral involvement of the frontal sinus was present in 9 patients (20%), in 5 of whom the tumour originated from the frontal sinus. Nasal obstruction was the most common symptom (32 patients, 67%), followed by headache, either as the main (7%) or associated complaint (31%). Nasal discharge was present in only 6 patients (14%) and anosmia in 3 (7%). Four patients (8%) were asymptomatic and diagnosed incidentally during head imaging for other causes.

Before treatment in our tertiary care referral centre, 30

patients had been already treated surgically elsewhere, almost all with an exclusive endoscopic approach (29 cases) except for one case treated with an external Caldwell-Luc procedure. Prior to surgery, the available imaging was a combination of CT scan and contrast-enhanced MRI in 38 cases (80%), CT scan alone in 5 cases (10%) and only MRI in 4 cases (9%). All clinical and demographic data are summarised in Table II.

Surgical procedure

Patients were divided in two groups: one group included all patients treated with an exclusive endoscopic endonasal approach, while the other one included all patients treated with a combined endoscopic-OPF approach. No case in the present series fulfilled the requirements for a classic or modified Riedel's procedure or for a classic craniofacial resection, hence these approaches were never performed.

A purely endoscopic endonasal approach (EEA) was used in 18 patients (38%): Type 1 resection was performed in 11 cases, Type 2 in 2 cases and Type 3 in 5 cases. In this group of patients, the frontal sinus was the site of origin of the disease in 3 cases (3/18, 17%). In 8 cases an endoscopic orbital transposition was performed in order to resect a lesion located in the supraorbital recess (Fig. 2). The frontal sinusotomy was a Draf type 1 in 2 cases (2/18, 11%), a Draf type 2a in 3 cases (3/18, 17%), a Draf type 2b in 11 cases (11/18, 61%) and a Draf type 3 in 2 cases (2/18, 11%). Figure 3 shows pre-operative extension and post-operative results of a patient successfully treated with an EEA. No case required conversion from a purely endoscopic endonasal procedure to an OPF.

Conversely, a combined EEA with OPF was necessary in 29 patients (62%), of whom 11 had the frontal sinus as a primary site of origin of the tumour (13/29, 45%) (Fig. 4). A Draf type 2b frontal sinusotomy was performed in 12 cases (12/29, 41%), while a Draf type 3 was performed in the remaining cases (17/18, 59%). Figure 5 shows pre-operative extension and post-operative results of a patient treated with combined EEA-OPF resection.

To note, choice of the most appropriate approach was driven not only by the origin site, but also by intraoperative evidence of diseased mucosa in the frontal sinus. Table III illustrates the different approached used, based on the sites encroached by the lesion. A combined EEA with OPF was more often required if the lesion involved either the anterior or posterior walls of the sinus or the supraorbital recess or multiple sites.

Table II. Clinical and demographic data of patients.

Number of patients	47	
Sex		
Male	34	72%
Female	13	28%
Mean age (range)	57 years (26-78)	
Side of lesion		
Right	21	45%
Left	17	36%
Bilateral	9	19%
Site of origin		
Frontal sinus	16	34%
Ethmoid	31	66%
Previous surgery		
None	17	36%
Endoscopic	29	62%
External	1	2%
Imaging		
CT	5	10%
MRI	4	9%
CT+MRI	38	81%
Type of surgery		
EEA (with OT)	18 (8)	38% (17%)
EEA + OPF	29	62%
Histology		
Inverted papilloma	46	98%
Oncocytic papilloma	1	2%
Associated histology		
None	37	79%
Mild dysplasia	3	6%
Moderate dysplasia	5	11%
Severe dysplasia	1	2%
Carcinoma in situ	–	–
SCC	1	2%
Recurrences		
No	45	96%
Yes	2	4%
Mean follow-up (range)	43 months (12-137)	

OT: orbital transposition; OPF: osteoplastic flap

Histology and classification

Final histology was consistent with inverted papilloma in 46 cases, while in one case it required a combined EEA with OPF in whom an oncocytic papilloma was diagnosed. Variable levels of dysplasia were observed within the surgical specimens: mild dysplasia in 3 cases, moderate in 5 cases and severe in 1 case.

In one patient, a 64-year-old female, a synchronous invasive squamous cell carcinoma was identified. The inverted papilloma originated in the left frontal sinus and extended in the ethmoidal compartment and nasal fossa. A combined EEA with OPF approach was used. Final histology showed focal invasive squamous cell carcinoma, moderately differentiated, involving the vegetating nasal portion of the lesion, without infiltration of the ethmoidal and frontal components. This case was discussed post-operatively during a multidisciplinary meeting and neither revision surgery nor adjuvant radiation therapy was deemed necessary.

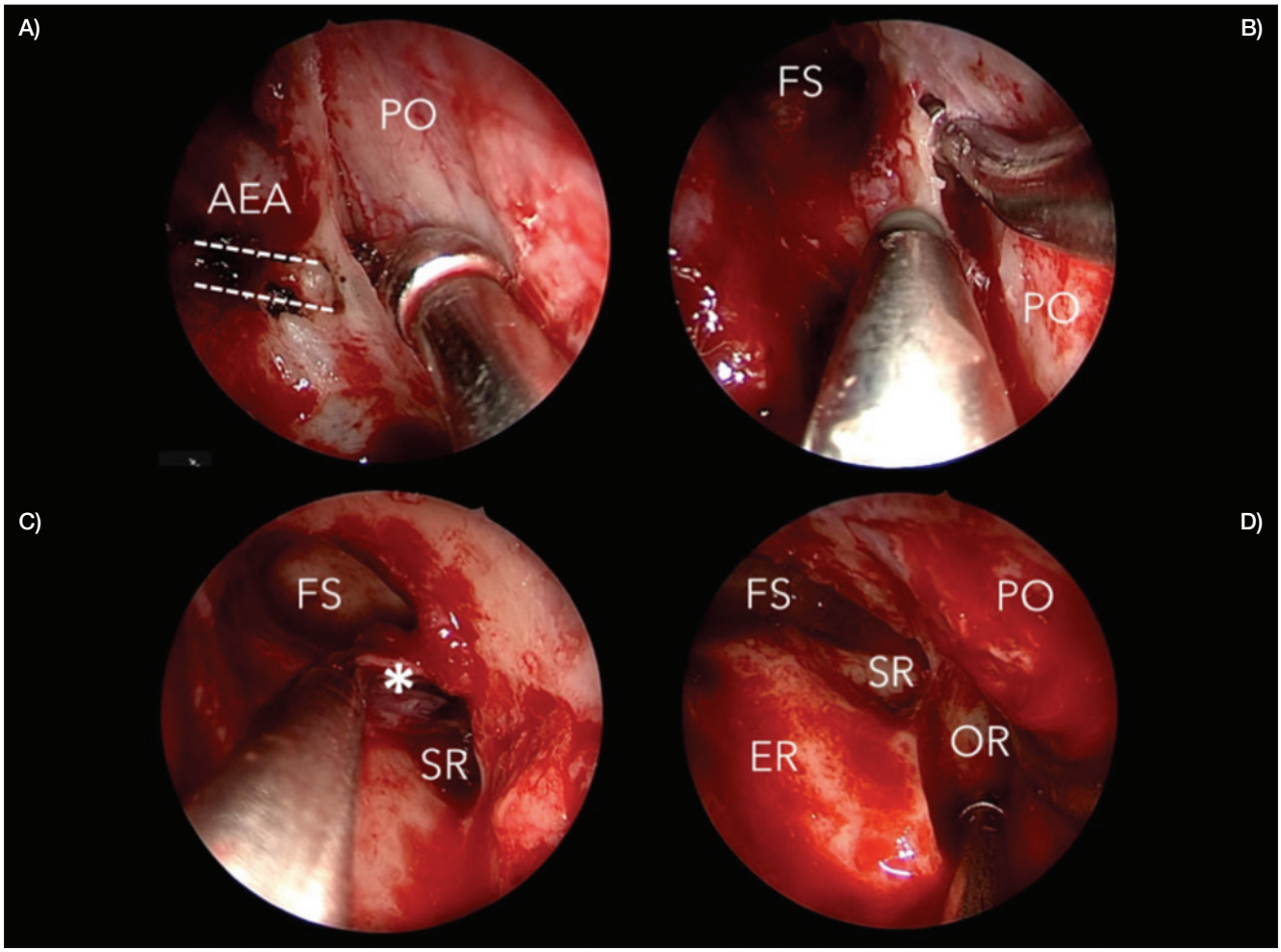


Fig. 2. Endonasal endoscopic orbital transposition to resect inverted papilloma involving the supraorbital recess. Once the periorbit has been exposed and the AEA cauterised and cut **(A)**, access to the supraorbital recess is gained by drilling the supero-medial orbital wall **(B)**, while the periorbit is pushed laterally to be protected and to expose completely the orbital roof; following removal of the most lateral portion of the lesion **(C)**, inspection of both the recess and the orbital roof is possible **(D)**. AEA: anterior ethmoidal artery; PO: periorbit; FS: frontal sinus; SR: supraorbital recess; ER: ethmoidal roof; OR: orbital roof; white asterisk marks the tumour.

According to Krouse staging of disease [13], involvement of the frontal sinus defines tumour as T3, and thus this was the final stage for all patients except for the one with associated synchronous carcinoma, defined as T4.

Complications and follow-up

In a single occasion, during a purely endoscopic endonasal approach, an intraoperative CSF leak occurred at the level of the left olfactory fissure, and thus a skull base reconstruction with a free graft of nasal mucoperiosteum placed overlay was performed. Neither recurrent leakage nor further complications were observed.

During follow-up (mean, 43 months; median, 32 months; range, 12-137 months), 17 patients (35%) presented with frontal stenosis, most of the time symptomless (12/17, 71%), 2 other patients (4%) with mucoceles and 1 additional patient (2%) with epiphora (Table IV). Of 17 cases with frontal stenosis, the frontal sinusotomy performed during resection of the IP was a Draf type 1 and a Draf type 2a in 1 case each, a Draf type 2b in 7 cases and a Draf type 3 in 8 cases. Both cases with mucoceles and 5 cases of frontal stenosis required revision surgery using an endoscopic endonasal approach. The patient complaining of epiphora was successfully treated with endoscopic dacriocystorhinostomy.

During follow-up, two patients (4%) experienced recurrence of disease and were consequently re-operated at, respectively, 8 and 40 months after the first surgical procedure. The first presented with inverted papilloma originating in the right posterior ethmoid and extending into the frontal sinus and was submitted to an EEA. He

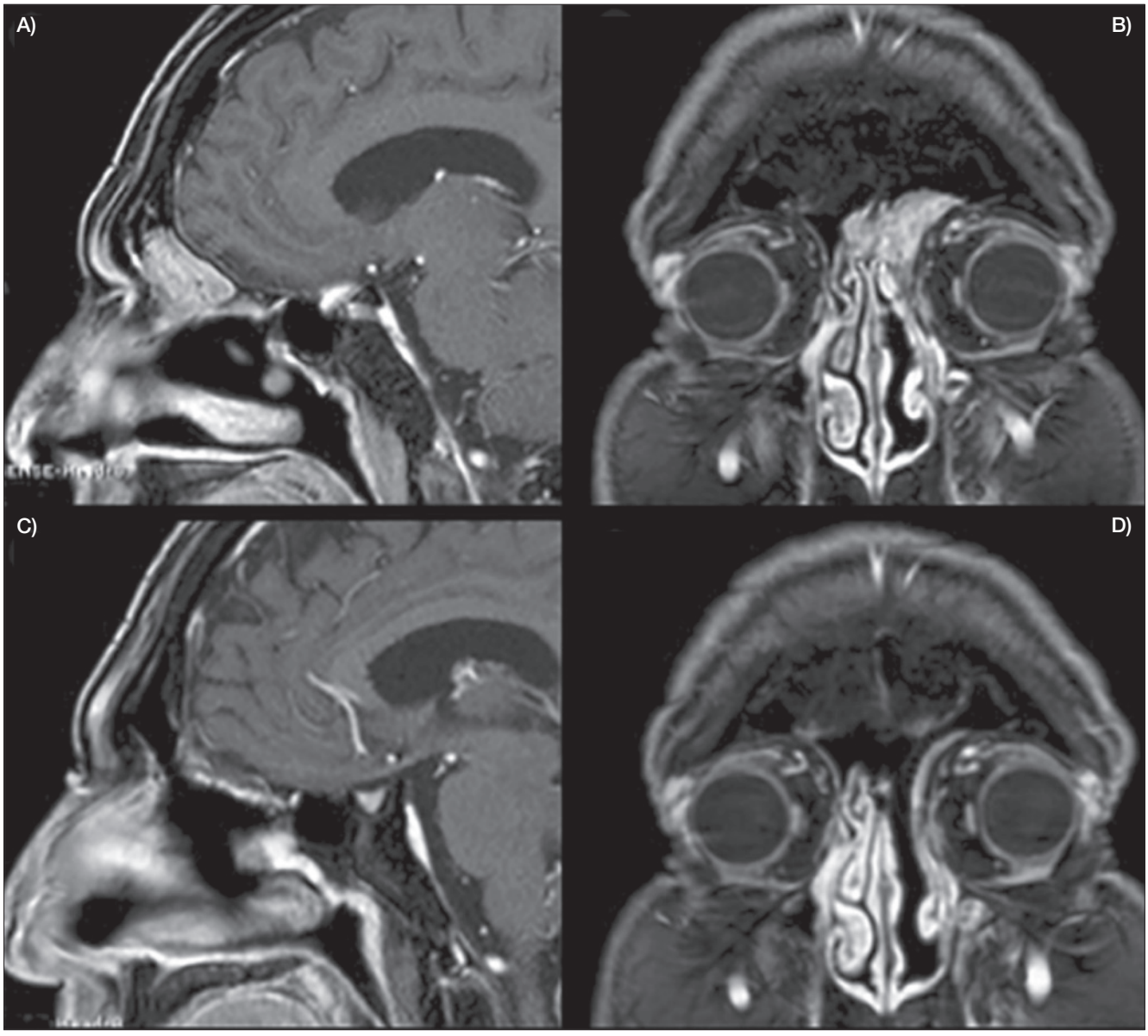


Fig. 3. T1-weighted MRI with gadolinium. Pre-operative **(A, B)** and post-operative **(C, D)** imaging of left fronto-ethmoidal inverted papilloma in sagittal and coronal views. Post-operative evidence of patent frontal drainage pathway and absence of disease is shown.

later developed a recurrence in the frontal sinus, which required a combined EEA with OPF. The second patient initially presented with inverted papilloma arising from the anterior wall of the right frontal sinus and extending into the ipsilateral ethmoidal compartment and maxillary sinus, and she was submitted to a combined EEA with OPF. She later developed frontal stenosis and complained of unbearable frontal headache, so she underwent revision surgery through a combined EEA with OPF: intraoperatively, suspicious tissue was removed from inside the frontal sinus and was compatible with IP at final histology. After 44 and 100 months of follow-up, respectively, these patients are alive without evidence of disease.

To note, the patient with diagnosis of synchronous squamous cell carcinoma was followed with stricter clinical endoscopic and radiological exams with contrast-enhanced MRI evaluations every 6 months and a total body CT scan once per year. She is currently alive without recurrence of disease after 96 months of follow-up.

Discussion

As already pointed out throughout the literature [2 8], resec-

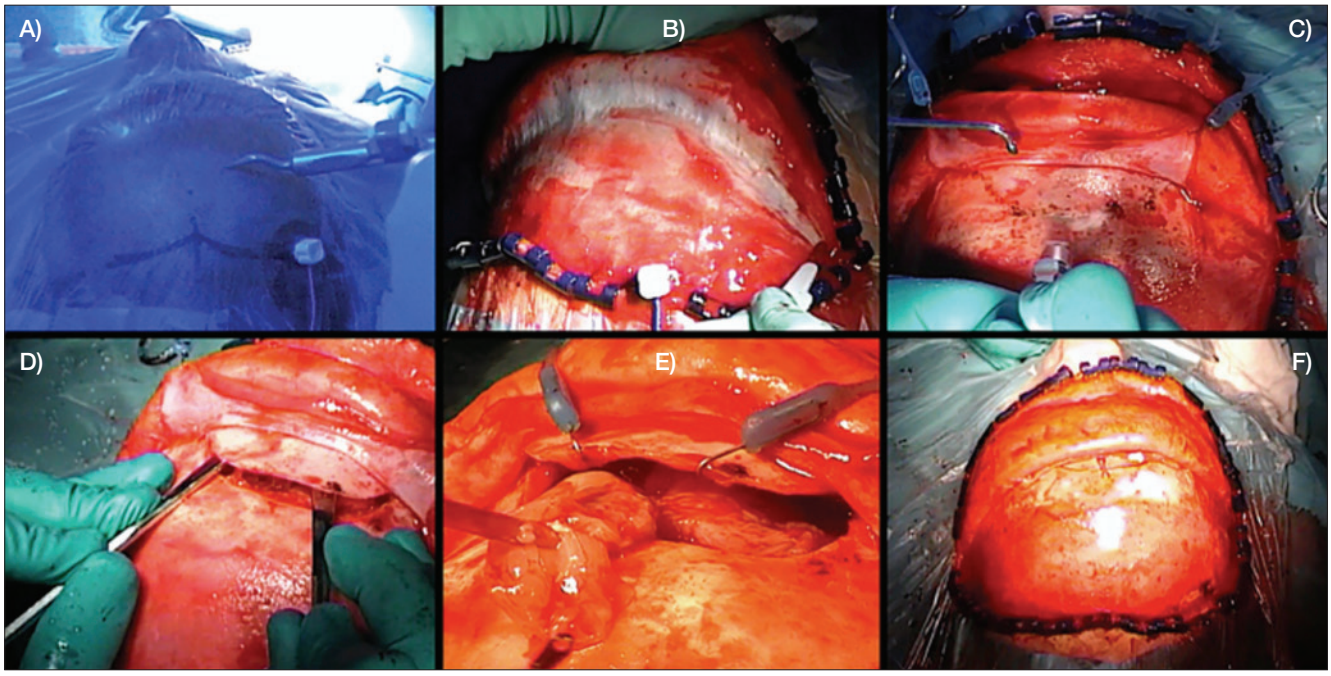


Fig. 4. Intraoperative views of an osteoplastic flap (OPF). After placement of a cranial pin and set up for magnetic navigation **(A)**, a cutaneous-galeal flap is raised **(B)**, followed by harvesting of a pericranial flap, which is held by small hooks **(C)**. Osteotomies are realised with an oscillating saw **(C)** and chisels **(D)** in order to create an inferiorly-pedicled osteoplastic flap and to gain access to the lesion inside the frontal sinus **(E)**. At the end of the procedure the osteoplastic flap is flipped back in place and screwed **(F)**.

tion of inverted papilloma should be particularly focused on the attachment site of the lesion: removal of the mucosa together with the periosteal layer followed by the drilling of the underling bone is crucial to avoid recurrences. This is the reason why the pre-operative identification of the tumour's site of attachment on radiological imaging is paramount. Endoscopic endonasal eradication is relatively accessible whenever the tumour involves the maxillary, ethmoid or sphenoidal sinuses; conversely, it can become difficult if the frontal sinus mucosa is interested by the tumour and the lesion does not simply vegetate inside the sinus. This is particularly true in case of extensive involvement of the sinus, which may preclude complete visualisation of the lesion and reduce the manoeuvrability of instruments.

Recently, a novel technique has been described to expand the EEA to lesions occupying the far lateral recess/supraorbital recess of the frontal sinus, the so-called endoscopic orbital transposition. This technique, based on a superomedial orbital wall decompression with preservation of the periorbital integrity, allows lateral dislocation of the orbital content, making the surgeon able to reach further in the lateral recess, thanks to a combined Draf type IIb or Draf type III frontal sinusotomy. As a consequence, inverted papilloma arising in the frontal sinus, laterally to a sagittal plane passing through the lamina papyracea, may no longer be considered as an absolute contraindication to EEA.

However, when the site of attachment is located on the superior, lateral, or anterior wall of the frontal sinus as well as in case of massive involvement of the frontal sinus mucosa or in case of a highly-pneumatised frontal sinus, endoscopic endonasal resection is highly challenging, as already stated by other authors [14 15]. In such cases, extended endoscopic approaches allow debulking of the tumour and identification of the sites of tumour attachment, but they may be not sufficient to eradicate the lesion; hence, open approaches are usually necessary, namely an osteoplastic flap (OPF) or an endoscopic frontal trephination (EFT). Of note, despite being mandatory to obtain preoperative plain CT scan and gadolinium-enhanced MRI to evaluate the origin and extension of the lesion and to plan the most suitable surgical approach, the final tumour encroachment can be clearly assessed only intraoperatively, aided by frozen sections, so that any possible site of attachment may be eradicated.

Recently, a new technique based on a combined endoscopic endonasal and transpalpebral orbitofrontal minicraniotomy has been proposed by Albathi et al. [16]. Though innovative, this experience is very limited, with only 4 cases described, and thus it is definitely too early to draw any conclusions about its efficacy and long-term outcomes.

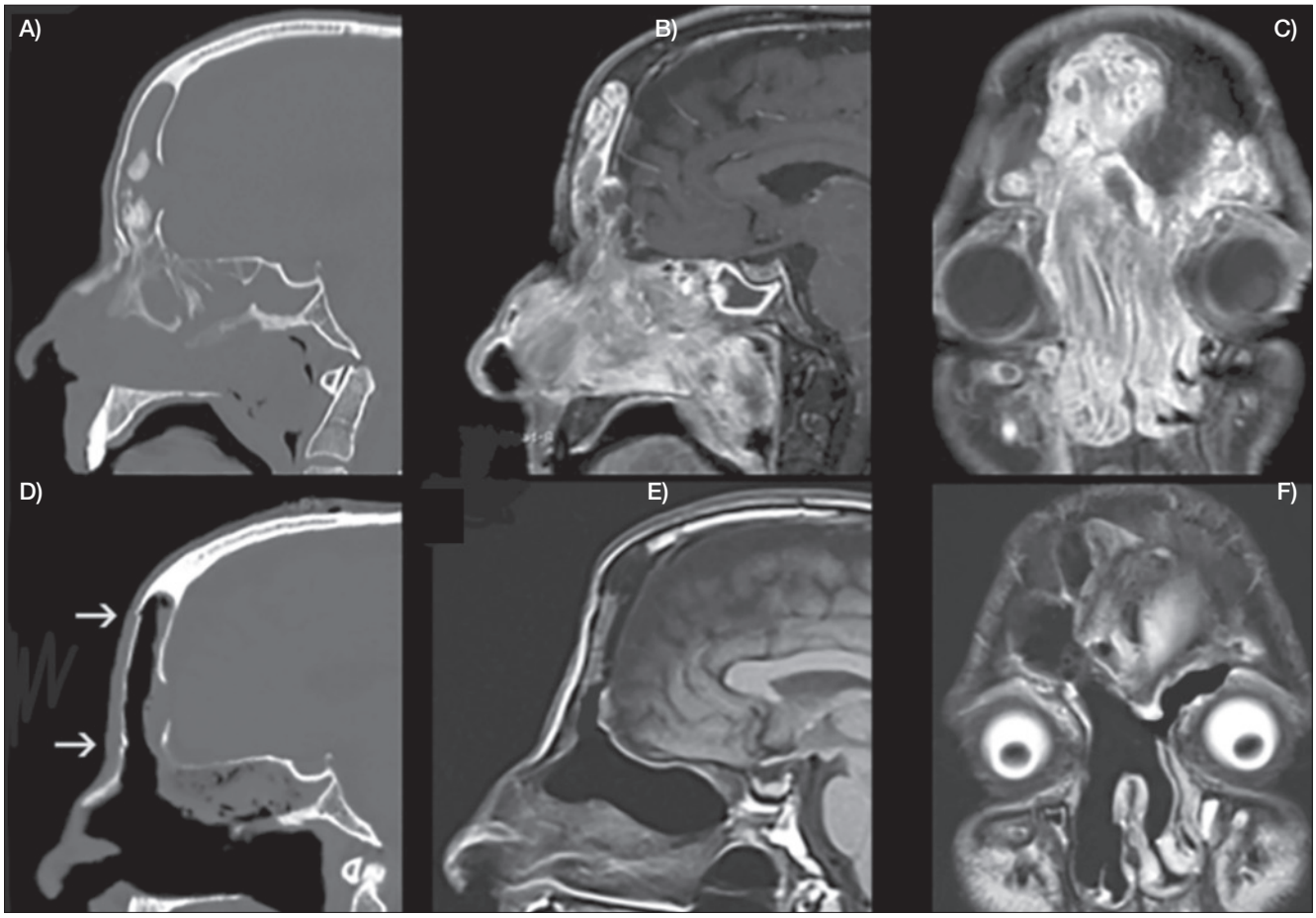


Fig. 5. Pre-operative imaging and post-operative outcomes of a massive inverted papilloma involving the frontal sinuses bilaterally with posterior wall bony erosion, successfully treated by combined endonasal with OPF approach. White arrows point out the osteotomies on the anterior frontal plate.

At present, in cases unfit for endonasal endoscopic eradication, we prefer to use the OPF because it offers better aesthetic results, allows complete access to the frontal sinus and is safer, since it can be performed using ENT magnetic navigation systems, as previously described [17]. At the end of this procedure, the bone flap is replaced and fixed with screws, without obliteration of the sinus. Whenever an OPF was required, this was carried out as a single stage operation, combining it with endoscopic endonasal surgery to simultaneously rehabilitate natural frontal sinus drainage. There is no need, in our opinion, to stage a second surgery as suggested by other studies [14]. Moreover, no major intraoperative or postoperative complications occurred in our series: this is consistent with the learning curve and acquired experience of the surgeons as well as the evolution of the technique since the first review was published [18]. Other authors reserve OPF for extreme cases and propose to use EFT, which is exploited to introduce instruments or endoscope [15]. However, in that paper, the non-negligible recurrence rate (22%) and associated complications [CSF leak in 1 of 5 cases (20%) with EFT] [15] suggest a limited use for this technique, and only in very well selected cases.

Inverted papilloma with intracranial extension is a rare finding with only 17 cases described in English literature and is usually seen in recurrent cases [11 12]. Anterior cranial fossa invasion occurs after destruction of the posterior table of frontal sinus or the roof of the nasal cavity. Data from the literature suggest that this uncommon condition can be effectively managed by craniofacial resection (CFR) [11 12]. Although no cases in our series required such an aggressive approach, this surgical option has been included within the rationale for management of these challenging tumours (Fig. 1).

Several case series analysing surgical management of frontal sinus inverted papilloma have been published recently [19-23], although numbers are obviously poor because of the rarity of the disease and the uncommon location. Table V provides a brief review of the English literature on articles concerning treatment of inverted papilloma of the frontal sinus from 2002 onwards.

Table III. Sites of attachment of IP inside the frontal sinus and surgical technique adopted.

Sites of attachment	EEA	EEA + OT	EEA + OPF	Total
PW	3	–	7	10
AW	1	–	4	5
MW	–	–	1	1
LW	–	–	1	1
SR	–	8	10	18
FR	5	–	2	7
PW+FR	1	–	1	2
PW+SR	–	–	1	1
PW+LW	–	–	1	1
AW+SR	–	–	1	1
Total	10	8	29	47

EEA: endoscopic endonasal approach; OPF: osteoplastic flap; PW: posterior wall; AW: anterior wall; MW: medial wall; LW: lateral wall; SR: supraorbital recess; FR: frontal recess.

Recently, Walgama et al published a review of the literature that was unable to demonstrate the superiority of one surgical approach over the others for successful removal of inverted papilloma of the frontal sinus [24]. The authors concluded that surgeons should be able to handle all different types of techniques and to be ready to convert from endoscopic to external approaches whenever dictated by intraoperative findings, possibly with a single-stage operation. The same review showed an overall recurrence rate of 22.4% which was lower in case of origin of the lesion from the posterior wall and in case of secondary disease, though without any statistical significance ($p = 0.051$ and $p = 0.074$, respectively). Posterior-wall lesions are probably the most accessible ones, and thus radical resection is achieved more often. As far as secondary lesions are concerned, this trend can be probably explained by a more aggressive approach adopted due to the natural history of the disease. We are not able to infer any data from our recurrent cases (2/47, 4%) because of insufficient statistical power and completely different features of the patients (combined approach for an IP originating from the frontal sinus; EEA for an IP originating from the anterior ethmoid). Of note, both patients presented with persistent/recurrent IP after being submitted to an endoscopic endonasal procedure at another centre, thus underlying the role of residual scar tissue and distorted anatomy in hindering the revision surgery, as already stated by other authors [20].

Table IV. Early and late post-operative complications according to surgical technique.

	Early complications	Late complications
EEA (18)	1 CSF leakage (1/18, 6%)	6 frontal stenosis (6/18, 33%) 1 epiphora (1/18, 6%)
EEA + OPF (29)	–	11 frontal stenosis (11/29, 38%) 2 mucoceles (2/29, 7%)
Total (47)	1 (1/47, 2%)	20 (20/47, 43%)

EEA: endoscopic endonasal approach; OPF: osteoplastic flap; CSF: cerebrospinal fluid

Globally, the recurrence rate of 4% reported in our study is similar to what is described in more recent studies [20]. When considering only papillomas originating from the FS, the recurrence rate is 1/16 (6%), which is definitely lower than the above-cited review [24] or more recent papers [25]. We believe that these data strongly support the efficacy and safety of the surgical algorithm herein proposed for the management of inverted papilloma involving the frontal sinus. As a general rule, we prefer an exclusively endoscopic endonasal approach whenever feasible, in order to decrease morbidity for patients and reduce hospitalisation time [26]. However, it is our opinion that some cases pose an absolute contraindication to pure EEA, which would result in incomplete resection of disease. Current contraindications for an EEA in the surgical management of frontal sinus inverted papilloma [10] are summarised as follows:

- small antero-posterior diameter of the frontal sinus (< 1 cm) and small interorbital distance;
- erosion of the posterior wall of the frontal sinus with intracranial extension;
- extension of the lesion through the anterior frontal plate;
- massive lateral supraorbital attachment of the lesion in laterally-pneumatised frontal sinus;
- attachment of the tumour to the anterior wall or to the upper half of the posterior wall of the frontal sinus;
- massive involvement of the mucosa of the frontal sinus and/or of supraorbital cell;
- histological evidence of SCC in IP at pre-operative biopsies or intraoperatively with frozen sections;
- presence of abundant scar tissue from previous surgery or relevant post-traumatic anatomic changes of the frontal bone.

Conclusions

To the best of our knowledge, this is the largest single-centre case series of inverted papilloma involving the frontal sinus, either as origin or extension. The practical algorithm for surgical treatment planning of such lesions is based on the site of attachment of the lesion and the anatomical conformation of the frontal sinus, and is supported by a very low recurrence rate (4%) and minimal complications observed.

Table V. Review of English literature on surgical treatment of frontal sinus inverted papilloma (2002-2017).

Author	Year	Total cases	Cases with FS involvement	Type of surgery	Results	No. of relapses	Type of surgery for relapse	Status	Follow-up (months)
Present study	2018	47	47	19 EE 28 combined	100% CR	2	2 OPF	100% NED	43
Albathi [16]	2018	4	4	EE + TrP	100% CR	0	–	100% NED	24
Adriansen [20]	2015	20	20	EE	100% CR	2	EE	100% NED	42
Ungari [27]	2015	35	5 FS 13 FE	OPF	100% CR	2	2 OPF	100% NED	> 12
Pagella [28]	2014	73	2 FS 8 FE	EE	100% CR	0	–	100% NED	58
Sciarretta [29]	2014	110	7 FR 4 FS	EE	100% CR	1 FR 1 FS	1 EE (FR) 1 OPF (FS)	100% NED	56.7
Kim [30]	2012	578	22 (origin)	10 EE 8 combined 4 external	100% CR	6	N/A	N/A	41
			89 (extension)	59 EE 20 combined 10 external		24			
Gotlib [21]	2012	2	2	EE	100% CR	N/A	N/A	50% NED 50% N/A	12
Walgama [24]	2012	49	49	31 EE 13 OPF 5 EFT	100% CR	11	8 EE 1 EFT 2 OPF	100% NED	27
Lian [31]	2012	26	1	EE	100% CR	N/A	N/A	100% NED	28.2
Kamel [32]	2012	119	6	EE	100% CR	0	–	100% NED	27
Bathma [33]	2011	13	4 FR	EE	100% CR	2[§]	EE	100% NED	40
Lombardi [34]	2011	212	11	EE	100% CR	2	1 EE 1 OPF	100% NED	53.8
Dragonetti [35]	2011	84	3 FS 5 FR	6 EE 2 OPF	100% CR	1 (FR)	OPF	100% NED	39.5
Gras-Cabrerizo [36]	2010	79	8 (extension)	5 EE 3 external	100% CR	N/A	N/A	N/A	> 12
Sham [37]	2009	56	3	1 EE 2 ExFS[+]	100% CR	3	2 ExFS 1 ExFS + Lothrop	89% NED 11% DOC	84
Yoon [15]	2009	18	18	2 OPF 5 EFT	100% CR	4	3 EE 1 EFT	100% NED	36.6
Eweiss [22]	2009	4	4	EE	100% CR	1	OPF	100% NED	N/A
Landsberg [38]	2008	30	2	EE	50% CR 50% PR	1	–	50% NED 50% AWD	40
Mackle [39]	2008	55	1	OPF	100% CR	N/A	N/A	N/A	> 36
Zhang [23]	2008	9	9*	EE	100% CR	0	– 1 OPF	100% NED	15.1
Sautter [19]	2007	5	5	4 EE 1 EFT	100% CR	0	–	100% NED	16.8
Mortuaire [40]	2007	65	3	N/A	100% CR	1	External	N/A	28
Woodworth [41]	2007	110	10 FR 9 FS	10 EE 5 OPF 2 EFT 2 EE + Lynch	100% CR	8	5 EE 1 EFT 1 EE + OPF 1 EE + Lynch	100% NED	40
Minovi [42]	2006	87	13	4 EE 9 OPF	100% CR	N/A	N/A	100% NED	74

Table V. Review of English literature on surgical treatment of frontal sinus inverted papilloma (2002-2017).

Author	Year	Total cases	Cases with FS involvement	Type of surgery	Results	No. of relapses	Type of surgery for relapse	Status	Follow-up (months)
Katori [43]	2005	39	2 (origin) 8 (extension)	EE, external	100% CR	5[#]	EE, external	N/A	35
Dubin [14]	2005	18	6	2 EE 1 OPF 3 EE + OPF	67% CR 33% PR	3°	2 EE 1 OPF	83% NED 17% DOC	13.3
Jameson [44]	2005	18	1 FS 1 FR	1 OPF 1 EE	100% CR	0	–	100% NED	29
Wolfe [45]	2004	50	3 FS 2 FR	3 EE 1 OPF 1 Lynch	100% CR	0	–	100% NED	31.1

FS: Frontal Sinus; FR: Frontal Recess; FE: Fronto-ethmoidal; EE: Endoscopic Endonasal; OPF: Osteoplastic Flap; EFT: Endoscopic Frontal Trephination; ExFs: External Frontal Sinusotomy; Lynch: external approach through Lynch incision; TrP: transpalpebral; CR: Complete Resection; PR: Partial Resection; NED: No Evidence of Disease; AWD: Alive With Disease; DOC: Dead of Other Causes; [§]: the 2 relapses occurred in the same patient; [+]: the external frontal sinusotomy was realised via an eyebrow incision; [*]: frontal sinus and frontal recess are considered altogether; [#]: 1 relapse in frontal sinus originally involved only the ethmoid, 2 patients recurred twice each after endoscopic and external approach (not furtherly specified); [°]: 2 out of 3 cases were in fact persistence: a staged OPF was performed because of suspicious partial resection after endoscopic approach, confirmed by pathology.

EEA should be used whenever feasible and able to obtain radical resection of inverted papilloma in the frontal sinus. On the other hand, a combined approach with an OPF has to be used whenever dictated by the localisation of the tumour, and particularly by its sites of attachment inside the frontal sinus, even when the point of origin is situated outside of the sinus (i.e. in the ethmoidal compartment). To note, a new approach to the far lateral frontal sinus, the so-called endoscopic orbital transposition [10], has lately changed our paradigm toward a totally endoscopic endonasal tumour removal in selected cases.

In conclusion, the present study emphasises that what really matters is complete tumour eradication, possibly using the least invasive approach for the patient. Endoscopic endonasal techniques have drammatically changed the approach to inverted papilloma, although the endoscope remains a very useful tool even if not the solution for every case.

Conflict of interest statement

None declared.

References

1 Lund VJ, Stammberger H, Nicolai P, et al. *European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base*. Rhinol Suppl 2010;22:1-143.

2 Lund VJ. *Optimum management of inverted papilloma*. J Laryngol Otol 2000;114:194-7.

3 Mirza S, Bradley PJ, Acharya A, et al. *Sinonasal inverted papillomas: recurrence, and synchronous and metachronous malignancy*. J Laryngol Otol 2007;121:857-64.

4 Karligkiotis A, Lepera D, Volpi L, et al. *Survival outcomes after endoscopic resection for sinonasal squamous cell carcinoma arising on inverted papilloma*. Head Neck 2016;38:1604-14.

5 Lawson W, Patel ZM. *The evolution of management for inverted papilloma: an analysis of 200 cases*. Otolaryngol Head Neck Surg 2009;140:330-5.

6 Karligkiotis A, Bignami M, Terranova P, et al. *Oncocytic Schneiderian papillomas: Clinical behavior and outcomes of the endoscopic endonasal approach in 33 cases*. Head Neck 2014;36:624-30.

7 Busquets JM, Hwang PH. *Endoscopic resection of sinonasal inverted papilloma: a meta-analysis*. Otolaryngol Head Neck Surg 2006;134:476-82.

8 Tomenzoli D, Castelnuovo P, Pagella F, et al. *Different endoscopic surgical strategies in the management of inverted papilloma of the sinonasal tract: experience with 47 patients*. Laryngoscope 2004;114:193-200.

9 Draf W. *Endonasal micro-endoscopic frontal sinus surgery: The fulda concept*. Oper Tech Otolayngol Head Neck Surg 1991;2:234-40.

10 Karligkiotis A, Pistochini A, Turri-Zanoni M, et al. *Endoscopic endonasal orbital transposition to expand the frontal sinus approaches*. Am J Rhinol Allergy 2015;29:449-56.

11 Mohan S, Nair S, Sharma M, et al. *Inverted papilloma of frontal sinus with intracranial extension*. Med J Armed Forces India 2015;71(Suppl 1):S152-5.

12 Vural E, Suen JY, Hanna E. *Intracranial extension of inverted papilloma: An unusual and potentially fatal complication*. Head Neck 1999;21:703-6.

13 Krouse JH. *Development of a staging system for inverted papilloma*. Laryngoscope 2000;110:965-8.

14 Dubin MG, Sonnenburg RE, Melroy CT, et al. *Staged endoscopic and combined open/endoscopic approach in the management of inverted papilloma of the frontal sinus*. Am J Rhinol 2005;19:442-5.

15 Yoon BN, Batra PS, Citardi MJ, et al. *Frontal sinus inverted papilloma: surgical strategy based on the site of attachment*. Am J Rhinol Allergy 2009;23:337-41.

16 Albathi M, Ramanathan M, Lane AP, et al. *Combined endonasal and eyelid approach for management of extensive frontal sinus inverting papilloma*. Laryngoscope 2018;128:3-9.

17 Volpi L, Pistochini A, Bignami M, et al. *A novel technique for tailoring frontal osteoplastic flaps using the ENT magnetic navigation system*. Acta Otolaryngol 2012;132:645-50.

[18] Hardy JM, Montgomery WW. *Osteoplastic frontal sinusotomy: an analysis of 250 operations*. Ann Otol Rhinol Laryngol 1976;85(4 Pt 1):523-32.

[19] Sautter NB, Citardi MJ, Batra PS. *Minimally invasive resection of frontal recess/sinus inverted papilloma*. Am J Otolaryngol 2007;28:221-4.

[20] Adriaensen GF, van der Hout MW, Reinartz SM, et al. *Endoscopic treatment of inverted papilloma attached in the frontal sinus/recess*. Rhinology 2015;53:317-24.

[21] Gotlib T, Krzeski A, Held-Ziółkowska M, et al. *Endoscopic transnasal management of inverted papilloma involving frontal sinuses*. Wideochir Inne Tech Maloinwazyjne 2012;7:299-303.

[22] Eweiss A, Al Ansari A, Hassab M. *Inverted papilloma involving the frontal sinus: a management plan*. Eur Arch Otorhinolaryngol 2009;266:1895-901.

[23] Zhang L, Han D, Wang C, et al. *Endoscopic management of the inverted papilloma with attachment to the frontal sinus drainage pathway*. Acta Otolaryngol 2008;128:561-8.

[24] Walgama E, Ahn C, Batra PS. *Surgical management of frontal sinus inverted papilloma: a systematic review*. Laryngoscope 2012;122:1205-9.

[25] Mak W, Webb D, Al-Salihi S, et al. *Sinonasal inverted papilloma recurrence rates and evaluation of current staging systems*. Rhinology 2018;56:407-14.

[26] Voultsos P, Casini M, Ricci G, et al. *A proposal for limited criminal liability in high-accuracy endoscopic sinus surgery*. Acta Otorhinolaryngol Ital 2017;37:65-71.

[27] Ungari C, Riccardi E, Reale G, et al. *Management and treatment of sinonasal inverted papilloma*. Ann Stomatol (Roma) 2016;6:87-90.

[28] Pagella F, Pusateri A, Giourgos G, et al. *Evolution in the treatment of sinonasal inverted papilloma: pedicle-oriented endoscopic surgery*. Am J Rhinol Allergy 2014;28:75-81.

[29] Sciarretta V, Fernandez IJ, Farneti P, et al. *Endoscopic and combined external-transnasal endoscopic approach for the treatment of inverted papilloma: analysis of 110 cases*. Eur Arch Otorhinolaryngol 2014;271:1953-9.

[30] Kim DY, Hong SL, Lee CH, et al. *Inverted papilloma of the nasal cavity and paranasal sinuses: a Korean multicenter study*. Laryngoscope 2012;122:487-94.

[31] Lian F, Juan H. *Different endoscopic strategies in the management of recurrent sinonasal inverted papilloma*. J Craniofac Surg 2012;23:e44-8.

[32] Kamel RH, Abdel Fattah AF, et al. *Origin oriented management of inverted papilloma of the frontal sinus*. Rhinology 2012;50:262-8.

[33] Bathma S, Harvinder S, Philip R, et al. *Endoscopic management of sinonasal inverted papilloma*. Med J Malaysia 2011;66:15-8.

[34] Lombardi D, Tomenzoli D, Buttà L, et al. *Limitations and complications of endoscopic surgery for treatment for sinonasal inverted papilloma: a reassessment after 212 cases*. Head Neck 2011;33:1154-61.

[35] Dragonetti A, Gera R, Sciuto A, et al. *Sinonasal inverted papilloma: 84 patients treated by endoscopy and proposal for a new classification*. Rhinology 2011;49:207-13.

[36] Gras-Cabrerizo JR, Massegur-Solench H, Pujol-Olmo A, et al. *Endoscopic medial maxillectomy with preservation of inferior turbinate: how do we do it?* Eur Arch Otorhinolaryngol 2011;268:389-92.

[37] Sham CL, Woo JK, van Hasselt CA, et al. *Treatment results of sinonasal inverted papilloma: an 18-year study*. Am J Rhinol Allerg 2009;23:203-11.

[38] Landsberg R, Cavel O, Segev Y, et al. *Attachment-oriented endoscopic surgical strategy for sinonasal inverted papilloma*. Am J Rhinol 2008;22:629-34.

[39] Mackle T, Chambon G, Garrel R, et al. *Endoscopic treatment of sinonasal papilloma: a 12 year review*. Acta Otolaryngol 2008;128:670-4.

[40] Mortuaire G, Arzul E, Darras JA, et al. *Surgical management of sinonasal inverted papillomas through endoscopic approach*. Eur Arch Otorhinolaryngol 2007;264:1419-24.

[41] Woodworth BA, Bhargave GA, Palmer JN, et al. *Clinical outcomes of endoscopic and endoscopic-assisted resection of inverted papillomas: a 15-year experience*. Am J Rhinol 2007;21:591-600.

[42] Minovi A, Kollert M, Draf W, et al. *Inverted papilloma: feasibility of endonasal surgery and long-term results of 87 cases*. Rhinology 2006;44:205-10.

[43] Katori H, Tsukuda M. *Staging of surgical approach of sinonasal inverted papilloma*. Auris Nasus Larynx 2005;32:257-63.

[44] Jameson MJ, Kountakis SE. *Endoscopic management of extensive inverted papilloma*. Am J Rhinol 2005;19:446-51.

[45] Wolfe SG, Schlosser RJ, Bolger WE, et al. *Endoscopic and endoscope-assisted resections of inverted sinonasal papillomas*. Otolaryngol Head Neck Surg 2004;131:174-9.

Received: August 13, 2018 - Accepted: October 15, 2018

How to cite this article: Pietrobon G, Karligkiotis A, Turri-Zanoni M, et al. *Surgical management of inverted papilloma involving the frontal sinus: a practical algorithm for treatment planning.* Acta Otorhinolaryngol Ital 2019;39:28-39. https://doi.org/10.14639/0392-100X-2313

Address for correspondence: Giacomo Pietrobon, Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences, University of Insubria, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi, via Guicciardini 9, 21100 Varese, Italy. Tel. +39 0332 393278. Fax +39 0332 39327. E-mail: giacomo.pietrobon@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:40-45; doi: 10.14639/0392-100X-2020

AUDIOLOGY

Hearing loss in children with congenital cytomegalovirus infection: an 11-year retrospective study based on laboratory database of a tertiary paediatric hospital

Ipoacusia e infezione congenita da citomegalovirus: i risultati di uno studio retrospettivo di 11 anni basato sui dati di laboratorio

S. PALMA[1], M.F. ROVERSI[2], M. BETTINI[3], S. MAZZONI[2], P. PIETROSEMOLI[4], L. LUCACCIONI[2], A. BERARDI[2], E. GENOVESE[5]

[1] Audiology, Primary Care Unit, Modena, Italy; [2] Neonatal Intensive Care Unit, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Italy; [3] Head and Neck Department, University of Modena and Reggio Emilia, Italy; [4] Microbiology and Virology Department, University Medical Hospital, Modena; [5] Audiology, Department of Diagnostic, Clinical and Public Health University of Modena and Reggio Emilia, Italy

SUMMARY

Congenital cytomegalovirus infection is considered the main cause of infantile non-genetic neurosensory hearing loss. Although this correlation was described more than 50 years ago, the natural history of internal ear involvement has not yet been fully defined. Hearing loss is the most frequent sequela and is seen in a variable percentage up to 30%; the hearing threshold is characterised by fluctuations or progressive deterioration. The purpose of this study was to evaluate the prevalence of hearing loss in cases of congenital CMV infection from Modena county, starting from the database of the microbiology and virology reference laboratory. All children undergoing urine testing for suspected CMV infection or viral DNA testing on Guthrie Card in the period between January 2004 and December 2014 were enrolled in the study. Family paediatricians were contacted and asked about clinical information on the possible presence at birth or subsequent occurrence of hearing loss, excluding cases where this was not possible. The results showed an annual prevalence of congenital cytomegalovirus infection among suspected cases that was stable over time despite the progressive increase in subjects tested. The prevalence of hearing loss was in line with the literature, whereas in long-term follow-up cases of moderate, medium-to-severe hearing loss with late onset were not detected. The introduction of newborn hearing screening in the county has allowed early diagnosis of hearing loss at birth as non-TEOAE-born births underwent a urine virus test. Moreover, despite all the limitations of the study, we can conclude that European epidemiological studies are needed to better define the relationship between congenital CMV infection and internal ear disease as the impact of environmental and genetic factors is still not entirely clarified.

KEY WORDS: Cytomegalovirus • Congenital infection • Hearing loss • Newborn screening • Late sequelae

RIASSUNTO

Il citomegalovirus è la più comune causa di infezione congenita nei paesi industrializzati, con una prevalenza stimata intorno allo 0.3-2% dei nati vivi. Di questi, il 10-15% presenta sequele tardive tra cui deficit visivi, uditivi, ritardo mentale. La infezione congenita da citomegalovirus, ad oggi, è ancora ritenuta la principale causa di ipoacusia neurosensoriale infantile su base non genetica. Sebbene tale correlazione sia stata descritta più di 50 anni fa, la storia naturale del coinvolgimento dell'orecchio interno non è stata ancora completamente definita. La ipoacusia neurosensoriale è la sequela più frequente ed in una percentuale variabile, a seconda delle casistiche fino al 30%, la soglia è caratterizzata da fluttuazioni o deterioramento progressivo. Lo scopo di questo studio è stato quello di valutare la prevalenza della ipoacusia nei casi di infezione congenita da CMV della provincia di Modena, partendo dal data base del laboratorio di Microbiologia e Virologia, centro di riferimento per la intera provincia. Inoltre, ci si è proposti di valutare la entità della ipoacusia come sequela tardiva. Sono stati arruolati tutti i bambini sottoposti ad esame delle urine per sospetta infezione da CMV o mediante ricerca del DNA virale su Guthrie Card, nel periodo compreso tra gennaio 2004 e dicembre 2014. Mediante il contributo dei pediatri di famiglia e del servizio di Audiologia di Modena sono state accolte le informazioni cliniche sulla eventuale presenza alla nascita o insorgenza successiva di ipoacusia, escludendo dallo studio i casi in cui ciò non è stato possibile. I risultati hanno dimostrato una prevalenza annuale di infezione congenita da citomegalovirus stabile nel tempo nonostante l'aumento progressivo dei nati sottoposti al test. La prevalenza della ipoacusia nei casi di infezione congenita è in linea con la letteratura mentre non sono emersi, nel lungo periodo, casi con ipoacusia media/severa bilaterale ad insorgenza tardiva. La introduzione dello screening audiologico neonatale nella nostra regione (2012) ha permesso una diagnosi precoce della ipoacusia in quanto i nati con esito fail alle TEOAE venivano sottoposti anche al test per la ricerca del virus nelle urine. Pur con tutti i limiti di uno studio basato su revisione di casistica, possiamo concludere che permane la necessità di studi epidemiologici europei che consentano di definire meglio la relazione tra infezione congenita da CMV e patologia dell'orecchio interno in quanto l'impatto dei fattori ambientali e genetici non è ancora del tutto chiarito. La sinergia tra screening audiologico neonatale ed esecuzione del test per la ricerca del virus nelle urine si è dimostrata molto proficua.

PAROLE CHIAVE: *Citomegalovirus • Infezione congenita • Ipoacusia • Screening neonatale • Sorveglianza audiologica*

Introduction

Congenital cytomegalovirus (cCMV) infection is currently estimated to be the main cause of non-inherited sensorineural hearing loss [1 2]. Considered the most common congenital infection in humans, cCMV has a prevalence in the hearing-impaired children population between 2% and 18% [3-5]. The virus can be transmitted to the foetus through placental blood, contact with infected vaginal secretions during delivery, breast milk, or blood transfusions after birth. The risk of transmission to the foetus is 30-35% and 1.1-1.7% for primary or non-primary maternal infection, respectively [6].

Although the association between cCMV and hearing loss was first noted 50-60 years ago, the natural history of the inner ear involvement is still unclear [7]. Even if 85-90% of cCMV are asymptomatic at birth, 10-15% of these infants may develop hearing, visual, or neurodevelopmental impairment [2 8]. Moreover, vestibular involvement, often underestimated, may contribute to delayed motor skill acquisition in these children [9 10]. In view of the fact that most newborns are asymptomatic at birth and that there are no specific screening protocols to detect infection, the actual impact of cCMV is still not completely known. Sensorineural hearing loss is the most common sequela, affecting from 33 to 65% of symptomatic newborns and from 7 to 15% of asymptomatic ones [11 12], presenting in 30% of the cases, with fluctuating auditory thresholds, characterised by deterioration or improvement over time [1 11-13].

As no effective prenatal therapy or vaccine exist, and since most patients with cCMV recover spontaneously, no universal screening program for cCMV has yet been implemented, although its value is an increasingly debated issue [14]. When urine and saliva cultures obtained within the first two weeks of life are positive for cCMV, clinicians carry out complete clinical and biochemical evaluation to identify whether the infection is symptomatic or asymptomatic. The outcome of these tests affects treatment decisions, as current guidelines recommend to treat only symptomatic infants with antiviral therapy during their first 30 days of life in the presence of central nervous system disorders or in cases of focal or severe organ diseases [15].

Materials and methods

Data were retrospectively collected from the laboratory database of the University Medical Hospital of Modena, the reference centre for diagnosis of viral infections for the entire county. All urinary CMV tests carried out between January 2004 (the starting point was linked to the introduction of new hospital software) and December 2014 were reviewed. As a first step, all children (0-12 years) with confirmed CMV infection were enrolled in the study. Diagnosis of CMV infection was carried out by testing urine samples using the shell vial assay (SVA). Cases of cCMV infection were defined as any newborn ≤ 14 days of age with a positive CMV urine test or with a positive polymerase chain reaction (PCR)-CMV test confirmed on Guthrie cards. The main reasons for performing a cCMV test were: incidental finding of maternal CMV during pregnancy, abnormal prenatal cerebral ultrasound, preterm delivery, microcephaly (head circumference < 3° percentile), persistent jaundice, thrombocytopenia, neutropenia. Family paediatricians were contacted and asked if their patients experienced hearing loss, and additional information regarding hearing loss was obtained from the records of the ENT/Audiology and Paediatric Departments. A new audiological evaluation was prescribed only in cases of doubt.

Since January 2012, neonates born in Modena county routinely undergo hearing testings in accordance with the screening program implemented in the Emilia Romagna region [16] (a two stage Transitory Evoked Otoacoustic Emission-TEOAE protocol, carried out in accordance with the recommendations of the American Academy of Pediatrics).

Before 2012 the Auditory Brainstem Response (ABR) test was carried out only at the time of diagnosis of cCMV. Starting from 2012, in accordance with Italian paediatric guidelines [17], children with cCMV infection routinely undergo ABR as part of a long-term audiological program for cCMV infected patients, which foresees assessments at 1-3 and 6 months and annual assessments up to the 6-year age for neonates with normal hearing.

The severity of sensorineural hearing loss was defined as follows: normal hearing (0-15 db), slight (16-25 db), mild (≥ 26 to < 40 dB); moderate (≥ 41 to < 55 dB), moderate-severe (≥ 56 to < 70 dB), severe (≥ 71 to < 90 dB) and profound (> 90 dB).

Demographic data were obtained from the Regional Health Agency. This study was approved by the Ethics Committee of Modena county (n. 166/14), informed consent was obtained through the family's paediatricians.

Results

Urinary CMV testing was carried out in 2966 children (3.9% of total live births) between 2004 and 2014, 1954 (65%) of whom were younger than 14 days (Fig. 1). Table I shows the prevalence of children tested positive or negative for cCMV in the county. CMV infection was confirmed in 339 children and information on hearing loss was available in 250 (73.8%): 45/250 were cCMV, while

Table. I. Number of newborns per year during the study period and number of children tested for suspected cCMV (age < 14 days of life). The prevalence calculated on our population are reported in brackets.

Year	Total newborns	Children tested for suspected cCMV (prevalence %)	Children resulted negative for cCMV (prevalence %)	Children resulted positive for cCMV (prevalence %) *	Prevalence of cCMV among tested population
2004	6553	80 (1.2%)	72 (1%)	8 [5] (0.1%)	10%
2005	6770	163 (2.4%)	157 (2.3%)	6 [5] (0.08 %)	3.7%
2006	6703	162 (2.4%)	158 (2.3%)	4 (0,04%)	2.5%
2007	6857	132 (1.9%)	128 (1.8%)	4 [3] (0.05%)	3%
2008	7201	121 (1.6%)	118 (1.6%)	3 (0,03%)	2.5%
2009	7151	151 (2.2%)	145 (2%)	6 [5] (0.08%)	4%
2010	7116	189 (2.6%)	184 (2.5%)	5 [4] (0.07%)	2.64%
2011	6949	224 (3.2%)	217 (3.1%)	7 [6] (0.1%)	3.1%
2012	6703	185 (2.7%)	185 (2.7%)	0	-
2013	6311	247 (3.9%)	240 (4%)	7 [5] (0.1%)	2.8%
2014	6040	300 (4.9%)	295 (5%)	5 (0,08%)	1.66%
Tot	74354	1954 (2.8%)	1899 (2.5%)	55 [45] (0.07%)	2.8%

**: The number of newborns with information about hearing impairment are reported in squared brackets.*

205/250 were acquired (Fig. 2). Figure 2 also details the rates of acquired and congenital infections according to the availability of hearing loss information. All these children had at least 2 years of follow-up, and 51% had at least 8 years.

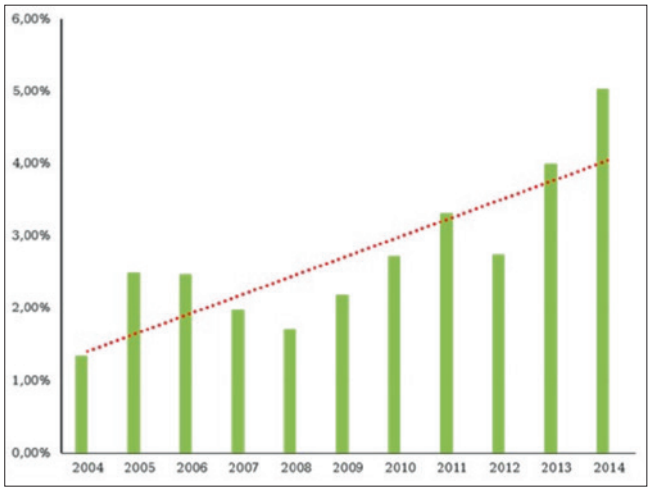


Fig. 1. Number of children screened for CMV compared to the number of newborns from 2004 to 2014.

A few children (n = 6/250-13%) with cCMV infection had confirmed hearing impairment. Among these, 2 were diagnosed after 2012 through the neonatal hearing screening program, and were positive by TEOAE. The number of children presenting with hearing loss, the severity of disease and side of hearing impairment are shown in Table II. The prevalence of symptomatic cCMV after the introduction of newborn hearing screening (2/10) was 20%, while the proportion of symptomatic cCmv with hearing loss before the screening was 11%. Among the 205 children (82%) with acquired CMV, 6 (2.9%) had moderate to severe hearing impairment: in one case the Guthrie card excluded cCMV and 2 cases were associated with syndromes. The remaining 3 cases could be attributed to delayed diagnosis of cCMV (Table II). All the 6 cases with acquired CMV were born before the implementation of the newborn hearing screening.

Although the total number of samples analysed increased over the years (from 1.2% in 2004 to 4.9% in 2014), and

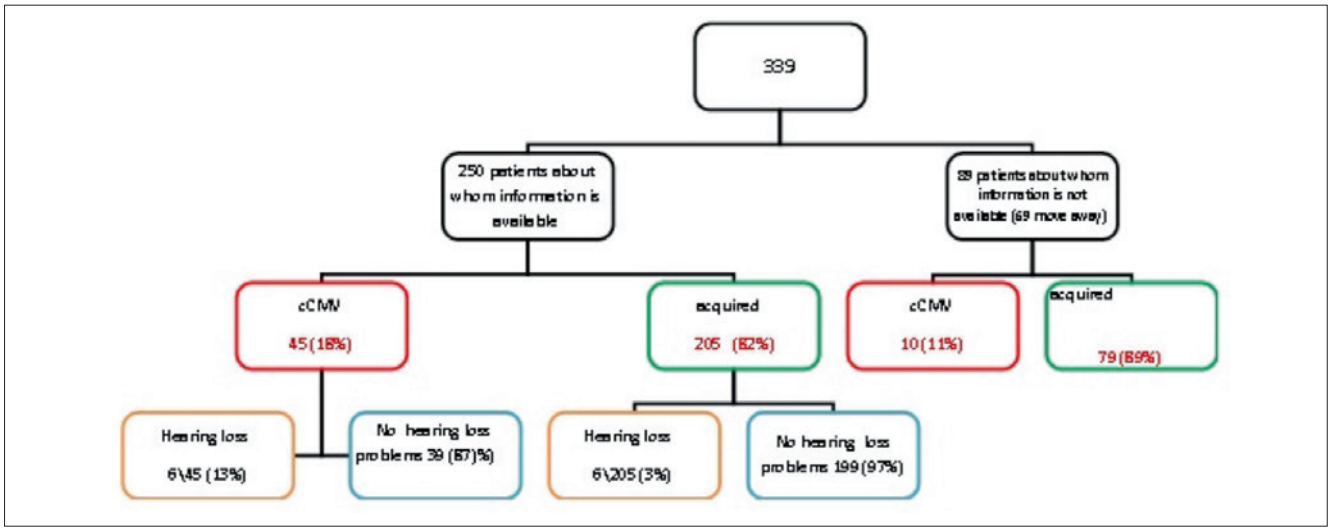


Fig. 2. Positive CMV testing.

in particular due to the introduction of the newborn hearing screening test, the prevalence of cCMV among tested children reduced from 10% to 1.6%. Figure 3 shows the number of cCMV cases detected per year.

Discussion

This retrospective study is based on the laboratory database of a tertiary university hospital, which is the reference center for the entire country.

We found that the number of tested infants increased almost four-fold during the study period, demonstrating the efforts of clinicians in identification of asymptomatic infants at least among the population at high risk (i.e. preterm infants, intrauterine growth retarded infants).

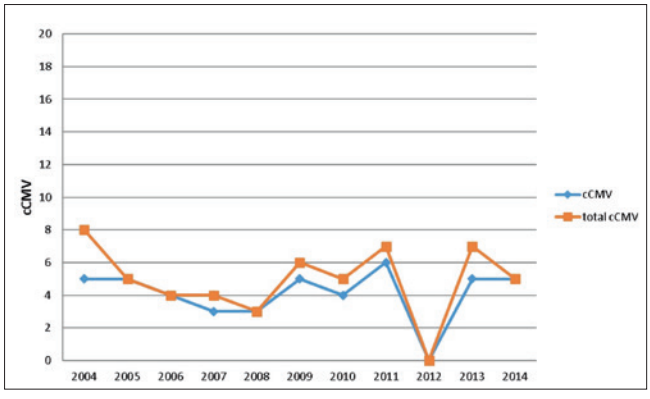


Fig. 3. The blue line shows the number of cases per year about which information on hearing loss was available, and the brown line indicates the total number of cases of cCMV diagnosed per year. In 2012 an earthquake struck the county, and only 3 of the 5 maternity wards were functioning for a 4-5 month period.

Table II. Number of children presenting with hearing loss.

Hearing loss	cCMV	aCMV
Bilateral		
Mild	1	1
Severe	2	1
Profound	1	0
Monolateral		
Mild	0	0
Severe	1	1
Profound	1	0
Tot	**6 (13%)**	**3**

In particular, during the first years of the study period, clinical suspicion of infection mainly led to the urine CMV test. Near the end of the study period, CMV screening was increasingly addressed to asymptomatic high-risk infants in order to improve early diagnosis and secondary prevention strategies.

Large prospective studies reported a prevalence of 0.4-0.53% of cCMV(14), a recent systematic review indicates a median prevalence of 0.58% [3]. In our sample, the prevalence of cCMV among tested children has showed fluctuations ranging from 1.6% to 10% that can be ascribed to the different sample size, the retrospective nature of the study and the type of population (clinical suspicion of congenital infection and/or high risk infants).

Interestingly, despite the increasing number of infants tested during the study period, the percentage of cCMV decreased, reaching the lowest percentage in the year with the larger number of infants tested. The greater and less

selected the tested population, the lower the prevalence of cCMV. In this regard, a recent review examining the disease burden in Europe suggested that more epidemiological knowledge of cCMV infection [18] is needed to assess its actual prevalence. Epidemiological patterns over the years show fluctuations in viral congenital infection rates and differences in prevalence registered in industrialised and non-industrialised countries, suggesting that other factors, e.g. environmental or genetic, may be involved [19]. Retrospective studies on populations of deaf children report a percentage of 2-18% of hearing loss cases due to cCMV, but its real prevalence is not yet precisely known, as in most countries CMV infection is not screened during pregnancy or in newborn [14 20 21]. In the last 20 years, it has also been assumed that asymptomatic cCMV can be a significant cause of hearing loss. The question is still complex as childhood hearing impairment is the result of the intersection of different factors such as genetic predisposition and intrauterine, as well as perinatal and postnatal factors.

In our sample, the prevalence of hearing loss in cCMV infection was 13.3%, similar to that reported in a systematic review by Goderis [3], indicating an overall 12.6% prevalence of cCMV with a 76% rate of severe to profound hearing loss. In detail, the proportion of symptomatic cCMV with hearing loss is higher after the year of implementation of prevention programs such as the newborn hearing screening and Italian paediatric guidelines [16 17].

It is well established that delayed identification of hearing loss can compromise a child's language acquisition and cognitive and psychosocial skills, but it is important to highlight that since hearing impairment may present after the neonatal period, a screening program at birth would fail to identify children with cCMV who will develop hearing loss later. In fact, in a recent study it was demonstrated that a cCMV screening program within the context of newborn hearing screening protocol can identify the majority of infants with CMV-related sensorineural hearing loss at birth, while missing cases at risk for late onset hearing impairment [5].

Currently there is a growing interest in the feasibility and benefit of linking screening for cCMV infection and neonatal audiological screening as many consider implementing a universal cCMV screening program to be an onerous solution [22-24].

The only way to measure the real impact of cCMV related hearing impairment on the infant population, especially in the late onset form, would be to exclude with all certainty other concomitant causes of hearing loss: for example, new hereditary sensorineural hearing loss are revealed every day, and it cannot be excluded that some genetic factors could facilitate virus-related damage to the inner ear.

None of the children of our study reported significant worsening of hearing loss after the neonatal period, and in particular none of the 51% with 8 years follow-up; this data confirms that delayed onset of hearing loss, even though possible, is not a predictable condition in cCMV infection. A recent study on a murine CMV-induced hearing loss model, which demonstrated that host derived inflammatory responses and not direct virus-mediated cytopathology may be responsible for hearing impairment [25], can explain the waywardness of cochlea-vestibular damage.

Long-term audiological follow-up for at least 6 years is recommended, and audiological surveillance of children together with monitoring of communicative skills are essential to minimise adverse consequences of hearing loss, and require a multidisciplinary approach to the problem.

This retrospective study has some limitations. Firstly, our sample accounts for only 2.6% of the infants born during the study period, and no information is added with respect to the prevalence of cCMV infection in the general population. Secondly, we cannot exclude that a few children who were scored normally hearing by paediatricians might suffer from slight/mild hearing loss or a monolateral loss whose signs were not reported by parents. Finally, due to organisational issues, we were unable to detect CMV DNA by PCR on neonatal dried blood spots when the urine sample was collected later than 14 days of life. Taking into account all these limitations, we agree on the necessity of more epidemiological European studies, mainly because the impact of environmental and genetic factors is still not fully understood. The synergy between universal newborn hearing screening program and cCMV testing for asymptomatic infants who failed the TEOAE test allows early diagnosis of congenital CMV infection and the beginning of follow-up strategies and secondary prevention programs.

Conclusions

Congenital CMV infection is still one of the main causes of hearing loss in the paediatric population and a large debate on the introduction of a universal newborn screening for cCMV infection is ongoing. The question is complex, as childhood hearing loss is the result of different factors such as genetic predisposition as well as perinatal and postnatal factors. A targeted CMV approach testing newborns who fail hearing screening is useful to identify most of children with CMV-related sensorineural hearing loss as the impact of environmental and genetic factors on viral infection rates is still not fully understood.

Conflict of interest statement

None declared.

References

1 Grosse SD, Ross DS, Dollard SC. *Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment.* J Clin Virol 2008;41:57-62.

2 Dollard SC, Grosse SD, Ross DS. *New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection.* Rev Med Virol 2007;17:355-63.

3 Goderis J, De Leenheer E, Smets K, et al. *Hearing loss and congenital CMV infection: a systematic review.* Pediatrics 2014;134:972-82.

4 Das VK. *Aetiology of bilateral sensorineural hearing impairment in children: a 10 year study.* Arch Dis Child 1996;74:8-12.

5 Fowler KB, McCollister FP, Sabo DL, et al. *A targeted approach for congenital cytomegalovirus screening within newborn hearing screening.* Pediatrics 2017;139:e20162128.

6 Kenneson A, Cannon MJ. *Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection.* Rev Med Virol 2007;17:253-76.

7 Medearis DN. *Viral infections during pregnancy and abnormal humana development.* Am J Obstet Gynecol 1964;90:1140-8.

8 Britt WJ. *Cytomegalovirus*. In: Remington JS, Klein JO, Wilson CB, et al., editors. *Infectious diseases of the fetus and newborn infant.* Philadelphia: Elsevier Saunders; 2011. pp. 706-55.

9 Teissier N, Bernard S, Quesnel S, et al. *Audiovestibular consequences of congenital cytomegalovirus infection.* Eur Ann Otorhinolaryngol Head Neck Dis 2016;133:413-8.

10 Zagólski O. *Vestibular-evoked myogenic potentials and caloric stimulation in infants with congenital cytomegalovirus infection.* J Laryngol Otol 2008;122:574-9.

11 Fowler KB, Boppana SB. *Congenital cytomegalovirus (CMV) infection and hearing deficit*. J Clin Virol 2006;35:226-31.

12 Rosenthal LS, Fowler KB, Boppana SB, et al. *Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection.* Pediatr Infect Dis J 2009;28:515-20.

13 Cannon MJ, Griffiths PD, Aston V, et al. *Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit?* Rev Med Virol 2014 ;24:291-307.

14 Foulon I, Naessens A, Foulon W, et al. *A 10 year prospective study of sensorineural hearing loss in infants with congenital cytomegalovirus infection.* J Pediatr 2008;153:84-8.

15 Kadambari S, William EJ, Luck S, et al. *Evidence based management guidelines for the detection and treatment of congenital CMV.* Early Hum Dev 2011;87:723-8.

16 GPG/2011/498. *Screening uditivo neonatale e percorso clinico ed organizzativo per i bambini affetti da ipoacusia in Emilia-Romagna. Approvazione linee guida per le aziende sanitarie.* 23 maggio 2011, N. 694, Boll. Uff. RER, 6 luglio 2011,18-49.

17 *Linee guida SIN*. www.simast.it/linee-guida/percorsi-diagnostico-assist/citomegalovirus.

18 Ludwig A, Hengel H. *Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe.* Eur Surveill 2009;14:26-32.

19 Marsico C, Kimberlin DW. *Congenital cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment.* Ital J Pediatr 2017;4:38.

20 Sculerati N. *Analysis of a cohort of children with sensory hearing loss using the SCALE systematic nomenclature.* Laryngoscope 2000;110:787-98.

21 Ohlms LA, Chen AY, Stewart MG, et al. *Establishing the etiology of childhood hearing loss.* Otolaryngol Head Neck Surg 1999;120:159-63.

22 Gantt S, Dionne F, Kozak FK, et al. *Cost-effectiveness of universal and targeted newborn screening for congenital cytomegalovirus infection.* JAMA Pediatr 2016;170:1173-80.

23 Williams EJ, Kadambari S, Berrington JE, et al. *Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss.* Arch Dis Fetal Neonatal Ed 2014;99:F230-F6.

24 Forli F, Giuntini G, Bruschini L, et al. *Aetiologic diagnosis of hearing loss in children identified through newborn hearing screening testing.* Acta Otorhinolaryngol Ital 2016;36:29-37.

25 Bradford RD, Yoo YG, Golemac M, et al. *Murine CMV-induced hearing loss is associated with inner ear inflammation and loss of spiral ganglia neurons.* Plos Pathol 2015;11:e1004774.

Received: November 21, 2017 - Accepted: February 18, 2018

How to cite this article: Palma S, Roversi MF, Bettini M, et al. *Hearing loss in children with congenital cytomegalovirus infection: an 11-year retrospective study based on laboratory database of a tertiary paediatric hospital.* Acta Otorhinolaryngol Ital 2019;39:40-45. https://doi.org/10.14639/0392-100X-2020

Address for correspondence: Silvia Palma, Audiology, Primary Care Unit Modena, University Hospital, Modena, via del Pozzo 71, 41100 Modena, Italy. Tel. +39 059 4223901. E-mail: silviapalma@inwind.it

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:46-52; doi: 10.14639/0392-100X-1963

AUDIOLOGY

Predictors of central vestibular compensation after surgery for vestibular schwannomas

Fattori predittivi di compensazione vestibolare centrale dopo chirurgia per lo schwannoma vestibolare

Z. ČADA[1*], Z. BALATKOVÁ[1*], O. ČAKRT[2], S. HRUBÁ[1], M. KOMARC[3], J. PLZAK[1], R. ČERNÝ[4]

[1] Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine Charles University in Prague and Motol University Hospital, Postgraduate Medical School; [2] Department of Rehabilitation and Sports Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Postgraduate Medical School; [3] Department of Anthropomotorics and Methodology, Faculty of Physical Education and Sport, Charles University in Prague;[4] Department of Neurology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Postgraduate Medical School

* These authors contributed equally to this work.

SUMMARY

Surgical removal of vestibular schwannoma causes acute vestibular symptoms, including postoperative vertigo which is the most negative factor affecting quality of life in patients after vestibular schwannoma surgery. The main aim of this study is to determine whether the results from routine electronystagmography with pathological visually-provoked responses can predict poor postoperative compensation. We also investigate whether postoperative central compensation is related to objective parameters such age, tumour size, length of surgery and persistent nystagmus. According to the results from preoperative electronystagmography, patients were divided into three groups: peripheral, central and combined vestibular syndrome. Signs of central compensation were evaluated by the presence of postoperative nystagmus, vertigo, deviation of subjective visual vertical and head impulse test. There were no statistically significant differences between groups in observed signs of compensation. These results suggest that pathological central oculomotor parameters are not a negative predictive factor for central vestibular compensation.

KEY WORDS: Vestibular function • Central compensation • Electronystagmography • Vertigo

RIASSUNTO

La rimozione chirurgica dello schwannoma vestibolare è causa di sintomi vestibolari acuti, inclusa la vertigine postoperatoria che rappresenta il fattore che influenza più negativamente la qualità della vita dei pazienti dopo questo tipo di chirurgia. Scopo principale di questo studio è stato quello di determinare se i risultati dell' elettronistagmografia con risposte provocate patologiche possano prevedere una scarsa compensazione postoperatoria. Abbiamo inoltre ricercato se la compensazione postoperatoria possa essere correlata con parametri oggettivi come l'età, le dimensioni del tumore, la durata della chirurgia e la persistenza del nistagmo. Sulla base dei risultati dell' elettronistagmografia preoperatoria, i pazienti sono stati divisi in tre gruppi: con sindrome vestibolare periferica, centrale o combinata. I segni di compensazione centrale sono stati valutati dalla presenza di nistagmo postoperatorio, vertigine, deviazione della verticale soggettiva ed "head impulse" test. Non vi sono state differenze statisticamente significative fra i due gruppi nei segni di compensazione osservati. Questi risultati suggeriscono che i parametri oculomotori centrali patologici non sono un fattore predittivo negativo per la compensazione vestibolare centrale.

PAROLE CHIAVE: *Funzione vestibolare • Compensazione centrale • Elettronistagmografia • Vertigini*

Introduction

Surgery for vestibular schwannoma leads to acute vestibular dysfunction in the postoperative period [1 2]. Surgery leads to acute vestibular syndrome due to vestibular asymmetry.

After each acute vestibular asymmetry, central compensation initiates but usually subsides over weeks to months. After surgery, patients compensate with variability in vertigo symptoms, but such variability is still poorly understood. With advancing age, internal and neurologic comorbidities slow down the process of compensation. Central compensation depends on functional integrity of central vestibular and cerebellar centres [3]. Older patients or those with additional central nervous disorders may have a problem with vestibular compensation that can be prolonged or even inadequate [3 4]. Patients with uncompensated unilateral vestibular loss typically suffer from chronic vertigo, instability, postural imbalance and per-

sistent spontaneous nystagmus. Patients with vestibular schwannomas may have impaired balance due to direct vestibular nerve compression or pressure on the brain stem and cerebellum.

According to the type of functional impairment, patients with vestibular schwannoma can be divided into three groups with a peripheral, central, or mixed (combined) vestibular syndrome pattern.

The primary endpoint of the study is smooth pursuit movements and/or optokinetic and saccadic responses in predicting poor compensation following vestibular schwannoma surgery.

Secondary end-points include correlation of compensation markers with age, gender, tumour size, duration of surgery and persistence of nystagmus.

Materials and methods

In this study, 47 patients (28 males and 19 females; mean age, 46 years; range, 19-74 years) who underwent surgery for vestibular schwannomas (retrosigmoid approach) between 2009 and 2010 were included. All patients were examined pre-operatively by neurologists, ENT specialists and an ophthalmologist, and determined to be candidates for surgery. Most patients had profound hearing loss on the tumour side (pure tone average > 55 dB). Five patients had mild hearing loss on the tumour side. The size of the tumour was classified according to the Koos classification (Table I). All patients were pre-operatively evaluated by neuro-otologists. A history of vertigo was documented in all patients before surgery. The examination included evaluation for spontaneous nystagmus, and testing of the vestibulo-ocular reflex by head impulse testing and subjective visual vertical examination. All patients were evaluated pre-operatively by electronystagmography. Electronystagmography was performed using a four-channel electronystagmograph (Toennies Nystagliner, Wuerzburg, Germany). Electronystagmographic examination (ENG) included examination of spontaneous nystagmus with and without fixation, gaze direction nystagmus, smooth pursuit test, examination of saccades, recording of optokinetic nystagmus, and rotational and caloric tests. Based on the results of the ENG battery, patients were classified into the following three categories: peripheral vestibular syndrome; central vestibular syndrome; and combined vestibular syndrome (Table II).

Central vestibular syndrome was defined as abnormal results in tests for smooth pursuit movements (SPEMs), abnormal saccades and optokinetic response. Vestibulo-ocular reflex gain, as examined by rotational and caloric tests, were within normal limits and no asymmetry was present. Central oculomotoric movements in the vertical plane are not routinely evaluated in our laboratory.

SPEM were considered abnormal when saccades intrusion and/or a staircase appearance was noted. The limits of norm of SPEM gain are shown in Table III.

Saccades abnormalities are defined as hypermetria or hypometria. The limits of norms are shown in Table II.

Table I. Characteristics of patients.

Patients	Total	Peripheral syndrome	Central syndrome	Combined syndrome	P value
Number of patients (%)	47 (100.0)	18 (38.3)	19 (40.4)	10 (21.3)	
Side of tumour/left (number, %)	27 (57.4)	9 (50.0)	11 (57.9)	7 (70.0)	0.590
Age/years (mean, SD)	46.1 (13.9)	45.1 (12.3)	48.1 (13.6)	44.4 (17.9)	0.741
Length of surgery/hours (mean, SD)	8.2 (2.1)	7.3 (1.9)	8.7 (2.5)	8.8 (0.6)	0.073
Vertigo (mean, SD)	0.4 (0.5)	0.3 (0.5)	0.4 (0.5)	0.7 (0.5)	0.175
• preoperatively 0 (number, %)	26 (55.3)	12 (66.7)	11 (57.9)	3 (30.0)	–
• preoperatively 1 (number, %)	21 (44.7)	6 (33.3)	8 (42.1)	7 (70.0)	–
• preoperatively 2 (number, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Spontaneous nystagmus	–	–	–	–	–
• preoperatively (number, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
• postoperatively (number, %)	26 (55.3)	11 (61.1)	8 (42.1)	7 (70.0)	0.293
SVV	–	–	–	–	–
• preoperatively (mean, SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	–
• postoperatively (mean, SD)	2.1 (3.6)	2.33 (2.74)	2.26 (4.83)	1.4 (2.32)	0.791
• 3 months after surgery (mean, SD)	0.8 (1.6)	1.22 (1.83)	0.68 (1.7)	0.2 (0.63)	0.263
Tumour stage (mean, SD)	3.5 (0.9)	2.9 (1.1)	3.7 (0.7)	3.8 (0.4)	0.008
• stage I (number, %)	2 (4.3)	2 (11.1)	0 (0.0)	0 (0.0)	–
• stage II (number, %)	7 (14.9)	5 (27.8)	2 (10.5)	0 (0.0)	–
• stage III (number, %)	6 (12.8)	3 (16.7)	1 (5.3)	2 (20.0)	–
• stage IV (number, %)	32 (68.1)	8 (44.4)	16 (84.2)	8 (80.0)	–

SD: standard deviation; SVV: subjective visual vertical.

Table II. Characteristics of vestibular syndromes.

	SpN	OKN	SPEM	Saccades	Rotational test	Caloric test
Central	– +	+	+	+	–	–
Peripheral	+	–	–	–	+	+
Mixed	+	+	+	+	+	+

SpN: spontaneous nystagmus; OKN: optokinetic nystagmus; SPEM: pursuit smooth movements; +: abnormal result; –: normal result; – +: abnormality is not obl.

Optokinetic nystagmus was classified as abnormal when nystagmus beats were absent or irregular or dysrhythmic. The quantitative parameters of abnormalities are presented in Table II.

The criteria for peripheral vestibular hypofunction were caloric or rotational hyporeflexia, positive head impulse testing and absence of the above-mentioned central oculomotor abnormalities [5-7].

Combined (mixed) vestibular syndrome was defined as the combination of pathologies in central and peripheral parameters.

The clinical examination included a search for nystagmus and corrective sacades in head impulse testing, stand and gait stability and subjective visual vertical. Two subjective scales were used (vertigo intensity and validated questionnaire [Dizziness Handicap Inventory {DHI}]). Vertigo intensity was assessed by subjective numerical rating scale in three degrees (0,1 and 2). Vertigo 0 indicates very slight instability without nausea or emesis. Vertigo 1 indicates instability provoked by fast movements of the head and/or body with slight nauzea and no emesis. Vertigo 2 means that patients have rotatory vertigo, poor stability, and nausea with possible emesis.

Patients were examined before surgery (Time 1) and shortly (2 to 4 days after surgery) after surgery (Time 2), and then at 3 weeks (Time 3) and 3 months after surgery (Time 4).

In all patients, both vestibular nerves (superior and inferior) were macroscopically resected together with the tumour using a retrosigmoid-transmeatal approach. All patients were postoperatively instructed to practice a vestibular training programme adopted for patients with acute vestibular loss [8]. The programme included gaze stability exercises, smooth pursuit and saccadic eye movements, and postural exercises to improve balance control and gait stability.

Questionnaires

The DHI contains 25 items with a score from 0 to + 100, with a higher score indicating more severe handicap.

Statistical analysis

Data are expressed as the mean ± SD, or summarised as absolute frequencies and percentages as appropriate. Differences between groups of patients with different types of vestibular syndrome (peripheral, central, and combined) were evaluated by one-way analysis of variance (ANOVA). A chi-square test was used to compare count variables. Changes in vertigo perception and DHI in patients with different types of vestibular syndrome were tested using two-way repeated ANOVA (time x group), followed by a series of LSD post-hoc tests. The Spearman correlation coefficient was calculated to express the magnitude of the relationship between particular variables. A two-tailed p value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS (version 22; IBM SPSS, Armonk, NY, USA).

Results

During the study period, 50 patients underwent surgery for vestibular schwannomas using a retrosigmoid-transmeatal approach. Three patients were excluded from the study because they declined inclusion for various reasons.

The tumour was situated on the left side in 27 patients (57.4%); 21(44.7%) patients had pre-operative dizziness. In 7 patients (14.9%) cerebrospinal fluid leaks were observed from spinal fluid pseudocysts. All cysts were con-

Table III. Limits of norms for ENG tests, 95% CI.

SPEM (0.29°/s) gain	OKN (36°/s) gain	OKN maximum velocity (°/s)	Saccade dissymmetry (%)	Saccade latency (ms)	Sinusoidal rotation test gain
0.65-1.07	0.52-1.15	19-42	Right eye right saccade 88-108 Left eye right saccade 89-110 Right eye left saccade 89-111 Left eye left saccade 88-108	129-255	0.24-0.85

SPEM: pursuit smooth movements; OKN: optokinetic nystagmus.

servatively treated by puncture and compression during the first postoperative week.

No patients had pre-operative spontaneous nystagmus and abnormal deviation of subjective visual vertical. Most of tumours were stage IV (32 patients [68.1%]). Six patients (12.8%) had stage III tumours, 7 patients (14.9%) had stage II tumours, and 2 patients (4.3%) had stage I tumours (Table I).

According to the results of ENG, patients were divided into three categories (peripheral, central and combined). Eighteen patients (38.3%) had peripheral vestibular syndrome, 19 patients (40.4%) had central vestibular syndrome and 10 patients (21.3%) had combined vestibular syndrome.

These three groups (peripheral, combined and central) did not differ with respect to age, presence of pre- and post-operative spontaneous nystagmus, sensation of vertigo, or deviation of subjective visual vertical ($p > 0.05$). Statistically significant differences were observed ($p < 0.05$) between size of tumour and type of syndrome, in which patients with large tumours had more central signs on ENG ($p < 0.05$; Table I). All patients had vertigo with nausea shortly after surgery.

Patients with central and peripheral pre-operative findings had post-operative non-significant reduction of vertigo in comparison with the preoperative level. At 3 weeks and 3 months post-operatively the vertigo sensation in these groups was non-significantly worse (Fig. 1, Table IV). A significant difference was observed ($p < 0.05$) in patients with combined findings who had smaller vertigo intensity at 3 weeks post-operatively compared with the pre-operative state (Fig. 1, Table IV).

These results were in contrast to the DHI results. There was a significant ($p < 0.05$) increase in the DHI score at 3 months post-operatively in the peripheral and central groups (Fig. 2, Table IV). In the combined group, there was also an increase in DHI scores, but statistical significance was not reached ($p = 0.056$).

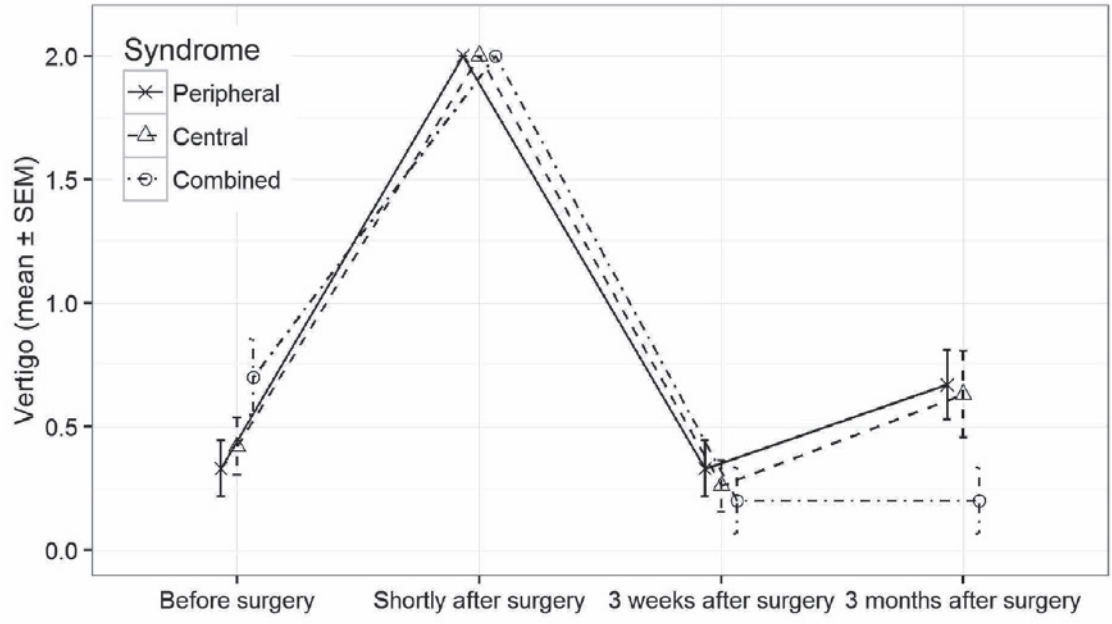
Other factors studied, such as age, side of the tumour and length of surgery did not influence the compensation (Table I).

Discussion

Resection of vestibular schwannomas is a good model of acute unilateral peripheral vestibular asymmetry. An episode of acute vestibular asymmetry leads to central compensation, which persists for approximately several weeks [9].

A central oculomotor pathology can be found, especially in patients with cerebellar dysfunction [4 10]. In this study, 29 patients (61.7%) had central abnormalities, which is higher than other reports [1 2 11], because most tumours were stages 3 or 4, which we assume represented cerebellar compression.

The primary aim of this study was to determine whether or not central pathological oculomotor findings measured



SEM: standard error of the mean.

Fig. 1. Changes in vertigo mean values (± standard error of the mean) in patients with different syndromes.

Table IV. Outcome parameters according to group.

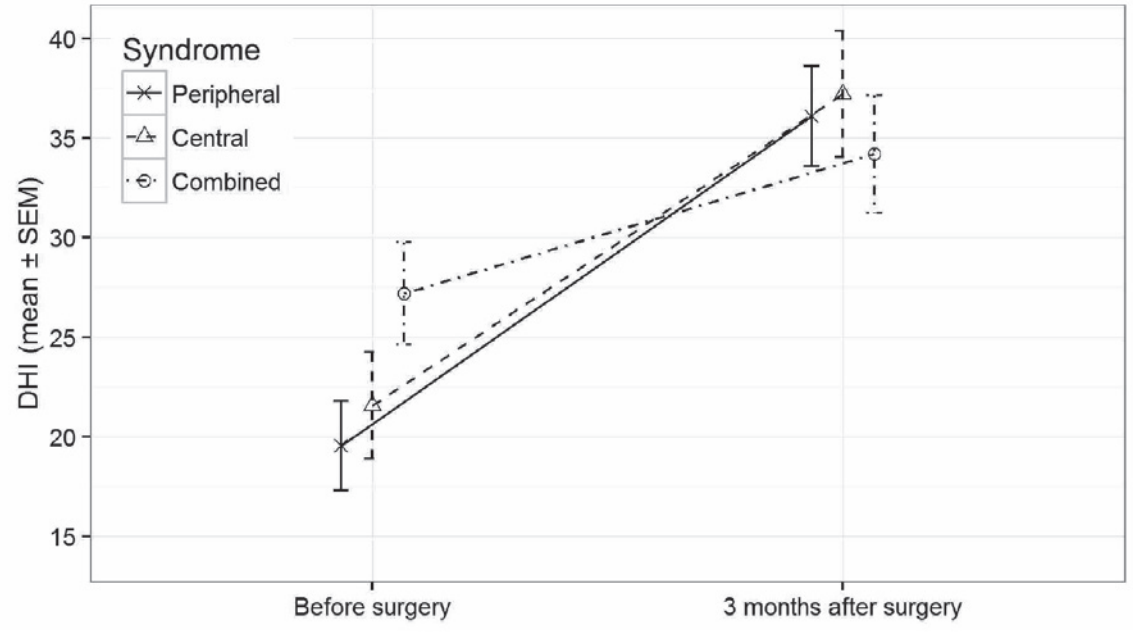
		Peripheral syndrome		Central syndrome		Combined syndrome		
		Mean (SD)	P value[w]	Mean (SD)	P value[w]	Mean (SD)	P value[w]	P value[b]
Vertigo	Time 1	0.33 (0.11)	$p^{1,3} = 1.000$	0.42 (0.12)	$p^{1,3} = 0.187$	0.70 (0.15)	$p^{1,3} = 0.015$	0.175
	Time 2	2.00 (0.00)	–	2.00 (0.00)	–	2.00 (0.00)	–	–
	Time 3	0.33 (0.11)	$p^{3,4} = 0.083$	0.26 (0.10)	$p^{3,4} = 0.110$	0.20 (0.13)	$p^{3,4} = 1.000$	0.754
	Time 4	0.67 (0.14)	$p^{1,4} = 0.083$	0.63 (0.17)	$p^{1,4} = 0.259$	0.20 (0.13)	$p^{1,4} = 0.052$	0.155
DHI	Time 1	19.56 (9.53)	$p^{1,4} < 0.001$	21.58 (11.70)	$p^{1,4} = 0.001$	27.2 (8.16)	$p^{1,4} = 0.056$	0.174
	Time 4	36.11 (10.68)	–	37.21 (13.81)	–	34.2 (9.35)	–	0.810

SD: standard deviation; p-value[w]: within-group differences tested by LSD post-hoc tests after repeated measures ANOVA; Time 1: before surgery; Time 2: shortly after surgery; Time 3: 3 weeks after surgery; Time 4: 3 months after surgery; $p^{1,3}$: p-value of the difference between Time 1 and Time 3; $p^{1,4}$: p-value of the difference between Time 1 and Time 4; $p^{2,4}$: p-value of the difference between Time 2 and Time 4; $p^{3,4}$: p-value of the difference between Time 3 and Time 4; p-value: between-group differences tested by one-way ANOVA.

pre-operatively by ENG (pursuit smooth movements, saccadic system and optokinetic system) are negative predictive factors for post-operative central compensation.

Post-operative central compensation was evaluated subjectively by questionnaires assessing sensation of vertigo and objectively by the presence of spontaneous pre- and post-operative nystagmus and subjective visual vertical. With respect to the presence of spontaneous nystagmus and abnormal deviation of subjective visual vertical (SVV) at 3 weeks and 3 months after surgery, our study did not find a significant difference between patients with central parameters pre-operatively. These results are in agreement with other studies [4 11].

We also attempted to determine whether or not the total DHI score and the vertigo intensity scale differed between patients with and without central signs. There were no significant differences between groups in DHI scores pre-operatively and 3 months postoperatively, and the same was true for the vertigo intensity questionnaire pre-operatively at 3 weeks and 3 months postoperatively. This result differs from a report in which central signs affected DHI scoring [11]. Our results are in line with that of the larger group of schwannoma patients in whom DHI deteriorated from preoperative values to higher scores at three months after surgery. The scores remained practically stable at 12-month follow-



SEM: standard error of the mean.

Fig. 2. DHI mean values (± standard error of the mean) before surgery and 3 months after surgery in patients with different syndromes.

up postoperatively. There was a trend to higher scores with larger tumour size [12].

Patients with central signs had decreased sensations of vertigo at 3 weeks after surgery compared with pre-operative sensations. In the combined group, the difference was statistically significant ($p < 0.05$). Three months post-operatively, the sensation of vertigo in the central and peripheral group was non-significantly worse than at 3 weeks postoperatively. In patients with combined syndrome, the sensation of vertigo at 3 weeks and 3 months post-operatively remained unchanged.

Combined vestibular syndrome has significantly low vertigo intensity in comparison to the other two groups at three months. DHI score of the combined group is lower than the score of peripheral and central groups, even if this was not statistically significant. This fact, as theoretically the most affected (combined) group has the best outcome, is not easy to explain. As combined syndrome subjects exhibited a higher DHI score in the pre-operative period, it is possible that they are better adapted to the chronic handicap and do not deteriorate further.

Significant findings were observed in all groups for DHI scoring pre-operatively and at 3 months post-operatively. This result suggests that the DHI questionnaire is more applicable for monitoring vestibular function in real life and the sensation of vertigo as an isolated symptom of one aspect of vestibular function is not sufficient for follow-up of subjective compensation in daily life.

Contrary to our expectations, we found that abnormal results of the oculomotor tests in the pre-operative period do not predict less favourable outcomes at 3 months post-operatively.

Specifically, there was no correlation between vertigo intensity and DHI scoring and SPEM, OKN and saccades performance. We have analysed this topic from several viewpoints; specifically, the entire ENG record was summarised and classified into three distinct groups (normal, central, peripheral, or mixed type abnormalities). There was no difference between these groups in terms of both vertigo intensity and DHI score at the 3-month follow-up evaluation. When analysing the subgroup with high DHI scores (unfavourable outcome), no significant accumulation of central type abnormities was found. There is little correlation between symptoms traditionally considered as important for central vestibular compensation and the real clinical outcome at 3 months post-neurectomy.

Vestibular compensation is a complex process based on changes in all levels of integration of vestibular afference. It cannot be constrained only to vestibular nuclei and archicerebellum. Participation of the posterior insular, superior temporal and parietal cortex on vestibular compensation was shown by voxel-based morphometry in the study of Helmchen et al. [13].

The exact site of affection in the central vestibular structures by the high grade vestibular schwannoma can differ substantially between cases, which can explain the variable clinical presentations observed in our study. It seems that detailed brainstem imaging would be necessary to explain why oculomotor abnormalities are observed in some high-grade schwannoma and absent in others with seemingly similar radiological presentation. Specifically, signs of flocculo-nodular lobe, olivo-cerebellar tracts, dorsolateral pontine nuclei and vermis should correlate with oculomotor tests more closely. This explanation would appear to be supported by similar studies [14 15]. In a study on cerebellopontine angle meningioma, cerebellar signs were observed in only 32% of cases, depending on the anatomical circumstances [16]. In the study by Berrettini, best diagnostic sensitivity was achieved by combination of ENG and brain stem auditory evoked potentials [17].

On the other hand, oculomotor abnormalities documented by ENG examination are highly specific and failure in these circuits does not interfere with the vestibular compensation, as shown by this study. This result is supported by the large study of Stipkovits, who did not find a consistent correlation between tumour size and level of compensation [18].

The main result of this study is the evidence that routine oculomotor tests in vestibular functional laboratory are poor predictors of the overall outcome following vestibular schwannoma surgery. There is a need for other factors to be implemented in presurgical evaluation with possibly better prediction capability. We speculate that the level of presurgical compensation of vestibular deficit is an important factor for final functional outcomes. This factor should be investigated with a higher level of detail using video head impulse test, vestibular evoked potentials, gain at high and low frequency rotatory stimulation and functional measures of postural stability. We also suggest that tests of overall fitness, factors affecting quality of life and personal traits should be included in future studies.

We see the main weakness of the study in the fact that routine preoperative imaging cannot identify the anatomical details needed for evaluation of central vestibular structures involvement by the pathological process.

Conclusions

Pre-operatively measured signs of central pathology have little impact on the process of vestibular compensation in acute complete unilateral vestibular lesions.

The results of this study can be clinically used in patients

with combined vestibular pathology (e.g. intractable Meniere disease after brain stroke) in which surgery is indicated, but central signs, which are usually present in patients after brain stroke, represent a contraindication to the surgery [19]. Compensation of vestibular loss is a complex process that includes central recalibration of vestibular reactivity and oculomotor functions, changes in postural strategy and important individually variable psychological factors [20]. From these, only oculomotor and vestibular responses can be evaluated by ENG examination. Clearly, important parts are missing. Future analyses should take into account parameters of postural stability, psychological factors and measures of quality of life. These functional factors probably have a higher influence on overall vestibular compensation than formal measures of vestibular function in the ENG laboratory.

From a practical standpoint, the results of the ENG battery should be considered with care. In particular, abnormal results of oculomotor subtests do not predict a poor efficacy of vestibular rehabilitation or a final functional outcome.

Acknowledgements

Supported by PROGRES Q28, UNCE 204013, GAUK 310216, and the Ministry of Health of the Czech Republic (grant No. 15-28933A).

Conflict of interest statement

None declared.

References

1. Vidal PP, de Waele C, Vibert N, et al. *Vestibular compensation revisited.* Otolaryngol Head Neck Surg 1998;119:34-42.
2. Barbara M, Ronchetti F, Manni V, et al. *Double localization of a unilateral sporadic vestibular schwannoma*. Acta Otorhinolaryngol Ital 2008;28:34-7.
3. Herdman SJ, Clendaniel RA, Mattox DE, et al. *Vestibular adaptation exercises and recovery:acute stage after acoustic neuroma resection.* Otolaryngology - Head And Neck Surgery 1995;113:77-87.
4. Furman JM, Balaban CD, Pollack IF. *Vestibular compensation in a patient with a cerebellar infarction.* Neurology 1997;48:916-20.
5. Szirmai A, Keller B. *Electronystagmographic analysis of caloric test parameters in vestibular disorders.* Eur Arch Otorhinolaryngol 2013;270:87-91.
6. Van Der Stappen A, Floris LW, Van De Heyning PH. *Computerized electronystagmography:normative data revisited.* Acta Otolaryngol 2000;120:724-30.
7. Jacobson GP, Newman CW, Kartush JM. *Handbook of balance function testing.* Mosby; 1992. p. 360.
8. Hirvonen M, Aalt H, Hirvonen TP. *Postural control after vestibular schwannoma resection measured with visual feedback posturography.* ORL J Otorhinolaryngol Relat Spec 2005;67:335-9.
9. Cohen HS, Kimball KT, Jenkins HA. *Factors affecting recovery after acoustic neuroma resection*. Acta Oto-Laryngologica 2002;122:841-50.
10. Čada Z, Balatková Z, Chovanec M, et al. *Vertigo perception and quality of life in patients after surgical treatment of vestibular schwannoma with pretreatment prehabituation by chemical vestibular ablation.* Biomed Res Int 2016;2016:6767216.
11. Thomeer H, Bonnard D, Franco-Vidal V, et al. *Prognostic factors of balance quality after transpetrosal vestibular schwannoma microsurgery: an instrumentally and DHI-based prospective cohort study of 48 patients.* Otol Neurotol 2015;36:886-91.
12. Humphriss RL, Baguley DM, Moffat DA. *Change in dizziness handicap after vestibular schwannoma excision.* Otol Neurotol 2003;24:661-5.
13. Helmchen C, Klinkenstein JC, Krüger A, et al. *Structural brain changes following peripheral vestibulo-cochlear lesion may indicate multisensory compensation.* J Neurol Neurosurg Psychiatry 2011;82:309-16.
14. Mohamed ES. *Predictors of central vestibular disorders from videonystagmography tests.* Egypt J Otolaryngol 2016;32:202-9.
15. Kumar A, Mafee M, Torok N. *Anatomic specificity of central vestibular signs in posterior fossa lesions.* Ann Otol Rhinol Laryngol 1982;91:510-5.
16. Voss NF, Vrionis FD, Heilman CB, et al. *Meningiomas of the cerebellopontine angle.* Surg Neurol 2000;53:439-46.
17. Berrettini S, Ravecca F, Sellari-Franceschini S, et al. *Acoustic neuroma: correlations between morphology and otoneurological manifestations.* J Neurol Sci 1996;144:24-33.
18. Stipkovits EM, Van Dijk JE, Graamans K. *Electronystagmographic changes in patients with unilateral vestibular schwannomas in relation to tumor progression and central compensation.* Eur Arch Otorhinolaryngol 1999;256:173-6.
19. Göksu N, Bayazit YA, Yilmaz M, et al. *Surgical treatment of peripheral vertigo and vertiginous diseases.* ORL J Otorhinolaryngol Relat Spec 2005;67:1-9.
20. Peusner KD, Shao M, Reddaway R, et al. *Basic concepts in understanding recovery of function in vestibular reflex networks during vestibular compensation.* Front Neurol 2012;3:17.

Received: December 18, 2017 - Accepted: February 22, 2018

How to cite this article: Čada Z, Balatková Z, Čakrt O, et al. *Predictors of central vestibular compensation after surgery for vestibular schwannomas.* Acta Otorhinolaryngol Ital 2019;39:46-52. https://doi.org/10.14639/0392-100X-1963

Address for correspondence: Jan Plzák, Department of Otorhinolaryngology and Head and Neck Surgery, 1st Faculty of Medicine, Charles University in Prague, Faculty Hospital Motol, Postgraduate Medical School, v. Úvalu, 84, 15006 Praha, Czech Republic. Tel. +420 224434301. E-mail: jan.plzak@fnmotol.cz

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:53-60; doi: 10.14639/0392-100X-2005

Otology

Quality of life and functional results in canal wall down vs canal wall up mastoidectomy

Qualità della vita e risultati funzionali nella timpanoplastica aperta vs timpanoplastica chiusa

D. LUCIDI, E. DE CORSO, G. PALUDETTI, B. SERGI

Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY

Social functioning and personal satisfaction about quality of life are issues in the spotlight in most fields of otolaryngology. However, in ear surgery, few studies performed standardised measurements through interviews and validated questionnaires. We enrolled 81 patients undergoing tympanomastoidectomy from January 2011 to December 2014, at the "A. Gemelli" Hospital of the Catholic University, Rome. 50 patients (61.7%) underwent non-obliterative Canal Wall Down (CWD) mastoidectomy, whereas 31 patients (38.3%) underwent Canal Wall Up (CWU) mastoidectomy. We administered the Chronic Ear Survey (CES) 3 and 12-months post-operatively and the Chronic Otitis Media Outcome Test-15 (COMOT-15) 12 months post-operatively. Results were compared to hearing threshold, sex and age. In the CWD Group, significant improvements were observed in all CES subscale scores and total scores over time ($p < 0.001$) whereas in the CWU Group we found a partial improvement. Inter-group comparison showed no significant differences in administration of CES in CWD vs CWU ($p > 0.05$ for all subsections and overall scores). A significant difference was found only in the COMOT-15 "Hearing Function" subsection, in favour of CWU over CWD (61 vs 39 respectively; $p < 0.05$). A significant association was found between PTA and COMOT-15 "Hearing Function" subsection scores. According to our results, a significant difference in the post-operative QoL between CWD and CWU should not be taken for granted.

KEY WORDS: Cholesteatoma • Middle ear • Mastoidectomy • Ear surgery • Quality of life • Canal wall up • Canal wall down • Chronic otitis media

RIASSUNTO

Il benessere sociale e la soddisfazione personale riguardo alla qualità di vita sono temi d'attualità nella maggior parte dei campi dell'otorinolaringoiatria. Tuttavia, nella chirurgia dell'orecchio, pochi studi utilizzano misurazioni standardizzate e/o questionari convalidati. Abbiamo arruolato 81 pazienti sottoposti a timpanoplastica da gennaio 2011 a dicembre 2014, presso l'Università Cattolica di Roma, Policlinico "A. Gemelli". 50 pazienti (61,7%) sono stati sottoposti a timpanoplastica aperta non-obliterativa (CWD), mentre 31 pazienti (38,3%) sono stati sottoposti a timpanoplastica chiusa (CWU). Abbiamo somministrato il questionario Chronic Ear Survey (CES) 3 e 12 mesi dopo l'intervento e il questionario Chronic Otitis Media Outcome Test-15 (COMOT-15) 12 mesi dopo l'intervento. I risultati dei tests sono stati correlati con la soglia uditiva, il sesso e l'età. Nel gruppo CWD sono stati osservati miglioramenti significativi dei punteggi di tutte le sottosezioni del CES e dei punteggi totali in funzione del tempo ($p < 0,001$), mentre nel gruppo CWU abbiamo riscontrato un parziale miglioramento. Il confronto tra timpanoplastica aperta e chiusa non ha mostrato differenze significative nella somministrazione del CES ($p > 0,05$ per tutte le sottosezioni e punteggi complessivi). Una differenza significativa è stata riscontrata solo nella sotto-sezione "Funzione uditiva" del COMOT-15, in favore del gruppo CWU (rispettivamente 61 versus 39; $p < 0,05$). Una correlazione significativa è stata riscontrata solo tra i punteggi della sottosezione "Funzione uditiva" del COMOT-15 e il PTA. Secondo i nostri risultati, una differenza significativa nella qualità della vita postoperatoria nel confronto tra timpanoplastica aperta e chiusa non dovrebbe essere data per scontata.

PAROLE CHIAVE: *Colesteatoma • Orecchio medio • Mastoidectomia • Chirurgia dell'orecchio • Qualità della vita • Timpanoplastica aperta • Timpanoplastica chiusa • Otite media cronica*

Introduction

Cholesteatoma surgery represents one of the most debated topics in otolaryngology. The main goals are radical excision of the disease, prevention of severe complications due to the erosive behavior, possibly through the achievement of a dry and infection-free ear, and improvement of quality of life (QoL). Canal Wall Up (CWU) and Canal Wall Down (CWD) mastoidectomy represent the most common surgical techniques. In CWU, the targets are achieved through preservation of both the external canal wall and middle ear volume and maintenance of a physiological position of the tympanic membrane. CWU allows to avoid both the need for frequent ear cleaning and the limitation of keeping the ear away from water. The majority of studies report better functional results obtained by

CWU compared to CWD [1-4]. However, an increased risk of recurrence/residual cholesteatoma and revision surgery is described [5 6]. Moreover, the residual/recurrent cholesteatomatous process is not easily detectable in a CWU cavity. The literature reports varying recurrence rates in both groups. A recent review [5], including six studies, describes higher recidivism after CWU (16.7-61%) versus CWD (0-13.2%). CWD allows easier outpatient follow-up and an early identification of cholesteatomatous foci or infection. On the other hand, in CWD some disadvantages may be present. The most common limitations are accumulation of keratin debris and need for frequent cleaning, higher susceptibility to infection with water exposure, risk of sudden dizziness associated with change of temperature in the external auditory canal and hearing aid discomfort [7]. To overcome such problems, many surgeons choose to obliterate the neo-cavity with different materials: bone patè, musculo-periosteal flaps, silicon material or cartilage, hydroxyapatite, or bioactive glass [8-10].

Comparison of the two surgical techniques, in terms of post-operative outcomes, is mostly based on auditory results, complications and recurrence rates; however, the most common complaints among patients are impediment to social interaction and daily activity, due to frequent discharge from the ear, pain, medical examinations and fear of complications. Few studies have been designed to assess post-operative QoL in cholesteatoma patients and few specific tools are available. The first post-operative questionnaires administered to patients with chronic otitis media (COM), such as Glasgow Benefit Inventory (GBI), Short Form-36 (SF-36), Hearing Handicap Inventory for Adults (HHIA) and modified Amsterdam Inventory for Auditory Disability and Handicap Score (mAIAD), proved to be inadequate to evaluate the specific characteristic of these patients, because they are too generic or because only partial features, such as hearing loss, are evaluated. More recently, specific surveys aimed at the evaluation of specific aspects of COM and the impact on daily life have been developed [11]. The Chronic Ear Survey (CES) is a statistically validated questionnaire, specific for patients affected by COM, first introduced by Nadol and colleagues at the Massachusetts General Hospital [12 13], which has significant correlation with the audiometric threshold, with other QoL surveys (HHIA, SF-36), and undergoing to a marked post-surgical improvement. The Chronic Otitis Media Outcome Test-15 (COMOT-15) was subsequently developed and validated by Baumann et al. [14] to allow self-assessment of symptom severity, whereas CES is based on symptom frequency.

The aim of our study was to assess the post-operative QoL in a population of patients operated for cholesteatoma. We compared the early and one year-postoperative results in CWD versus CWU without obliteration of the surgical cavity using the CES and COMOT-15 surveys. We finally compared subjective outcomes with age, sex and post-operative hearing threshold.

Materials and methods

We enrolled 81 patients admitted for cholesteatomatous otitis media at the Department of Head and Neck Surgery, Catholic University School of Medicine and Surgery, Rome, Italy. Patients underwent tympanomastoidectomy from January 2011 to December 2014. All enrolled patients showed recurrent otorrhoea and associated hearing loss and were treated with repeated cycles of antibiotics and corticosteroid therapy with poor improvement of the clinical picture. Micro-otoscopy and pure tone audiometry were performed in all patients. The diagnosis was confirmed by CT scan of the temporal bone, which showed inflammatory tissue in the middle-ear with partial erosion of adjacent bone structures.

All patients were candidates for surgery: in 50 patients (61.7%) a CWD technique was performed, due to the large extent of the pathology, anatomical conformation and/or erosion of the external ear canal (CWD group). In 31 patients (38.3%), we performed a CWU tympanomastoidectomy due to the limited extent of the disease (CWU group). In 5 patients, a sequential bilateral tympanoplasty was performed with analogous technique (3 CWD and 2 CWU). Standard surgery was performed under general anaesthesia, as an inpatient service, and in all cases a retroauricular incision with a tympanomeatal flap was made. We used temporal fascia for reconstruction of the tympanic membrane. CWU was performed in two stages, while CWD was carried out in a single stage. No obliteration of the neo-mastoid cavity was performed. Histological study confirmed a cholesteatomatous pattern in all cases, with keratinising squamous epithelium. All patients underwent standard pure-tone audiometry for testing conventional frequency range (0.25 to 8 kHz), using an Amplaid 319 audiometer (Amplaid Inc., Milan, Italy) in a double-walled, soundproof room. Pure-tone average (PTA) values were calculated as the mean of 0.5, 1, 2, and 4 kHz thresholds. Audiological assessment performed 24 hours preoperatively and 12 months post-operatively were compared.

Exclusion criteria were: patients younger than 18 years or older than 70 years, patients undergoing revision surgery, patients with bilateral disease who underwent a different surgical technique in the two ears, patients undergoing

tympanoplasty without mastoidectomy, patients affected by petrous apex cholesteatoma and patients affected by severe general diseases influencing the degree of perceived quality of life or unable to fill out the questionnaire.

The Chronic Ear Survey questionnaire was assessed in all patients within the first 3 months after surgery (early post-operative administration). At one-year postoperative assessment (mean time after surgery 12.6 ± 3 months), all patients underwent a second administration of the Chronic Ear Survey together with the Chronic Otitis Media Outcome Test-15 (COMOT-15).

The Chronic Ear Survey is a 13-item survey, divided in 3 subscales: activity restriction (AR), symptoms (S) and medical resources (MR). The Chronic Otitis Media Outcome Test-15 (COMOT-15) consists of 15 items and 3 subscales: ear symptoms (ES), hearing function (HF) and mental health (MH); in addition, a single question regarding a general evaluation on QoL (GE) and a single question on frequency of doctor visits (FDV) were included. Total scores were normalised in percentiles (0-100, with 0 indicating maximum restriction of quality of life). This study was approved by the Ethics Committee of the Faculty of Medicine of the Catholic University of the Sacred Heart in Rome and was carried out in accordance with the Declaration of Helsinki. All patients received appropriate and comprehensible information about the surgical procedures and tests and gave their written consent.

Statistical analysis of results was performed using SSPS for Windows. Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between groups were performed by Pearson's chi square test and Student's t-test. The strength of the correlation between the two parameters was obtained by Spearman's rank correlation test. The results were considered significant for p values < 0.05.

Results

The mean age at the time of surgery was 47 years (range = 18-70; SD = ± 15.9) and the male/female ratio was 1.25 (45 males and 36 females). In the CWD group, the mean age was 48.5 years (range = 15-70; SD = ± 12.1) and the male/female ratio was 1.3 (28 males and 22 females). In the CWU group, the mean age was 44.6 years (range = 15-70; SD = ± 16.8) and the male/female ratio was 1.2 (17 males and 14 females). The mean follow-up time was 22 months (range = 15-36 months; SD = ± 6). At the time of data analysis, no patient was diagnosed with recurrent or residual cholesteatoma.

Pre-operatively, the overall mean PTA was 50 dB (range = 10-90; SD = ± 18). In the CWD group, the mean pre-operative PTA was 55 dB (range = 16-90; SD = ± 18), whereas in the CWU group the mean pre-operative PTA was 42 dB (range = 10-90; SD = ± 19). The difference between the mean pre-operative PTA in the two groups was statistically significant ($p < 0.05$). At the 12-month post-operative assessment, the overall mean PTA was 48 dB (range = 10-90; SD = ± 19). In the CWD group, the mean post-operative PTA was 52 dB (range = 22-81; SD = ± 18), whereas in the CWU group the mean post-operative PTA was 41 dB (range = 16-65; SD = ± 18). The difference between the mean post-operative PTA in the two groups was statistically significant ($p < 0.05$). Significant differences between the pre- and post-operative PTA were not found ($p > 0.05$) in either the CWD or CWU groups. The pre- and post-operative audiological results of both groups are reported in Table I.

We compared the intra-group results obtained in the early (3 months) and late (12 months) post-operative administration of the Chronic Ear Survey. In the CWD group, significant improvements were observed in all the three mean subscale scores and total scores over time ($p < 0.001$). In the CWU group, we found a significant improvement in the mean activity restriction subscale score and overall score ($p < 0.001$) whereas the mean symptoms and medical resources subscale scores were not significantly different in the two administrations ($p > 0.05$). The intra-group results of both groups are reported in Figure 1.

We compared the inter-group mean scores at both the early and late CES administration. At the early post-operative administration of CES, a significant difference was obtained only in the mean symptoms subscale score, in favour of the CWU group ($p < 0.05$). However, at the late CES administration the mean subscale scores and total scores were not significantly different between groups ($p > 0.05$). Data regarding the early and late CES administration is summarised in Table II. The one-year post-operative administration of COMOT-15 shows the absence of a significant difference between the mean scores obtained in the CWD and CWU groups in the total scores and subsections, except for the hearing function subscale, in favor of the CWU group ($p < 0.05$). The COMOT-15 results are shown in Table III. No significant difference was found in the administration of COMOT-15 and CES, according to sex ($p > 0.05$ in all subsections and overall scores). We performed linear regression analysis to evaluate the association between the post-operative hearing threshold (PTA) and both CES and COMOT-15 subsections and overall scores. A significant linear association was found only between the PTA and the COMOT-15 "hearing function" subsection scores (rs coefficient = 0.721; $p < 0.005$; Fig. 2). Moreover, a significant correlation between the

Table I. Pre- and post-operative audiological data in both groups.

		500 Hz	1000 Hz	2000 Hz	4000 Hz	Mean PTA
CWD	Pre-op PTA (dB) ± SD	54 ± 19*	55 ±19	51 ± 19*	60 ± 21*	55 ± 18*
	Post-op PTA (dB) ± SD	48 ± 19§	51 ±19	53 ± 19§	56 ± 20	52 ± 18§
	Delta PTA (dB) ± SD	6 ± 18	4 ± 20	- 2 ± 18	4 ± 22	3 ± 19
CWU	Pre-op PTA (dB) ± SD	41 ± 19*	44 ± 19	39 ± 20*	45 ± 21*	42 ± 19*
	Post-op PTA (dB) ± SD	35 ± 19§	43 ± 19	39 ± 19§	46 ± 20	41 ± 18§
	Delta PTA (dB) ± SD	6 ± 20	1 ± 18	0 ± 20	- 1 ± 19	1 ± 18

*Delta PTA: pre-operative minus post-operative PTA; * and §: p < 0.05 for inter-group comparison.*

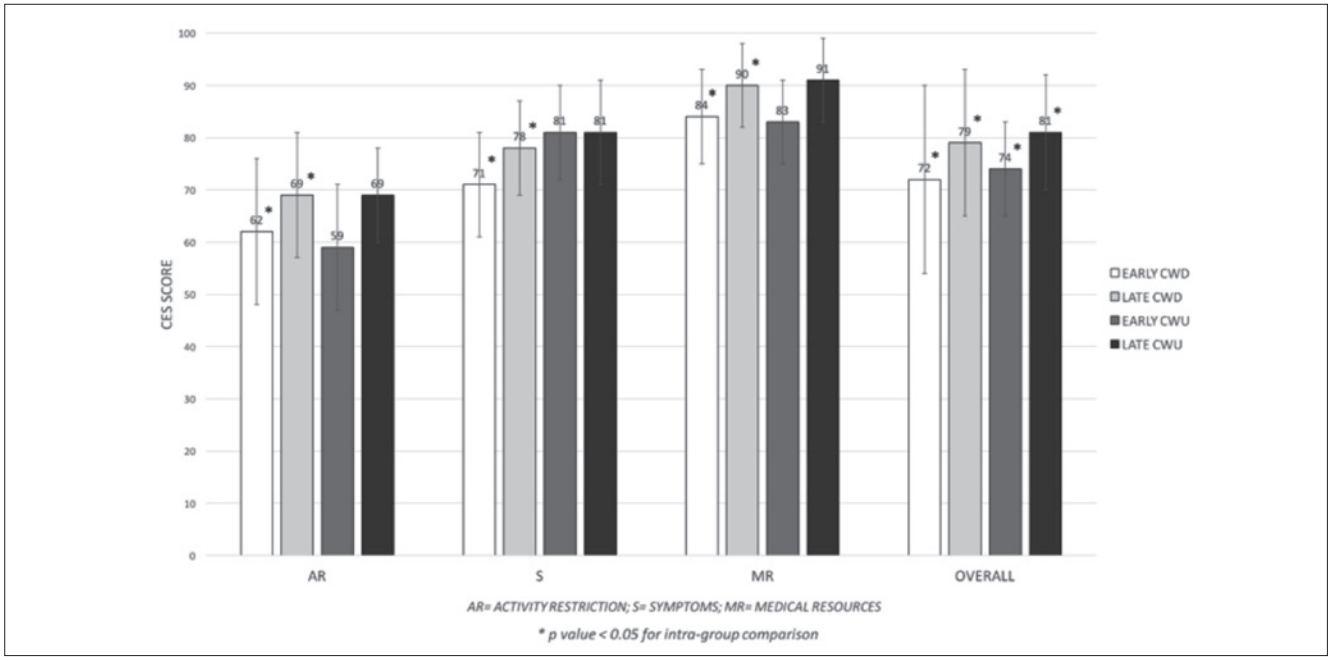


Fig 1. Comparison of 3-month (early) and 12-month (late) post-operative administration of CES in the CWD and CWU groups.

CES and COMOT-15 scores and age was not found ($p > 0.05$ in all the subsections and overall scores).

Discussion

Over the past 30 years, the concept of health-related quality of life has gradually gained large consensus to evaluate post-operative results in most fields of otolaryngology. Historically, CWD has been associated with a poorer quality of life, compared to CWU due to the limitations of the wide neo-mastoid cavity [15]. However, standardised measurements obtained through interviews and validated questionnaires are lacking.

In our study, we demonstrated the absence of a significant difference, in terms of self-perceived quality of life, in patients undergoing CWU compared to CWD. Our results are consistent with those reported by other authors [9 12 16].

The study conducted by Lailach et al. [16] which compared QoL outcomes among CWD, CWU and exclusively transcanalar technique (ETC) demonstrated that CWD showed similar results in QoL compared to CWU, whereas the ETC group reported significantly higher performances. All previous scientific comparisons, however, were conducted on CWD with mastoid obliteration versus CWU. Accordingly, it is suggested that the overlapping results are due to a decreased incidence of neo-mastoid cavity disadvantages in the CWD group [8 9 16 17].

Dornhoffer et al. [18] reported that most patients subjected to revision surgery for a draining cavity (including mastoid obliteration and cartilage reconstruction of the tympanic membrane) have increased self-perceived QoL. Similarly, Kurien et al. [7] suggested that secondary mastoid obliteration provides subjective benefit to patients, which is more

Table II. Inter-group comparison of early and late CES scores.

			AR	S	MR	Overall
Early administration	CWD	Mean score ± SD	62 ±14	71 ± 10 *	84 ± 9	72 ± 18
	CWU	Mean score ± SD	59 ± 12	81 ± 9 *	83 ± 8	74 ± 14
	Delta CWU minus CWD		- 3	10	- 1	2
Late administration	CWD	Mean score ± SD	69 ± 12	78 ± 9	90 ± 8	79 ± 14
	CWU	Mean score ± SD	69 ± 9	81 ± 10	91 ± 10	81 ± 11
	Delta CWU minus CWD		0	3	1	2

AR: activity restriction; S: symptoms; MR: medical resources ($p < 0.05$ in comparison of symptoms subscale at early administration only).*

Table III. Inter-group comparison of COMOT-15 scores.

	ES	HF	MH	GE	FDV	Overall	
CWD	Mean score ± SD	75 ± 14	39 ± 12 *	74 ± 19	44 ± 22	80 ± 19	64 ± 20
CWU	Mean score ± SD	75 ± 16	61 ± 18 *	78 ± 16	34 ± 22	88 ± 16	60 ± 20
Delta CWD minus CWU		0	22	4	- 10	8	- 4

ES: ear symptoms; HF: hearing function; MH: mental health; GE: general evaluation on QoL; FDV: frequency of doctor visits ($p < 0.05$ in comparison of hearing function subscale only).*

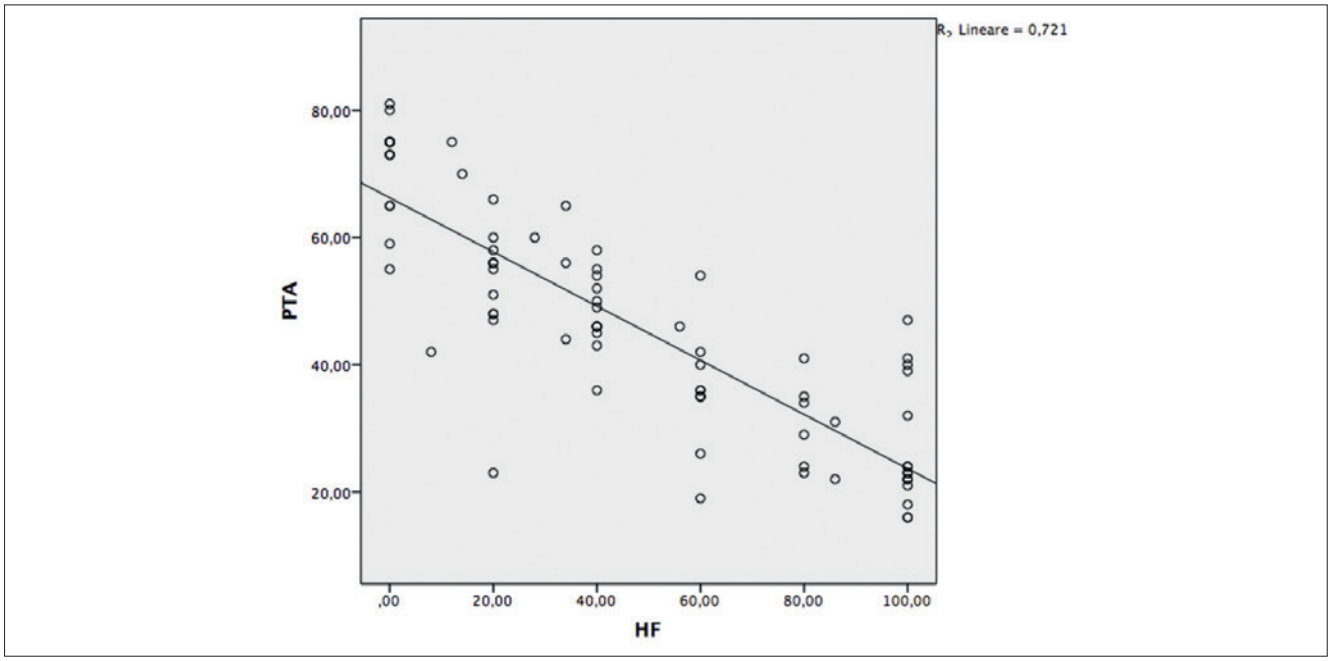


Fig 2. Scatter plot showing correlation between PTA levels (dB) and hearing function subsection scores at COMOT-15.

pronounced compared to primary mastoid obliteration. Both studies performed QoL assessment using the Glasgow Benefit Inventory (GBI), which is a generic tool for post-surgical evaluation and does not consider specific topics, such as otorrhoea, hearing loss, or water restriction. Moreover, the above-cited reports did not compare QoL obtained with different surgical techniques, but only analysed CWD patients undergoing obliteration of the mastoid cavity.

Our study is the first to demonstrate analogous results, in terms of QoL, in CWD with no mastoid obliteration versus CWU. Although promising long-term results following obliteration in CWD are described in the literature [8], some critic aspects are reported by a recent overview [19]. Atrophy/resorption of muscle flaps, relapsing otorrhoea/infection associated with reactive granulation tissue, often leading to surgical revision, are among the most fre-

quently reported disadvantages. Moreover, a mild and not otherwise confirmed increase in the recurrence rate, associated with difficult exposure of the surgical cavity ("silent cholesteatoma" hidden in the obliterative tissue) is described [8 19]. We found that at 3-month post-operative assessment by CES, CWD patients reported a slightly lower mean score at the "symptoms" subsection (including the following entries: drainage, smell, hearing loss, pain), compared to CWU patients. This difference, however, was not statistically significant at the 12-month post-operative assessment. Patients undergoing CWD mastoidectomy, in fact, tend to have delayed healing of the surgical cavity and higher initial psycho-social impairment compared to CWU patients, due to water restrictions and frequent post-operative medical examinations [20]. Moreover, the presence of exposed bone delays epithelisation of the mastoid bowl, leading to a higher risk of early post-operative otorrhoea.

However, in our experience, some precautions might be useful to accelerate the epithelial lining spread and to prevent otorrhoea, in the absence of obliteration of the mastoid cavity. We suggest avoiding bony overhanging in the hedges of the cavity and blind spots/pouches, to lower the facial ridge as much as possible, to remove all inflammatory tissue and to create an adequately sized meatoplasty. These measures allow satisfying epithelisation of the bowl in a few months [21]. This might explain the significant improvement reported by CWD patients in self-perception of ear symptoms over time. Accordingly, intra-group results obtained in comparison of early versus late administration of CES, demonstrated, in the CWD group, a significant improvement in all subsections (including "symptoms") and overall score. Together with ear-related symptoms, in CWD patients, distress related to the medical examinations and activity restriction (mainly water restrictions) becomes significantly less severe over time. On the other hand, in the CWU group, only "activity restriction" subsection and overall score significantly improved over time, whereas subjective assessment of distress related to "symptoms" and "medical resources" remained stable compared to the first trimester assessment. This is easily explained by the preservation of the physiological middle and external ear structure and the lower hospitalisation times. As reported by Nadol et al. [12], perceived quality of life, assessed by CES scores, improves over time in patients subjected to tympanomastoidectomy, which is consistent with our results and, as previously described, is highly significant in CWD patients.

Overlapping outcomes were obtained by the administration of COMOT-15: only the "hearing function" subsection was characterised by significantly poorer results obtained by CWD versus CWU patients. Decreased auditory function remains the most disabling symptom experienced by patients undergoing to CWD compared to CWU [22 23]. This is consistent with the poorer functional results obtained by this cohort. COMOT-15 assessment allowed us to demonstrate a significant difference between groups in terms of self-perceived hearing disability. It is, in fact, provided with a dedicated section. On the contrary, the CES questionnaire includes hearing discomfort in the symptoms subsection, together with drainage, smell and pain. COMOT-15 represents, in our opinion, a useful and complementary tool in assessment of quality of life in patients affected by COM, also thanks to the ease of administration (individual entries have 5 answer options each, whereas answer options vary from 4 to 6 in CES) and focus on symptom severity. Moreover, the COMOT-15 is provided with a specific section regarding mental health, which is not taken into account by the CES and which might be a critical issue in patients affected by chronic inflammatory disease and hearing impairment. Bakir and colleagues [24] have shown a high prevalence of psychiatric symptoms such as depression, anxiety, phobia and somatisation in a population of patients affected by COM. Our results, however, do not demonstrate a high incidence of psychosomatic impairment or a significant difference in CWD versus CWU patients.

We compared post-operative hearing threshold and questionnaire scores, demonstrating that PTA (dB) has only a linear correlation with the COMOT-15 "hearing function" subscale, thus confirming the validity of the test. However, no association was found between PTA levels and other CES and COMOT-15 subsection rates or overall scores. The relationship between audiometric threshold and questionnaire scores is a controversial topic: according to Nadol et al. [12], the CES survey is specifically designed according to hearing levels and strong correlation between PTA and overall score is seen. Baumann et al. [14] demonstrated a relationship only between hearing threshold and COMOT-15 HF and MH subscales. Lailach et al. [16] demonstrated a moderate correlation between PTA and COMOT-15 overall score and strong correlation between PTA and the hearing function subscale. Other studies [25 26] showed only partial or no association at all between PTA and the questionnaire's subsections, consistent with our results. Our data imply that a patient with hearing impairment does not necessarily show subjective impairment in the overall quality of life. We believe that objective measurements, such as hearing threshold, are not sufficient to assess patient satisfaction. Other ear-related symptoms (such as smell, otorrhoea, pain, water restriction) and mental status are important

in post-operative assessment for comparison of different techniques. Accordingly, administration of subjective assessment tests seems pivotal, in association with the collection of objective parameters, for post-operative assessment of COM patients.

This study has some limitations: CWD are performed in extensive cholesteatoma, and therefore patients may have a severe clinical outset. CWU patients often had small limited cholesteatoma with a mild pre-operative clinical picture. This might influence the early post-operative self-evaluation. All the studies comparing CWD versus CWU show this well-known limitation, since randomisation of the technique is not ethically acceptable.

Also, QoL results were collected on average 12 months post-operatively and although a longer follow-up time was administered for detection of cholesteatoma recurrence, this might only partially predict life-long results. We believe that one year after surgery epithelisation of the mastoid cavity is complete, allowing patients to provide a reliable self-assessment about quality of life. We also agree with the work by Nadol et al. [12], who recognised that perceived quality of life improves over time and reaches its apex on the 12th post-operative month. However, long-term results are also influenced by recurrence and a repeated surgical procedure could be considered reliable after at least 5 years follow-up.

The results in this study were collected in a limited cohort from a single institution and reproducibility was not demonstrated. Experience of the surgeon, social and cultural factors are crucial factors affecting outcomes. Potential confounders due to demographic features were avoided, since the two cohorts have consistent demographic characteristics, although the number of patients is not broad.

Moreover, the impact of recurrence and possible surgical reoperation on QoL could not be considered. In our institution, recurrence rates vary between 20-30% in CWU and 5-9% in CWD, in agreement with other reports [5]; however, at 22 months postoperative evaluation no patient enrolled in the study was diagnosed with recurrent cholesteatoma.

We believe that follow-up duration may not be sufficient to consider this result as conclusive. Indisputably, any future reoperation could compromise overall QoL, although at present it is not known if one group will be significantly more affected by recurrence than the other [27].

Conclusions

Our data, although collected on a small sample, suggest that at one-year postoperative follow-up no differences exist in terms of quality of life between CWD with no mastoid obliteration and CWU surgeries. Long-term results are needed, and we propose to address this important topic in a future study.

Conflict of interest statement

None declared.

References

1 Whittemore KR Jr, Merchant SN, Rosowski JJ. *Acoustic mechanisms: canal wall-up versus canal wall-down mastoidectomy*. Otolaryngol Head Neck Surg 1998;118:751-61.

2 Stankovic MD. *Audiologic results of surgery for cholesteatoma: short- and long-term follow-up of influential factors*. Otol Neurotol 2008;29:933-40.

3 Schmerber S, Troussier J, Dumas G, et al. *Hearing results with the titanium ossicular replacement prostheses.* Eur Arch Otorhinolaryngol 2006;263:347-54.

4 De Corso E, Marchese MR, Sergi B, et al. *Role of ossiculoplasty in canal wall down tympanoplasty for middle-ear cholesteatoma: hearing results.* J Laryngol Otol 2007;121:324-8.

5 Kerckhoffs KG, Kommer MB, van Strien TH, et al. *The disease recurrence rate after the canal wall up or canal wall down technique in adults.* Laryngoscope 2016;126:980-7.

6 Neudert M, Lailach S, Lasurashvili N, et al. *Cholesteatoma recidivism: comparison of three different surgical techniques.* Otol Neurotol 2014;35:1801-8.

7 Kurien G, Greeff K, Gomaa N, et al. *Mastoidectomy and mastoid obliteration with autologous bone graft: a quality of life study.* J Otolaryngol Head Neck Surg 2013;23:42-9.

8 Yamamoto Y, Takahashi K, Morita Y, et al. *Long-term follow-up results of canal wall down tympanoplasty with mastoid obliteration using the bone pate plate for canal wall reconstruction in cholesteatoma surgery.* Otol Neurotol 2014;35:961-5.

9 Quaranta N, Iannuzzi L, Petrone P, et al. *Quality of life after cholesteatoma surgery: intact-canal wall tympanoplasty versus canal wall-down tympanoplasty with mastoid obliteration.* Ann Otol Rhinol Laryngol 2014;123:89-93.

10 Bernardeschi D, Nguyen Y, Russo FY, et al. *Cutaneous and labyrinthine tolerance of bioactive glass S53P4 in mastoid and epitympanic obliteration surgery: prospective clinical study.* Biomed Res Int 2015;2015:242319.

11 Phillips JS, Yung MW. *A systematic review of patient-reported outcome measures for chronic suppurative otitis media.* Laryngoscope 2016;126:1458-63.

12 Nadol JB Jr, Staecker H, Gliklich RE. *Outcomes assessment for chronic otitis media: the chronic ear survey.* Laryngoscope 2000;110:32-5.

13 Ralli G, Milella C, Ralli M, et al. *Quality of life measurements for patients with chronic suppurative otitis media: Italian adaptation of "Chronic Ear Survey".* Acta Otorhinolaryngol Ital 2017;37:51-7.

14 Baumann I, Gerendas B, Plinkert PK, et al. *General and disease-specific quality of life in patients with chronic suppurative otitis media - a prospective study.* Health Qual Life Outcomes 2011;9:48.

15 Bhatia S, Karmarkar S, DeDonato G, et al. *Canal wall down mastoidectomy: causes of failure, pitfalls and their management.* J Laryngol Otol 1995;109:583-9.

16 Lailach S, Kemper M, Lasurashvili N, et al. *Health-related quality of life measurement after cholesteatoma surgery: comparison*

of three different surgical techniques. Eur Arch Otorhinolaryngol 2015;272:3177-85.

17 Clark MP, Bottrill I. *SerenoCem-glass ionomeric granules: a 3-year follow-up assessment of their effectiveness in mastoid obliteration.* Clin Otolaryngol 2007;32:287-90.

18 Dornhoffer JL, Smith J, Richter G, et al. *Impact on quality of life after mastoid obliteration.* Laryngoscope 2008;118:1427-32.

19 Alves RD, Cabral Junior F, Fonseca AC, et al. *Mastoid obliteration with autologous bone in mastoidectomy canal wall down surgery: a literature overview.* Int Arch Otorhinolaryngol 2016;20:76-83.

20 Bastier PL, Leroyer C, Lashéras A, et al. *Early and late surgical site infections in ear surgery.* Acta Otorhinolaryngol Ital 2016;36:127-34.

21 Thiel G, Rutka JA, Pothier DD. *The behavior of mastoidectomy cavities following modified radical mastoidectomy.* Laryngoscope 2014;124:2380-5.

22 Pontillo V, Barbara F, De Robertis V, et al. *Treatment of cholesteatoma with intact ossicular chain: anatomic and functional results.* Acta Otorhinolaryngol Ital 2018;38:61-6.

23 Artuso A, di Nardo W, De Corso E, et al. *Canal wall down tympanoplasty surgery with or without ossiculoplasty in cholesteatoma: hearing results.* Acta Otorhinolaryngol Ital 2004;24:2-7.

24 Bakir S, Kinis V, Bez Y, et al. *Mental health and quality of life in patients with chronic otitis media.* Eur Arch Otorhinolaryngol 2013;270:521-6.

25 Jung KH, Cho YS, Hong SH, et al. *Quality-of-life assessment after primary and revision ear surgery using the chronic ear survey*. Arch Otolaryngol Head Neck Surg 2010;136:358-65.

26 Choi SY, Cho YS, Lee NJ, et al. *Factors associated with quality of life after ear surgery in patients with chronic otitis media.* Arch Otolaryngol Head Neck Surg 2012;138:840-5.

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

Received: November 10, 2017 - Accepted: August 3, 2018

How to cite this article: Lucidi D, De Corso E, Paludetti G, et al. *Quality of life and functional results in canal wall down vs canal wall up mastoidectomy.* Acta Otorhinolaryngol Ital 2019;39:53-60. https://doi.org/10.14639/0392-100X-2005

Address for correspondence: Daniela Lucidi, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, largo A. Gemelli 1, 00168 Rome, Italy. Tel. +39 06 30154439. Fax +39 06 30151194. E-mail: dani.lucidi@gmail.com

ACTA OTORHINOLARYNGOLOGICA ITALICA 2019;39:61-64; doi: 10.14639/0392-100X-1753

Case series and reports

A new lateral cervical approach for salvage total laryngo-pharyngectomy

Un nuovo approccio latero-cervicale per la faringo-laringectomia totale di recupero

G. SPRIANO[1], G. MERCANTE[1], V. MANCIOCCO[1], G. CRISTALLI[1], G. SANGUINETI[2], F. FERRELI[1]

[1] Department of Otolaryngology, Head & Neck Surgery, [2] Department of Radiation Oncology, Regina Elena National Cancer Institute, Rome, Italy

SUMMARY

Total laryngectomy with subtotal pharyngectomy is the standard treatment of persistent/recurrent laryngeal and/or pharyngeal cancer. Salvage surgery can be complicated by pharyngo-cutaneous fistula because of previous treatment. The aim of this paper was to verify the feasibility of salvage total laryngectomy with subtotal pharyngectomy with a minimally invasive technique through a lateral cervical approach using the same skin incision used for resection of primary, synchronous neck dissection and pharyngeal flap reconstruction. This approach allowed harvesting of the anterior-myocutaneous flap including skin, subcutaneous tissue, platysma, anterior jugular veins, sterno- and homohyoid muscle in order to preserve as much tissue not involved by the tumour as possible. This technique is feasible and safe; further studies should confirm its advantages in terms of reduction of complications.

KEY WORDS: Salvage total laryngectomy • Recurrent laryngeal cancer • Larynx • Cancer • Cervical approach

RIASSUNTO

La laringectomia totale con faringectomia subtotale rappresenta il trattamento di scelta per le persistenze/recidve dei tumori maligni laringei e/o faringei. La chirurgia di recupero può essere complicata da una fistola faringo-cutanea correlata ai precedenti trattamenti chemio-radioterapici. L'obiettivo di questo studio è stato quello di verificare la fattibilità della faringo-laringectomia di recupero mediante una tecnica mini-invasiva attraverso un approccio cervicale laterale utilizzando la stessa incisione cutanea per la resezione del tumore, lo svuotamento linfonodale del collo e la ricostruzione faringea. Questo approccio ha consentito l'allestimento di un lembo mio-cutaneo anteriore costituito da cute, tessuto sottocutaneo, platisma, vene giugulari anteriori, muscolo sterno- e omoioideo al fine di preservare il tessuto non interessato dalla neoplasia. Questa tecnica è fattibile e sicura; ulteriori studi potranno confermare i vantaggi in termini di riduzione di fistola faringo-cutanea.

PAROLE CHIAVE: *Laringectomia totale di salvataggio • Carcinoma laringeo recidivato • Laringe • Cancro • Approccio laterale*

Introduction

NCCN guidelines recommend total laryngectomy (TL) as the first option for patients with loss of physiological voice and T4-laryngeal cancer involving the skeleton, while an organ preservation protocol using concurrent chemo-radiotherapy is preferred for T3-laryngeal and hypopharyngeal cancers. TL is the only choice in case of persistent or recurrent cancer of the larynx and/or pharynx. Salvage surgery is technically more difficult than upfront surgery and is associated with a higher number of complications such as haematoma, oedema, suture dehiscence, subcutaneous abscess and tissue necrosis with consequent pharyngo-cutaneous fistula. A second surgical procedure for closing the pharyngo-cutaneous fistula may be necessary if wound dressing and spontaneous healing are not adequate. Surgical pearls and suggestions have been proposed for preventing fistulas; nonetheless, pedicle or free flaps harvesting from non-irradiated areas is one of the most used techniques.

Some authors have recently proposed endoscopic or transoral robotic-assisted TL, with the goal of sparing as much healthy tissue as possible compared to an external approach [1-3]. In fact, dedicated equipment and extensive expertise are required in these minimally invasive techniques. Furthermore, patients with laryngeal recurrences are at high risk of nodal metastasis, and neck dissections are therefore recommended [4]. However, considering these minimally invasive techniques, neck dissections should be staged as a second surgical procedure after complete healing of pharyngeal tissues. In the early 20th century, lat-

eral pharyngotomy was described for limited resection of pharyngeal carcinomas [5], but this approach has never been proposed for advanced pharyngeal/laryngeal carcinomas with nodal metastasis.
The aim of this paper was to verify the feasibility of salvage total laryngectomy with subtotal pharyngectomy (SPTL) using a lateral cervical approach through the same skin incision for synchronous neck dissection and pharyngeal flap reconstruction.

Materials and methods

Surgical technique

The patient was placed in the head extension position. Surgical procedure was performed under general anaesthesia, with orotracheal intubation. A naso-gastric feeding tube (NGFT) was inserted. A monolateral 8-cm neck incision was made at the level of the anterior border of the sterno-cleido-mastoid muscle. An anterior myo-cutaneous (AMC) flap including skin, subcutaneous tissue, platysma, anterior jugular veins and sterno- and homohyoid muscle was harvested to create a space between these two muscles and the sterno-thyroid and thyro-hyoid muscles (Fig. 1).
The second step involved performing an ipsilateral selective neck dissection (II-IV) through the same incision. Next, the thyroid isthmus was divided and the thyro-hyoid muscles were cranially separated from the inferior border of the hyoid bone (Fig. 2). The pre-epiglottic space was also dissected. On the contralateral side of the incision, the superior laryngeal pedicle was ligated and sectioned, the inferior constrictor muscle was incised at the level of the lateral margin of thyroid cartilage and the pyriform sinus was detached from the internal thyroid cartilage with blunt dissection to free the larynx on the side that did not involve the neoplasia. All these surgical steps were done through a single unilateral skin incision.

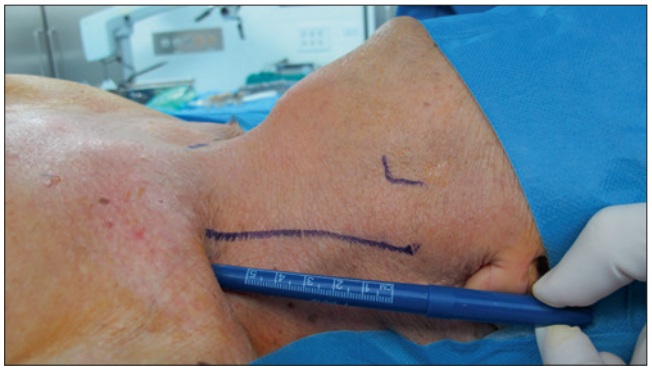


Fig. 1. Pictures of the lateral skin incision along the anterior margin of the sterno-cleido-mastoid muscle in lateral view.

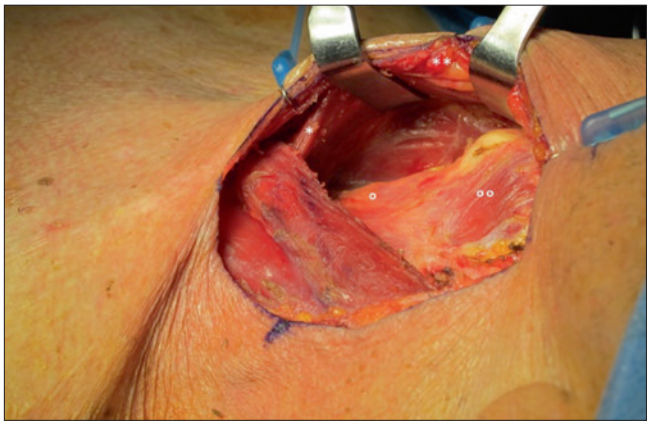


Fig. 2. Anterior myo-cutaneous (AMC) flap is harvested between the sterno- and homo-hyoid muscles and the sterno-thyroid and the thyro-hyoid muscles.
*white**: sterno-hyoid muscle; white*: homo-hyoid muscle; white°: thyro-hyoid muscle; white°°: sterno-thyroid muscle.*

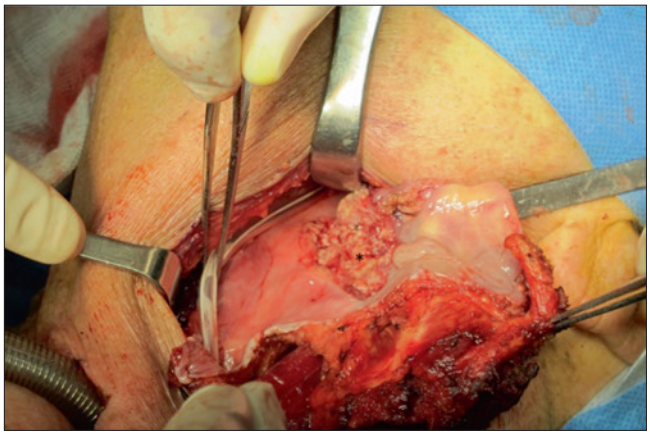


Fig. 3. The lesion involving the left pyriform sinus in vivo.
black: tumour of the left pyriform sinus.*

The pharynx was opened through the vallecula and en-bloc resection was performed under direct vision. The surgical removal of the specimen extended from the posterior wall of the hypopharynx to the lower pole of the tonsillar fossa, including the omolateral thyroid lobe (Fig. 3). A second oval horizontal incision with a 3-cm diameter was made in the jugular area to perform a definitive tracheostoma and the respiratory tube was removed from the larynx while a new one was passed into the tracheostoma. Direct closure of the pharynx was not possible due to the small amount of residual pharyngeal mucosa (2-cm in width); as a result, a myocutaneous pectoralis major pedicle flap was used to close the defect and reconstruct the neo-hypopharynx (Fig. 4). A by-pass salivary stent was placed in which the NGFT was positioned. The pectoralis flap was sutured to the remnant mucosa using the lateral cervical incision without any limitations of visualisation during flap

insetting. Closure was completed once repositioning of the mycocutaneous flap over the pectoralis flap took place.

Results

Case report

A 71-year old man, smoker, affected with squamous cell carcinoma of the hypopharynx involving the piriform sinus and the posterior wall, extending to the hemilarynx and the tonsillar fossa, staged cT3N1-G2, was treated with concurrent chemo-radiotherapy (total dose of 70 Gy + CDDP 30 mg/weekly for 6 weeks). The patient developed a loco-regional recurrence, stage yrT3N0 cancer after 1 year of initial treatment. MRI showed a recurrent lesion involving the same primary subsites (Fig. 5).

Biopsies confirmed recurrence, and salvage SPTL using a lateral approach was planned. Neck dissection, tumour resection and pharyngeal reconstruction with pectoralis major pedicle flap were performed as previously described. The total time of surgery was 185 minutes.

The postoperative period was uneventful and the cervical and thoracic drains were removed within 3 days. Oral intake of liquids started 2 weeks after surgery. The hospitalisation time was 20 days and the salivary stent was removed after 40 days in an outpatient setting.

The final pathology report showed ypT3N1 hypopharyngeal tumour with free margins.

No local complications or comorbidities were observed. The patient did not refer symptoms related to pharyngeal stenosis after stent removal.

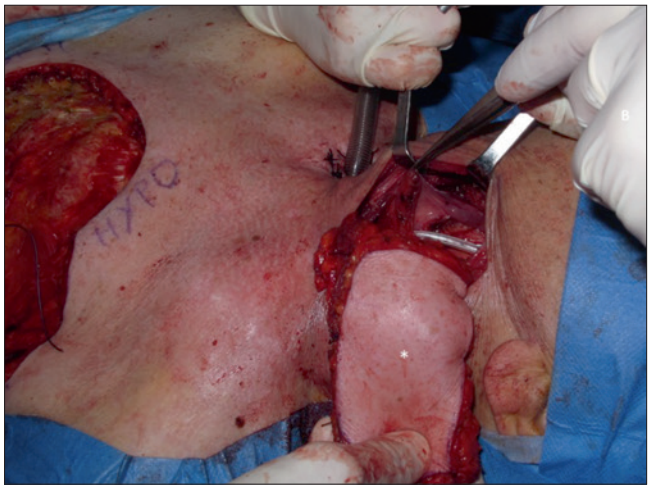


Fig. 4. The myocutaneous pectoralis major pedicle flap is rotated into the neck over the residual pharyngeal mucosa.
white: pectoralis major flap.*

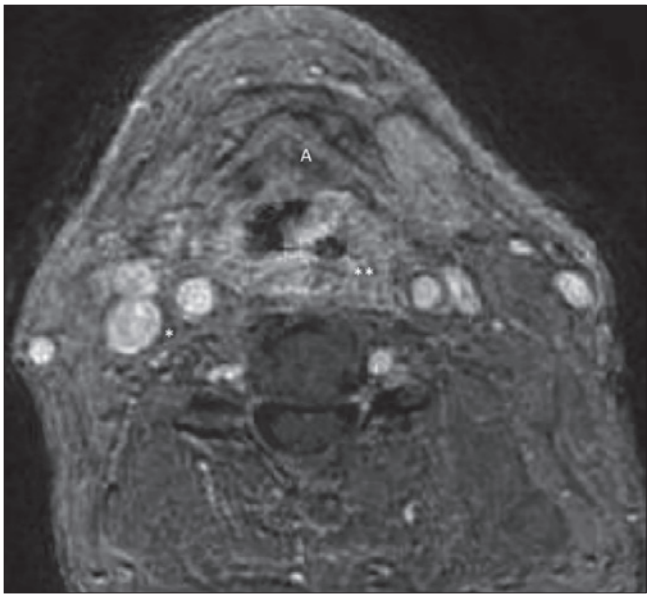


Fig. 5. Axial T1-weighted MRI with contrast after chemio-radiaton treatment, showing the hypopharyngeal recurrence.
*white**: recurrence of tumour.*

Discussion

Salivary fistulas may consequently occur in patients undergoing salvage surgery of laryngo-hypopharyngeal cancer after chemoradiotherapy. Radiotherapy and chemotherapy target cancer cells but, in spite of modern techniques, surrounding healthy tissue is irradiated as well. Tissue damaged by radiation must undergo repair. During the repair process, injured tissue may be replaced by normal functioning tissue. On the other hand, tissue repair mechanisms may cause replacement of normal tissue with fibrotic tissue. Tissues become noncompliant, contracted and atrophic resulting in altered function and significant symptom burden. Surgery represents a further insult that previously irradiated tissue may not sustain. After chemoradiotherapy, there is a time window (usually from 4-6 weeks after the end of treatment until 4-5 months of follow up) during which salvage surgery may be undertaken at limited or no extra morbidity. Afterwards, hypoxic and avascular irradiated normal tissues may not be able to further repair surgical damage. This aspect gives rise to complications such as suture dehiscence and subsequent fistulas.

Classic SPTL using a transcervical approach requires a wide exposure to stage the neck dissection. The common skin flap is a superior base “apron shaped” flap including the skin, the subcutaneous fat and platysma muscle which are detached from the cervical fascia. The anterior jugular veins as well as the strap muscles are resected and the hyoid

bone to which the larynx and suprahyoid muscles are attached causing the sacrifice of healthy tissues and ischaemia. Tissue trauma and the sequelae of the chemo-radiotherapy increase the risk of post-operative complications; therefore, some authors have proposed the interposition of a flap between the pharynx and the skin flap to prevent pharyngo-cutaneous fistula [4]. Furthermore, the extension of the resection involving the hypopharynx and simultaneous neck dissection increases the risks of complications. Lawson [1] using the Da Vinci system and Férnandez-Férnandez [2] adopting an ultrasonic device demonstrated the feasibility of the transoral salvage laryngectomy with sparing healthy tissue around the larynx. More recently, Funk confirmed in biological models the possibility of performing a transoral laryngectomy even with the Medrobotics flex system [3]. Lawson stated that one limitation in using the transoral technique is that the extension of the neoplasia limited to the laryngeal box. Furthermore, these transoral procedures need dedicated technologies, the ability to perform a single transoral pharyngeal suture and a second surgical step represented by therapeutic or elective neck dissection, mostly bilateral, when healing is completed.

The surgical technique of salvage SPTL with a lateral cervical approach presented herein represents one of the most challenging situations because of tumour extension in the hemilarynx, pyriform sinus and posterior hypopharyngeal wall. At the end of the resection, a myo-cutaneous pectoralis major pedicle flap was harvested to complete the circumference of the digestive tube because the pharyngeal mucosa was not sufficient for direct closure. In spite of this, all surgical steps (neck dissection, laryngopharyngeal resection and reconstruction) were performed through a single 8-cm cervical lateral incision. The AMC flap has the advantage of sparing healthy tissue not involved by the tumour. The preservation of the hyoid bone and its muscle insertions contributes to respecting tissue for covering the suture line. Another advantage could be represented by a better lateral cosmetic profile of the neck avoiding the posterior retraction of the classic TL.

This surgical procedure seems to be indicated in the laryngeal and hypopharyngeal tumours without anterior spread outside the external pericondrium and/or invasion of the hyoid bone or its inserted muscles, both as upfront and/or salvage surgery.

Conclusions

Salvage SPTL through a lateral cervical approach after chemo-radiotherapy failure is feasible. The key point of this technique is represented by harvesting of an AMC flap that spares healthy tissue in comparison to the classic technique. Neck dissection, tumour resection and reconstruction can all be performed through the same incision. Further studies are needed to confirm its advantages in terms of reduction of pharyngo-cutaneous fistulas compared to other techniques.

Acknowledgements

The authors acknowledge Ms Tania Merlino for English language editing.

Conflict of interest statement

None declared.

References

1 Lawson G, Mendelsohn AH, Van Der Vorst S, et al. *Transoral robotic surgery total laryngectomy.* Laryngoscope 2013;123:193-6.

2 Fernandez-Fernandez MM, Montes-Jovellar Gonzalez L, Ramirez Calvo CR, et al. *Transoral ultrasonic total laryngectomy (TOUSS-TL): description of a new endoscopic approach and report of two cases*. Eur Arch Otorhinlaryngol 2016;273:2689-96.

3 Funk E, Goldenberg D, Goyal N. *Demonstration of transoral robotic supraglottic laryngectomy and total laryngectomy in cadaveric specimens using the Medrobotics Flex System.* Head Neck 2017;39:1218-25.

4 Spriano G, Piantanida R, Maffioli M. *Salvage surgery after unsuccessful radiotherapy of cancer of the larynx.* Acta Otorhinolaryngol Ital 1989;9:161-8.

5 Trotter W. *A Method of lateral pharyngotomy for the exposure of large growths of the epilaryngeal region.* Proc R Soc Med 1920;13:196-8.

Received: May 10, 2017 - Accepted: May 21, 2017

How to cite this article: Spriano G, Mercante G, Manciocco V, et al. *A new lateral cervical approach for salvage total laryngo-pharyngectomy.* Acta Otorhinolaryngol Ital 2019;39:61-64. https://doi.org/10.14639/0392-100X-1753

Address for correspondence: Fabio Ferreli, via Elio Chianesi 53, 00144 Rome, Italy. Tel. +39 06 52666770. E-mail: fabio_ferreli@yahoo.it

Vieri Galli,
In Memoriam

L'8 febbraio è scomparso Vieri Galli, già Professore Ordinario di Otorinolaringoiatria nella Facoltà di Medicina e Chirurgia dell'Università Federico II di Napoli, membro del Consiglio Superiore di Sanità.
Aveva iniziato il suo percorso professionale sulla scia del padre Mario, che lo aveva indirizzato nella scelta della specializzazione. Ha proseguito la sua carriera universitaria presso l'Ateneo di appartenenza con una parentesi prolungatasi dal 1981 al 1994 come professore ordinario presso la Facoltà di Medicina e Chirurgia dell'Università della Magna Grecia di Catanzaro.
Ricordiamo Vieri, uomo leale e di profonda onestà intellettuale, libero nel pensiero e nei comportamenti, sempre pronto ad affrontare a viso aperto le battaglie in cui credeva, incapace di rancori. Amava anche la politica che aveva svolto attivamente come esponente di spicco del partito popolare ma ancor di più l'Accademia di cui avvertiva il prestigio e sapeva viverne le contraddizioni senza falsi pudori o moralismi ma cercando di affrontarle con spirito positivo e costruttivo. Sempre disponibile verso i colleghi e i pazienti che avevano in lui una fiducia incondizionata, attento alla persona nella sua interezza, coniugava la sua grande professionalità con una umanità che andava oltre il rapporto formale. Nella professione era noto per la scrupolosità, il senso del dovere, la passione innata per la chirurgia, il rispetto e la generosità con cui seguiva i pazienti e le varie generazioni di allievi che si sono succedute negli anni.
Chi lo ha conosciuto ha incontrato un galantuomo prima ancora che un professionista di valore, un esempio per tutti di bontà, rettitudine ed onesta.

Maurizio Maurizi

Otorhinolaryngologica Italica

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

What's new?

Single platform

New on-line submission

New web site

www.actaitalica.it

Available on Google Scholar

Cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, DOAJ, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

Journal Citation Reports:
Impact Factor 1.196

Editor-in-Chief: M. Ansarin

PACINI EDITORE MEDICINA