



Head and neck

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HEAD AND NECK

Surgical site infections after parotidectomy: management and benefits of an antibiotic prophylaxis protocol

Infezioni del sito chirurgico dopo parotidectomia: la gestione e i vantaggi dell'antibioticoprofilassi

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SUMMARY

The use of perioperative prophylactic antibiotics in uncontaminated head and neck surgery is still controversial. The aim of this study was to assess the efficacy of an institutional antibiotic prophylactic protocol in preventing surgical site infection after parotidectomy. The medical charts of 448 patients who underwent parotidectomy were reviewed. Patients were divided in two groups according the use of perioperative administration of intravenous cefazolin or post-operative week course of antibiotics. Surgical site infection was registered in 29 (6.5%) cases, 16 (5.7%) within the group before the application of the perioperative protocol and 13 (7.9%) within the antibiotic prophylaxis protocol group. The univariate and multivariate logistic regression analyses showed that predictors for surgical site infection were the amount of drain output ≥ 50 ml in the first post-operative 24 hours (OR: 4.86; 1.59-14.82 95% CI; $p < 0.01$) and history of a previous parotid acute infection (OR: 13.83; 5.31-36 95% CI; $p < 0.01$). The majority of post-surgical infections (82%) were treated with intravenous antibiotic therapy. The remnants were treated surgically. Perioperative antibiotic treatment is recommended for patients undergoing parotid gland surgery and intravenous antibiotics during the post-operative course are highly suggested in case of history of previous acute parotid infection and drain output ≥ 50 ml in first 24 hours.

KEY WORDS: Surgical site infection • Parotidectomy • Surgery • Prophylaxis • Antibiotic

RIASSUNTO

L'uso dell'antibioticoprofilassi perioperatoria nella chirurgia della testa e del collo non contaminati è ancora oggetto di dibattito. La valutazione dell'efficacia del protocollo istituzionale di antibioticoprofilassi per la prevenzione dell'infezione del sito chirurgico dopo parotidectomia è l'obiettivo del nostro studio. Per tale scopo sono state rivalutate le cartelle cliniche di 448 pazienti sottoposti a parotidectomia. I pazienti sono stati divisi in due gruppi in base all'uso della somministrazione endovenosa perioperatoria di cefazolina oppure di ciclo settimanale di antibioticoterapia post-operatoria. L'infezione del sito chirurgico è stata registrata in 29 casi (6,5%) di cui 16 (5,7%) all'interno del gruppo prima dell'applicazione del protocollo perioperatorio e 13 (7,9%) all'interno del gruppo dell'antibioticoprofilassi. Le analisi di regressione logistica univariata e multivariata hanno mostrato che i fattori predittivi per l'infezione del sito chirurgico erano la quantità di raccolta nel drenaggio ≥ 50 ml nelle prime 24 ore postoperatorie (OR: 4,86; 1,59-14,82 95% CI; $p < 0,01$) e l'anamnesi positiva per una precedente infezione acuta parotidea (OR: 13,83; 5,31-36 95% CI; $p < 0,01$). La maggior parte delle infezioni post-chirurgiche (82%) sono state trattate con terapia antibiotica endovenosa. Le restanti hanno richiesto un intervento chirurgico. L'antibioticoprofilassi è raccomandata per i pazienti sottoposti a chirurgia parotidea mentre la terapia antibiotica nel decorso post-operatorio è fortemente consigliata in caso di storia di precedenti infezioni acute parotidee e di quantità di materiale raccolto nel drenaggio ≥ 50 ml nelle prime 24 ore.

PAROLE CHIAVE: Infezione del sito chirurgico • Parotidectomia • Chirurgia • Profilassi • Antibiotico

Introduction

Antibiotic stewardship is critical, but there is limited evidence to guide surgeons on the most appropriate regimen for antibiotic prophylaxis during head and neck surgery. Antibiotic prophylaxis in clean-contaminated head and neck surgery is mandatory. The efficacy of perioperative

antibiotic administration during major head and neck surgery in which the wound is contaminated by saliva has been clearly established. Some head and neck surgeons believe that during parotidectomy a direct connection between the oral cavity and the surgical field is formed with possible retrograde flow of saliva from the contaminated oral cavity

into the clean wound. Hence, they advocate the use of prophylactic perioperative antibiotic treatment in parotid gland surgery. Slattery et al.¹ found that perioperative antibiotic prophylaxis for 24 hours is sufficient to prevent wound infections in clean, uncontaminated neck dissections. However, the use of perioperative prophylactic antibiotics in uncontaminated head and neck surgery remains controversial². Furthermore, the choice of specific antimicrobial agents and duration of treatment are controversial, and incidence of the reported wound infections in head-neck surgery is still high^{3,4}. Cephalosporins have emerged as the drug of choice for perioperative prophylaxis because of their wide antibacterial spectrum and low incidence of side effects⁵.

The purpose of this study is to compare the efficacy of our institutional antibiotic prophylaxis protocol with a cefazolin regimen given as a single dose rather than as a one week course of antibiotic in preventing surgical site infection (SSI) after parotidectomy.

Materials and methods

This study was approved by the Institutional Review Board. The medical charts of consecutive patients who underwent parotidectomy at our department between November 2004 and March 2016 were evaluated retrospectively. Data collected for the analysis were: age, sex, comorbidities, pathology, postoperative complications and follow-up data, including postoperative wound infection, drainage amount, type and route of antibiotics administration and type of surgery. Patients were excluded if they had undergone previously parotid surgery, if there was missing information about wound infection, or missing information about the receipt of antibiotics. All patients were prepared and draped for surgery in the same fashion using povidone-iodine, 10%, topical solution. At our institution before 2013, surgeons administered oral amoxicillin/clavulanic acid 1 gm every 8 hours for one week in the post-operative course. If penicillin allergy was noted, ciprofloxacin 500 mg each 12 hours for a week or clarithromycin 500 mg each 12 hours for a week. After 2013, a perioperative antibiotic prophylaxis institutional protocol was introduced. Immediately before the skin incision, intravenous cefazolin 2 gm is currently administered. If penicillin allergy was registered, intravenous clarithromycin 500 mg or, as second choice, ciprofloxacin 500 mg is given in a single shot.

The SSI was defined as local oedema, erythema and tenderness, starting no less than 48 hours postoperatively.

Statistical analysis

To test the differences among groups Fisher's exact test

was used for categorical data, while the Student's t-test was used for continuous data. The role of each possible prognostic factor (univariate analysis) and their independent effect (multivariate analysis) was explored using logistic regression model or Cox-proportional hazard model as appropriate. Probability values lower than 0.05 were considered statistically significant. All analyses were performed with STATA 12.1 software (Stata Corp, College Station, TX, USA).

Results

A total of 448 patients met inclusion criteria. The patients were divided in two groups according the perioperative antibiotic prophylactic protocol. The cohort's characteristics are shown in Table I. Perioperative antibiotic treatment was given to 165 patients (36.8%). No significant differences were found between groups, except for the extent of parotidectomy ($p < 0.01$). More radical parotidectomies within the group before the application of perioperative antibiotic prophylaxis protocol were recorded. However, the groups can be considered homogenous. SSI was registered in 29 (6.5%) of 448 cases, 16 (5.7%) within the group before the application of antibiotic prophylaxis protocol and 13 (7.9%) within the antibiotic prophylaxis protocol group ($p = 0.43$). The majority of SSIs (82%) were treated with intravenous antibiotic therapy. Four patients needed a surgical drainage of the pus collection, while only one patient needed complete surgical revision for extension of the neck abscess in the deep fascial plane surrounding the main neurovascular bundle.

Of note, 132 Warthin's tumours were found and at least one previous infection's episode was noted in 10.6% of cases. Moreover, previous parotid infections were registered in 81% of chronic sialoadenitis with calculi. Univariate and multivariate logistic regression analyses (Table II) showed that predictors for SSI were the amount of drain output ≥ 50 ml in the first post-operative 24 hours (OR: 4.86; 1.59-14.82 95% CI; $p < 0.01$) and history of previous acute parotid infection (OR: 13.83; 5.31-36 95% CI; $p < 0.01$).

Discussion

Despite remarkable advances in the use of surgical techniques and prophylactic antibiotics and environmental/ergonomic improvements in the operating room, SSIs remain a significant cause of patient morbidity and mortality, and are the third-most common source of hospital-acquired infection⁶. Of concern is that SSIs occur in up to 30% of all surgical procedures, and yet most are preventable^{6,7}.

Table I. Clinical characteristics of 448 patients undergoing parotidectomy.

	No perioperative prophylaxis (%)	Perioperative prophylaxis protocol (%)	p
Sex			
Males	162 (57.2)	87 (52.7)	0.38
Females	121 (42.8)	78 (47.3)	
Age (mean \pm SD)	57.8 \pm 16.4	59 \pm 16	0.46
Diabetes			
Yes	24 (8.5)	7 (4.2)	0.12
No	259 (91.5)	158 (95.8)	
Histology			
Benign	250 (88.3)	147 (89.1)	0.88
Malignant	33 (11.7)	18 (10.9)	
Type of parotidectomy			
Superficial/partial	250 (88.3)	156 (94.6)	p < 0.01
Total	16 (5.7)	8 (4.9)	
Radical	17 (6)	1 (0.6)	
Neck dissection			
Yes	30 (10.4)	9 (5.4)	0.08
No	253 (89.4)	156 (94.6)	
Drain output first 24 hours			
< 50 ml	136 (48.1)	67 (40.6)	0.14
\geq 50 ml	147 (51.9)	98 (59.4)	
Previous infection			
Yes	21 (7.42)	18 (10.9)	0.23
No	262 (92.58)	147 (89.1)	
Surgical site infection			
Yes	16 (5.7)	13 (7.9)	0.43
No	267 (94.3)	152 (92.1)	

SD = standard deviation.

The economic impacts on the health care system are substantial, including increased hospital length of stay and escalating hospital costs, rising from twofold to fivefold⁸. These human and economic effects are compounded by overstretched health care systems, suboptimal integration in clinical processes and fragmented approaches used by health professionals in wound-care management. Necessarily, there is a growing emphasis on the prevention of SSI. Unfortunately, no randomised controlled studies hitherto are present in literature analysing the best care in preventing SSI after parotidectomy. Recently, Shkedy et al.⁹ demonstrated that female sex, neck dissection and drain output > 50 ml within 24 hours were predictive of postoperative wound infection after parotidectomy and found no benefit for routine prophylactic perioperative antibiotic treatment in patients undergoing parotid gland surgery. On the other hand, our results confirm, at univariate and multivariate logistic regression analysis, that drain output > 50 ml within 24 hours (p < 0.01) and, further, a

history of previous parotid infections (p < 0.01) were predictive of SSIs. Interestingly, the slightly high prevalence but not statistically significant of SSIs in the antibiotic prophylaxis group (7.9% vs 5.7%) might be explained by the fact that cases with a history of previous infections require antibiotics postoperatively and the prophylaxis is not adequately sufficient.

In the literature, few studies have evaluated the efficacy of antibiotic prophylaxis in prevention of SSIs in head and neck surgery, and most of them addressed purely major oncological surgery not discussing parotid gland surgery as a separate entity. Simo and French¹⁰ found that prophylactic antibiotic use in clean-contaminated major oncological head and neck surgery is mandatory to reduce the risk of infection. Ogihara et al.¹¹ concluded that in order to minimise SSI, patients with head and neck tumours should have a thorough understanding of the risk factors leading to postoperative infections, such as blood loss, previous chemotherapy and clean-contaminated sur-

Table II. Univariate and logistic multivariate regression analysis of predicting factors for surgical site infection.

	Univariate			Multivariate				
	Number of surgical site infections (%)	Odds ratio	p	Odds ratio	Std. Err.	z	p	95% Confidence interval
Sex								
Males	21 (8.5)	2.2	0.65	1.89	0.89	1.36	0.17	0.76, 4.75
Females	8 (4)	1 (Reference)				1 (Reference)		
Age at diagnosis								
< 60 years	13 (5.8)	1 (Reference)				1 (Reference)		
≥ 60 years	16 (7.14)	1.25	0.57	1.05	0.46	0.10	0.92	0.44, 2.46
Diabetes								
Yes	2 (6.5)	1 (Reference)				1 (Reference)		
No	27 (6.5)	1	1	1.18	0.99	0.19	0.85	0.22, 6.2
Histology								
Benign	24 (6.1)	1.69	0.31	3.46	2.28	1.89	0.06	0.95, 12.6
Malignant	5 (9.8)	1 (Reference)				1 (Reference)		
Type of parotidectomy								
Superficial/partial	25 (6.2)	1.56	0.19	1.23	0.68	0.38	0.71	0.42, 3.65
Total	1 (4.2)	1 (Reference)				1 (Reference)		
Radical	3 (16.7)	1 (Reference)				1 (Reference)		
Neck dissection								
Yes	4 (10.3)	1.76	0.32	0.52	0.46	- 0.75	0.45	0.09, 2.91
No	25 (6.1)	1 (Reference)				1 1 (Reference)		
Drain output first 24 hours								
< 50 ml	4 (2)	1 (Reference)				1 (Reference)		
≥ 50 ml	25 (10.2)	5.65	< 0.01	4.86	2.76	2.78	< 0.01	1.59, 14.82
Previous infection								
Yes	13 (33.3)	12.28	< 0.01	13.83	6.75	5.38	< 0.01	5.31, 36
No	16 (3.91)	1 (Reference)				1 (Reference)		
Perioperative antibiotics								
Yes	13 (7.9)	1 (Reference)				1 (Reference)		
No	1 6(5.7)	0.7	0.36	1.19	0.53	0.39	0.69	0.5, 2.8

Std. Err. = standard error.

gery. Lee et al.¹² recommended preventive measures or close monitoring in these patients to reduce the likelihood of postoperative SSIs. Busch et al.¹³, in a retrospective study, demonstrated that long-term (more than 7 days) antibiotic prophylaxis is not associated with a further decrease in SSI rates in head neck oncologic surgery. Conversely, Carrau et al.² did not demonstrate the efficacy of prophylactic antibiotics in uncontaminated neck dissections.

Selection of the appropriate antimicrobial agent for a specific surgery should take into account characteristics of the ideal agent, comparative efficacy of the antimicrobial agent for the procedure, safety profile and the patient's medication allergies. To achieve these goals, an antimicrobial agent should be active against the pathogens most likely to contaminate

the surgical site; given in an appropriate dosage and at a time that ensures adequate serum and tissue concentrations during the period of potential contamination, and administered for the shortest effective period to minimise adverse effects, development of resistance and costs. Generally, for most surgical procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety and low cost¹⁴. In case of unresponsive SSIs to antibiotics, surgical intervention remains the mainstay of treatment, especially in severe cases of deep neck infections. Indications for surgery include airway impairment, septicemia, de-

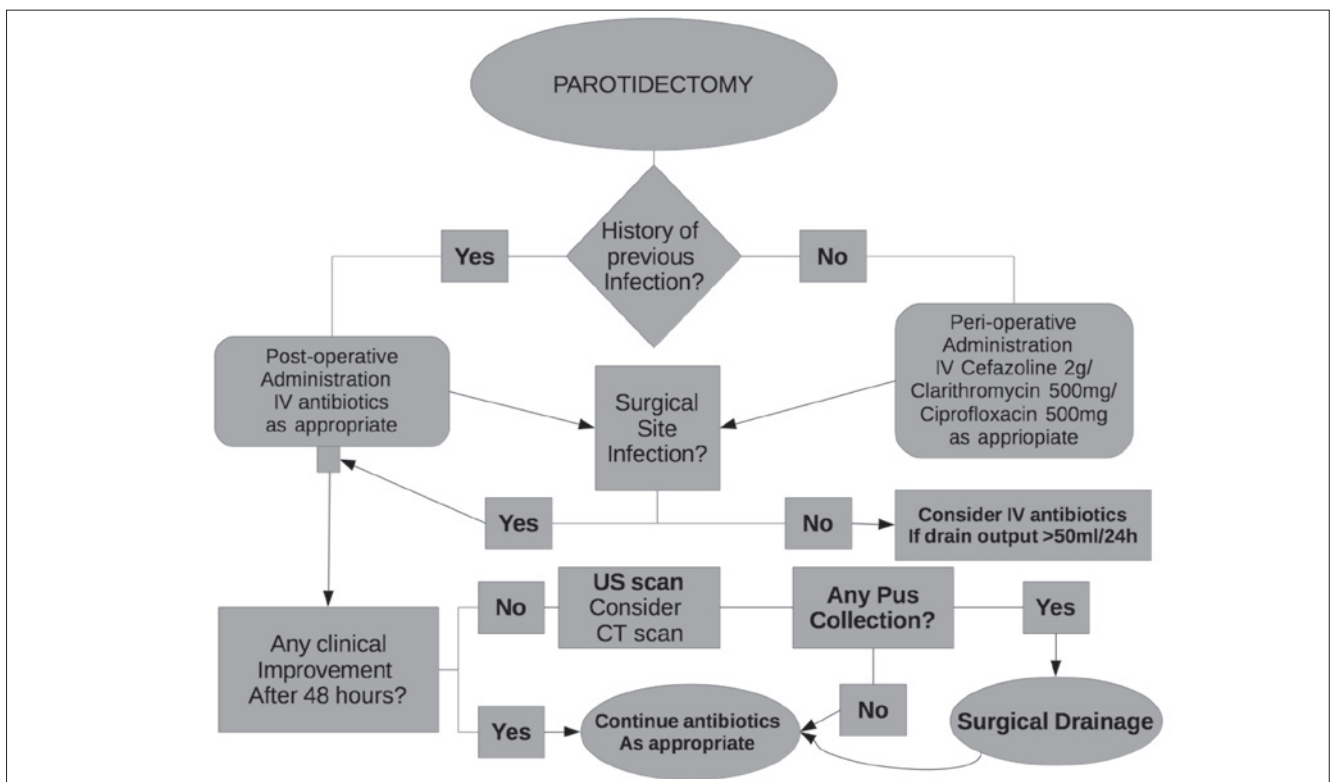


Fig. 1. Institutional algorithm of decision-making and management of post-operative course after parotidectomy.

scending infection, diabetes mellitus, or no clinical improvement within 48 hours from intravenous antibiotic administration¹⁵. In addition, abscesses > 3 cm in diameter that involve the prevertebral, anterior visceral, or carotid spaces, or that involve more than two spaces, should be surgically drained¹⁶. Conventionally, once surgical drainage has been completed, drainage tubes, usually in continuous aspiration, are placed in the surgical field to remove all secretions and prevent new pus collection from forming in the postoperative course. Recently, the VAC therapy has gained wide acceptance for the management of complex wound infections¹⁷. Gallo et al.¹⁸ used this device in deep neck abscess with promising results.

In our point of view, we strongly support the use of VAC in case of extended and/or severe cases of SSIs needing surgical drainage, although attention should be given avoiding the direct application on the facial nerve. Nevertheless, this device permits to obtain a larger surface area under negative pressure. This characteristic makes VAC more effective in eliminating the biofilm that protects bacteria from antibiotics and in promoting healing through the enhancement of granulation tissue formation¹⁹.

Furthermore, as SSIs are a key indicator of quality care, it is important to implement strategies that promote team-

based approaches in their prevention. For these reasons, we developed an algorithm for prophylactic antibiotic and relative SSI treatment in parotid gland surgery to help clinicians in decision-making and patient management (Fig. 1).

Conclusions

Perioperative antibiotic treatment is recommended for patients undergoing parotid gland surgery and intravenous antibiotics during the post-operative course are highly suggested in case of history of previous acute parotid infection and of drain output ≥ 50 ml in first 24 hours.

Conflict of interest statement

None declared.

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HEAD AND NECK

Free flap head and neck reconstruction in the elderly: what is the impact on quality of life?

Ricostruzione testa-collo mediante lembi rivascolarizzati nella popolazione anziana: quale impatto sulla qualità della vita?

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SUMMARY

Morphofunctional reconstruction is a pivotal aspect in the surgery of head and neck neoplasms: nowadays, microvascular free flap surgery represents the gold standard. In choosing the surgical technique, the effects on residual quality of life, especially in elderly people, usually considered more fragile and so often excluded from microsurgical procedures, must be taken into account. This multicentre study evaluated the quality of life index in patients more than 75 years of age and who underwent to head and neck microsurgical reconstruction. Data from patients aged > 75 years at the time of major head and neck reconstruction conducted with free flaps between 1 January 2005 and 30 June 2015 were analysed retrospectively. We administered the Italian version of Quality of Life questionnaire SF-36, at least 24 months after surgery. Results were compared to those for the general Italian population of the same age. We enrolled 39 patients with an average age of 80.6 years. The results did not differ significantly from the reference population. The international literature has already shown that chronologic age is not a valid parameter to determine the surgical treatment modality. Even considering the quality of residual life, our study supports the indication for free-flap reconstruction of head and neck defects in the elderly, confirming its effectiveness in this population.

KEY WORDS: Head and neck cancer • Free tissue flaps • Reconstructive microsurgery • Quality of life • Patient health questionnaire

RIASSUNTO

La ricostruzione dei difetti della regione testa-collo costituisce un momento fondamentale del trattamento delle neoplasie di questo distretto in considerazione delle criticità estetiche e funzionali delle strutture coinvolte. In tale contesto le tecniche microvascolari rappresentano ad oggi il gold-standard. Tuttavia, le indicazioni a tali tecniche dovrebbero tenere in considerazione anche l'impatto delle procedure sulla qualità della vita residua, in particolare nella popolazione anziana, generalmente considerata più fragile e pertanto spesso non candidata a metodiche microchirurgiche. Lo studio, condotto con un disegno multicentrico, mira a valutare la qualità della vita nei pazienti anziani sottoposti a ricostruzione con lembi liberi per verificare l'appropriatezza delle indicazioni in questa particolare popolazione. Sono stati raccolti i dati di tutti i pazienti di età > 75 anni al momento della ricostruzione microvascolare testa-collo, tra il 1 gennaio 2005 e il 30 giugno 2015. Il questionario per qualità della vita SF36 è stato quindi somministrato ad almeno 24 mesi di follow up. Dai risultati dell'SF36 abbiamo inoltre estrapolato anche i valori sintetici PCS (Physical health Composite Score) e MCS (Mental health Composite Score). I risultati sono stati confrontati con gli score della popolazione normale della stessa fascia di età. Sono stati arruolati 39 pazienti, con età media di 80,6 anni, con follow-up medio di 49,3 mesi. La letteratura internazionale conferma che è il profilo biologico del paziente e non l'età anagrafica che dovrebbe determinare l'indicazione alla ricostruzione microvascolare. Pochi lavori hanno invece analizzato l'outcome del paziente in termini di qualità della vita residua. Questo studio conferma che le metodiche microvascolari possono essere utilizzate con sicurezza anche nella popolazione over 75, senza impattare significativamente sulla qualità di vita residua.

PAROLE CHIAVE: Tumori testa e collo • Lembi liberi microchirurgici • Microchirurgia ricostruttiva • Qualità della vita • Questionari di valutazione della salute

Introduction

The global increase in the mean lifespan and improvements in medical science have raised issues related to surgical approaches in elderly patients ¹. In particular, when primary functions such as swallowing, breathing

and speaking are impaired, as is inevitable when treating malignancies in the upper aero-digestive tract, the importance of patient recovery and impact on the quality of residual life after surgical treatment should not be underestimated ^{2,3}. Many authors have recently examined these

issues, with particular focus on indications, success rates, complications and perioperative morbidity related to free-flap reconstruction in elderly patients with oral cavity tumours ⁴⁻⁸. Most authors have concluded that comorbidities and performance status, rather than age, should be considered as risk and predictive factors ⁹, as free-flap techniques are believed to be relatively safe in the elderly population ^{10 11}.

However, little research has focused on the impact of such reconstruction on the quality of life (QOL) of elderly patients. Thus, we require a better understanding of patients' QOL after tumour treatment, in terms of surgery-related long-term morbidity, social life impairment and the psychological implications of such major interventions in a subset of patients usually considered to be frail. Comprehensive insight into this matter is of primary importance to better determine whether these procedures are indicated in the elderly population, as the quality of residual life (which is obviously shorter than in younger patients) is a primary issue that should be taken into account when treating these patients. In this study, we analyse the impact of major resection and reconstructive procedures on QOL in the population of patients over the age of 75.

Patients and methods

This multicentre retrospective review of medical records involved five Italian academic tertiary-care institutions: the University Hospital of Parma, University Hospital Maggiore Policlinico of Milano, "Sant'Anna" Hospital of Como, University Hospital "Federico II" of Napoli, and "Casa Sollievo della Sofferenza" Hospital of San Giovanni Rotondo. Data from patients aged > 75 years at the time of major head and neck reconstruction conducted with free flaps between 1 January 2005 and 30 June 2015 were analysed retrospectively. The data collected included age, sex, American Society of Anesthesiologists (ASA) status, alcohol and tobacco habits, history of oncological pathology, and comorbidities in four major areas (cardiovascular, kidney, liver, and lung). Data related to treatment included diagnosis, staging, site involved, need for neck dissection, free flap type, adjuvant treatments and need for permanent feeding or breathing support (i.e., tracheostomy, percutaneous endoscopic gastrostomy [PEG]).

The validated Italian version of the Medical Outcome Study's (MOS's) 36-item Short-Form Health Survey (SF-36), administered at least 24 months after surgery, was used to assess QOL ¹². The SF-36 investigates eight fields of global health, focusing on emotional and physical aspects, with scores ranging from 0 to 100. The Short Form 12 (SF-12) can be used to condense SF-36 scores into the medical

component summary (MCS) and physical component summary (PCS) scores, simplifying analysis of data ¹³. Results with the SF-12 were compared to those for the general Italian population of the same age using a database of 61,434 questionnaires completed by Italian subjects ¹⁴.

Results

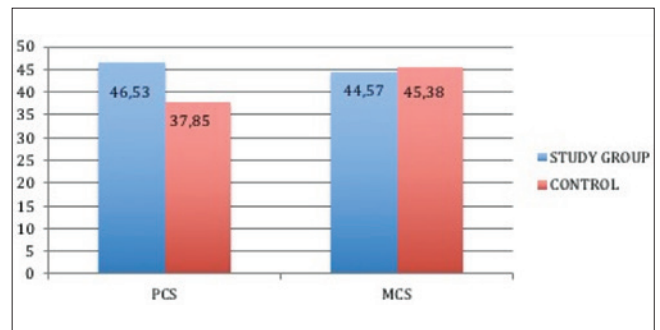
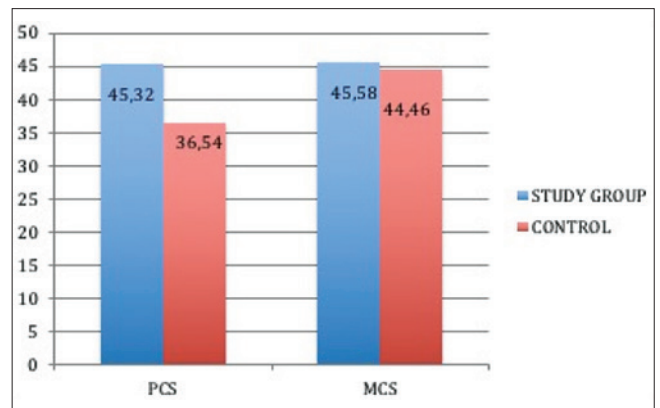
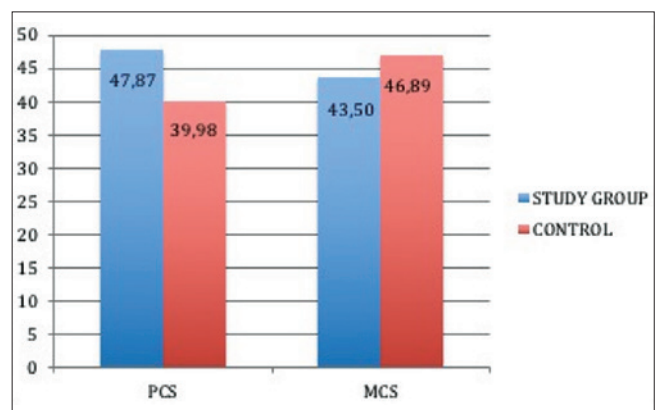
For the period considered, 115 patients met inclusion criteria. 76 (66.1%) of patients died before data collection and were not included. Thus, the study cohort consisted of 39 patients (19 males and 20 females) with an average age at the time of surgery of 80.6 ± 4.40 years (maximum age, 89 years; Table I). The average follow-up duration was 49.3 months (range, 24-132 months). Comorbidities (86% of which were cardiovascular disease) were recorded in 32 patients. ASA indices were 3 for 59% of patients, 2 for 33% of patients, 4 for 5% of patients and 1 for 2% of patients. In all, 15 patients were smokers, 11 abused alcohol and 8 had both habits. All patients required microvascular reconstruction due to malignant pathology: 33 patients had squamous cell carcinoma of the oral cavity, 4 had cutaneous squamous cell carcinoma, 1 was treated for basal cell carcinoma infiltrating the maxilla and 1 had adenocarcinoma of the minor salivary gland. The most frequently involved oral-cavity site was the mandible (in 36% of patients), followed by the tongue (21%), cheek (13%), maxilla (13%), and floor of the mouth (8%). The skin was involved in 10% of patients. 20 (51%) patients had advanced (stage IV) disease, six had stage III, 9 had stage II and 4 had stage I disease. Bone-containing free flaps were used in 7 patients (five fibula flaps, two iliac crest flaps), and the most frequently used flap was the radial forearm free flap ($n = 20$). Other flaps harvested were the latissimus dorsi ($n = 10$) and antero-lateral thigh (ALT; $n = 2$) flaps. Neck dissection was performed in 30 patients. 23 patients underwent post-surgical adjuvant radiotherapy, two underwent chemotherapy and 1 patient was given both treatments. No permanent tracheostomies were recorded; three patients underwent permanent PEG. We recorded 10 cases of disease relapse, and three patients died after completing the questionnaire.

The questionnaire results are summarised in Table II. The average score for all patient scales was 68.29 ± 27.30 ; the highest score was for physical function (76.92 ± 25.35) and the lowest score was for energy/fatigue (60.25 ± 19.26). SF-12 results are shown in Figures 1-3. We divided the cohort into two groups according to sex and compared our results with those from the control group, which comprised 5,283 Italian

Table I. Patient characteristics (n = 39).

	N (%)
Sex	
Male	19 (49%)
Female	20 (51%)
Comorbidities	
Yes	22 (56%)
Renal	0 (0%)
Pulmonary	2 (5%)
Cardiovascular	19 (49%)
Hepatic	1 (2%)
No	17 (44%)
Smoking	
Yes	15 (38%)
No	24 (62%)
Alcohol	
Yes	11 (28%)
No	28 (72%)
ASA	
I	1 (2%)
II	13 (33%)
III	23 (60%)
IV	2 (5%)
Pathology	
Squamous cell carcinoma oral cavity	33 (87%)
Cutaneous squamous cell carcinoma	4 (9%)
Cutaneous basal cell carcinoma	1 (2%)
Adenocarcinoma salivary gland	1 (2%)
Tumour site	
Mandible	14 (36%)
Tongue	8 (21%)
Maxillary bone	5 (13%)
Cheek	5 (13%)
Floor of the mouth	3 (8%)
Skin	4 (9%)
Disease stage	
I	4 (9%)
II	9 (24%)
III	6 (16%)
IV	20 (51%)
Type of flap	
Forearm	20 (51%)
Fibula	5 (13%)
Iliac crest	2 (5%)
ALT	10 (26%)
Latissimus dorsi	2 (5%)
Neck dissection	
Yes	7 (18%)
No	32 (72%)
Adjuvant therapy	
Yes	26 (67%)
No	13 (33%)

people aged > 75 years. The most evident difference was in the PCS score (46.53 vs 37.85), which indicated that our patients perceive themselves to have a better physical status than their counterparts from the general population.

**Fig. 1.** SF-12 results, all patients.**Fig. 2.** SF-12 results, female group.**Fig. 3.** SF-12 results, male group.

Discussion

When surgical results after head and neck resection and reconstruction in the elderly population are analysed, several major issues must be considered. The most relevant issues are that most of these patients are extremely frail, and long-term follow-up is difficult to achieve due to death of subjects resulting from multiple possible events (e.g., cardiovascular events, sec-

Table II. Results obtained in the 8 fields of SF-36 questionnaires.

SF-36	Mean	Average	SD	Min	Max
Physical functioning	85	76.92	± 25.35	0	100
Role limitations due to physical health	100	66.66	± 41.09	0	100
Pain	74	72.76	± 27.18	0	100
General health	61	60.48	± 17.85	25	100
Energy/fatigue	60	60.25	± 19.26	15	95
Social functioning	75	72.23	± 24.87	0	100
Role limitations due to emotional problems	100	67.46	± 43.62	0	100
Emotional well-being	72	69.53	± 19.15	28	100

ondary tumour development). Our case series confirms this trend, as two-thirds of patients died before our retrospective evaluation, which makes assessment of the real impacts of these procedures on patient survival and the effectiveness of reconstructive surgery in terms of QOL extremely difficult. Moreover, recruitment of survivors introduces selection bias because this group likely includes only those with the highest performance status, partially affecting comparison with the general population of the same age. This bias was further increased in our series because we considered only patients who were candidates for free-flap surgery, resulting in the exclusion of those in worst general condition at the time of treatment.

No consensus has been reached in the international literature on the official definition of “elderly”, with various cut-off ages used in different studies¹⁵⁻¹⁷. However, 75-80 years of age is considered worldwide to be a well-defined landmark, probably because the percentage of comorbidities and general performance status are more constant in individuals who have reached this age range than in the younger population, in which these parameters can markedly differ among patients of the same age and are usually considered the most important criteria in patient evaluation.

All of these findings underline the difficulty of dealing with this specific group of patients and partially explain the relative paucity of papers with a large series of elderly patients¹⁸. Our inclusion criteria were thus quite broad, and the data were not stratified based on surgical site or adjuvant treatment. This approach was taken in part due to the small sample, and in part based on our goal of examining the impact of free-flap surgery in these subjects. We believe that it was adequate for the examination of patients in this cohort.

Few studies have focused on QOL in these elderly subjects, probably due to the difficulty of analyses. A multicentric study design is mandatory to achieve a sufficiently large study cohort for such analyses. Although its importance is often underestimated, long-term QOL is of ex-

treme relevance in analyses of surgical results because it represents a final assessment of treatment; thus, it should be considered a real outcome to measure¹⁹, particularly for patients with relatively short remaining life expectancies, such as octogenarians. The intent is to assess whether major surgical procedures, usually considered the best reconstructive options in the general population²⁰, are justified by the achievement of satisfactory QOL, or whether possible associated risks and shortcomings^{21,22}, which can lead to impairment and other consequences that compromise final outcomes, outweigh potential benefits.

QOL should be assessed through analyses of daily life activities and functions, and questionnaires are considered among the best methods by which to investigate this parameter^{23,24}. When results from the general population are available, comparison with cohort data can further improve the value of the results and provide a more objective view of the scores. This consideration is the main reason that we chose to use the SF-36 and SF-12. Our choice was also made with consideration of the availability of the questionnaire in patients' native language and its international validation¹². The results of this study are quite encouraging, particularly in consideration of physical impairment; the mean general physical function was 76.92/100, and pain (72.76/100) was not an issue for our patients. Energy/fatigue and general health were the most relevant problems, with scores of 60.25 and 60.48/100, respectively, but these factors are probably those most biased by the age of the subjects. SF-12 scores were comparable with those of the general population; the PCS score was slightly better than that of the control group, and the MCS score was basically the same as that from the general population. Considering the selection of the “healthiest” subjects based on the indication for free-flap procedures, this analysis showed that free-flap reconstruction does not worsen the quality of residual life in elderly patients. These findings, together with those from the literature, confirm that free-flap success rates and complications in this population are comparable to those in

younger patients, which should help surgeons in surgical planning, reducing concerns about elderly patients' post-surgical daily lives.

Conclusions

Our data support the indication for free-flap reconstruction of head and neck defects in the elderly population. In particular, the quality of residual life seems to be comparable to that in the general population of the same age. Further studies should be conducted to assess whether the high mortality rate is related only to general age-related risks, or whether major surgical procedures play a contributing role.

Conflict of interest statement

None declared.

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HEAD AND NECK

Comparative intraindividual ablative tissue effects of diode laser 980 nm versus radiofrequency in tonsillar hypertrophy management

Effetti tissutali ablativi intraindividuali comparabili del laser diodo 980 nm rispetto alla radiofrequenza nella gestione dell'ipertrofia tonsillare

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SUMMARY

Tonsillotomy (tonsillar ablation) using diode laser and radiofrequency has been introduced for management of tonsillar hypertrophy as it is associated with fewer hazards to deep structures. We compared tissue volume and histological changes in the tonsils following radiofrequency tonsillotomy versus diode laser tonsillotomy in tonsillar hypertrophy. 40 tonsils excised from 20 patients were included in this study. Twenty tonsils were subjected to radiofrequency tonsillotomy (RFT) group 1, and the other 20 tonsils were subjected to diode laser 980 nm tonsillotomy (DLT) group 2. Both procedures were followed by cold dissection tonsillectomy for macroscopic and histological examination of tonsils. Tonsillar volume reduction was evident in both groups with a non-significant difference between groups. Histological changes were evident in both groups. In our study, both radiofrequency and diode laser were effective in tonsillar ablation in terms of volume reduction and keeping the histological pattern intact.

KEY WORDS: Hypertrophic tonsils • Tonsillotomy • Diode laser • Radiofrequency • Histological examination

RIASSUNTO

La tonsillotomia (ablazione tonsillare) usando il laser a diodi e le radiofrequenze è stata introdotta nel trattamento dell'ipertrofia tonsillare per ridurre i rischi di complicanze a carico delle strutture profonde. Questo studio si propone di paragonare il volume tissutale e le modificazioni istologiche provocate nella tonsilla ipertrofica rispettivamente dalla ablazione tonsillare con radiofrequenza e da quella con laser. Abbiamo analizzato 40 tonsille escisse a 20 pazienti. Venti tonsille (gruppo 1) sono state escisse mediante radiofrequenza (RFT), le altre venti (gruppo 2) mediante laser a diodi 980 nm (DLT). Entrambe le procedure sono state seguite da dissezione fredda della tonsilla per esame macroscopico e istologico della stessa. La riduzione del volume tonsillare è stata evidente in entrambi i gruppi con una differenza non significativa fra i due. Le modificazioni istologiche erano evidenti in entrambi i gruppi. Nel nostro studio, sia la radiofrequenza che il laser a diodi consentono di eseguire una efficace ablazione tonsillare, mantenendo intatto il pattern istologico.

PAROLE CHIAVE: Tonsille ipertrofiche • Tonsillotomia • Laser a diodi • Radiofrequenza • Esame istologico

Introduction

Tonsils are aggregates of lymphoid tissue that play a large role in immunology and defense mechanisms, and especially in IgA production ¹. Tonsillectomy is performed for diverse indications including recurrent episodes of acute tonsillitis (the most common), in addition to tonsillar hypertrophy causing obstructive sleep apnoea syndrome ². The traditional technique of “cold” dissection was introduced about 100 years ago. Since then, many different techniques have been introduced to speed up the operation, keep intraoperative bleeding to a minimum

and reduce postoperative morbidity ^{3,4}. Besides the risk of haemorrhage, postoperative pain represents a major issue in tonsillectomised patients due to disruption of mucosa and glossopharyngeal and/or vagal nerve fibers with consecutive inflammation and spasm of pharyngeal muscles leading to ischaemia and a protracted cycle of pain ⁵. As extensively studied by Hultcrantz et al. ⁶, risk of haemorrhage, postoperative pain and morbidity were significantly reduced, as well as accelerated recovery, when tonsillotomy was performed rather than tonsillectomy. It has been reported that in the case of laser tonsillotomy,

the tonsils are merely reduced in size and maintain their function as an immunocompetent lymphoid tissue, and also reduce the risk of bleeding, postoperative pain and morbidity ⁷.

Different types of lasers have been used in tonsillotomy and tonsillectomy such as KTP, carbon dioxide and NDYAG ^{8,9}. The diode laser has a potent thermal perifocal effect in tissues and a shallow penetration depth, and is associated with fewer hazards to deep structures. Diode laser tonsillar surgery is thus a low-complication modality with very satisfactory postoperative results ⁷.

Radiofrequency tonsillar ablation has been described in recent years and was introduced as an alternative ablative device for tonsillar hypertrophy, which has a lower tissue heating with the advantage of mucosal sparing and sufficient tissue reduction ^{10,11}.

The aim of this clinical study was to introduce diode laser 980 nm as a tonsillar ablative tool and assess the volume reduction and histological outcomes compared to radiofrequency tonsillar ablation.

Materials and methods

This study was designed to examine volume reduction and histological changes in 40 tonsils excised from 20 patients between 8 and 16 years old, after being subjected to tonsillotomy. Each patient was subjected to radiofrequency tonsillar ablation on one side (group 1) and diode laser 980 nm tonsillar ablation on the other side (group 2) in order to minimise problems caused by interindividual variation. The tonsils were removed by cold dissection tonsillectomy and the procedure was performed by the same surgeon.

Inclusion criteria included patients with chronic hypertrophic tonsils and obstructive tonsillar hypertrophy with sleep apnoea that was accurately diagnosed to exclude other causes of apnoea. Inclusion criteria also met the American Academy of Otolaryngology guidelines for tonsillectomy. Tonsillotomy followed by tonsillectomy was imposed in these patients as a therapeutic necessity. Exclusion criteria were cases of unilateral tonsillar hypertrophy suspicious of neoplasms, and general contraindications for tonsillectomy such as bleeding tendency.

The local ethics committee approved the study protocol and written informed consent was obtained from parents of all children enrolled in the study.

A research assistant discussed participation requirements and completed eligibility assessment and the consent process.

All procedures were performed under general anaesthesia using the same anaesthetic and surgical technique. The standard and general safety precautions while using the

laser were taken into consideration to avoid injury to the endotracheal tube and included placement of a 4 cm wide soaked saline packing around the tube. Medical personnel wore safety goggles for the appropriate wavelength and irradiation.

In radiofrequency tonsillotomy (ablation) the surgical procedure was started by using a radiofrequency surgical device (Dr. Oppel ST-501, Korea) spectrum of 4 mHz; a single RF electrode (tip exposure, 2 cm) (Fig. 1) was inserted interstitially at 5 points in the tonsil. The RF patient plate was placed in contact with the patient's body, and at a power of 10 watts and continuous mode for 30 sec, the energy was delivered with a total of 1500 joule per tonsil during the procedure.

Diode laser interstitial tonsillotomy (ablation) was performed using a Boyle Davis mouth gag and a 980 nm wavelength diode laser (Quanta, Solbiate Olona, Italy), and pulses were delivered using a bare optical fibre (320 µm) (Fig. 2). The procedure was performed by inserting the optical fibre about 2 cm interstitially in the tonsil and delivering laser pulses into five adjacent, non-overlapping spots, avoiding injury to the tonsillar bed. A continuous 10-watt power mode was used for 30 sec at 300 J/cm². The total energy delivered was 1500 joule per tonsil. The mean operative time was 4 min per tonsil.

After both procedures ended, the tonsils were excised by cold instrumental dissection to allow macroscopic examination of the tonsils to detect any gross changes (volume measurements, features), and histological examination of the tonsils followed both procedures.

Adequate gross dissection and sampling of tonsillar tissue at 3 mm thickness were done. Tissue sections were fixed for 24 hours in 10% neutral buffered formalin then dehy-



Fig. 1. Radiofrequency tonsillotomy surgical procedure.

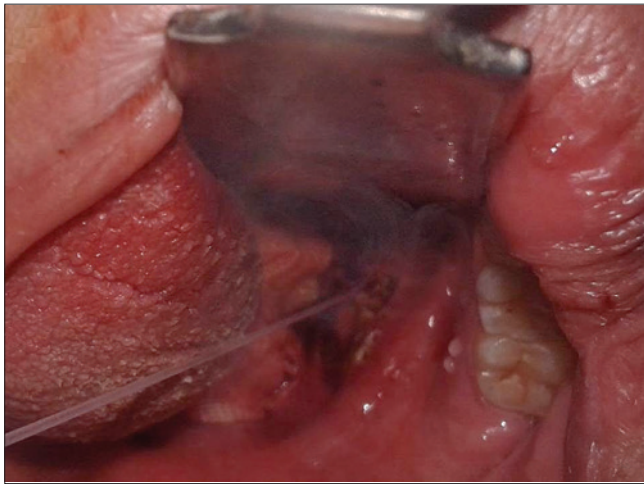


Fig. 2. Diode laser interstitial tonsillotomy surgical procedure.

drated, cleared and embedded in paraffin wax according to routine processing procedures. The paraffin wax blocks were cut in 5 μ m sections and stained with haematoxylin and eosin for histopathological examination.

Statistical analysis

Data collected processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantitative data expressed as means \pm SD, while qualitative data was expressed as numbers and percentages. Student's *t* test used to test the significance of difference for quantitative variables that follow a normal distribution.

Results

We conducted this study on two tonsillotomy groups: radiofrequency (group 1) and diode laser 980 nm (group 2). The mean age of patients was 14 ± 7 years. Of the 20 patients, 18 (90%) underwent adenotonsillectomy surgery. It is noteworthy that bleeding during ablation and dissection of the tonsils was minimal in group 2 in comparison with group 1 since the diode laser is a better coagulator than radiofrequency. Also, postoperative pain perception was at the level expected after cold steel tonsillectomy. All patients were given postoperative medications and recovered normal activity after one week to 10 days.

Concerning histological analysis in group 1 (RFT), the specimens showed widespread starting necrotic foci in the form of pyknosis, karyorrhectic debris and karyolysis (faint dissolved nuclei) of cells in tonsillar tissue, and vacuolar degeneration of the tonsillar epithelium was also seen. The architecture of the lymphoid germinal centres was normal as well as the extent and type of vascularisation (Fig 3).

The histological picture of group 2 (DLT) specimens showed mild focal necrotic changes; areas of charring surrounded by zones of congestion were evident grossly (Fig. 4) and microscopically (Fig. 5). The tonsillar epithelium preserved a normal structure of the multilayer squamous epithelium, apart from focal vacuolar degeneration of the epithelium close to points of charring and haemolysed RBCs. Submucosally, there were no other abnormalities apart from focal necrotic foci and evident vascularity close to sites of charring; the architecture of the lymphoid germinal centres was also normal as well as the extent and type of vascularisation (Fig. 5).

The volume of the tonsils was calculated prior to surgery by transcutaneous ultrasound. Using a standard sonographic formula, the longitudinal, transverse and anteroposterior dimensions of tonsils was 0.523.

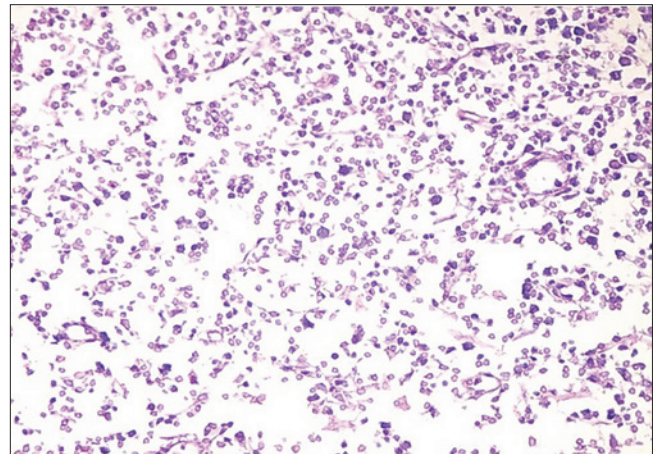


Fig. 3. Radiofrequency tonsillotomy showed karyolysis [faint dissolved nuclei] of the cells of the tonsillar tissue x200.

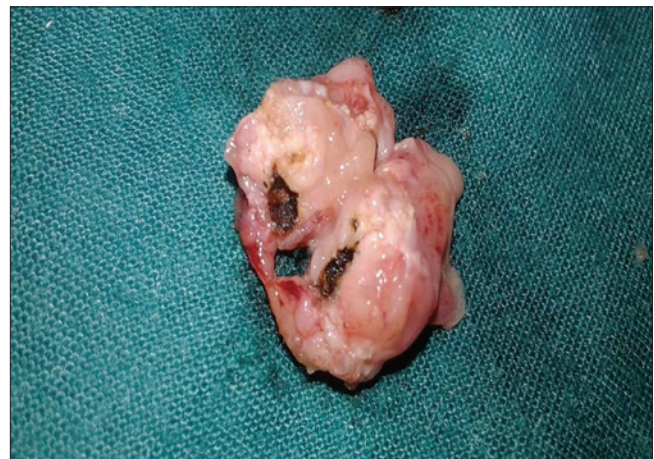


Fig. 4. Diode laser tonsillotomy showed areas of charring.

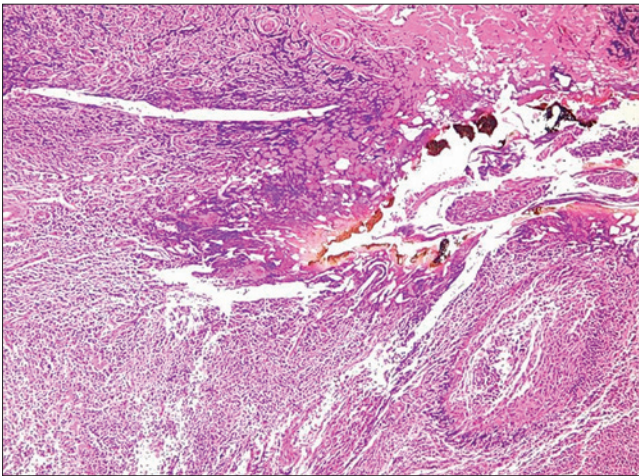


Fig. 5. Diode laser tonsillotomy showed charring and haemolysed RBCs, thermal injury of cells next to haemolysed RBCs, hyaline degeneration of tonsillar vessels (upper half of image) and degenerative changes of epithelium (lower right side) x200.

Regarding the gross picture and volume of the tonsillar specimens in group 1 (RFT), there were no superficial charring points, and the mean tonsillar preoperative volume (\pm SD) was $7.18 \text{ cm}^3 (\pm 2.94)$, while postoperatively it was $4.9 \text{ cm}^3 (\pm 3.14)$, which showed significant volume reduction.

In group 2 (DLT), the points of charring on the surface of the tonsils were evident and the mean tonsillar preoperative (\pm SD) volume was $7.36 \text{ cm}^3 (\pm 2.78)$, while postoperatively it was $4.79 \text{ cm}^3 (\pm 2.89)$, showing significant volume reduction. The results summarised in Table I show that there was no significant difference in volume reduction between the two groups.

Discussion

Tonsillectomy is still the most common operation performed in the paediatric population in order to reduce obstruction from enlarged tonsils, treat recurrent tonsillar infections, or both. There is no agreement on the ideal method for performing tonsillectomy. Various methods have been described which are frequently compared and discussed in the otolaryngology literature^{3,4,12-14}. Introduction of tonsillar ablation techniques such as radiofrequency

and laser has been used to achieve the ideal modality for management of tonsillar hypertrophy, hence avoiding both intraoperative and postoperative bleeding, besides preserving immunological function of the tonsils^{6,7,9-11}. Friedman and Ibrahim¹⁵ concluded that radiofrequency modality in tonsillar tissue volume reduction was efficient and safe with a low risk of postoperative morbidity. Terk and Levine¹⁰ reported that volume reduction of tonsillar tissue by radiofrequency energy was achieved with minimal postoperative pain, which was attributed to the avoidance of mucosal interruption, in addition to the absence of fibrosis and preservation of the histological architecture of the tonsils.

On the other hand, the near infrared diode laser 980 nm has energy and wavelength characteristics that specifically target soft tissues in addition to its affinity for haemoglobin and melanin. Due to these characteristics, it is more efficient and better equipped to address soft tissue problems¹⁶. Besides this, we adopted the 320 μm fibre optic diameter as it was the safest due to the selectivity of minor vessel coagulation and minimal damage to surrounding tissue. The energy released by the diode laser transforms into heat, resulting in immediate tissue vaporisation¹⁷. The long wavelength of the diode laser furnishes a short depth of penetration and high energy density, making it more selective to interaction with water and haemoglobin, resulting in high tissue ablation properties with good homeostasis¹⁸.

In this study, we applied a diode laser at 980 nm in tonsillar ablation, which to our knowledge has not been performed before, aiming to assess outcomes compared to the well documented efficient radiofrequency in managing tonsillar hypertrophy. The intraindividual design of this work fulfilled our goal since the same total amount of energy was delivered to the same patient either by diode laser at 980 nm or by radiofrequency, so that each patient acted as his own control, thus avoiding interindividual variation such as pain perception and bleeding tendency. In our study, both groups, RFT group (1), and DLT group (2) showed a significant volume reduction of tonsils after ablation procedures, which were 31.6% and 34.9%, respectively. However, there was no significant difference between groups.

Table I. Comparison of tonsillar volume before and after operation in the two groups.

Tonsillar volume (ml)	Before operation		After operation		T test	P value
	Mean	\pm SD	Mean	\pm SD		
RFT (group 1)	7.18	2.94	4.91	3.14	2.17	0.033*
DLT (group 2)	7.36	2.78	4.79	2.89	2.41	0.025*

* Statistically significant; RFT: Radiofrequency tonsillectomy; DLT: Diode laser tonsillectomy

Terk and Levine¹⁰ reported that using radiofrequency with a power setting (2 watt) an insufficient tissue volume reduction was recorded, which they attributed to the low power setting. They concluded that energy application at a higher power setting would have affected tonsillar tissue volume reduction more. On the other hand, Nelson¹¹⁻¹⁹ reported a 30% to 60% reduction in tonsillar size depending on the energy settings applied. Regarding group 1 (RFT), our results are in agreement with the two preceding authors as 31.6% volume reduction was achieved by using 10-watt power setting.

Concerning group 2 (DLT), the comparatively greater results achieved in tissue volume reduction can be attributed to the effect of heat released by the interstitial insertion of the diode fiber into the tonsil, which resulted in faster and efficient denaturation of proteins and collagen followed by vaporisation of water molecules contained in tonsillar tissues. Our results are in accordance with Sedlmaier et al.⁷, who reported sufficient tonsillar volume reduction on applying diode laser in contact mode (812 nm, continuous wave, 13 W) for tonsillotomy, and described the procedure's effectiveness in long-term results for snoring, obstructed respiration, apnea, lack of appetite and susceptibility to infection as very good. Moreover, Havel et al.²⁰ concluded in their study that the coagulative and haemostatic effect of carbon dioxide laser might not be as efficient in well-perfused tonsillar tissue as that of the diode laser at 1470 nm.

Although there was no significant difference in volume reduction between the two groups, group 2 showed higher volume reduction which can be attributed to the fact that the coagulation and ablative effects of diode laser are better than radiofrequency since diode laser at 980 nm shows a high absorbance in water, which provides a better coupling to aqueous environments²¹.

The histological findings showed that the tissue damage due to radiofrequency surgery was less than that due to the diode laser, which is likely to occur since radiofrequency would cause an increase in tissue temperature to a maximum of 80°C²² compared to more than 300°C using a diode laser²³. This was manifested by areas of charring surrounded by zones of congestion both grossly and microscopically in group.

The mucosa of the tonsillar bed showed no abnormal gross changes in either ablation procedure because both were applied interstitially. Tonsillectomy was performed immediately after the ablation procedure and excised tonsils were subsequently subjected to macroscopic examination and prepared for histological study. Otherwise, if there was time delay between tonsillotomy and tonsillectomy, the results would have differed.

Conclusions

In obstructive tonsillar hypertrophy, tonsillotomy is often preferred over tonsillectomy due to diminished postoperative pain, decreased risk of secondary bleeding and preservation of tonsillar architecture. In our study, both radiofrequency and diode laser at 980 nm were effective in tonsillar ablation with better volume reduction and less intra- and postoperative bleeding with the latter. As both techniques were submucosal, the lymphoid germinal centres were kept intact as well as the extent and type of vascularisation, thus preserving the immunological function of the tonsils. Hence, both procedures can be beneficial in management of tonsillar hypertrophy.

Conflict of interest statement

None declared.

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HEAD AND NECK

Repeatedly recurring pleomorphic adenoma: a therapeutic challenge

Adenoma pleomorfo plurirecidivante: una sfida terapeutica

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SUMMARY

Pleomorphic adenoma (PA) is the most common tumour of the salivary glands, and can recur even after proper surgery. The extent and timing of surgery for recurrent tumours remains controversial, and multiple recurrences pose a special challenge. We evaluated all recurrent PAs (RPAs) treated at the Helsinki University Hospital through 2004-2013 focusing on patients with multiple recurrences. Follow-up data were obtained until January 2018. Of the 47 patients, 70% were women and the median age was 33.5 years. Most of the RPAs were located in the parotid gland (87%), and six (13%) in the submandibular gland. One-third (17/47) of tumours had been primarily excised. This patient population experienced 75 recurrent events in total with two or more recurrences in 14 patients (30%). The time interval between recurrences shortened after each recurrent event and the tumour was more likely to be multifocal. At the end of the follow-up period, 15% had recurrent disease and malignant transformation had occurred in 6%. Treatment for PA and RPA is challenging and requires centralised management. Patients with RPA are often young and recurrences may cause lifelong morbidity, especially when the tumour recurs repeatedly. The utilisation and timing of postoperative radiotherapy needs to be discussed as well as the potential risk for malignant transformation in this patient population.

KEY WORDS: Salivary gland • Pleomorphic adenoma • Adenoma • Treatment • Outcome

RIASSUNTO

L'adenoma pleomorfo è il tumore più frequente delle ghiandole salivari. È caratterizzato da un elevato rischio di recidiva anche dopo un'accurata chirurgia. L'estensione ed il corretto timing della chirurgia è controverso soprattutto nei casi di tumori plurirecidivanti. In questo lavoro abbiamo valutato tutti i casi di adenoma pleomorfo plurirecidivante (RPAs) trattati presso l'Helsinki University Hospital dal 2004 al 2013. I dati di follow-up sono stati raccolti sino al gennaio 2018. Dei 47 pazienti considerati, 70% erano donne con un'età media di 33,5 anni. La maggior parte dei RPAs erano localizzati a livello della ghiandola parotide (87%), sei (13%) a livello delle ghiandole sottomandibolari. Un terzo (17/47) dei tumori sono stati rimossi chirurgicamente. All'interno di questa popolazione di pazienti sono stati documentati 75 eventi di recidiva di malattia, 14 pazienti (30%) hanno avuto 2 o più recidive. L'intervallo di tempo intercorso fra le singole recidive si è gradualmente accorciato con un incremento progressivo del rischio che il tumore si ripresentasse a livello multifocale. Al termine del periodo di follow up, 15% dei pazienti hanno avuto recidiva di malattia, nel 6% si è verificata la degenerazione maligna del tumore. Il trattamento dell'adenoma pleomorfo plurirecidivante rappresenta una sfida terapeutica e richiede un management centralizzato. I pazienti affetti da RPA sono spesso di giovane età, il trattamento delle forme plurirecidivanti è gravato da un'elevata morbidità negli anni. L'impiego ed il timing di un'eventuale radioterapia post operatoria nonché il rischio di degenerazione maligna sono parametri da prendere in considerazione per una corretta gestione multidisciplinare dei RPA.

PAROLE CHIAVE: Ghiandole salivari • Adenoma pleomorfo • Adenoma • Trattamento • Risultati

Introduction

Pleomorphic adenoma (PA) is the most common tumour of the salivary glands with an incidence rate between 4.2-4.9/100,000 person-years^{1,2}. Recurrences occur despite proper surgery. Treatment of recurrent PA (RPA) remains a challenge, and some tumours may even be incurable. The occurrence of satellite nodules and pseudopodia of PA may

occur due to incomplete capsule of the tumour³, which may lead to residual disease, especially after limited surgery such as enucleation. Rupture of the capsule results in spillage of tumour cells and increases the risk for recurrences 14- to 21-fold^{4,5}. Also, positive surgical margins increase the risk of recurrence, but in these circumstances the term residual disease instead of recurrence may be more accurate. In close proximity of a tumour of the parotid gland to the facial nerve

(FN), the tumour needs to be dissected extracapsularly⁶, which may result in recurrences even after proper superficial parotidectomy (SP). Since not all tumours with rupture of the tumour capsule recur, and some recur after adequate surgery, the causes for RPA seem multifactorial.

Some studies report that age^{7,8} and gender⁸ have an influence on the potential of PA to recur, but others show no influence^{4,5,9}. Controversies exist between the risk for RPA and cellular composition of PA primarily. The most likely reasons for RPA to date are rupture of the capsule leading to tumour spillage and positive surgical margins⁴, although as pointed by Colella et al.¹⁰, studies supporting this conception are limited. The abandonment of enucleation and preferring more extended surgery seem to have led to a dramatically decreased recurrence rate of PA from up to 45% to as low as 1%^{5,6,10}. Favouring extracapsular dissection (ECD) nowadays in parotid PA over routine SP does not result in a higher recurrence rate^{6,10}, but does minimise the risk for FN dysfunction and other complications¹¹. Furthermore, a recent meta-analysis on parotid PAs reported that the recurrence rate after ECD was half that after SP in experienced hands¹⁰. The aim of the present study was to evaluate RPA treated at our institution over a 10-year period. We report the treatment and outcome of 47 consecutive patients and discuss the reasons for recurrences and treatment of RPA with special focus on multiple recurrences.

Patients and methods

Patients with any recurrence of PA diagnosed at the Helsinki University Hospital between January 1, 2004 and January 1, 2014 were included. We collected information on patient demographics, clinical history, diagnostics, clinical and pathological features of tumours, recurrences and their treatment, FN function and follow-up data. To gather further follow-up data after diagnosis of RPA, all events until January 2018 were recorded. This study was approved by the institutional Research Ethics Board (192/13/03/02/16) and study permission was granted.

During the study inclusion period, 47 patients with RPA were diagnosed. During the same period, 796 patients were operated for a benign salivary gland PA, including the RPAs, at our institution.

We included also RPA with malignant changes, i.e. CX-PA. An additional search revealed 14 patients with CXPA during the period, but only one had presented with a previously treated PA.

Results

Of the 47 patients, 33 were women (70%) and 14 were

men (30%). The median age at time of diagnosis of the primary tumour was 33.5 years (range, 10-65). Most of the tumours were located in the parotid gland (n = 41; 87%), and six (13%) in the submandibular gland. We found no RPAs of the minor salivary glands. Altogether, 75 recurrent events occurred in this patient population. Of all patients, 33 had one recurrence, seven had two, four had three, one had four, one had five and one patient experienced seven recurrences. In 41 patients, the primary surgery had been carried out before the study inclusion period (January 1, 2004) (Fig. 1). Of the recurrent events, 12 occurred before this date, and further recurrences after the study inclusion period were diagnosed in two patients.

Primary tumours and treatment

The initial treatment of the primary tumours was performed during 1969-2009 by various head and neck surgeons. In 23 cases, treatment had been executed at other institutions, even some in other countries (n = 4), limiting available information on the initial phase of treatment.

Of the 41 parotid gland tumours, 38 were initially located in the superficial lobe, two in the deep lobe and one was extended to both lobes. Surgery of parotid gland tumours consisted of removal of the tumour only in 15 patients, superficial or partial parotidectomy in 22 patients and total parotidectomy in three patients. In one patient, surgical data remained unavailable. Of the six patients with a submandibular gland tumour, four had had removal of the gland with the tumour, and two had had limited surgery with a purpose of tumour removal only.

Rupture of the tumour capsule and direct spillage of tumour cells was reported in eight (17%) patients. None of the primary tumours were multifocal.

First recurrence

The median time between primary treatment of the tumour and first recurrence was 10.3 years (mean, 13.3; range, 1.3-39.4). All except one of the 47 patients underwent surgery for the first recurrence. Surgery for 40 parotid gland RPAs consisted of resection of single adenomas in 18 patients (45%), partial or superficial parotidectomy in 15 patients (38%), total parotidectomy in six (15%) and radical surgery in one patient (3%). Surgery for submandibular gland RPA included resections of a single adenoma in two patients, or at least level I B dissection in four.

Rupture of the tumour capsule and direct spillage of tumour cells was reported in four cases (9%). In three cases surgery was non-radical, and these patients had persistent disease at the end of follow-up. On histopathological examination, positive surgical margins were reported in 19 cases (41%), and multifocal disease in 27 cases (59%).

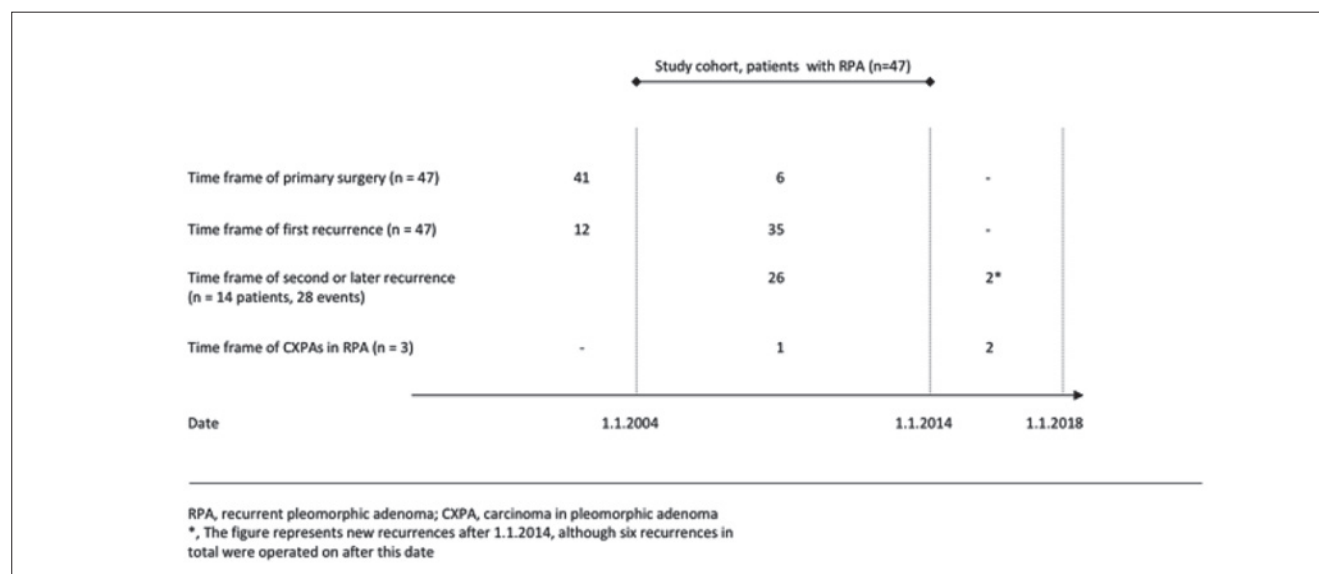


Fig. 1. Time frames of the diagnosis of the primary tumours and recurrences.

Radiotherapy (RT) with 60 Gy was administered in three patients after a benign recurrent tumour, in all after the first recurrence.

Second and later recurrences

The majority (n = 31; 70%) of the patients had a single recurrent event, whereas a second recurrence (i.e. two or more recurrent events) occurred in 14 (30%) patients. 11 (79%) emerged in the parotid gland, and three (21%) in the submandibular gland.

Of the 14 patients undergoing additional surgery for second recurrence, rupture of the tumour capsule and direct spillage of tumour cells was reported in four cases (29%). Histopathological examination revealed positive surgical margins in two patients (14%), and multifocal disease in eight cases (57%).

A third recurrence (i.e. three or more recurrent events) was observed in seven patients (15%), six in the parotid gland and one in the submandibular gland. The recurrence was multifocal in five of these patients (71%). Further recurrences occurred in three patients. Their surgery included excision of single adenomas.

The time interval between recurrences shortened after each recurrent event with a median of 5.8 years (mean, 7.5; range, 1.2-20.1) between the first and the second recurrence.

At the end of the follow-up period (January 1, 2018), seven patients presented with recurrent disease: one patient who had been treated with postoperative RT presented with an unchanged parapharyngeal space recurrence within a 3-year follow up. Surgery had been non-radical in three patients with multifocal disease and they had been fol-

lowed up without further treatment. In the remaining three cases, multiple tumours after repeated recurrences had been followed up and their status had remained almost unchanged for 4-9 years.

Carcinoma ex pleomorphic adenoma

Three patients experienced a carcinoma in their recurrent tumours. In one patient, this occurred in the first recurrence 14 years after the treatment of the primary tumour. The patient had two palpable tumours, which had grown within 3-4 years, but MRI and histology revealed numerous carcinomatous lesions. In the two other patients, multifocal carcinoma was diagnosed in the third recurrent event. These appeared at 20 and 37 years after the treatment of the primary tumour (7 and 16 years after previous recurrences). Fine needle aspiration cytology (FNAC) was taken in two of these patients, and in one patient it was highly suspicious of malignancy and in the other it was slightly suspicious.

Discussion

We had 47 RPA cases, 14 of whom (30%) later experienced further recurrences. During our study period, the rate of recurrences of all PAs operated on at our institution was 6%. However, this does not reflect the true recurrence rate, as many of the tumours had initially been operated on decades ago, and at several other hospitals. Notwithstanding, our results are in line with Valstar et al.¹ and Colella et al.¹⁰. The latter meta-analysis reported the recurrence rate to vary according to the type of surgery from 1-8%. Women were more often affected in the present study, and

this has also been shown by others^{1 2 12 13}. Andreasen et al.² reported in a national study a median age for PA to be over 50 years, and showed a tendency for younger age among patients who experienced recurrences. This tendency was also obvious in the current study.

We and others nowadays favour MRI as the preferred imaging method in RPA¹⁴. It is superior in detecting multinodularity, but the smallest nodules still remain undetectable¹⁴. In our series, MRI was used rarely in superficial lesions. Instead, ultrasound (US) and US-guided FNAC was used in many cases. The sensitivity of FNAC for detecting salivary gland neoplasms is generally around 83%¹⁵, and even higher for PA^{16 17}, and was 67% in the present study (data not shown). Heaton et al.¹⁶ have shown that FNAC combined with MRI can offer highly confident preoperative diagnosis of PA¹⁶. Of note, Zbären et al.¹⁸ reported that the sensitivity of FNAC to detect CXPA was only 47%, and the malignancy of PA was known preoperatively in only 42% of cases. Therefore, FNAC does not seem to be adequate in defining the eventual malignant nature of a recurrent tumour. In our series, FNAC indicated malignancy correctly, but was obtained in only two of three CXPAs.

Basically, despite the surgical method, all techniques for superficial parotid PA expose the tumour capsule focally⁶. A meta-analysis shows that a rupture of the capsule of the primary tumour and tumour spillage are strongly associated with recurrence⁶. However, rupture of a capsule does not always lead to recurrence, and several reports have shown no association of tumour cell seeding with recurrences^{6 13 19}. Dell'Aversana et al.²⁰ showed that favouring ECD in superficial parotid gland tumours instead of SP seems to decrease possible postoperative complications, but may carry a higher risk for rupture of the capsule and an increase in recurrences, although not all support this conception⁶. In our cohort, surgery for the primary tumour included removal of the tumour only in 36% of cases. Knowledge of tumour biology and education of the appropriate treatment are vital.

In our cohort, tumour spillage after rupture of the capsule of the primary tumour was known only infrequently. Obviously, a structured surgical and histopathological worksheet should be outlined to complete clinically relevant tumour characteristics and possible complications during surgery. The primary treatment of PA should therefore be carefully planned, executed and centralised in experienced centres. Valstar et al.¹ showed that positive resection margins increased the risk for recurrence over four-fold, and Espinosa et al.¹³ reported the risk to be even 49 times higher.

Incomplete capsule, capsule penetration, pseudopodia, or

satellite tumours are common in PA. Zbären and Stauffer¹² reported these features to be present in 73% of a cohort of 218 tumours. Satellite nodules increase the risk for RPA, as they are observed in 60% of RPAs compared to 10% in non-recurrent tumours⁴. Thus, negative surgical margins do not guarantee successful surgery in terms of tumour recurrence²¹. Satellite nodules seem to be more common in tumours over 4 cm^{4 22 23}, as they are observed in 33% of such tumours compared to 6-10% in those smaller than 4 cm²². We had only two (12%) tumours that were over 4 cm. Delays in treatment may also increase the size of the recurrent tumour and thus increase treatment-related complications²⁴. Some studies show that the myxoid histologic subtype of PA with incomplete encapsulation has a higher risk for RPA^{12 23} and some show no significance of the cellular subtype^{4 13}, while another study indicated that the risk appears to be higher in hypercellular tumours⁷. Multinodular tumours and tumours with local excision only are more likely to recur repeatedly⁹. Redaelli de Zinis et al.⁹ reported an overall recurrence rate of 33% for second recurrences, reflecting our results (32%). None of their patients with a parotid RPA with a single node recurred. They found that patients with multiple nodules who did not undergo at least SP were at higher risk to recur. In our cohort, after every recurrence, the tumour was more often multifocal and thus complicating the surgical treatment. Thus, limited surgery consisting of resection of single nodules was more often executed in the second recurrence.

Additional surgery for RPA increases the risk for FN paralysis^{8 14}. This was also obvious in our patient cohort, but comprehensive data were difficult to extract retrospectively from hospital records. A recent prospective study assessing the complications of parotid gland surgery reported immediate postoperative FN paralysis in 40% of patients when the slightest changes were taken into account²⁵, although nerve monitoring and the use of microscope decrease the risk²⁶. A review by Witt et al.¹⁴ revealed that after surgery of a parotid gland RPA, temporary FN injury occurred in 90-100%, and permanent FN injury in 11-40% of cases. This highlights the importance of adequate treatment of RPA in the first recurrent event. Postoperative RT should be discussed in cases of PA with negative prognostic factors²⁷. In some cases RT is an option to preserve FN function²⁸, and some have administered RT for PA with close or positive surgical margins^{29 30} with good local control. Witt et al.¹⁴ summarised local tumour control after postoperative RT and it seems that RT improves treatment outcomes in patients with multinodular tumours with several recurrences. RT should be administered after surgery: Douglas et al.³¹

reported postoperative RT to result in a 100% 15-year locoregional control among patients with microscopic disease compared to 76% for patients with macroscopic disease. Many studies included only a few patients who received RT. Conclusions on indications of RT are thus hard to outline. Furthermore, it is unclear after which recurrent event is RT beneficial and should be recommended. Also, since patients usually present tumours at an early age, the side effects of RT need to be considered, and whether RT can induce the growth of other nodules in the future. We had only three patients who received RT for benign RPA. Furthermore, half of the patients who had a second recurrence developed further recurrences, and even malignancy. Thus, we might speculate that more extensive utilisation of postoperative RT could have deferred further recurrences. Based on the results from our series and the current literature, postoperative RT seems warranted in multifocal recurrent disease and in patients for whom additional surgery would most likely cause significant morbidity. We had several patients who had been followed up after detection of repeated recurrence. Among these, additional surgery was considered impossible without sacrifice of the facial nerve, and RT was not optimal because of macroscopic disease. It is noteworthy that even 6% of patients in our series developed CXPA and patients in follow-up are still in high risk of developing a malignancy. This clinical dilemma supports administration of postoperative RT for RPA.

The majority of CXPA are diagnosed as de novo cases^{2,18}, although PA may undergo malignant transformation with an increased risk over time¹⁴. If PA is left untreated, recent studies show that the risk for malignant transformation is generally considered to be around 1.1-1.7%^{1,2}. RPA gains potential for malignant transformation after repeated recurrences^{14,21}. On the other hand, 12% of CXPA have been shown in patients with a previous operation for PA, and the rate of malignant transformation in RPA has been reported around 3-4%³², reflecting the results of the present study. As Suh et al.²¹ show, younger patients are at higher risk for developing recurrences and therefore malignancies in the future.

The causes which lead to subsequent recurrences occur most likely at the time of the primary surgery²⁷, but the subsequent recurrences become clinically evident later. Therefore, we can contemplate that treatment of RPA had been inadequate in several cases. The mean time interval from the treatment of the primary tumour to diagnosis of first recurrence was as long as 12 years in the present study. Another study also reported that tumours commonly recur more than 10 years after initial surgery¹⁹. Zbären et al.⁷ reported a mean nine-year interval between the first

and second recurrence, reflecting the mean 7.5-year interval in the present study, but a recent study reported a much shorter interval of two years¹. The time interval between recurrences in our cohort, however, shortened after every recurrence, as reported in another study²¹. We can speculate whether a follow-up period instead of immediate surgery after detection of RPA would be warranted. This could reveal whether there will appear several additional lesions since MRI fails to show all small nodules. Thus, the extent of surgery could be planned more adequately to avoid multiple surgeries. Significant morbidity after additional surgery probably limits the desire to proceed with more radical surgery among young patients.

Conclusions

Treatment for PA, and especially RPA, is challenging, and surgery of salivary gland tumours thus needs to be centralised. Patients with RPA are often young and recurrences may cause lifelong morbidity, especially in cases with multiple recurrences. Thus, in some cases, follow-up instead of additional surgery might be an option. The role of RT in the management of RPA needs consideration as the risk for malignant transformation is significant. Future research is required to develop new follow-up methods and management options for RPA in order to avoid further recurrences.

Conflict of interest statement

None declared.

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LARYNGOLOGY

Voice prosthesis rehabilitation after total laryngectomy: are satisfaction and quality of life maintained over time?

Riabilitazione vocale mediante protesi fonatoria dopo laringectomia totale: soddisfazione e qualità di vita sono mantenute nel tempo?

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SUMMARY

Total laryngectomy is the standard of care for advanced laryngeal/hypopharyngeal cancer. Effective voice rehabilitation is mandatory and tracheo-oesophageal speech (TES) has progressively gained approval. In 2011, we evaluated quality of life (QoL) and satisfaction after TES rehabilitation, demonstrating its efficacy in highly motivated subjects. The aim of the present study was to investigate whether those results are maintained over time within the same selected cohort. 15 of 24 patients were left with a minimum 12 year-follow up after voice prosthesis (VP) implantation. Short Form 36-Item Health Survey (SF-36) for QoL assessment and a study-specific structured questionnaire for evaluation of TES-related satisfaction were employed. The 9/24 patients who dropped out from the follow-up were excluded from the original count and the former results were recalculated. A control group of subjects with minor ENT diseases was used for SF-36 analysis. Many SF-36 items (RP, BP, SF, RE) significantly improved over time, approaching the results of the control group. VP duration also increased (6.3 ± 3.1 against 3.0 ± 1.8 months). TES-related satisfaction items did not change in a statistically significant way. Three patients (20.0%) would not have chosen the same kind of voice restoration: these subjects are those more distant from our institution (230 km and 462 km, respectively, against a mean distance of 15.4 ± 13.8 km for other patients). With the present work, we highlight how the striking results of TES can not only be maintained over time (i.e. TES-related satisfaction), but also substantially improve (i.e. QoL). An integrated, widespread network of centres for VP management is needed to optimise patient follow-up and allow studies on larger series.

KEY WORDS: Total laryngectomy • Voice prosthesis • Voice rehabilitation • Tracheo-oesophageal speech

RIASSUNTO

La laringectomia totale è ancora oggi gold standard terapeutico per molti carcinomi ipofaringeo-laringei in stadio avanzato. Una corretta riabilitazione vocale postoperatoria è indispensabile e la voce tracheo-esofagea (VTE) ha progressivamente raccolto consensi crescenti in quest'ambito. Abbiamo in precedenza (2011) valutato la qualità di vita (QoL) e la soddisfazione riguardante la riabilitazione mediante VTE, dimostrando la sua efficacia in soggetti altamente motivati. Scopo del presente lavoro è di indagare se tali risultati siano mantenuti nel tempo all'interno della medesima coorte di pazienti. Dei 24 soggetti originari solo 15 rimangono ad oggi intervistabili, con un follow-up minimo di almeno 12 anni dopo il posizionamento della protesi fonatoria (PF). La QoL è stata indagata mediante Short Form 36 (SF-36) mentre la soddisfazione associata alla riabilitazione con VTE attraverso un questionario specifico ad essa dedicato. I risultati concernenti i 9 pazienti usciti dalla coorte originaria sono stati esclusi dal computo iniziale e lo stesso ricalcolato per evitare "selection bias". Per quel che concerne l'analisi con SF-36, è stato utilizzato un gruppo di controllo costituito da soggetti afferenti al nostro istituto per problematiche ORL minori. Molti item della valutazione SF-36 (RP, BP, SF, RE) sono incrementati significativamente nel tempo, approssimandosi ai risultati del gruppo di controllo. Anche la durata media delle singole PF è cresciuta negli anni ($6,3 \pm 3,1$ mesi contro $3,0 \pm 1,8$). Al contrario gli item associati all'analisi della soddisfazione correlata alla riabilitazione mediante VTE non si sono modificati in misura statisticamente significativa. Tre pazienti (20,0%), inoltre, non sceglierebbero di nuovo tale tipologia di riabilitazione vocale: questi soggetti sono anche i più distanti dal nostro ospedale (230 e 462 km, contro una distanza media di $15,4 \pm 13,8$ km negli altri pazienti). Il presente lavoro rileva come i risultati positivi della riabilitazione vocale mediante VTE possano non solo mantenersi nel tempo (i.e. soddisfazione), ma anche migliorare sensibilmente (i.e. QoL). Si rende tuttavia necessaria la creazione di un network integrato di centri deputati alla gestione delle PF per ottimizzare il follow-up dei pazienti e consentire valutazioni cliniche su più larga scala.

PAROLE CHIAVE: Laringectomia totale • Protesi fonatorie • Riabilitazione vocale • Voce tracheo-esofagea

Introduction

Laryngeal carcinoma accounts for about 130,000 new cases per year worldwide with 80,000 deaths annually¹. Hypopharyngeal carcinoma with laryngeal extension is generally less frequent, although its prognosis is usually worse². When diagnosed at an early stage, the disease is amenable for organ-preservation surgery or radiation therapy alone, with excellent oncological outcomes and good functional results³. However, in more advanced stages, especially in case of invasion of the laryngeal cartilaginous framework, total laryngectomy (TL) remains essential to achieve satisfying loco-regional control. Concurrent chemo-radiotherapy (CRT) may still represent a valid alternative in patients whose local and general conditions allow this approach⁴. Whatever organ-preservation protocol is adopted firstly, TL can be taken into account as salvage treatment in case of local persistence/failure⁵.

Despite ensuring good oncological outcome in many loco-regionally advanced cases, TL is associated with substantial physical and psychological sequelae, affecting basic life functions such as breathing, swallowing and oral communication. Permanent tracheostomy and loss of natural voice worsen patients' quality of life (QoL), resulting in social stigma and consequent psychological discomfort⁶. Even dysphagia, changes in taste and smell, neck or shoulder dysfunctions can play a role in increasing postoperative disability⁶.

Although speech alteration is not the only factor reducing patients' QoL after TL, it is usually perceived as a major contributor: significant issues in dealing with strangers and also relatives are reported⁷. Therefore, rapid and effective voice rehabilitation becomes crucial to help patients coping with their new condition. To date, available solutions are oesophageal speech (ES), electro-larynx (EL) and tracheo-oesophageal speech (TES)⁸. The latter can be performed at the same time of TL (primary tracheo-oesophageal puncture - TEP) or as a second-stage procedure (delayed or secondary TEP). There are no substantial differences in voice rehabilitation efficacy between these two approaches^{9,10}. Furthermore, primary TEP does not seem to increase peri-procedural complication rates¹¹, even in the setting of a salvage TL with vascularised free-tissue reconstruction¹²; thus, it is nowadays considered as first choice, whenever feasible¹³. Secondary TEP may be preferred when extensive pharyngeal resections are required, since the risk of fistula formation is very high in these settings¹⁴, or to test the patients' real commitment to TES¹⁵. Regardless of when TEP is performed, TES has gradually become the gold standard for voice restoration after TL over ES and EL^{13,16,17}.

We have previously performed a study assessing QoL and

degree of satisfaction in TL patients after VP rehabilitation, demonstrating its good efficacy in highly motivated subjects¹⁸. The aim of the present work is to investigate whether this satisfaction is maintained over time within the same selected cohort, evaluating the long-term effects and possible pitfalls of TES.

Materials and methods

In our previous study¹⁸, we selected 42 patients who had undergone TL for hypopharyngeal or laryngeal cancer between January 2003 and January 2006. We offered them two possibilities for voice restoration: ES or TES. Twenty-four (57.1%) chose TES and underwent implantation of Provox2 VP (Atos Medical, Hörby, Sweden). During TL a section of sternal heads of sternocleidomastoid muscles and a short anteriorly positioned cricopharyngeal muscle myotomy have always been performed, reducing the chances of deep stoma evolution (which would increase the risk of vertical slit tracheostomal stenosis and difficulty in VP management) and hypertonicity of the pharyngo-oesophageal segment (which would make voicing harder in both ES and TES). Video-fluoroscopy and Taub test were also routinely realised before planning a secondary TEP procedure. The selected cohort consisted of 22 males and 2 females, aged from 46 to 72 years (mean age: 63.6 ± 4.2 years). As a rule, TEP was performed as a secondary procedure, generally 6 months after TL (6.5 ± 1.3 months), at the end of the patients' course of treatment: the presumed need for extensive pharyngo-laryngeal resections, frequently in salvage settings and/or post-operative irradiation play a role in the decisional algorithm. We investigated QoL and satisfaction within this cohort (group A) in comparison to TL patients trained for ES (group B) and subjects with minor ENT diseases referring to our clinic (group C; control group). QoL was assessed through Short Form 36-Item Health Survey (SF-36); satisfaction of TES patients was evaluated with a study-specific structured questionnaire. Both questionnaires were administered one year after TEP procedure during regular, ENT follow-up visits.

With the present work we reconsidered QoL and TES-related degree of satisfaction within the same cohort of patients, wondering whether those early, positive results were maintained over time. Of the original group A (24 subjects), 2 patients died of progressive disease (8.4%, 2/24), and 4 of unrelated causes (16.8%, 4/24). Three patients were lost to follow-up (12.5%, 3/24). All the remaining 15/24 patients had at least a 12-year follow-up period after VP implantation (range: 12-15 years). Patient characteristics are summarised in Table I. A survey was conducted using the same questionnaires. To obtain comparable results and avoid selection bias, the 9/24 patients who dropped out from the follow-up were

excluded from the original count and the former results recalculated. Likewise, in our previous work, a control group of subjects with minor ENT diseases referring to our facility (homogeneous by demographics characteristics to the present study cohort) was employed for SF-36 analysis.

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the principles stated in the Declaration of Helsinki "Ethical Principles for Medical Research Involving 'Human Subjects'", adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and as amended most recently by the 64th World Medical Assembly, Fortaleza, Brazil, October 2013.

Statistical analysis was performed with SPSS statistical package (IBM Corp., version 20). Satisfaction of TES voice rehabilitation was compared with 2011 results through Fisher's exact test, when feasible. Paired samples Student's t-test was used to assess variation of QoL through the years. A $p < 0.05$ was considered significant.

Results

QoL assessment

Results of the SF-36 survey are shown in Table II, comprehensive of outcomes control group. We found a substantial in-

crease in terms of QoL in role physical (RP) area ($p < 0.001$), bodily pain (BP) area ($p < 0.001$), social functioning (SF) area ($p < 0.001$) and role emotional (RE) area ($p = 0.03$) in comparison with the 2011 results¹⁸. Also, other sections demonstrated a trend towards a better-perceived long-term QoL, although not in a statistically significant manner. The present QoL outcomes, in particular, approached the results of the control group, without statistically significant differences, except for the bodily pain (BP) area in which TES patients achieved even better scores ($p < 0.001$).

TES-related satisfaction survey

Long-term degree of satisfaction was assessed through a study-specific structured questionnaire (Table III), the same survey we used in our previous analysis¹⁸. The answers were grouped two by two to allow statistical comparison using Fisher's exact test, when feasible. Voice clarity, loudness, tone, fluency and clarity on the telephone seemed to improve slightly over time, with a higher percentage of patients perceiving those parameters as "good" or "reasonable". However, this subtle difference was not statistically significant. Also, voice-related QoL seemed to ameliorate over the years, with 86.7% of patients (13/15) reporting an improvement with TES (73.3% in 2011, 11/15), while overall satisfaction behaved in the opposite way, with 93.3% of patients "satisfied" or "very satisfied" in 2011 vs 80.0% at present. Nevertheless, neither of these differences reached statistical significance.

VP replacement occurred more frequently in 2011 (every 3.0 ± 1.8 months) than at present (6.3 ± 3.1 months). Leakage through VP (i.e. trans-prosthetic leakage) and/or impaired voicing, both caused by loss of one-way valve function as a consequence of fungal-bacterial colonisation, followed by leakage around VP (i.e. peri-prosthetic leakage) were the main reasons for valve replacement both previously and currently (Table III). This latter condition is indeed a troublesome issue to cope with, since VP substitution is frequently not sufficient to resolve it. In our case, we added a peri-prosthetic, tailored silastic collar to cover the defect on the tracheal side. Daily cleaning routine was not substantially modified over the years (2.5 times per day in our previous analysis, 2.0 in the present one).

The capacity to be understood by relatives or strangers, even on the telephone, was essentially preserved over time, with no significant differences (Table III). However, an increased difficulty in noisy environments was noted. Two patients (13.3%, 2/15) reported to have sometimes considered removing the VP, as in our previous analysis. Interestingly, 20.0% of our cohort (3/15) would not choose the same kind of voice restoration (i.e. TES) if they could turn back time. None of the patients reported the same will in 2011. Sub-

Table I. Patient characteristics.

Demographics	Age at surgery	65.2 \pm 9.8 years
	Age at follow-up	76.2 \pm 9.1 years
	Gender	Male: 13/15 (86.7%) Female: 2/15 (13.3%)
	Heavy smokers (> 10 PY)	14/15 (93.3%)
	VP placement delay	6.2 \pm 2.1 months
T site	Larynx	12/15 (80.0%)
	Hypopharynx	2/15 (13.3%)
	Thyroid	1/15 (6.7%)
Tumour stage	III	2/15 (13.3%)
	IV	13/15 (86.7%)
Surgery	Laryngectomy	10/15 (66.7%)
	Pharyngo-laryngectomy	5/15 (33.3%)
Neck dissection	Bilateral	15/15 (100.0%)
Timing of surgery	Primary	7/15 (46.7%)
	Salvage	8/15 (53.3%)
Radiotherapy	Primary treatment	8/15 (53.3%)
	Adjuvant	7/15 (46.7%)
	Overall	15/15 (100.0%)
Concomitant chemotherapy	Yes (CCDP)	13/15 (86.7%)
	No	2/15 (13.3%)
Pharyngeal mucosa reconstruction*	Primary closure	10/15 (66.7%)
	Pedicle PMMF	2/15 (13.3%)
	RFFF	3/15 (20.0%)

PY: pack/year; VP: voice prosthesis; CCDP: cisplatin; PMMF: pectoralis major myocutaneous flap; SCAIF: supraclavicular artery island flap; *: pedicle/free flap harvested for interposing purposes are excluded from the count.

Table II. Short Form 36-Item Health Survey (SF-36) analysing quality of life (QoL) in total laryngectomy patients one year after voice prosthesis implantation¹⁸ and over time (11 years or more after trachea-oesophageal puncture) and in the control group. Paired samples Student's t-test was used in order to assess variation of perceived QoL.

	2011 ¹⁸	2017	Control group
PF	73.2 ± 27.5	82.3 ± 20.0	89.3 ± 10.1
RP	50.1 ± 30.7	83.3 ± 32.3	85.7 ± 9.5
BP	73.1 ± 14.1	94.8 ± 13.8	80.3 ± 12.5
GH	58.7 ± 16.3	63.0 ± 20.2	66.3 ± 14.2
VT	67.8 ± 13.6	69.3 ± 17.5	71.3 ± 13.7
SF	72.1 ± 12.7	88.3 ± 16.7	90.7 ± 7.6
RE	69.4 ± 24.0	84.5 ± 30.5	85.7 ± 18.5
MH	69.9 ± 15.3	71.5 ± 21.2	71.9 ± 11.5

PF: physical functioning area, concerning limitations to everyday activities; RP: role physical area, evaluating the influence of physical limitations on activities or work; BP: bodily pain, related to pain and its influence on everyday life; GH: general health, estimating the actual health status and self-expectation about future health development; VT: vitality, related to the feeling of being full of energy or exhausted; SF: social functioning, related to the influence of physical or mental limitations on social activities; RE: role emotional, evaluating the influence of emotional problems on activities or work; MH: mental health, concerning general mental health including depression, anxiety and mood; NSS: not statistically significant.

jects who referred these two issues are those more distant from our facility (230 km and 462 km, respectively, against a mean distance of 15.4 ± 13.8 km for the other patients).

Discussion

TL remains the standard of care for advanced laryngeal/hypopharyngeal carcinoma, either as primary procedure or as salvage treatment after failure of chemo-radiation protocols^{4,5}. Despite its straightforward oncological efficacy, TL results in dramatic physical and functional changes: permanent tracheostomy and loss of natural voice are especially perceived as the major contributors⁶. Rapid, effective voice rehabilitation is essential^{7,8}.

Since its introduction as a viable approach for voice restoration after TL, TES has gradually become the gold standard^{13,16,17}. The achieved vocal quality is generally superior to ES and EL from both objective and subjective points of view¹⁶ and acoustically more comparable to normal laryngeal speech¹⁹. Our initial policy was to perform almost exclusively secondary TEP, since we deal generally with extremely advanced diseases, often as CRT failure, often requiring extensive pharyngo-laryngeal resections and/or adjuvant therapies: this is why our former cohort includes only “secondary” patients¹². This also allowed us to verify patients’ adaptability to ES and eventual commitment to TES, since many subjects preferred not to undergo another surgical operation and, mostly, to develop a kind of hospital-addiction for VP replacement¹⁵. Nowadays our attitude has greatly changed toward a primary TEP philosophy, accord-

ing to well-known evidence underplaying the role of adjuvant radiation in increasing the risk of perioperative complications²⁰. The worse prognosis associated with salvage TL²¹ could also favour a primary TEP approach, offering patients a better residual QoL.

Our previous study helped to emphasise the positive effects of TES rehabilitation on QoL of TL patients¹⁸. In comparison with ES, we found that TES helped to improve patients’ self confidence and limit postoperative social disability¹⁸. With this evidence in mind, we tried reassessing QoL and degree of satisfaction many years after TEP procedure, wondering whether those positive results were maintained over time.

Despite the small size of our cohort, we interestingly found that QoL outcomes were better today (12 years or more after VP implantation) than at one year after TEP (Table II), despite the natural aging of the sample. Through the SF-36 survey, we detected a significant improvement in role physical (RP), bodily pain (BP), social functioning (SF) and role emotional (RE) areas and a trend towards a better-perceived long-term QoL in other sections in comparison with the 2011 results¹⁸. These striking evidences could be explained by many reasons, not necessarily related to TES itself, and firstly the progressive healing of surgical sequelae and CRT side effects and decreasing chances of disease relapse²². It is well known that head and neck cancer patients taking QoL surveys more than 12 months after diagnosis and treatment report better outcomes in many domains²³. Moreover, patients tend to be accustomed to their laryngectomy-condition, demanding for greater social integration²²: the similarity of SF-36 outcomes between the present results and the control group (Table II) can indeed support these interpretations.

If QoL seemed to improve, long-term degree of satisfaction of TES as source of voice restoration remained approximately stable over time (Table III). Although roughly increased, the results in term of voice clarity (“good” or “reasonable” for 73.3% of patients against 60.0% in 2011), voice loudness (66.7% vs 60.0%), tone (66.7% vs 60.0%), fluency (73.3% vs 60.0%) and clarity on the telephone (60.0% vs 53.3%) did not achieve significant differences. Also, the specific, positive effect of TES voice restoration on QoL seemed to increase in comparison to our previous analysis (86.7% of patients perceived their QoL as “a lot” or “quite a bit” improved by TES against 73.3% in 2011); in the same way, overall satisfaction with TES seemed to worsen (93.3% of patients “satisfied” or “very satisfied” in 2011, 80.0% today); however, neither of these two changes reached statistical significance. The increased difficulty in noisy environments reported by a few patients (13.3%) could be considered as a consequence of the above-mentioned greater need for social integration. Long-term maintenance of TES-related satisfaction is actu-

Table III. Questionnaire for assessment of the degree of satisfaction of vocal rehabilitation with tracheo-oesophageal puncture (TEP) and voice prosthesis (VP) implantation evaluated one year after TEP procedure ¹⁸ and over time (11 years or more after VP insertion).

		2011 ¹⁸	2017	p
Satisfaction				
Are you satisfied with your voice after the positioning of the VP?	(1) "Not satisfied" or "somewhat satisfied" (2) "Satisfied" or "very satisfied"	1 (6.7%) 14 (93.3%)	3 (20.0%) 12 (80.0%)	NSS
How would you rate the clarity of your voice?	(1) "Poor" or "moderate" (2) "Reasonable" or "good"	6 (40.0%) 9 (60.0%)	4 (26.7%) 11 (73.3%)	NSS
How would you rate the loudness of your voice?	(1) "Poor" or "moderate" (2) "Reasonable" or "good"	6 (40.0%) 9 (60.0%)	5 (33.3%) 10 (66.7%)	NSS
How would you rate the tone of your voice?	(1) "Poor" or "moderate" (2) "Reasonable" or "good"	6 (40.0%) 9 (60.0%)	5 (33.3%) 10 (66.7%)	NSS
How would you rate the fluency of your voice?	(1) "Poor" or "moderate" (2) "Reasonable" or "good"	6 (40.0%) 9 (60.0%)	4 (26.7%) 11 (73.3%)	NSS
How would you rate the clarity of your voice on the telephone?	(1) "Poor" or "moderate" (2) "Reasonable" or "good"	7 (46.7%) 8 (53.3%)	6 (40.0%) 9 (60.0%)	NSS
Do you think the VP has improved your quality of life?	(1) "No" or "a little" (2) "Quite a bit" or "a lot"	4 (26.7%) 11 (73.3%)	2 (13.3%) 13 (86.7%)	NSS
Voice prosthesis replacement				
On an average, how often the VP has been replaced?	Every:	3.0 ± 1.8 months	6.3 ± 3.1 months	
Reasons for replacement:	(1) Leakage through prosthesis and/or impaired voicing (2) Leakage around prosthesis	13 (86.7%) 2 (13.3%)	14 (93.3%) 1 (6.7%)	NSS
Voice prosthesis cleaning				
Is the VP easy to clean?	(1) Yes (2) No	15 (100.0%) /	14 (93.3%) 1 (6.7%)	NA*
Do you use a brush/pipette?	(1) Yes (2) No	15 (100.0%) /	15 (100.0%) /	NA*
If yes, how many times per day?		2.5 per day	2.0 per day (1-5)	
Understanding				
Are you able to be understood easily by strangers?	(1) "Always" or "frequently" (2) "Rarely" or "never"	15 (100.0%) /	15 (100.0%) /	NA*
Are you able to be understood easily by strangers on the telephone?	(1) "Always" or "frequently" (2) "Rarely" or "never"	14 (93.3%) 1 (6.7%)	13 (86.7%) 2 (13.3%)	NSS
Are you able to be understood easily by relatives?	(1) "Always" or "frequently" (2) "Rarely" or "never"	15 (100.0%) /	15 (100.0%) /	NA*
Are you able to be understood easily by relatives on the telephone?	(1) "Always" or "frequently" (2) "Rarely" or "never"	13 (86.7%) 2 (13.3%)	12 (80.0%) 3 (20.0%)	NSS
Are you able to be understood easily in noisy environments?	(1) "Always" or "frequently" (2) "Rarely" or "never"	15 (100.0%) /	13 (86.7%) 2 (13.3%)	NA*
Have you ever wanted to remove the VP?	(1) Yes (2) No	2 (13.3%) 13 (86.7%)	2 (13.3%) 13 (86.7%)	NSS
If you could turn back time, would you choose the same kind of voice restoration?	(1) Yes (2) No	15 (100%) /	12 (80.0%) 3 (20.0%)	NA*

NA*: Fisher's exact test not applicable because one of the variables is a "constant"; NSS: not statistically significant.

ally an expected result, as the natural consequence of thorough, initial patient selection. In fact, it is essential to predict patients and caregivers' long-lasting commitment to TES in order to achieve a good, durable functional outcome: for this purpose, ES trial and eventual secondary TEP may still represent a valid option, despite the present shift towards a primary TEP philosophy ¹³.

The significant lengthening in VP duration we noticed could be related to many factors: increased expertise in valve management (both by patients and physicians), the progressive implementation of new-generation VPs (i.e. Provox Vega, Atos Medical, Hörby, Sweden) ²⁴ and the systematic introduction of long-term PPI therapy in TES patients, due to the emerging evidence that gastro-oesophageal reflux disease

(GERD) on tracheo-oesophageal fistula integrity^{25 26}, especially in subjects who underwent radiation therapy¹⁵. These aspects are particularly meaningful in our selected cohort, since all patients were submitted to pre- or post-operative irradiation (Table I).

As previously stated, trans-prosthetic leakage and/or impaired voicing were the only reasons for valve replacement in most patients (93.3% today, 86.7% in 2011). These conditions are caused by abnormal *Candida* spp-bacterial biofilm formation on the valve structures despite regular cleaning, causing improper VP closure and loss of one-way valve function²⁷. The progressive introduction of new-generation VP (i.e. Provox Vega) could obviously play a role in increasing VP lifespan²⁴, even if no special VP (e.g. Provox Activale, Atos Medical, Hörby, Sweden) was employed¹³. We also generally administered an oral antifungal suspension (e.g. nystatin) as long as patients reported an increase in trans-prosthetic leakage.

Leakage around VP (13.3% in 2011, 6.7% today) is a fistula-related problem that we tackled by placing a peri-prosthetic, tailored silastic collar to cover the defect on the tracheal side as well as replacing VP with a shorter one. Both conservative measures and surgical ones are considered when dealing with peri-prosthetic leakage²⁸: we generally approach it by reducing VP size or putting in place a tracheal, peri-prosthetic washer at first, leaving fistula shrinkage, tissue augmentation and use of Provox Vega XtraSeal (Atos Medical, Hörby, Sweden) as further options in case of failure. We do not usually perform purse-string sutures. Systematic use of long-term PPI therapies is an essential supplement, as advocated in the literature²⁵.

Despite all this favourable evidence, there is still one main pitfall to consider: although the proportion of subjects who has thought about removing VP remained the same through the years (13.3% in 2011 and today), some of our patients (3/15, 20.0%) would not choose the same type of voice restoration (i.e. TES) if they could turn back time. That could apparently jeopardise TES efficacy in voice restoration over time. Curiously, patients who reported these two issues are almost the same and those more distant from our institution (230 km and 462 km, respectively, against a mean distance from our clinic of 15.4 ± 13.8 km for other patients). We could explain these facts as signs of intolerance towards periodical dependence for VP management from the facility where they underwent TEP and VP implantation, which is far away from their residence: this issue can affect indeed patients' overall satisfaction related to TES without impairing their QoL, which is mostly associated to the relational possibilities offered by TES than to its maintenance cost. This finding is not surprising, as people belonging to lower socio-economic classes or living in remote areas of countries cannot afford

travelling to receive repeated health care^{29 30}: however, it is curious in a relative small country like Italy. This once more raises the need of creating an integrated, widespread network of centres for VP management and replacement, irrespective of the institution where TEP was performed. Beyond helping patients in dealing with VP management, this could also help to extend this kind of analysis to larger series and confirm the long-term efficacy of TES as the gold standard approach for voice rehabilitation after TL.

Conclusions

Since its introduction, TES has gradually become the gold standard for voice restoration after TL, replacing EL and ES. Our previous study tried to emphasise the positive effects of TES rehabilitation on QoL of TL patients. With the present work we highlight how those results can not only be maintained over time (i.e. TES-related satisfaction), but also substantially improve (i.e. QoL). However, we also show how distance of residence from a referral institution can potentially jeopardise these aspects. An integrated, widespread network of centres for VP management and replacement is needed to overcome the problem and allow studies on larger series.

Conflict of interest statement

None declared.

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RHINOLOGY

Multiple gene expression profiling suggests epithelial dysfunction in polypoid chronic rhinosinusitis

Il profilo di espressione genica multipla rivela una disfunzione epiteliale nella rinosinusite cronica polipoide

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SUMMARY

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disorder resulting from a complex gene-environment interaction. Although its aetiology remains elusive, numerous studies reported gene expression alterations of factors apparently implicated in all aspects of the inflammatory response. However, most investigations are limited, unconfirmed analyses of a single gene. Moreover, studies concerning multiple gene expression analyses, usually on inflammatory mediators (e.g. cytokines), show contrasting outcomes in part due to use of heterogeneous samples or methodologies with limited power. In this scenario, our goal was to simultaneously evaluate the expression of a panel of selected genes (*AQP5*, *MUC5AC*, *CAV1*, *LTF*, *COX2*, *PGDS*, *TNFα*, *TGFβ1*, *MGB1*) potentially involved in CRS inflammatory mechanisms. While most of the samples collected were excluded from the analysis because of poor quality RNA, we were able to demonstrate statistically significant downregulation of the *AQP5*, *CAV1*, *LTF*, *MGB1* genes in a specific subset of polypoid CRS (patients without typical comorbidities), which might suggest relevant underlying epithelial dysfunction. Further studies are needed to enrich our knowledge on the pathogenesis of CRS. Forthcoming approaches might utilise next-generation RNA sequencing and comprehensive bioinformatics analyses to better characterise the transcriptome profiles of CRS endotypes.

KEY WORDS: Chronic rhinosinusitis • Nasal polyps • qPCR • Epithelial damage • Inflammatory cytokines • Tissue remodelling • Immune barrier

RIASSUNTO

La rinosinusite cronica (CRS) è un disturbo infiammatorio eterogeneo risultante da una complessa interazione genetico-ambientale. Sebbene l'eziologia rimanga tuttora sfuggente, numerosi studi riportano alterazioni nell'espressione genica di diversi fattori implicati nell'ambito della risposta infiammatoria. Tuttavia, la gran parte di queste sono analisi isolate, non replicate, che prendono in considerazione un singolo gene alla volta. Inoltre, gli studi riguardanti analisi di espressione genica multipla, solitamente su mediatori infiammatori (es. citochine), spesso presentano risultati contrastanti, che in parte possono essere dovuti all'eterogeneità dei campioni o a metodologie analitiche di potenza limitata. In quest'ottica, il nostro obiettivo è stato di verificare simultaneamente l'espressione genica di un pannello di geni (*AQP5*, *MUC5AC*, *CAV1*, *LTF*, *COX2*, *PGDS*, *TNFα*, *TGFβ1*, *MGB1*) potenzialmente coinvolti nei meccanismi infiammatori della CRS. Nonostante la gran parte dei campioni sia stata esclusa dall'analisi a causa del deterioramento dell'RNA tissutale, siamo stati in grado di dimostrare una riduzione statisticamente significativa dell'espressione dei geni *AQP5*, *CAV1*, *LTF* e *MGB1*, in uno specifico sottogruppo di pazienti affetti da CRS nella variante con polipi nasali senza le tipiche comorbidità frequentemente associate (asma, allergia, intolleranza all'acido acetil-salicylico). Questi dati sembrano suggerire una disfunzione della barriera epiteliale nella CRS polipoide. Ulteriori studi saranno necessari per incrementare ulteriormente la nostra conoscenza sulla patogenesi della CRS. A tal proposito l'applicazione delle nuove e più potenti tecniche di sequenziamento, come la next-generation RNA sequencing, e la disponibilità di analisi bioinformatiche più complete potranno migliorare la caratterizzazione del transcriptoma negli endotipi della CRS.

PAROLE CHIAVE: Rinosinusite cronica • Poliposi nasale • qPCR • Disfunzione epiteliale • Citochine infiammatorie • Rimodellamento tissutale • Barriera immunitaria

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disorder characterised by persistent symptomatic inflammation of the nasal and paranasal sinus mucosa.

The interest of research in CRS arises from several factors. First, CRS is one of the most commonly reported diseases, estimated as the second most prevalent chronic health condition and affecting 10.9% of the European population. Second, the burden of CRS to society is considerable, with substantial negative impact on several aspects of quality of life and considerable medical costs. Lastly, the current treatment options struggle to be widely effective ¹.

The aetiology of CRS remains unclear. It is becoming widely accepted that CRS arises from genetic, epigenetic, microbial and environmental factors; several conditions, such as asthma, damage of ciliated mechanical barrier, obstruction of nasal drainage, induction of inflammatory cytokines and impairment of the immune system, have been recognised as predisposing or associated factors to CRS ¹. For these reasons, current research has attempted to elucidate the factors leading to persistent sinus inflammation, focusing on innate and acquired immunological mechanisms ².

Numerous studies have reported alterations in the gene expression of factors apparently implicated in all aspects of the inflammatory response. However, most investigations are limited, unconfirmed analyses of a single gene. In addition, studies concerning multiple gene expression analyses, usually on inflammatory mediators (e.g. cytokines), demonstrate contrasting outcomes in part due to heterogeneous samples or methodologies with limited power ³.

Furthermore, even the site of tissue sampling seems to influence the results; indeed, there is evidence of a topographic gene expression in the sinonasal cavities. In particular, nasal polyps in CRS have been shown to exhibit a unique transcriptional pattern, typical of the polypoid tissue itself and not simply related to chronic mucosal inflammation or regional variations ⁴. In this scenario, our goal was to simultaneously evaluate, in healthy samples and CRS with nasal polyps (CRSwNP), the expression of a panel of genes involved in: (1) defects in the epithelial barrier and in both innate and adaptive host defence functions (Aquaporin 5-*AQP5*, Mucin 5AC-*MUC5AC*, Caveolin 1-*CAV1*, Lactoferrin-*LTF*); (2) alterations of eicosanoid pathways (Cyclooxygenase 2-*COX2*, Prostaglandin D Synthase-*PGDS*); and (3) induction of inflammatory cytokines and aberrant remodelling processes (Tumour necrosis factor alpha-*TNFα*, Transforming growth factor

beta 1-*TGFβ1*, Mammaglobin 1-*MGB1*). Inclusion criteria for CRS patients were tight and painstaking and care was taken in collecting tissue samples in order to minimise the above-mentioned distortions.

Materials and methods

Participants

A retrospective study was carried out on a total of 85 individuals, comprising 52 cases (CRSwNP) and 33 controls (CTL). The local Institutional Review Board approved this study. All participants provided informed consent to use their samples for research purposes. Research was carried out in compliance with the Helsinki Declaration.

As the case group, we recruited patients affected by CRSwNP as defined by the European guidelines ¹, aged from 18 to 75 years. All cases presenting with immune-deficiency, autoimmune diseases, genetic disorders, history of sinonasal trauma, tumours, or loco-regional radiotherapy were excluded. Moreover, only CRSwNP patients without asthma, allergy, aspirin sensitivity, or hyper-eosinophilia (> 10%) were considered suitable for enrolment.

As the control group, we recruited subjects undergoing nasal surgery for other reasons (septoplasty, turbinoplasty, skull base reconstruction after trauma, spontaneous cerebrospinal fluid leaks, endoscopic approaches to sellar region), matched to patients for age and sex. We adjusted the control selections for geographic region and ethnicity in order to minimise the environmental differences with the cases. Exclusion criteria consisted of a positive history of asthma, allergy and acute or chronic rhinosinusitis.

Sample collection

Arbitrarily, 20 days before surgery patients suspended local steroid treatment in order to dispose of “pharmacological wash-out” mucosal samples, eliminating the potential effects of steroids on gene expression. At the time of surgery, the absence of acute inflammatory and infectious conditions was verified both in patients and controls. Biopsy specimens of CRSwNP and CTL mucosa were obtained from the anterior ethmoid (uncinate process or bulla ethmoidalis, when available) under general or local anaesthesia and immediately stored at -80°C until further analysis.

RNA extraction and reverse transcription

Total RNA was isolated from 100 mg of tissue using the TRIzol solution (Invitrogen™, Italy) according the standard protocol. The extracted RNA was quantified by

QuantiFluor fluorometer (Promega, Italy) using QuantiFluor® RNA System dye and its quality and integrity was assessed by 1% gel electrophoresis. The first strand cDNA was synthesised using the iScript™ cDNA Synthesis Kit (BioRad, Italy), according to the manufacturer's instructions and stored at -20°C.

Quantitative PCR

For quantitative PCR (qPCR), six genes were chosen as housekeeping genes (glyceraldehyde-3-phosphate dehydrogenase-*GAPDH*, beta-2 microglobulin- β 2M, hypoxanthine phosphoribosyltransferase 1-*HPRT1*, Actin_beta-*Actin* β , TATA box binding protein-*Tbp* and ribosomal protein L13-*RPL13*) and the most stable three genes (*GAPDH*, β 2M and *Actin* β) were selected according to Palombella et al. ⁵. Selected target genes are reported in Table I. qPCR was performed using iTaq™ Universal SYBR®Green-Supremix (BioRad, Italy). Specific primers were designed using the Beacon Designer Program (BioRad, Italy) within the sequences of the genes shown in Table II. Each reaction was performed according to Rossi et al. ⁶. Briefly, 7.5 μ l of SYBR Green Supremix (2x), 1 μ l of forward and reverse primers (6 μ M), 5 ng of cDNA and water to a final volume of 15 μ l were mixed and run in a CFX 96 Thermocycler (BioRad, Italy). The thermal cycle was as follows: 5 min at 95°C, 10 sec at 95°C and 30 sec at 60°C for 40 cycles. Each experiment was repeated three times.

Statistical analysis

Comparative cycle threshold method (Δ Ct) was used for qPCR analysis and gene levels expressed as $2^{-\Delta Ct}$ (Δ Ct = CtTarget – CtHousekeeping). Data analysis were performed by Student's t-test. Results were statistically significant with $p < 0.05$.

Results

Despite the large number of samples processed and the maximum care during the sample collection and manipulation, we encountered much difficulty in obtaining good quality RNA from biopsies; among the 85 selected individuals (52 CRSwNP and 33 CTL), only a total of 24 samples, comprising 11 CRSwNP and 13 CTL, were considered suitable for the study, due to extraction of poor-quality RNA.

As can be seen in agarose gel electrophoresis of specimens from both CRSwNP and CTL Groups (Figs. 1, 2), in some samples the RNA appeared to be partially degraded. This occurred particularly in CRSwNP specimens (Fig. 1), showing that the problem was probably due to the extraction of pathologic tissue with poor cellular content.

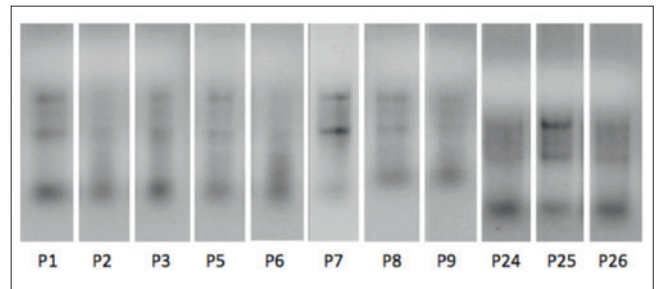


Fig. 1. 1% Agarose gel electrophoresis of some specimens of CRSwNP Group, in which RNA is seen to be partially degraded.

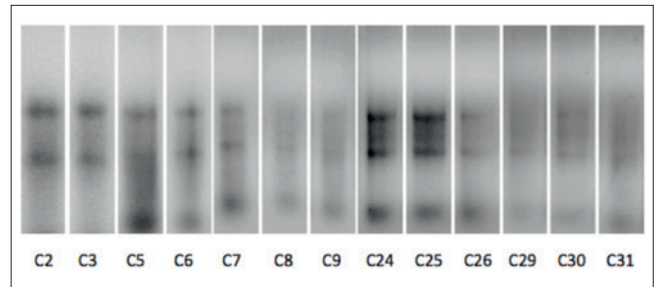


Fig. 2. 1% Agarose gel electrophoresis of specimens of the CTL Group in which RNA is less degraded compared to pathological tissue.

This problem was clearly less evident in biopsies taken from healthy mucosa from CTL Group (Fig. 2).

In the first group of selected genes, those related to the epithelial barrier and immune functions, *APQ5*, *CAVI* and *LTF* genes were significantly downregulated in CRSwNP samples compared to CTLs, as reported in Figure 3 ($p < 0.05$). In the other two groups of genes, statistically significant downregulation was observed for *COX2* and *MGB1* genes in CRSwNP samples compared to CTLs ($p < 0.05$), as reported in Figures 4 and 5, respectively.

Discussion

It is increasingly acknowledged that CRS is not a single pathological entity, but has a rather broad clinical presentation, histopathology and response to therapy. Several pathophysiological pathways seem to exist, ending in the common point of sinonasal mucosal inflammation. Once chronic inflammation has become apparent, the activation of other pathways inevitably masks the possibility to identify the early cause. Determining which cellular and molecular characteristics of CRS represent the underlying factors that induce inflammation, or more simply the downstream consequences, remains a challenge in the ongoing field of research ⁷.

In this context, in the attempt to give our contribution

Table I. Target genes selected for qPCR analysis.

Gene title	Gene symbol	Family	Subcellular localisation	Molecular functions	Gene ontology biological process
Aquaporin 5	AQP5; PPKB	MIP/aquaporin (TC 1.A.8)	Apical cell membrane; Multi-pass membrane	Water channel activity; protein binding	Transport; water transport; excretion; carbon dioxide transport; pancreatic juice secretion
Mucin 5AC	MUC5AC; LeB; TBM	Mucins	Secreted	Extracellular matrix structural constituent	Stimulatory C-type lectin receptor signalling pathway; O-glycan processing; phosphatidylinositol-mediated signalling
Caveolin 1	CAV1; MSTP085; BSCL3; LCCNS; VIP21; CGL3; PPH3	Caveolin	Golgi apparatus membrane; peripheral cell membrane	Receptor binding; patched binding; structural molecule activity; protein binding; cholesterol binding	Negative regulation of transcription from RNA polymerase II promoter; MAPK cascade; inactivation of MAPK activity; angiogenesis; vasculogenesis
Lactoferrin	LTF; GIG12; EC 3.4.21; HEL110; HLF2	Transferrin	Secreted; cytoplasmic granule; cytoplasm	Lipopolysaccharide binding; DNA binding; serine-type endopeptidase activity; cysteine-type endopeptidase inhibitor activity; iron ion binding	Ossification; regulation of cytokine production; retina homeostasis; innate immune response in mucosa; immune system process
Cyclooxygenase 2	COX2; PHS II; PGHS-2; EC 1.14.99; GRIPGHS; PGG/HS; HCox-2; PHS-2	Prostaglandin G/H synthase	Microsome membrane; peripheral membrane; endoplasmic reticulum membrane;	Peroxidase activity; prostaglandin-endoperoxide synthase activity; protein binding; lipid binding; oxidoreductase activity	Prostaglandin biosynthetic process; angiogenesis; lipid metabolic process; fatty acid metabolic process; fatty acid biosynthetic process
Prostaglandin D Synthase	PGDS; EC 5.3.99.2; PGDS2 PDS; L-PGDS; LPGDS; PGD2	Lipocalins	Rough endoplasmic reticulum; nucleus membrane; Golgi apparatus; cytoplasm, perinuclear region; Secreted.	Prostaglandin-D synthase activity; transporter activity; retinoid binding; fatty acid binding; protein binding	Prostaglandin metabolic and biosynthetic process; lipid metabolic process; fatty acid metabolic and biosynthetic process;
Tumour necrosis factor alpha	TNF α ; TNFSF2; TNFA; APC1; TNLG1F; DIF	Tumour necrosis factor	Cell membrane	Protease binding; cytokine activity; tumour necrosis factor receptor binding; protein binding	Protein import into nucleus, translocation; negative regulation of transcription from RNA polymerase II promoter; MAPK cascade; activation of MAPK activity
Transforming growth factor beta 1	TGF β 1; DPD1; LAP; CED	Endogenous ligands	Secreted; extracellular space; extracellular matrix	Glycoprotein binding; antigen binding; type II transforming growth factor beta receptor binding; cytokine activity; transforming growth factor beta receptor binding	Protein import into nucleus, translocation; negative regulation of transcription from RNA polymerase II promoter; MAPK cascade; vasculogenesis; ureteric bud development
Mammaglobin 1	MGB1; SCGB2A; UGB2	Secretoglobins	Secreted; Extracellular matrix	Protein binding	Biological process

to better clarify and understand the molecular patterns involved in CRS, we selected healthy and CRSwNP individuals and investigated the expression of several key genes involved in crucial points of CRS pathogenesis.

Despite the attention during tissue collection by the surgeon, the expertise of the laboratory technician in manipulating tissue and the care taken in all the steps to preserve the quality and the integrity of biological samples,

Table II. Primers used for qPCR analysis.

Gene Name		Sequence 5'-3'	Melting Temperature (°C)	Sequence Accession Number
GAPDH	FW Primer	ATCATCAGCAATGCCTCCT	60.9	M17851.1
	Rev Primer	GAGTCCTTCCACGATACCAA	60.5	
β 2M	FW Primer	CTATCCAGCGTACTCAA	59.5	AF072097.1
	Rev Primer	GAAACCCAGACACATAGC	59.5	
Actin β	FW Primer	ATGGGTCAGAAGGATTCC	59.8	NM_001101.3
	Rev Primer	CTCGATGGGGTACTTCAG	60.3	
AQP5	FW Primer	GCTCAACAACAACACAACG	62.1	NM_001651.3
	Rev Primer	TCAGTGGAGGCGAAGATG	62.9	
CAV1	FW Primer	TGAGCGAGAAGCAAGTGATC	64.2	BT007143.1
	Rev Primer	GTCATCGTTGAGGTGTTTAGGG	65.1	
COX2	FW Primer	GTCTGGTGCCTGGTCTGA	65.3	M90100.1
	Rev Primer	GTCTGGAACAAGTCTCATCA	64.5	
MGB1	FW Primer	GAAGTTGCTGATGGTCCTC	62.0	NM_002411.3
	Rev Primer	TTGTGGATTGATTGCTTGGGA	61.7	
MUC5AC	FW Primer	CATAACTTGTGGTCTGGAACCTA	63.9	L46721.1
	Rev Primer	CCGAGATTGTGCTGGTTGTA	64.2	
PGDS	FW Primer	TGTAACCTGGGCGAGCTTCTACT	65.3	NM_014485.2
	Rev Primer	GCAGGAATGGCTTGGACTT	64.6	
TNF α	FW Primer	ATGGCGTGGAGCTGAGAG	65.3	HQ201306.2
	Rev Primer	TGAAGAGGACCTGGGAGTAGAT	65.8	
TGF β 1	FW Primer	CTGCCAGAGTGGTTATC	65.9	NM_000660.5
	Rev Primer	GTGTTATCCCTGCTGTCA	65.4	
LTF	FW Primer	CTAATCTCTGTGCTCTGTGTATTG	63	M93150.1
	Rev Primer	CCAGTGTAGCCGTAGTATCTC	63.2	

GAPDH: glyceraldehyde-3-phosphate dehydrogenase, β 2M: beta-2 microglobulin, Actin β : Actin_beta, AQP5: Aquaporin 5, CAV1: Caveolin 1, COX2: Cyclooxygenase-2, MUC5AC: Mucin 5AC, PGDS: prostaglandin D, TNF α : tumour necrosis factor alpha, TGF β 1: transforming growth factor beta-1, LTF: Lactoferrin. Fw: forward, Rev: reverse.

the present work showed some limitations. First, only 24 samples of the 85 collected were deemed suitable for the study due to poor-quality RNA. It is well known that RNA is very susceptible to degradation during sampling, handling and storage ⁸. Moreover, previous studies demonstrated a higher concentration of RNases in nasal polyps compared to normal tissue as well as an increased enzyme activity ^{9 10}.

Second, the selection of patients was flawed by inclusion criteria established exclusively on a clinical basis (patients with polypoid CRS, either without asthma, allergic sensitization, aspirin intolerance or peripheral blood hypereosinophilia) when it is now clear that a clinical phenotypic differentiation does not adequately mirror the underlying immunological profile ¹¹. As a consequence, our results, though significant, should be interpreted in the light of this deliberate bias.

Disrupted epithelium

The “epithelial barrier hypothesis” of CRS pathogenesis

indicates that an intact barrier with tight epithelial junctions is necessary for healthy nasal mucosa. Defects in this protective barrier, including the epithelium itself and its mucous lining, mucociliary clearance, intercellular junctions, ion channels and secreted antimicrobial proteins and enzymes, may cause the passage of pathogenic microbes across the epithelium and subsequent dysregulation of the inflammatory cascade ¹². With the aim of exploring epithelial barrier functionality, we chose to verify the expression of the *AQP5*, *MUC5AC*, *CAV1* and *LTF* genes. As reported in Figure 3, the expression of all these genes in CRSwNP samples was downregulated compared to CTLs, and the differences in *AQP5*, *CAV1* and *LTF* were statistically significant (Fig. 3a-c).

In detail, *AQP5* acts as a key tight junction in regulating water transport and cell volume and in maintaining water homeostasis in the epithelium ². In CRS, a downregulation of *AQP5* has been associated with oedema and polyp formation and production of thick secretion, typical features of CRSwNP ¹³ (Fig. 3a).

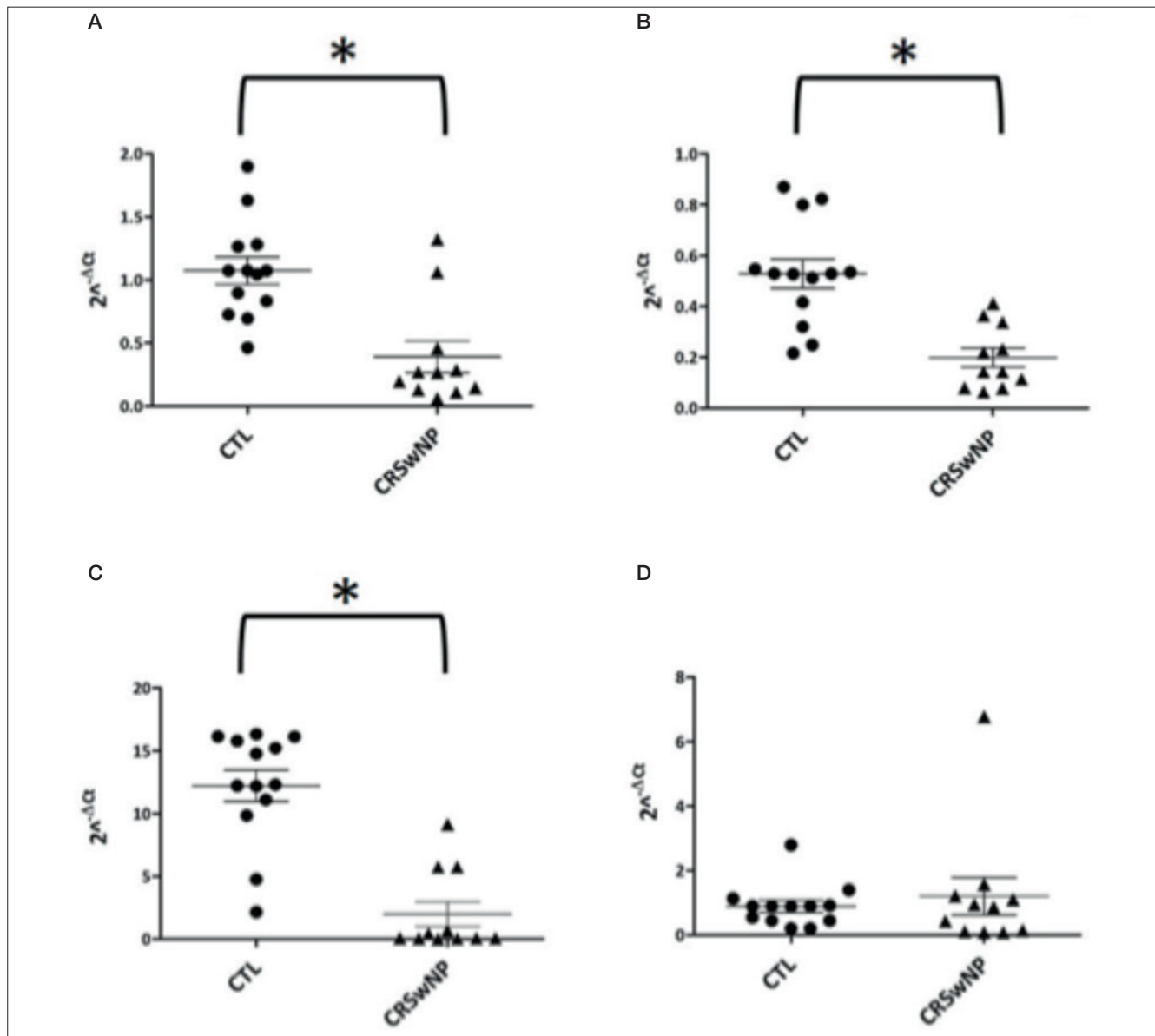


Fig. 3. Molecular expression of *AQP5* (a), *CAV1* (b), *LTF* (c) and *MUC5AC* (d) in healthy subjects (CTL) and in CRS patients with nasal polyps (CRSwNP) by qPCR. CTL: 13 cases; CRSwNP: 11 cases. (*) indicates statistically significant data ($p < 0.05$) obtained by Student's t-test.

CAV1 is a scaffolding membrane protein implicated in vesicular transport, endocytosis and regulation of signal transduction. Moreover, this gene plays a central role in defence against infections¹⁴. Downregulation of *CAV1* has been reported to cause dysregulation of membrane trafficking in the airway epithelium¹⁵ (Fig. 3b).

LTF possess diverse functions, including antibacterial, antifungal and antiviral activities, as well as immune regulatory and anti-inflammatory actions¹⁶. There is evidence that *LTF* is significantly decreased particularly in polypoid CRS patients with bacterial biofilms¹⁷ (Fig. 3c).

Taken together our results tend to confirm previous literature reports.

Contrarily, in our analysis, *MUC5AC* was slightly down-regulated in CRSwNP compared to CTL, albeit with no significant difference. *MUC5AC* is one of the predominant gel-forming mucins in human nasal mucosa¹⁸ and its upregulation, induced by various stimuli such as bacteria and allergens, was found in CRSwNP subjects^{19,20}. Although the increased production of mucus allows for better trapping and clearance, mucin overproduction may lead to airway obstruction and exacerbation of pre-exist-

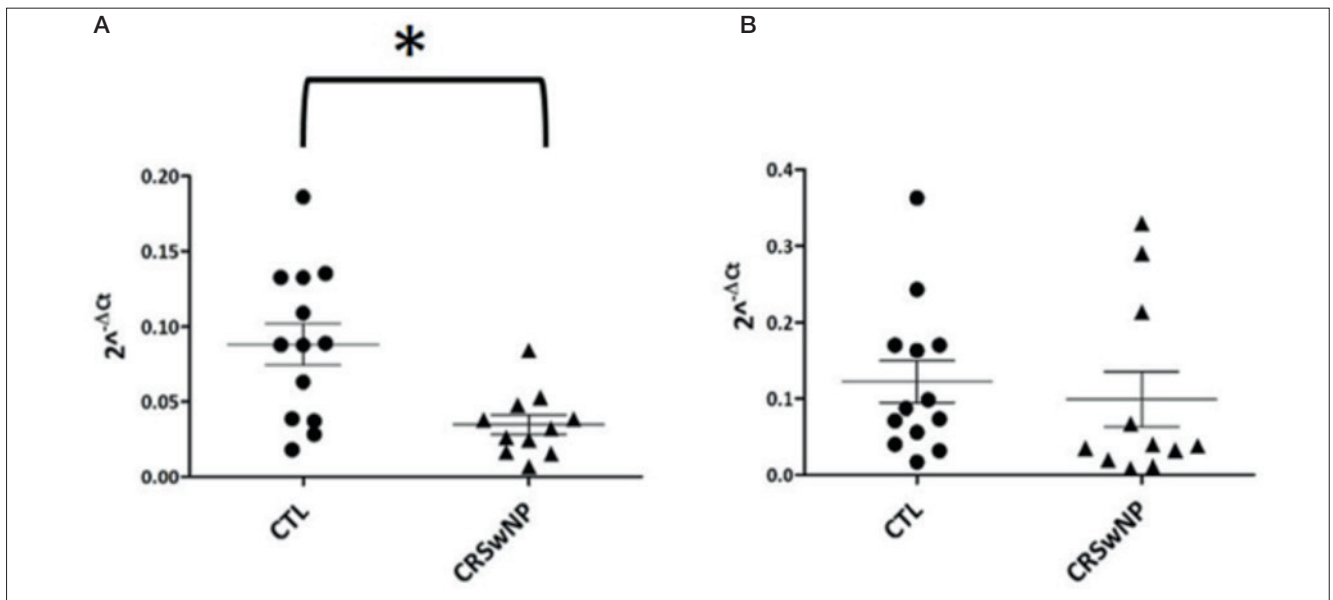


Fig. 4. Molecular expression of *COX2* (a) and *PGDS* (b) genes in healthy subjects (CTL) and in CRS patients with nasal polyps (CRSwNP) by qPCR. CTL: 13 cases; CRSwNP: 11 cases. (*) indicates data statistically significant ($p < 0.05$) obtained by Student's t-test.

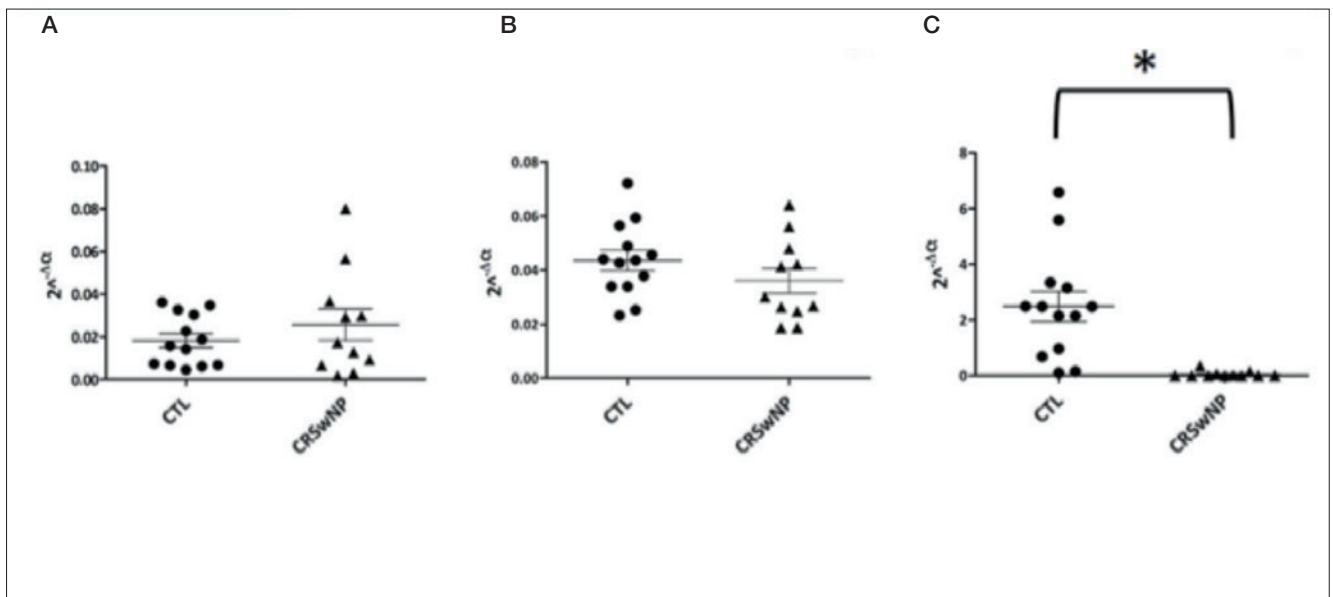


Fig. 5. Molecular expression of *TNFα* (a), *TGFβ1* (b) and *MGB1* (c) genes in healthy subjects (CTL) and in CRS patients with nasal polyps (CRSwNP) by qPCR. CTL: 13 analysed cases; CRSwNP: 11 analysed cases. (*) indicates statistically significant data ($p < 0.05$) obtained by Student's t-test.

ing inflammation and infection²¹. Our data showed a single sample with a very high level of *MUC5AC* compared to the other 10 samples (Fig. 3d).

Defects in eicosanoid metabolism

Defects in eicosanoid metabolism, particularly involving leukotriene (LT) and prostaglandin (PG), seem to be asso-

ciated to CRS, especially in the polyp variant. *COX2* has a key role in the synthesis of biologically active prostaglandins that possess different functions²². For instance, prostaglandin D2 (PGD2) prolongs the survival of eosinophils and induces the migration of Th2 lymphocytes, whereas prostaglandin E2 (PGE2) stimulates bronchodilation and demonstrates anti-inflammatory effects by reducing

the production of LTs. In CRSwNP, increased levels of PGD2 and PGD2 synthase (PGDS) were positively correlated with the eosinophil infiltrate²³, and imbalance in PGD2/PGE2 metabolism contributes to CRS associated to aspirin intolerance²⁴. In line with these findings, in our CRSwNP series, *COX2* expression was significantly reduced (Fig. 4a). However, there are controversial reports in the literature on the behaviour of *COX2* in CRS. It has been shown that *COX2* mRNA displays different kinetics in nasal mucosa and nasal polyps, obliging us to consider that even the sampling site may affect the results²⁵. The reduced expression (not significant) of *PGDS*, apparently in contrast to what previously reported, may be justified by the fact that our population did not include cases of aspirin intolerance, a clinical feature that appears to be strongly associated to eicosanoid metabolism imbalance in favour of the PGD2 cascade (Fig. 4b).

Inflammatory cytokines and remodelling processes

Numerous cytokines have been reported to be expressed at altered levels in CRSwNP tissues²⁶. We decided to explore the inflammatory status, remodelling pattern and immune-modulating activities, respectively, through the analysis of expression of the *TNF α* , *TGF β 1* and *MGB1* genes (Fig. 5).

Increased levels of *TNF α* have already been demonstrated in nasal polyp tissues, together with other pro-inflammatory cytokines²⁷, and protein levels are elevated in nasal secretion of CRSwNP patients²⁸. Although not statistically significant compared to CTL, our CRSwNP samples showed overexpression of *TNF α* mRNA (Fig. 5a).

In CRS, chronic inflammation results in structural changes referred to as a remodelling process, which tends to balance extracellular matrix production and degradation by several regulation mediators, such as *TGF β 1*. Previous studies have confirmed its pivotal role in these processes, showing significantly lower expression of *TGF β 1* in CRSwNP compared to controls^{26,29}. The downregulation signalling pathway results in oedema formation and lack of collagen production, histologic features that are typical of nasal polyps. *TGF β 1* gene expression was also lower in our CRSwNP group, although a significant difference was not reached (Fig. 5b).

Lastly, our results showed a significant downregulation of the *MGB1* gene in CRSwNP samples compared to CTLs (Fig. 5c). The role of *MGB1* in CRS remain uncertain, but it is known that other proteins of the mammaglobin family are secretory proteins involved in modulation of inflammatory processes, and *MGB1* overexpression in nasal polyps has been associated with neoplastic-like growth³⁰.

Conclusions

The intent of the present study was to enrich data reported in the literature by analysing, at the same time, the expression of several genes implicated in various inflammatory aspects of CRSwNP. We believe that confirmatory studies are unavoidable in research which strengthen the current knowledge about CRS pathogenesis and allow better definition of endotypes in order to achieve “tailored” treatment³¹. Forthcoming approaches might take into account next-generation RNA sequencing and comprehensive bioinformatics analyses (e.g. hierarchical clustering) to characterise the transcriptome profiles of CRS subgroups. In summary, our attempt at gene expression profiling allowed us to depict a specific subset of CRSwNP (without typical comorbidities), which showed significant downregulation of *APQ5*, *CAV1*, *LTF*, *COX2* and *MGB1* genes, data that might suggest relevant epithelial dysfunction in polypoid chronic rhinosinusitis.

Difficulty in mRNA extraction has to be taken into account for future studies, and in this regard the synergy between surgeon and laboratory is of great importance; the surgeon must have full knowledge of what happens during laboratory processing and what is needed. Additional genes could be selected from the literature for similar studies, or the same genes could be retested. In any case, the present results need further study on larger samples.

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Conflict of interest statement

None declared.

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AUDIOLOGY

Improvement of speech perception in noise and quiet using a customised Frequency-Allocation Programming (FAP) method

Miglioramento della percezione del parlato in condizioni di silenzio e rumore mediante il metodo FAP (Frequency-Allocation Programming) personalizzato

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SUMMARY

The objective of this study is the evaluation of speech recognition of experienced CI recipients with standard MAP settings using the default frequency-allocation tables with the optimised frequency-allocation MAP. This is an observational, cross-sectional and quantitative approach study on 50 adult cochlear implant recipients, 20 bilateral and 30 unilateral implant recipients. 23 men (46%) and 27 women (54%). All subjects were ≥ 18 years old. Differences between the means of the thresholds in tone audiometry in free fields were statistically significant in both unilaterally and bilaterally implanted patients; similar results were obtained between average benefits in disyllabic for both unilaterally and bilaterally implanted patients ($p < 0.005$). The differences between the means of scores were statistically significant for unilaterally and bilaterally implanted patients, similarly occurred with the average in HINT test between standard SRT50% programming and frequency allocation fitting ($p < 0.005$). Patients using the frequency allocation method, which assigns frequencies based on fundamental frequencies, showed better perception of disyllabic words and open-set sentences in quiet and in noise than patients previously fitted with standard fitting techniques. The method can be applied to different processors and used with different strategies of stimulation. It allows reduction of current intensity levels as well as an increase in the dynamic range and improves the quality of the representation of the signal.

KEY WORDS: Cochlear implant • Speech perception • Programming Method

RIASSUNTO

L'obiettivo di questo studio è la valutazione della discriminazione verbale da parte di soggetti esperti portatori di impianto cocleare con impostazioni MAP standard, utilizzando le tabelle predefinite di allocazione di frequenza con un MAP di frequenza ottimizzato. Questo è uno studio osservazionale, trasversale e quantitativo su 50 adulti con impianto cocleare, 20 bilaterali e 30 monolaterali. 23 maschi (46%) e 27 femmine (54%). Tutti i soggetti erano maggiorenni. Le differenze tra i valori medi di soglia nell'audiometria tonale in campo libero sono risultati statisticamente significativi nei pazienti impiantati sia monolateralmente che bilateralmente; risultati simili sono stati ottenuti nei test bisillabici nei pazienti impiantati sia monolateralmente che bilateralmente ($p < 0,005$). I pazienti che hanno utilizzato il metodo di allocazione di frequenza, che assegna le frequenze sulla base di quelle fondamentali, hanno mostrato una percezione delle parole bisillabiche e delle frasi libere in quiete e nel rumore migliore rispetto ai pazienti con dispositivo precedentemente regolato con tecniche standard. Il metodo può essere applicato a diversi processori e utilizzato con differenti strategie di stimolazione. Permette la riduzione degli attuali livelli di intensità così come un aumento del range dinamico e migliora la qualità della rappresentazione del segnale.

PAROLE CHIAVE: Impianto cocleare • Percezione del parlato • Mappatura impianto

Introduction

Cochlear implants were originally designed to allow speech perception in the absence of noise. While success has been achieved in restoring speech-in-quiet understanding, their performance with respect to music and speech in background noise is less than ideal ¹⁻³. Processor fitting is based on subjective responses to stimuli presented in different channels of the electrode array. This subjectivity

becomes a problem when dealing with patients who are not cooperative (e.g. toddlers), or who have difficulties with language development and communication skills ⁴. In these cases, the use of information obtained from objective measurements is useful in assessing electrode functionality and thresholds of hearing (T-levels) and thresholds level of comfort (C-levels) estimates. Examples of these include the stapedius reflex evoked by electrical stimulation,

neural response telemetry and electrically evoked potentials. However, listening to subjective information provided by the patient is an important aspect to keep in mind⁵⁻⁸.

Proper adjustment of the speech processor of the cochlear implant is essential to provide good quality of sound perception and speech intelligibility. For fitting a multichannel cochlear implant, the channels must be checked in order to verify the functionality of stimulation that is sent to each of the electrodes, estimate the perception threshold (T-level) of the electrical impulses and estimate the maximum level of comfort (C-level) or maximum level of stimulation that the patient accepts without feeling discomfort. The T and C-levels yield the dynamic ranges for each electrode⁹.

Frequency-allocation fitting improves musical and melodic auditory recognition in cochlear implant patients. It can be applied to different processors and different stimulation strategies. The outcome of applying the frequency allocation method allows reduction of current intensity levels and an increase in the dynamic ranges, which decreases band-overlapping when mapping and improves audio quality of the representation of the signal⁸.

Music and human voices, far from being made up of pure tones, are made up of fundamental notes and a series of harmonics added to the fundamental frequency, which distinguishes one instrument from another, for example. The harmonics are integer multiples of the fundamental note. As one gets further away from the fundamental, the volume decreases and becomes practically inaudible as the sixth or seventh harmonic is approached^{9,10}.

Sound-processing strategies for cochlear implants represent a set of rules that defines how the sound processor analyses acoustic signals and codes them for delivery to the cochlear implant. The most commonly used coding strategy, the ACE (Advanced Combination Encoder), takes advantage of the 22 closely spaced intracochlear electrodes and the place-pitch selectivity of the cochlea to deliver spectral resolution. The places of stimulation in the cochlea greatly depend upon ongoing spectral analysis as each of the 22 electrodes are associated with a frequency-band. A primary function of a MAP (program) is to translate the spectral information in the incoming acoustic signal into instructions for channel stimulation. The frequency-to-channel allocation is assigned by programming software depending on the coding strategy, type of speech processor and number of channels available for stimulation. While in routine clinical practice frequency table are assigned by defaults, the original impetus for our work was to understand if, by customising frequency-to-channel allocation, it would be possible to improve the differentiation of complex sound and, as a result, improve speech understanding and music recognition.

A spectrum analyser computes the Discrete Fourier Transform (DFT), a mathematical process that transforms a waveform into the components of its frequency spectrum, of the input signal and is, therefore, a useful tool to predict how the speech processor will extract the spectral components of a sound. Prior work was carried out with the spectrum analyser (*Spectra LAB FFT Special Analysis System version 4.32.11 by Sound Tecnologic Inc*) in order to create WAV files containing complex sounds to be used to customise the frequency-to-channel allocation (Frequency Table). Chords were executed and recorded between the 3rd and 6th octave, containing harmonic and non-harmonic sounds, altered and unaltered scales and ascending and descending tone scales. Piano, guitar, trumpets, trombone, soprano saxophone and violin were selected for their specific fundamental frequency and interpreted at the same intensity and tempo.

In our previous work, aiming to improve music recognition, we successfully used these WAV files to optimise a MAP frequency-allocation table for a CI user⁸. Based on these earlier findings, in this comparative performance study, we assessed speech recognition of experienced CI recipients with the standard MAP settings using the default frequency-allocation tables with the optimised frequency-allocation MAP.

Materials and methods

Study design

An observational, cross-sectional and quantitative-approach study was performed in 50 consecutively implanted, experienced adult cochlear implant recipients being treated routinely in our implant clinic. With respect to the cross-sectional nature of this study, it must be specified that the post-treatment auditive test was performed after a three-month period because of the particularities of the patient's evolution and responses to the treatment/intervention. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Ethics Committee of our Hospital.

Subjects

Subjects comprised 20 bilateral implant recipients, 11 men (55%) and 9 women (45%), mean age 45.6 years (SD = 11.54), with an age ranging from 33 years and 69 years. The average value of auditive thresholds previously to the implantation were 86.11 dB (SD = 10.08) for the right ear and 88.33 dB (SD = 8.40) for the left ear; the average value in percentage for the logaudiometry was

38.89% (SD = 13.32) and 30 unilateral implant recipients: 16 men (53.33%) and 14 women (46.67%), mean age 35.82 years (SD=7.68), and age ranging from 19 years and 48 years; The average value in the auditive thresholds prior to the implantation was 86.59 dB (SD = 8.78) in the implanted ear, being their average percentage in logoaudiometry 34.55% (SD = 14.79). All the patients had a Nucleus® 24 Contour Advanced implant with full electrode insertion.

Surgeries were performed in the same implant centre by the same surgical team.

All patients were short-term deafened, i.e. under 5 years, pre-implantation. At the time of their enrollment in the study, all patients were experienced users with a minimum of 1-year post-implantation CI use in, at least, one ear, and had a stable map with a minimum of 18 active channels (i.e. to allow modification of the full set of frequency-allocation bands). All the patients used the Freedom or CP810 sound processor programmed with the ACE signal processing strategy with a stimulation rate between 900 Hz and 1,200 Hz.

Patients with incomplete insertions and comorbidities preventing them from cooperating with the modified programming and evaluations were excluded from the study.

Fitting procedure

Cochlear Custom Sound Suite, version 5.0 was used as the software platform to MAP all sound processors using standard clinical procedures at first and subsequent fittings, deactivating extra-cochlear electrodes. For the comparison, the modified mapping technique involving modified frequency-allocation bands was created using the same software. Performance with both the standard and modified MAP was compared on speech recognition test measures acutely and after a short take-home trial with the modified MAP.

Principals of the customised Frequency MAP

The Frequency Allocation Table (FAT) defines the frequency range (frequency bandwidth) that is assigned to each active channel in the map. Each channel covers a specific frequency range and a given channel receives stimulation when its bandwidth has sufficient energy to be selected as a maxim. Increasing a band width of a channel may change the electrode associated with a given frequency to the lower adjacent one. For example, increasing channel 11 frequency band from (1688-1938) to (1688-2019) will result in representing the frequency 2,000 Hz with electrode 11 instead of electrode 10. Changing the electrodes used to transmit the electrical stimulation inside the cochlea changes the pitch perception of the user; therefore, optimising frequency table has the potential to

improve discrimination of complex sounds. Also, enlarging the bandwidth increases the potential for the electrode to be stimulated.

As per the standard ACE strategy, to optimise speech recognition, the aim is to present the fundamental frequencies selecting the maximal energy bands from an acoustic sound signal. The principle of the modified frequency allocation adjustments is focused on individually tailoring and improving resolution for the identification of fundamental frequencies.

The specific steps for the modified Frequency MAP were as follows for each subject enrolled:

1. Standard MAP.

As per the routine standard MAP procedure, only activated intracochlear electrode channels are used with T and C-levels set in response to subjective responses and balanced.

(Note that electrodes in areas of sparse neuronal population are routinely deactivated as detected by NRT and impedance measures).

2. Modified MAP and global adjustment of T and C levels.

Prior to adjusting the frequency bands, the electrode channels from the standard MAP are balanced and a global reduction of 25% for both T and C is implemented.

3. With the full MAP created, switching into live-voice mode, with the clinician's voice as stimulus, the C-levels are modified globally until a dynamic range of at least 47 is reached. As the patient becomes accustomed to the sound quality and intensity during the fitting session, the dynamic range stabilises between 49 and 51 current levels, enabling increased intensity resolution.

4. Modification of bands and frequency.

Using the WAV sound files created in our prior work that represent the fundamental frequency and first harmonic of a range of preselected musical instruments for the modified frequency MAP, the boundaries of the frequency-allocation channels are reallocated via programming software for stimulation to the corresponding cochlear implant channels. These values are based on the patient's listening ability to audibly detect the difference between each set of instrument WAV files presented within each stimuli series (Table I).

The stimuli versus response

- Commencing with electrode 22, changing to lower limit of 205 Hz, to avoid the poorer sound quality below 200 Hz, the upper limit frequency boundary is modified based on the patient's responses to each stimuli pair based on an audible difference task.

- For each audible difference task, the patient, listening in live-voice mode, is presented a pair of different WAV file stimuli corresponding to the targeted frequency band (Table I).
- Following presentation of each stimuli WAV file pair, the patient is asked if they can detect an audible difference between the two stimuli or not.
- Up to 5 different stimuli pair presentations can be presented for each respective electrode.
- When an audible difference is detected between the stimuli pair, the upper frequency limit boundary is set for use as the stimuli presentation and the clinician moves on to testing the next adjacent channel.
- However, in the event no audible difference is detected between the stimuli pair after 3 “no difference” responses to 3 consecutive stimuli pairs, the upper limit of the default frequency boundary is then augmented by + 50 Hz.
- Moving on to each adjacent electrode in sequence, the stimuli - response procedure is repeated for each corresponding frequency channel using the boundary guidelines proposed in Table I.

The electrode test sequence

- Focusing on the reference fundamental frequencies for the various instrument WAV files, following reallocation of the upper-frequency limit for channel 22, channels 21-20-19 and 18 were tested, representing the frequencies in the 250 to 500 Hz range, testing the minimal audible difference for stimuli pairs presented

Table I. WAV file stimuli corresponding to each consecutive series of channels used to determine the individual frequency reallocations for the Modified Frequency Allocation (FAP) ⁸.

Fundamental note	125 Hz - 250 Hz	3 rd octave chord piano (C-F)	Channel 22 205 Hz 210 Hz
	250 Hz - 500 Hz	3 rd octave chord guitar-piano (C-F)	Channels 21-20-19-18
	400 Hz - 1 kHz	4 th octave chord trumpet-trombone sax soprano (C)	Channels 21-20-19 18-17-16
	800 Hz - 2 kHz	4 th octave chord piano-string (C)	Channels 17-16-15 14-13-12
Harmonics	2 kHz - 4 kHz	5 th octave chord piano (C-F)	Channels 11-10-9 8-7-6
	4 K Hz - 8 kHz	Vowels and consonants Use of familiar voices (specific to each individual)	Channels 6-5-4 3-2-1

from the WAV file corresponding to the 3rd octave of a piano and a guitar.

- Then, electrodes 17 and 16 were tested with the frequency range 400 to 1,000 Hz as reference, which is where most musical elements are found (e.g. voice, guitars and keyboards), running the WAV file corresponding to the 4th octave chord of trumpet, trombone, saxophone and soprano.
- Still focusing on the reference musical fundamental frequencies, electrodes 15-14-13 and 12 were included, focusing on the frequency range 800 to 2,000 Hz, running the WAV file corresponding to the 4th octave chord for piano and string instruments.
- Representation of the remaining sound signal harmonics involves modification and emphasis of the differences between channels 11 through to 1. This involves frequencies between the 2 and 7.9 kHz range.
- Electrodes 11-10-9-8-7 and 6 with the reference frequency range between 2,000 to 4,000 Hz were tackled next. Importantly, this area should not be over-enhanced as it may result in a nasal quality perceived in voices ⁸. The WAV file used corresponds to the 5th octave chord of the piano.
- Finally, electrodes 5-4-3-2 and 1 were checked, with the frequency range 4,000 to 8,000 Hz as reference. This is where the clarity of voices is found, over-enhancing in this range can produce a lisp or over emphasis of the “s” in spoken voice. As stimuli, familiar voices combining vowels and consonants are used in this area (e.g. family members in attendance, clinicians voice etc.) ⁸.
- The time used in patient coding to perform the total modification of the MAP, in our experience, requires around 20 minutes.
- The Modified Frequency Allocation Map is saved, and the patient is asked to use the FAP at home for a one-month home trial.

Figure 1 shows the electrodiagram obtained with the Nucleus Implant Communicator (NIC); the variance between Standard Fitting and Frequency Fitting. For it a WAV file of the 4th-octave F-chord (Between 400 Hz and 1000 Hz) was used for the coding session, and only the frequency bands were modified; whereas the Dynamic Range, the T level (threshold) and the levels C (comfort) were not altered.

The power of signal in a given frequency band $[f1, f2]$ is:

$$P_{FrequencyBand} = 2 \int_{f1}^{f2} S_{xx} (2\pi f) df$$

So, if we expand the frequency band, $f_1 <$ and $f_2 > f_2$, the the power of the signal in the new frequency band will, most likely, increase.

$$P'_{FrequencyBand} \geq P_{FrequencyBand}$$

This may help to describe why after the frequency mapping some channels seem to show increased current levels.

Evaluation schedule

All subjects were assessed with recorded Spanish speech materials in the sound field with the subjects seated at a 1 meter distance from the speaker with both their standard MAP and their individually tailored modified FAP MAP. Subjects were assessed at visit 0 with their optimised standard MAP. Following fitting of the FAP MAP and fine tuning, as needed, and after a 3-month take home trial, all subjects were reassessed using the same test materials and conditions.

Evaluation materials

Aided Tone audiometry in free field. Aided hearing thresholds for warble tones in the free field for 250, 500, 1,000, 2,000, 4,000 and 6,000 Hz were measured for each ear and bilaterally, where applicable, with the patient seated 1 metre away from the speaker. Results are shown for the mean thresholds of frequencies 500, 1,000 and 2,000 Hz.

For bilateral CI users, ears were assessed simultaneously with each of two speakers located at $+45^\circ$.

Hearing in Noise Test (HINT). The HINT sentence test measures a person's ability to hear speech in quiet and in noise. The HINT test is used in its validated Spanish version. The sentence test consists of lists of 20 phonetically balanced sentences with a total of 100 words presented with adaptive signal-to-noise ratio (SNR) or in quiet. The HINT test battery consists of four test conditions. For each test, the speech stimuli are presented from a speaker located directly in front of the subject at 0° azimuth, one metre from the subject's head. For each of the four test conditions, the subject is required to listen to a sentence and repeat it. The four test conditions are: (1) sentences with no competing noise, (2) sentences with competing noise presented directly in front of the patient (S0N0), (3) noise presented at 90° to the right of the patient, and (4) noise presented at 90° to the left of the patient. In all conditions, the competing noise is presented at a fixed loudness of 65 dB SPL. The loudness of the sentences presented is varied throughout the test, depending on whether the patient repeats it correctly or not. The software automatically adaptively modifies the noise level by varying the SNR until a result 50% correct speech recognition is achieved in silence. The resulting score is the SNR at which 50% was achieved and is called sentence reception threshold at 50% (SRT50%). For automation of the test and scoring, a test version of a software application for Windows was used: *HINT for Windows*. Only the S0N0 configuration was applied¹¹.

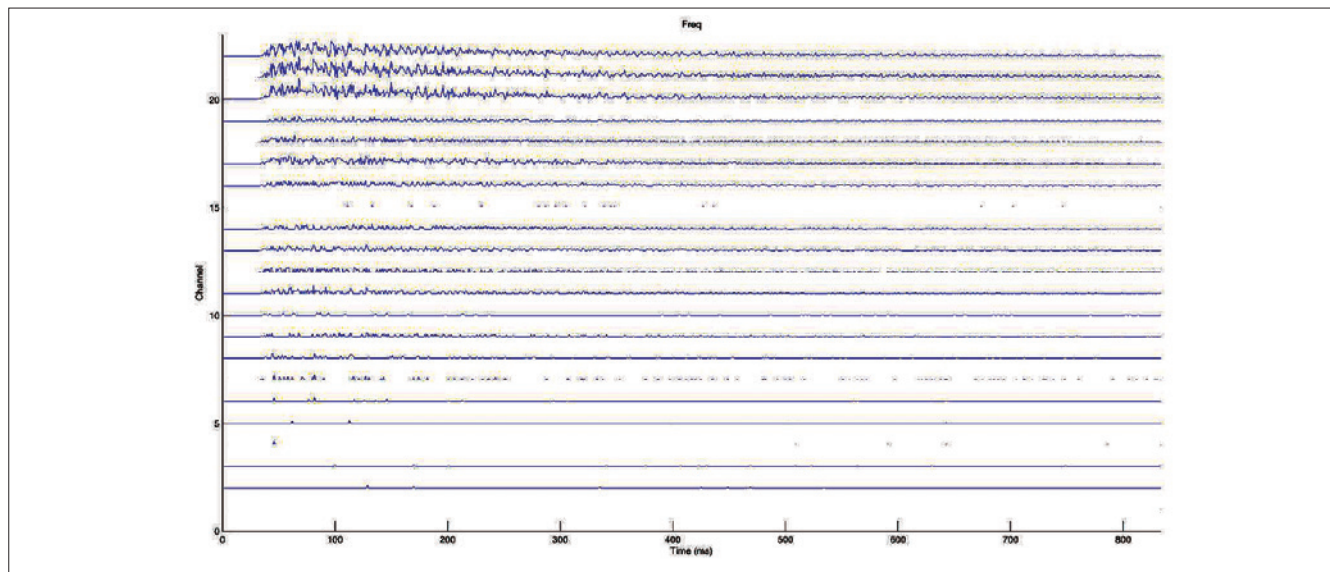


Fig. 1. Difference Standard Coding Electrodeogram vs Frequency Coding Electrodeogram. In this case, it can be seen that small differences are observed for the apical electrodes, 1-5, and that higher differences are observed for electrodes 21-11. Our observations suggest, however, that even the minor differences shown for all the electrodes can affect sound quality.

Disyllabic Word Test. The speech recognition test in quiet was conducted in a calibrated sound field with patients seated 1 metre away and an at an azimuth angle of 0° to the speaker stimulus using CD-recorded, calibrated speech stimuli. The test was performed according to the “Protocol for the assessment of hearing and speech in Spanish Language in a program for cochlear implants” with two lists of 25 words presented for each condition at 65 dB SPL with the percent-correct word score recorded for each ¹².

Open-set Spanish Sentences Test. Recorded sentence materials were presented in quiet at a fixed level of 65 dB SPL in the free field with the subject seated 1 metre away from the speaker at 0 azimuth. The materials consist of a Spanish adaptation of the “Everyday sentences test” (CID Sentence test) ¹². Materials were comprised of 100 sentences making up 10 lists. Percent-correct word scores are recorded for the daily listening condition for each patient (i.e. unilateral or bilateral CI use).

Statistical analysis

For statistical data processing, SPSS (version 21.0) was used. Hypothesis testing was considered statistically significant when the corresponding p-value was less than 0.05. The statistical comparison for independent samples was performed by using the Student t-test.

Results

Tone audiometry in free fields

The means of the warble tonal thresholds of patients with standard programming were 30.4 dB (unilateral) and 34.2 dB (bilateral), and with frequency programming were 21.9 dB (unilateral) and 24.7 dB (bilateral). The differences between the means of the thresholds were statistically significant in unilaterally and bilaterally implanted patients, ($p < 0.005$). In the box plots of Figure 2, the distribution of means of warble-tone thresholds were evaluated for unilateral and bilateral patients by using the standard and FAP MAPs.

Disyllabic tests

The average score achieved for the disyllabic test was 73% (unilateral) and 83.2% (bilateral) in patients with standard fitting, and 85.25% (unilateral) and 92.5% (bilateral) in patients with frequency allocation fitting. The differences between average benefits in disyllabic tests were statistically significant for both unilaterally and bilaterally implanted patients ($p < 0.005$).

Open-set sentence test

The average benefit for open-set sentence scores was 75.7% (unilateral) and 85% (bilateral) in patients with a standard fitting, and 87.5% (unilateral) and 96% (bilateral) in patients with frequency allocation fitting. The differences between the means of scores were significant for unilaterally and bilateral implanted patients ($p < 0.005$). In the box plots of Figure 3, the distribution of the percentage-correct scores for the disyllabic and sentence tests for the two different groups, unilateral and bilaterally implanted patients are shown.

HINT test

In the box plot in Figure 4, SRT50% distribution for the conditions Standard Programming vs FAP is shown. The mean SRT50% values for patients with conventional programming was 19.3 and 9.8 for unilateral and bilateral patients with frequency allocation fitting, respectively. Differences between mean values of standard SRT50% programming and frequency allocation fitting were significant ($p < 0.005$).

Discussion

The methodology presented herein is supported by the fundamental physiological principles presented in the place theory of Hermann von Helmholtz in the XIX century, which was later verified and modified by Georg von Békésy. Our method is also based on frequency principles; moreover, the auditory nerve’s frequency selectivity is considered ¹³⁻¹⁶. Following these principles, our method relies on the fundamental frequency. The allocation is independent of the electrode within the cochlea and of the neural response of the area.

To allocate the remaining frequencies, a study of postlingually deafened adults with auditory memory was used. Music files were used, which introduces a subjective element in the methodology since all the patients that participated had music melody memory. Once the dynamic range is established in the different channels, for each patient. This remains stable along the electrode array, because of the physiology of the inner ear. It was assumed that hearing deprivation in this case is insufficient to produce alterations or degenerations in the hearing neural paths ¹⁷.

The clinical impact of cochlear implants has been extremely successful. The search for ways to optimise the benefit of cochlear implants has been ongoing to improve not only speech understanding in quiet, but also in noise and for music perception; both are difficult situations for most CI users ^{18,19}.

Cochlear implant processors should be properly fitted with at least some degree of customisation. The goal is to establish a set of parameters that define the electrical im-

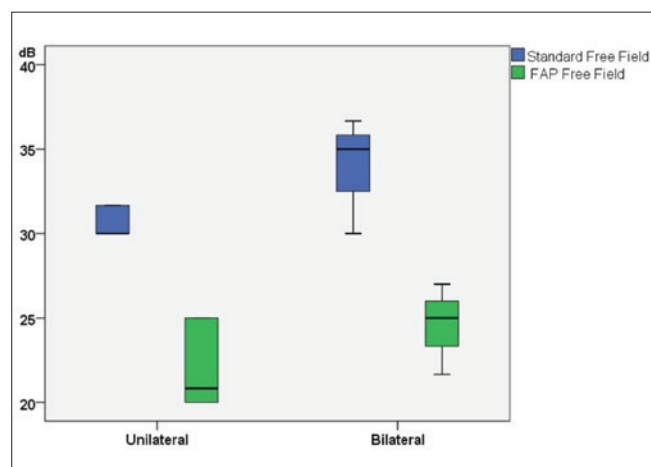


Fig. 2. The distribution of means of warble-tone thresholds were evaluated for unilateral and bilateral patients using the standard and FAP MAPs.

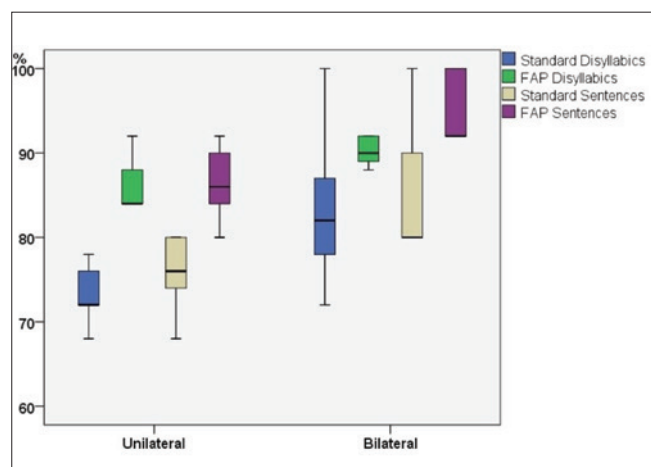


Fig. 3. The distribution of the percentage-correct scores are shown for the disyllabic and sentence tests for unilaterally and bilaterally implanted patients.

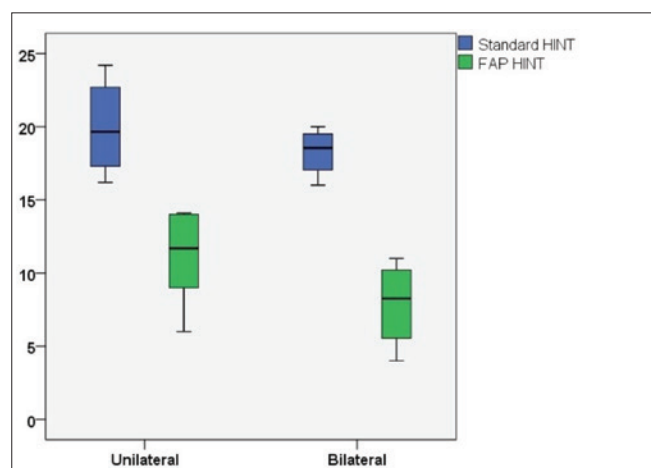


Fig. 4. SRT50% distribution is shown for the Standard Programming conditions vs FAP.

pulses generated by the device in response to sound that yield optimum speech intelligibility. Quality programming of the cochlear implant system is crucial^{19,20}.

It is important to remember that programming the speech processor is not the sole determinant in good performance of a patient. The age of implantation, family support, duration of deafness, the communicative context in which the patient lives, cognitive ability and use of the device are among the variables that can affect performance^{3,20,21}.

CI users who perform well on tests of speech and sentences in quiet often report difficulty understanding in everyday noisy environments²²⁻²⁴.

Baudhuin and colleagues studied implanted children to evaluate the parameters that influence better speech perception. Evaluating the findings of their study, they confirmed the need to create an individualised configuration for the fitting of each child, as well as the importance of speech recognition testing as follow-up checks, both in quiet and in noise²⁵. In the Zhou and Pflingst studies, it can be concluded that the site-specific adjustments of the T-level settings improved modulation sensitivity at low levels and speech-perception thresholds²⁶. In addition, as in Baudhuin's study²⁵, our current study also included T-level estimates.

Performance optimisation of patients in their daily lives is the goal of using frequency allocation fitting. By harnessing the full potential of the cochlea, stimulating throughout the spiral ganglion in each sampling window, it is possible to provide further spectral and temporal interaction. It was previously observed that the use of the frequency allocation method allowed better musical and melodic perception and recognition compared to standard fitting⁸.

The results of this investigation indicate that subjects showed significant improvements when using the frequency allocation method. The test data clearly demonstrate that patients show better speech recognition in quiet, as well as better speech recognition in noise.

The study performed by Matthias Meeuws should be noted, namely "Computer-assisted CI fitting: Is the learning capacity of the intelligent agent FOX beneficial for speech understanding?"²⁷: the processor was programmed with a predictive mode after their patient's responses to verbal and tonal stimuli. In our study, responses to music frequency bands are considered.

In implanted patients whose native language is a tonal language, the described method is of special importance due to specific characteristics of those languages. It is also important to specify that all patients (10/10) chose to continue using the map optimised by using frequency allocation. As this is a new method developed at our centre, it has not been possible to compare the results with other studies on the same type of changes in the parameters.

Conclusions

Patients using the frequency allocation programming method, which assigns frequencies based on fundamental frequencies, showed better perception of disyllabic words and open-set sentences in quiet and in noise than patients previously fitted with the standard fitting techniques. The method can be applied to different processors and used with different strategies of stimulation. It allows reduction of current intensity levels as well as an increase in the dynamic range, which enables a less disturbing mapping of each audio band and improves the quality of the signal representation.

Conflict of interest statement

None declared.

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VESTIBOLOGY

Saccades and driving

Saccadi e guida

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SUMMARY

Driving is not only a physical task, but is also a mental task. Visual inputs are indispensable in scanning the road, communicating with other road users and monitoring in-vehicle devices. The probability to detect an object while driving (conspicuity) is very important for assessment of driving effectiveness, and correct choice of information relevant to the safety of driving determines the efficiency of a driver. Accordingly, eye fixation and eye movements are essential for attention and choice in decision making. Saccades are the most used and effective means of maintaining a correct fixation while driving. In order to identify the features of the most predisposed subjects at high driving performances and those of the high-level sportsmen, we used a special tool called Visual Exploration Training System. We evaluated by saccade and attentional tests various groups of ordinary drivers, past professional racing drivers, professional truck drivers and professional athletes. Males have faster reaction time compared to females and an age below 30 seems to guarantee better precision of performance and accuracy in achieving all visual targets. The effect on physical activity and sports is confirmed. The performances of the Ferrari Driver Academy (FDA) selected students who were significantly better than those of a group of aspiring students and amateur racing drivers probably thanks to individual predisposition, training and so-called 'neural efficiency'.

KEY WORDS: Saccades • Driving • Racecar driver • Eye-tracking • High-level sportsmen

RIASSUNTO

Guidare non è solo un compito fisico, ma anche mentale. Gli input visivi sono indispensabili per la scansione della strada, la comunicazione con gli altri utenti della strada e il monitoraggio dei dispositivi di bordo. La probabilità di rilevare un oggetto mentre si guida (conspicuity) è molto importante per la valutazione dell'efficacia della guida e la scelta corretta delle informazioni rilevanti per la sicurezza determina l'efficienza di un conducente. Di conseguenza la fissazione visiva e il movimento degli occhi sono essenziali per l'attenzione e la scelta nel prendere decisioni. I movimenti saccadici sono il mezzo più usato ed efficace per mantenere una corretta fissazione durante la guida. Per identificare le caratteristiche dei soggetti più predisposti alle alte prestazioni di guida e quelle degli atleti di alto livello, abbiamo utilizzato il Visual Exploration Training System. Abbiamo studiato con test saccadici e attentivi vari gruppi di conducenti ordinari, di piloti professionisti, di camionisti professionisti e di altri atleti professionisti. I maschi hanno un tempo di reazione più veloce rispetto alle femmine e l'età inferiore ai 30 anni sembra garantire una migliore precisione delle prestazioni e nel raggiungere tutti gli obiettivi visivi. L'effetto dell'attività fisica e lo sport sono confermati. Le performance degli allievi selezionati della Ferrari Driver Academy sono significativamente migliori, in particolare rispetto al gruppo di aspiranti studenti e piloti dilettanti, probabilmente grazie alla predisposizione individuale e sulla cosiddetta 'efficienza neurale' dovuta sia ad un utilizzo ridotto delle risorse che al miglioramento nell'elaborazione delle informazioni, grazie a una migliore comunicazione tra le aree del cervello correlate alle attività.

PAROLE CHIAVE: Saccadi • Guida • Piloti sportivi • Eye-tracking • Sportivi di alto livello

Introduction

Driving is not only a physical task, but is also a mental task.

Our behaviour while driving depends from various factors: external non-modifiable elements (e.g. weather), external modifiable elements (mechanical equipment) and those dependent on our body (physical characteristics, psychological and adaptive factors). We live in a multi-sensorial environment: visual information (such as objects, persons, animals, buildings, locations), acous-

tic information (like sounds, voices, noises), vestibular information from the labyrinths (like linear and angular acceleration, head position), proprioceptive information (body position) and tactile information (skin perception of posture and movement) are fundamental for adaptive programs to every environmental condition.

Many subjective cognitive processes, like attention, memory, learning, motivation, decision and psychological factors, are able to influence information processing and the ability to adapt quickly to modifications. Human errors such as misperception, information processing errors and

poor decision making are frequently identified as causes of accidents¹⁻⁵.

Visual inputs are indispensable in scanning the road, communicating with other road users and monitoring in-vehicle devices. The probability to detect an object while driving (conspicuity) is very important for assessment of driving effectiveness, and correct choice of information relevant to the safety of driving determines efficiency of a driver.

Accordingly, eye fixation and eye movements are essential for attention and choice in decision making⁶⁻⁹.

The main goal of eye movements is to maintain foveal control of the most important visual target in every static or dynamic condition, but drivers need to acquire relevant information using both central and peripheral vision, the so-called useful field of view (UFOV).

Various eye movements are used to perceive information in driving: smooth pursuit (SP), optokinetic reflex (OKR), vestibulo-oculomotor reflex (VOR), vergence movements and saccadic movements (SM). These various systems are closely connected to control of the head (eye-head coordination mechanism) and total body movements (posture and gait control).

The eyes are never really fixed, because physiological micro-movement is continuous and has a nature of low-amplitude ($< 1^\circ$) and high-frequency vibrations (50-100 Hz). SM constitute the vast majority of ocular movements.

Saccadic Reaction Time (RT) exhibits temporal variability that is largely accounted for by the time necessary for visuo-motor and motor neurons to reach a specific threshold. The velocity is proportional to movement amplitude and reaches 900°/sec in humans. The saccade-generating system cannot respond to subsequent changes in the position of the target during eye movement and a second saccade must be made to correct the error. Any shift of gaze larger than about 20°-30° is accompanied by a head movement (so-called eye-head coordination). The head is moving at least 20-50 msec later and the vestibulo-ocular-reflex (VOR) causes the eyes to roll back in the head to keep gaze on the target.

SM may be reflexed or voluntary, peripherally-visually guided or centrally guided, and can be of various kinds. With regards to driving, the most important kind of saccades are the pro-saccades (reflexive saccade triggered exogenously by the appearance of a peripheral stimulus, or by the disappearance of a fixation stimulus), the scanning saccades (triggered endogenously for the purpose of exploring the visual environment), the anti-saccades (the eyes move away from the visual onset toward another direction), the memory guided saccade (the eyes move toward a remembered point, with no visual stimulus) and the predictive saccades (the eyes are kept on an object

moving in a temporally and/or spatially predictive manner; saccades often coincide with or anticipate the predictable movement of an object).

Voluntary saccades are much more frequent in everyday life. A simple visually guided saccadic eye movement requires at least two mental processes: target selection and motor preparation. These processes are carried out by a network of cortical and subcortical structures¹⁰⁻¹¹. The frontal eye fields, parietal eye field, the motion-sensitive area (MT/V5), the precuneus (V6), and the angular and the cingulate gyri were more activated in reflexive saccades than in voluntary saccades. No significant difference in activation was found in the cerebellum. Working memory may be involved in anticipatory drifts¹² and different cortical resources may be recruited when prediction is utilised, resulting in reduced latency, increased peak velocity and anticipatory movements. The cerebellum is crucial for synchronising saccades with learned or planned temporal events and the cerebellar vermis IV/V is involved in temporal prediction for saccadic movements. Usually antisaccadic responses show an increased latency and number of errors compared to prosaccadic response and the antisaccadic task also allows evaluation of the capacity to inhibit reflexive saccades and produce voluntary saccades. Its neuronal related network is still discussed¹³⁻¹⁵. To explore our environment, we make on average three saccades per second. Most of these saccades are of small amplitude ($< 10^\circ$ of visual angle) and in conjunction with head and or trunk movements¹⁶. Saccade motor control is highly stereotyped and automatised. Its long-term maintenance is served by an oculomotor learning process called saccadic adaptation which has to monitor success after the saccade and learn from observed errors in order to fine-tune planning parameters for future saccades¹⁷. The ability to generate antisaccades in the direction away from a new visual stimulus is fundamental in order to maintain an adequate level of attention. The antisaccade requires the capacity to inhibit a reflexive saccadic response in favour of complex volitional behaviour¹⁸⁻²². Saccadic movements can be trained and within half an hour healthy subjects become able to progressively improve saccadic control²³⁻²⁷. Activity in the inferior premotor cortex is significantly modulated and decreased during the progress of learning. Saccadic movements involve a problem of visual perception. During each, the visual scene sweeps across the retina with high-speed motion with inevitable blurring of the image, as the retina is sweeping the visual field. Object positions in retinal coordinates change, the entire visual image is not updated and humans become effectively blind, but usually we are not aware of this blur during eye movement. We do not perceive very fast disturbing motion or jumps of the

visual scene because there is a mechanism that “cuts off” the processing of retinal images when it becomes blurred. This lack of perception or omission is linked to a phenomenon called masking or saccadic suppression²⁸, which reduces the impact of retinal motion during the saccade on the visual system. This phenomenon is characterised by the inability to detect changes in the location of a target when the change occurs immediately before, during, or shortly after the saccade (120 msec). Because saccadic suppression starts before the actual onset of the saccade, it cannot be triggered by retinal motion and must be centrally activated by the brain. In this way, the cognitive individual system is able to reconstruct, “in real time”, all the details of the retina caught in a glimpse, but not yet focused, through a “filling in” process. For this reason, the spatial reconstruction of the environment that surrounds us takes effect on a central level by comparing memorised past experiences²⁹. However, each scene contains many different objects, few of which are relevant to behaviour at any given moment. Therefore, attentional mechanisms are also needed to select relevant objects. For this reason, the entire visual image is not updated during each saccade and large sudden changes in a visual scene can go undetected (change blindness).

Since the 1980s many authors have understood the important role of vision in driving and have measured eye movements, in daily practice, in sports, on heavy vehicles, at intersections without traffic lights, or in search of parking spaces, and have evaluated the effect of central de-structuring of eye movements due to alcohol intake³⁰. There is evidence that the pattern of eye movements of the driver depends on the number of objects and on the complexity of the landscape^{31,32} and on anticipation, which in turn depends on experience, and which can modify the reaction times. OKR is important while driving curves and at night, when solicitation of the peripheral retina is given by curbs, or, for instance, billboards, trees or tribunes. Too many optokinetic stimulations can be dangerous because of the large number of provoked saccadic phases. The angular VOR (from semicircular canals) makes a fundamental contribution to the maintenance of dynamic visual acuity while moving the head on horizontal and vertical planes. The linear VOR (from otolithic macular receptors) is very important during linear accelerations and decelerations. Unfortunately, the role of the substitutional SM which are typical of vestibular loss patient and which are able to increase the risk of saccadic visual suppression and blindness has not been evaluated.

However, saccades are the most widely used and effective means of maintaining a correct fixation while driving and the frequency of blinking, and saccade characteristics are a parameter to determine the level of fatigue and of attention³³.

In the task of driving, saccades can be frequent and can be shorter than 200 msec.

Typically, drivers tend to fixate straight ahead when driving, usually towards the location where the vehicle will be in the next few seconds, at least on straight and undemanding roads. Drivers may adopt different search strategies when they need to perceive objects located in front of and behind their own car by using the rear and side mirrors or when they drive on a straight road (stable driving), and mainly perceive objects located in front of their own car with few mirror glances. The reflexions in the outside rear view mirror images, passing through double-glazed windows of the car, may provoke misperceptions. When approaching an intersection, drivers made repeated saccadic gaze movements; after entering the intersection, saccadic gaze movements are directed in the direction of turning. One of the most complex visual tasks when driving is exiting a multistory car park, which involves the scanning of hundreds of parked vehicles with an average fixation time of approximately 100 msec. The total time spent fixating on a likely hazardous vehicle is longer for people in the driving-only condition than for those talking on a mobile phone with less exploring saccades.

It can easily be argued that not looking in the right place almost certainly guarantees that drivers will not react to the risk appropriately. Common sense suggests that drivers should “keep their eyes on the road” and “look where they are going.” During navigation, a driver tends to choose a target point in the field of view, allowing him/her to anticipate direction of travel of the vehicle. This tendency can cause 2 types of conflict: emergence of a number of points that can be “target points” in the same visual task, or occurrence of a number of elements that could be important for driving, but related with a variety of other visual tasks, as pedestrian detection or visual control of navigation system. Car drivers can employ various visual strategies. The tangent point strategy is based on the use of the tangent point (TP). This is a point on the lane edge on the inside of the curve where the line of sight is tangential to the lane edge, and corresponds to the point in the driver’s visual field where the visual orientation of the projection of the edge-line is reversed. The TP at a specific moment in time coincides with the apex point of a corner. The “gaze-sampling strategy” proposes to fixate points on the future path and measure the curvature of optic flow vectors, which can inform drivers whether they over- or under-steer and drivers direct their gaze on their future path, approximately 1 to 2 sec ahead of the vehicle³⁴. In general, the TP condition is preferred, and previewing the road curvature by tracking a distant point contributes to the stability of steering³⁵. During daytime

driving, visual distractions, such as billboards located on the roadside of a highway, increase the frequency of errors. Older people need more fixation than younger ones to follow the same scene, as well as more fixation to recognise the scene in circumstances of poor visibility (fog, rain, etc.). Furthermore, older people respond more slowly than younger people, they are less accurate in capturing scenes viewed while driving and make smaller saccades than young drivers³⁶. The literature suggests that expert athletes do not differ from non-experts in elementary abilities such as visual acuity, colour vision, or peripheral response time³⁷, but the former respond faster and more accurately to task-specific cues than non-experts^{38 39}. However, despite the extensive body of knowledge on the technological aspects of racecars, comparatively little is known about the motor, perceptual and cognitive skills of athlete performance in motorsports^{40 41}. Knowledge of these skills may aid in designing training methods for racing drivers and improve driver-vehicle interfaces for not only motorsport applications, but also road vehicles^{42 43}. Both professional and naïve drivers may share the common knowledge necessary for ordinary road driving but driving a racing-car implies a number of additional skills, from the use of different controls to the management of braking and rapid accelerations.

It is well established that practice is a prerequisite for achieving high levels of performance⁴⁴. Many studies have examined the effects of driving experience on eye movements using driving settings^{45 46}. During stable driving, eye movements are less variable in trained drivers than in untrained drivers⁴⁷, and by varying driving conditions the difference becomes more evident. Experienced drivers seem to rely less on foveal vision and more on peripheral vision for steering control. Experienced or safer drivers seem to collect more information of the scene and to be able to move their locus of attention quicker than novices⁴⁶. They also direct their gaze further ahead than novices. Horizontal scanning can be different. Experienced drivers tend to exhibit a wider horizontal search strategy with shorter eye-movement distances and longer fixation durations. On a dual-carriageway road, horizontal variances of fixation positions seem to be larger and fixation durations seem to be shorter in the experienced group than in the novice group; on a rural road experienced drivers seem to have smaller variances of fixation positions and longer fixation durations than novice drivers. Expert drivers are significantly more likely to gaze at areas of the roadway that contain information relevant to the reduction of risks than untrained drivers⁴⁶⁻⁴⁸. Their visual search depends on expectancy or anticipation skills based on experience. Therefore, the trained drivers may

anticipate the locations where potential dangerous events and relevant objects are likely to appear. Those with better attentional function, as measured by avoidance of objects, exhibit faster and larger saccades when driving.

Advanced age hardly affects older drivers' ability to perceive hazards⁴⁹. Novice drivers check the road more and estimate uninfluenced targets. They prioritise fixating on points on the road which aid steering, for example, "future path" points⁵⁰ or fixate closer to the vehicle to maintain lane position. They also look more at side pavements for possible pedestrians stepping out, inspecting slippery roads more often for adjoining traffic or look around for possible undertaking or overtaking vehicles in more demanding situations. This type of visual behaviour is important because wider scanning may result in more peripheral hazards.

In simulated driving there are fewer significant differences in a spatial distribution of fixation points. The differences in visual strategy seem to be linked not only to experience (i.e., how long someone has driven), but also to expertise in a particular field (policemen, truck drivers, racing drivers). Through practice and experience, task performance improves when actions become more automated and there is less of a requirement for conscious intervention^{51 52}. With driving, it may be the case that through experience, fewer conscious resources are required to control the vehicle as driving skill becomes automatic and this frees up resources to allocate visual attention to other parts of the scene. At the tactical level, racing drivers show a different gaze strategy, adjusting their gaze as they drive through the corner and choose different driving lines and optimise their driving lines to increase corner exit speeds. However, racing drivers drive statistically significantly lower best lap times than non-racing drivers not only thanks to eye movements, but also to different eye-head coordination. The driver directs his gaze at a horizontal offset from the TP, and this offset is different for each corner, illustrating that the TP itself is not the main area of visual attention while driving through corners, but also with strong correlation between head rotation and the vehicle's rotational speed approximately one second later. The eyes-in-head angle remains relatively constant throughout the lap with large differences in the head yaw angle for racing drivers compared to non-racing drivers. Racing drivers turn their head nearly twice as often as non-racing drivers while cornering. Racing drivers also steer their head more into corners than non-racing drivers and vary their gaze direction as a function of travelled distance, whereas non-racing drivers keep a more constant gaze location, close to the vicinity of the TP. As racing drivers enter a corner, they direct their gaze away from the TP towards the outside of the corner, and as they progress

through the corner they move their gaze towards the TP and beyond the TP. As the racing drivers exit the corner, they direct their gaze again towards the outside of the corner and subsequently look again towards the TP.

Brain functional studies have begun to indicate that skill acquisition in motor or cognitive domains may be associated with both increased or decreased response in task-related regions⁵³⁻⁵⁹. These findings suggest that neural efficiency may be associated with a greater automaticity and a reduced attentive load during task execution compared to 'ordinary' individuals^{60,61}.

Contextual cueing is a concept in psychology that refers to the manner in which the human brain gathers information from visual elements and their surroundings. It is defined as an attentional guidance or facilitation effect derived from past experiences of (mostly hidden) regularities of the (mainly visual) world. In other words, visual attention can be guided by incidentally acquired knowledge about spatial invariants. The attention decides to select or ignore the visual targets. Recent evidence collected in various highly skilled populations suggests that exceptional abilities, such as elite athletes, professional dancers, archers, divers and musicians, may be associated with specific changes in the morphological and functional architecture of the brain^{56,59,62-78}.

Skills and expertise are accompanied by relevant brain functional modifications even in drivers, and a distinct brain functional organisation emerges even during relatively simple visuo-motor tasks. Just 2 hours of practice with a driving simulator are sufficient to induce structural changes^{79,80}. Indeed, recent fMR studies^{81,82} showed both quantitative and qualitative differences between professional and naïve drivers. During the motor reaction, both naïve and professional drivers recruited similarly distributed networks (bilateral visual occipital, posterior temporal and parietal cortex, sensorimotor, motor and premotor areas, insula, striatum, cerebellum, cingulate, middle and inferior frontal cortex, prefrontal and precentral cortex, precuneus, parahippocampus, thalamus, lentiform nucleus), which include areas devoted to visuo-spatial processing, motor control and executive functions. However, comparative evaluation shows significant differences. Skilled car drivers are characterised by: reduced brain cortical activation and reinforced connectivity measures between task-relevant areas, consistent functional recruitment of driving-related brain regions (including vigilance, visuo-spatial monitoring, navigation, action preparation and motor control), increased grey matter density in basal ganglia, sensory-motor cortex, inferior frontal gyrus, retrosplenial cortex, fusiform/lingual gyrus and parahippocampus. Naïve car drivers are characterised by consistent modulation of brain response mostly limited to visual brain areas,

and to regions devoted to spatial information processing, greater and more extensive response in supplementary motor area, left middle frontal and precentral cortex, bilateral inferior parietal lobule, right superior parietal, and postcentral cortex, cerebellum, and bilateral striatum and greater recruitment of task-related brain areas, including sensorimotor, parietal and prefrontal regions.

Materials and methods

In order to identify the features of the most predisposed subjects with high driving performances and those of high-level sportsmen, we used a special tool called Visual Exploration Training System (VET by SVEP) which consists in: personal computer (PC), eye-tracking system (120 Hz frequency analysis) and a new specific software by SVEP, according to the literature on the subject³⁰.

We examined 174 subjects:

- group 1 (FDA): 6 Ferrari Driver Academy (FDA) students; 6 males (M) aged 15 to 20 years (mean 17.2 ± 2.17);
- group 2 (ARD): 20 FDA aspiring students and amateur racing drivers; 19 M and 1 females (F) aged 14 to 27 years (mean 22.07 ± 5.23);
- group 3 (PRD): 7 past professional racing drivers; 7 M aged 36 to 55 years (mean 42.83 ± 7.13);
- group 4 (BVP): 35 professional basket and volley ball players (Italian top league); 22 M and 13 F aged 19 to 32 years (mean 23.43 ± 5.27);
- group 5 (ORD): 87 ordinary road drivers; 58 M and 29 F, aged 15 to 53 years (mean 33.92 ± 10.16);
- group 6 (PTD): 19 professional truck drivers; 19 M aged 35 to 47 years (mean 41.35 ± 4.73).

Both FDA-selected students and FDA-aspiring students as well as amateur racing drivers had prior experience in go-kart races and/or international high level races with different types of cars.

No participant had any history of balance disorder or asymmetric deficits of auditory or visual function. None was taking any medication.

Subjects were seated in front of a monitor wearing the eye-tracking system.

Two tests were performed.

In the first test (saccade test; ST), the subject had to fix a target point that appeared randomly on the monitor in 31 different positions in 23 sec.

We evaluated:

1. average start time (msec) of ocular movements, defined as the interval of time between the presentation of the stimulus appearance and start of appropriate response in the subject (RT);

2. target reaching time (msec) with 80% accuracy (TRT);
3. average percentage of accuracy in achieving all targets (AP1).

In this way we evaluated the ability to produce repeated saccades for random stimuli maintaining a high level of attention.

In the second test (attentional test; AT), the subject had to maintain fixation on a target point that appeared randomly on the monitor in 50 different positions in 50 sec even during the recurrent appearance of new distracting images (car, humans, animals, road-signals). The distractive images progressively increased in number (from 1 to 4) and type every 10 sec.

A possible saccade towards the distracting image requires a corrective antisaccade, which is more difficult to perform compared to a prosaccadic task. Given the greater difficulty of this task with respect to prosaccadic tasks, heightened control is needed for its success.

We evaluated:

1. number of centred target points or precision of performance (PP);
2. number of saccades not directed towards the target point or attention deficit index (ADI);
3. average percentage of accuracy in achieving all targets (AP2).

The study was developed according to Declaration of Helsinki for Ethical Principles for Medical Research In-

volving Human Subjects of World Medical Association (WMA). All participants were volunteers and were informed about the study procedures and risks involved. All participants retained the right to withdraw from the study at any moment.

Results

Average start time (RT) for the series of 31 random reflexive saccades was shorter in FDA and in BVP (Table I). Target reaching time with 80% accuracy (TRT) was shorter in FDA, ARD and BVP. The average percentage of accuracy in achieving all targets (API) was higher in FDA, ARD and BVP. The highest number of centred target points or rather precision of performance in AT(PP) was in FDA and the lowest was in PTD.

Average percentage of accuracy in achieving all targets (AP2) was higher in FDA, ARD, PRD and BVP.

In AT, there were no significant differences between groups regarding the number of saccades not directed towards the right target point or attention deficit index (ADI).

The subjects aged less than 30 years (Table II) showed significantly better values for the target reaching time, with 80% accuracy (TRT) in ST and for the number of centred target points (PP) and for average percentage of accuracy in achieving all targets (AP2) in AT.

Table I. Mean and sd of the various parameters in ST and AT in various groups and significant differences (p t-test) between ordinary road drivers (ORD) and other groups.

	RT (msec)	TRT (msec)	AP1	PP (N)	ADI (N)	AP2
FDA	238.0 - sd 32.2	337.5 - sd 7.7	74.8 - sd 1.0	50.5 - sd 0.7	39.3 - sd 10.3	69.0 - sd 3.5
ARD	268.3 - sd 31.3	380.0 - sd 29.6	65.9 - sd 7.7	44.0 - sd 4.6	50.3 - sd 32.5	65.2 - sd 3.5
PRD	257.0 - sd 35.8	410.7 - sd 28.0	64.4 - sd 5.5	44.8 - sd 3.1	37.7 - sd 5.2	66.5 - sd 3.1
BVP	252.4 - sd 24.6	339.7 - sd 26.3	70.2 - sd 5.9	45.6 - sd 4.4	48.9 - sd 14.7	67.6 - sd 4.6
ORD	285.7 - sd 39.4	423.7 - sd 39.0	61.5 - sd 8.2	45.0 - sd 5.9	45.8 - sd 21.3	61.0 - sd 7.0
PTD	299.1 - sd 31.1	423.7 - sd 25.8	62.7 - sd 6.2	42.9 - sd 4.1	54.8 - sd 17.9	63.2 - sd 4.4
ORD/FDA	0.0047	0.0000	0.0002	0.0001		0.0069
ORD/ARD		0.0000	0.0309	0.0002		0.0106
ORD/PRD				0.0033		0.0428
ORD/BVP	0.0000	0.0000	0.0000			0.0000
ORD/PTD				0.0001		

Table II. Mean and sd of the various parameters in ST and AT of ordinary road drivers groups (ORD) aged less (29 cases) or more (58 cases) than 30 years.

	RT (msec)	TRT (msec)	AP1	PP (N)	ADI (n)	AP2
ORD < 30 y	284.55 - sd 36.39	367.11 - sd 42.76	61.5 - sd 8.2	48 - sd 5.89	40.62 - sd 25.17	64.8 - sd 5.16
ORD > 30 y	284.11 - sd 38.20	387.45 - sd 35.22	61.6 - sd 8.3	43.38 - sd 5.11	48.66 - sd 18.37	58.8 - sd 7.04
t-test		0.0205		0.0006		0.0001

In ordinary road drivers, there were differences between males and females. RT was slightly longer in females than in males (Table III). The number of saccades not directed towards the target point, i.e. the attention deficit index (ADI) was significantly higher in females and was associated with a lower average percentage of accuracy in achieving all targets (AP2).

This likely indicates a greater number of antisaccades in order to achieve all the correct targets.

The difference in number of saccades not directed towards the target point (ADI) was more significant in subjects aged less than 30 years: males made many fewer exploring saccades than females (Table IV). However, in this range of age the average accuracy in achieving all targets (AP2) was greater in females.

There were significant differences between ordinary road drivers and sports subjects (Table I). The average start time (RT) was shorter in FDA and in BVP.

Target reaching time with 80% accuracy (TRT) was shorter in FDA, ARD and BVP.

In ST, average percentage of accuracy in achieving all tar-

gets (API) was higher in FDA, ARD and BVP and in AT (AP2) in FDA, ARD, PRD and BVP.

Both males (Table V) and females among professional basket and volley ball players showed better performance in the tests, and the female disadvantage was almost completely reduced by practice. The number of saccades not directed towards the target point (ADI) in AT was higher in females.

A probable difference also emerges due to individual predisposition. Indeed, in our tests the performances of FDA-selected students were significantly better than those of the group of aspiring students and amateur racing drivers (ARD) (Table VI).

Discussion

The level of attention and collaboration was high in all groups. Indeed, in the AT there were no significant differences between groups regarding the number of saccades not directed towards the right target point or attention deficit index (ADI).

Table III. Mean and sd values of the various parameters in ST and AT in 58 males (M) and 29 females (F) of ordinary road drivers groups (ORD).

	RT (msec)	TRT (msec)	AP1	PP (NJ)	ADI (N)	AP2
F ORD	294.17 - sd 39.19	381.13 - sd 42.24	62.0 - sd 9.9	46.18 - sd 3.40	52.5 - sd 25.66	59.0 - sd 8.11
M ORD	277.88 - sd 34.76	378.31 - sd 35.45	61.5 - sd 7.3	44.74 - sd 6.05	40.76 - sd 15.90	62.5 - sd 5.72
t-test	0.0516				0.0102	0.0222

Table IV. Mean and sd of the various parameters in ST and AT in 21 males (M) and 8 females (F) of ordinary road drivers groups (ORD) aged less than 30 years.

	RT (msec)	TRT (msec)	AP1	PP (n)	ADI (N)	AP2
F ORD < 30 y	278.46 - sd 41.12	358.0 - sd 41.15	67.7 - sd 7.1	47.71 - sd 2.45	64.37 - sd 37.59	68.6 - sd 5.61
M ORD < 30 y	283.75 - sd 24.59	366.0 - sd 19.69	63.6 - sd 3.0	48.09 - sd 6.67	31.57 - sd 8.99	63.2 - sd 4.3
t-test			0.0349		0.0007	0.0098

Table V. Mean and sd of the various parameters in ST and AT in 58 males (M) ordinary road drivers (ORD) and 22 of professional players group (BVP) and in 29 females (F) ordinary road drivers and 13 of professional players group (BVP).

	RT (msec)	TRT (msec)	AP1	PP (N)	ADI (N)	AP2
M ORD	277.88 - sd 34.76	378.31 - sd 35.45	61.5 - sd 7.3	44.74 - sd 6.05	40.76 - sd 15.90	62.5 - sd 5.72
M BPV	252.2 - sd 27.3	345.2 - sd 26.2	69.1 - sd 6.2	45.9 - sd 3.8	44.9 - sd 10.7	67.2 - sd 4.4
t-test M BPV/ORD	0.0026	0.0002	0.0000			0.0008
F ORD	294.17 - sd 39.19	381.13 - sd 42.24	62.0 - sd 9.9	46.18 - sd 3.40	52.5 - sd 25.66	59.0 - sd 8.11
F BPV	252.8 - sd 20.1	330.3 - sd 24.5	72.1 - sd 5.0	45.4 - sd 5.3	54.6 - sd 18.0	68.4 - sd 4.8
t-test F BPV/ORD	0.0009	0.0002	0.0033			0.0004
F BPV	252.8 - sd 20.1	330.3 - sd 24.5	72.1 - sd 5.0	45.4 - sd 5.3	54.6 - sd 18.0	68.4 - sd 4.8
M BPV	252.2 - sd 27.3	345.2 - sd 26.2	69.1 - sd 6.2	45.9 - sd 3.8	44.9 - sd 10.7	67.2 - sd 4.4
t-test M/F BPV					0.0429	

Table VI. Mean and sd of various parameters in ST and AT in males (M) aged less than 30 years: 6 of Ferrari Driver Academy (FDA), 21 ordinary road drivers (ORD) and 19 aspiring students and amateur racing drivers (ARD).

	RT (msec)	TRT (msec)	AP1	PP (N)	ADI (n°)	AP2
FDA	238.0 - sd 32.2	337.5 - sd 7.7	74.8 - sd 1.0	50.5 - sd 0.7	39.3 - sd 10.3	69.0 - sd 3.5
ARD	268.3 - sd 31.3	380.0 - sd 29.6	65.9 - sd 7.7	44.0 - sd 4.6	50.3 - sd 32.5	65.2 - sd 3.5
t-test FDA/ARD	0.0047	0.0000	0.0002	0.0025	0.0005	0.0069

Usually the mean reaction time to detect visual stimuli and to produce a reactive saccade is approximately 180–200 msec. Reaction time shortens with age through childhood and gradually lengthens during adulthood; it also depends on attention and inter-individual variability is evident⁸³. However, the values remained stable in the age range of our study. Probably in our examination conditions RT in ST (Table I) was higher depending on the particular conditions of examination. In fact, we evaluated the average time for a long series of 31 random reflexive saccades. In agreement with the literature, in our study males had faster RT as compared to females. The age below 30 seems to guarantee better target reaching time (TRT), precision of performance (PP) and accuracy in achieving all targets (AP2). The effect of physical activity and doing sports on improving RT and accuracy in achieving all visual targets is confirmed.

The performances of females professional players are better compared with female ordinary road drivers and in our study the female disadvantage was almost completely reduced by practice^{84–87}. The performances of professional truck drivers were similar to those of ordinary road drivers, but were also characterised by lower precision of performance in the ST. These performances are significantly worse compared with those of racing drivers of the same age. Likely this is related to the problem of driving tasks. In driving, many tasks are performed and drivers may adopt different search strategies depending on the current driving task. For example, when drivers are passing, they need to perceive objects located in front of and behind their own car by using rear and side mirrors in preparation for maneuvering. In contrast, when drivers drive on a straight road (stable driving), they perceive mainly objects located in front of their own car with few mirror glances. Large vehicles only have side mirrors and therefore require different visual control strategies. In fact, it has been shown that the number of gaze movements was significantly greater in drivers of large vehicles. The amplitude of eye movements is significantly broader when driving large vehicles (truck, bus) than during driving a small car.

Finally, the performances of FDA-selected students were significantly better than those of the group of aspiring

students and amateur racing drivers probably thanks to individual predisposition based on so-called '*neural efficiency*', which postulates more efficient cortical functioning based on both a reduced utilisation of resources and an improvement in information processing, thanks to a better communication between task-related brain areas. Indeed, selected populations of individuals achieve very high levels of skills and performance in fields ranging from arts to sport activities as a consequence of intensive training and, probably, of some genetic predisposition⁷². However, the role of genetic predisposition and/or of acquired experience is not yet clear.

Conclusions

Both professional and naïve drivers may share the common knowledge necessary for ordinary road driving, but naïve individuals simply watch the race, while professional drivers imagine themselves to race.

In order to improve both safety and performances during daily or sports driving, it is important "what and where to look". Visual environmental control requires that foveal vision is maintained on specific targets (reference objects, trajectory points) and experience aimed at creating specific neuronal networks able to satisfy the most appropriate eye-test-body motor control strategy.

Indeed, the sensory-motor decision processes interact via functional information-processing loops in the brain to produce complex, adaptive behaviours⁸⁸. To achieve this goal, it is necessary to maintain adequate levels of visual attention even in the presence of distracting targets, reduce saccadic movements (with relative blindness and possible loss of environmental information from sections of the route that increase with increasing speed) and train the ability to perform eventual corrective antisaccades.

These abilities are essential for any high-level sporting activity, particularly for drivers. Athletic men and women acquire these performances with experience and training. The acquired attentional capacity tends to remain high even over time, mostly in racing drivers. Women generally show lower level performances, but they can significantly improve with training. The gaze is considered a good method of evaluation for assessment of attention

while driving⁸⁹ and a correct strategy of visual control of the environment through saccadic and anti-saccadic movements adapted to the situation is of fundamental importance in sport and driving. Our easy-to-use diagnostic method seems to be able to identify the most predisposed subjects at high driving performances and thus those to be submitted to specific training⁴⁵ to improve the function of saccadic exploration and safety in driving.

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Conflict of interest statement

None declared.

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OTOLOGY

The impact of intra-operative factors in otosclerosis outcomes: retrospective study in a tertiary centre

L'impatto dei fattori intra-operatori sul risultato della chirurgia dell'otosclerosi: studio retrospettivo in un centro di terzo livello

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SUMMARY

The aim of the study was to assess results from a large cohort of patients undergoing otosclerosis surgery with respect to the impact of intra-operative variables on post-operative hearing function and complications. We enrolled 384 patients affected by otosclerosis who were subjected to stapes surgery between 2004 and 2013 at a single institution. Surgery was performed in all cases under local anaesthesia, using a manual perforator and/or microdrill. Teflon-piston prosthesis was used in all patients. Audiological data obtained preoperatively and at last follow-up examination (minimum 12 months) were compared. Statistical analysis was performed using the multiple regression model. Peripheral rim otosclerosis and diffuse otosclerosis were associated with better functional results compared to the obliterative pattern ($p < 0.05$). Mean post-operative Air-Bone Gap was significantly higher in the 0.4 mm, compared to 0.6 mm piston group at 0.5 kHz ($p < 0.001$) and 1 kHz ($p < 0.02$); in the stapedotomy group a statistically significant difference was found between 0.4 and 0.6 mm piston groups, in favour of the latter ($p < 0.05$). No differences were encountered in terms of average hearing threshold and complications. Intra-operative variables cannot be fully predictable and our data could help in stratification of the results and as a landmark for the surgeon's decisions.

KEY WORDS: Otosclerosis • Stapedectomy • Stapedotomy • Hearing threshold

RIASSUNTO

Lo scopo dello studio è stato di valutare i risultati ottenuti in un'ampia coorte di pazienti sottoposti a intervento chirurgico per otosclerosi e determinare l'impatto delle variabili intraoperatorie sulla funzione uditiva e sul tasso di complicanze. Abbiamo arruolato 384 pazienti affetti da otosclerosi e sottoposti a intervento chirurgico tra il 2004 e il 2013 in una singola clinica. L'intervento è stato sempre effettuato in anestesia locale e mediante perforatore manuale e/o microdrill. In tutti i pazienti è stata utilizzata una protesi in teflon. I dati audiologici pre-operatori e post-operatori (almeno 12 mesi dopo l'intervento) sono stati confrontati. Le forme di otosclerosi "periferica" e "diffusa" si associavano a migliori risultati funzionali rispetto allo forma "obliterativa" ($p < 0,05$). L'Air Bone Gap post-operatorio medio risultava significativamente maggiore nel gruppo in cui era stato utilizzato il pistone con diametro 0,4 mm rispetto al gruppo con pistone 0,6 mm alle frequenze 0,5 kHz ($p < 0,001$) e 1 kHz ($p < 0,02$); nei pazienti sottoposti a stapedotomia è stata riscontrata una differenza statisticamente significativa tra i gruppi in cui era stato utilizzato il pistone da 0,4 e da 0,6 mm, a favore di quest'ultimo ($p < 0,05$). Non sono state riscontrate differenze in termini di soglia uditiva media e di complicanze tra i due gruppi. Le variabili intra-operatorie non sono completamente prevedibili nel pre-operatorio e i nostri dati potrebbero costituire un aiuto nella stratificazione del risultato e come guida per le decisioni del chirurgo.

PAROLE CHIAVE: Otosclerosi • Stapedectomia • Stapedotomia • Soglia uditiva

Introduction

Otosclerosis is a bone remodelling disorder involving the otic capsule, which leads to a fixation of the stapes footplate and to progressive hearing loss ^{1,2}. In 1958 Shea ³ performed the first total stapedectomy and since then several technological advances have been introduced ^{4,5}. Nowadays surgeons may choose among several techniques and materials and the iden-

tification of prognostic factors is crucial ⁶⁻⁸. Surgical technique (stapedotomy versus partial and total stapedectomy) and prosthesis characteristics have been evaluated as prognostic factors ⁹. Over the years several prostheses have been proposed in terms of size, material, fixation mechanism and shape. At the present time, reviews show conflicting results regarding the role of piston diameter: Wegner et al. ¹⁰ demon-

strated that it does not represent a prognostic factor, whereas Laske et al.¹¹ reported better outcomes for a 0.6-mm piston. Controversial results have been also reported regarding the surgical technique¹²⁻¹⁵; recently, a meta-analysis on 21 studies¹⁶ found no evidence for the superiority of laser versus conventional fenestration.

Besides surgical techniques, intrinsic characteristics of the pathology may influence the intra- and post-operative course. Gristwood¹⁷ classified otosclerosis lesions into 9 types, although he ultimately compared “obliterated” versus “non-obliterated” patterns, demonstrating a better prognosis in the latter group. Portman’s classification¹⁸ includes 5 types of otosclerosis characterised by progressive diffusion of the otosclerotic process, with type 1 corresponding to a small otosclerotic focus, localised at the fissula ante fenestram and type 5 corresponding to a complete obliteration of the footplate and oval window niche. The Portmann classification implies an increasing stapes fixation and surgical risk, based on the extension degree. Malafronte et al.¹⁹ proposed a simpler classification of otosclerosis, based on the appearance of the stapes footplate: blue footplate, white footplate and obliterative footplate. Identification of colour variation before removal of the superstructure seems to be associated with the incidence of footplate complications. The latter classification refers to histologic patterns and thickness of the footplate (fragile/vitreous versus elastic/resistant).

The aim of the present study was to evaluate the effect of intra-operative variables on post-operative results and complications in a large cohort of patients affected by otosclerosis and operated on at our Department.

Materials and methods

From January 2004 to December 2013, 429 consecutive patients were subjected to stapes surgery at the Otolaryngology Unit, University of Bari. All surgical procedures were performed by one surgeon, namely the first author. The diagnosis of otosclerosis was based on normal otoscopic findings, a progressive conductive hearing loss as air conduction pure tone average > 30 dB in the range of 0.5 to 4 kHz and the absence of cochleostapedial reflexes. Tympanometry was not considered essential for diagnosis since it is almost universally normal or shows stiffness of the ossicular chain. Tympanometric data suggesting otitis media or tympanosclerosis led to exclusion of the surgical candidacy. Pre-operative CT scan was not considered as part of routine evaluation.

Subjects whose audiological reports before and/or after surgical treatment were not available and patients whose follow-up time was less than 12 months were excluded. Patients

undergoing revision surgery, affected by tympanosclerosis, congenital anomalies, epitympanic fixation of the malleus or incus were also excluded. We enrolled 384 patients (248 females and 136 males) with a mean age of 47 years (range: 20-75 years) for data analysis. All patients had at least 12 months of post-operative follow-up. The study was approved by the Local Ethical Committee and was conducted in accordance with the ethical standards of the Declaration of Helsinki. Patients received adequate and comprehensible information about the surgical procedures and gave their written consent.

The following factors were evaluated: pre- and post-operative hearing threshold, surgical technique (partial stapedectomy, total stapedectomy, stapedotomy), diameter of the Teflon-piston (0.6 mm or 0.4 mm), intra- and post-operative complications (vertigo, facial palsy, tinnitus, sensorineural hearing loss) and type of otosclerosis pattern. Otosclerosis pattern was classified as: peripheral “well-delimited” rim fixation, diffuse and obliterative.

All patients were subjected to standard surgery under local anaesthesia using a transcanal approach as previously reported¹². The choice between partial stapedectomy (partial posterior platinectomy), or stapedotomy was only based on the amount of footplate that came out using the micro-hook. In case of obliterative otosclerosis a microdrill was used to perform a stapedotomy. According to the oval window niche anatomy and footplate opening dimensions, a 0.4 or 0.6 mm Teflon prosthesis was placed directly into the vestibule and the oval window niche was sealed with earlobe fat and blood.

Audiological evaluation was performed according to the guidelines of the American Academy of Otolaryngology Head and Neck Surgery²⁰: average thresholds were calculated at 500 Hz, 1 kHz, 2 kHz and 3 kHz. Last follow-up evaluation was performed on average at 30 months after surgery (range: 12-70 months).

Statistical analysis

Multiple linear regression analysis was performed. Mean post-operative air-bone gap (ABG), high frequency bone conduction (HFBC), calculated as the pre-operative minus the post-operative pure tone bone conduction average, obtained at least 6 weeks after surgery at 1, 2 and 4 kHz, bone conduction pure tone average (BCPTA) and pure tone average (PTA) were considered as the dependent variables, whereas independent variables were: type of otosclerosis, type of surgery, diameter of the piston, intra and post-operative complications. ANOVA and Chi-Square test were used to compare the groups. Statistical software (Statistica 8.0) was used for analysis and significance was set for $p < 0.05$.

Results

The otosclerosis involved the peripheral rim in 186 patients (48%), and was diffuse in 172 patients (45%) and obliterative in 26 patients (7%). One hundred thirty-seven patients underwent partial stapedectomy (35.6%), 232 patients stapedotomy (60.4%) and 15 patients (4%) “unplanned” total stapedectomy, which was usually performed in case of footplate dislocation during surgical manoeuvres. A 0.6 mm piston was used in 221 patients (57.4%) and a 0.4 mm piston in the remaining 163 patients (42.6%). In Table I patients are classified according to the technique and prosthesis diameter. No patients developed major complications such as dead ear or permanent facial palsy; minor complications such as temporary vertigo, tinnitus and facial palsy occurred in 60 patients (15.6%): namely 40 patients developed transient vertigo (10.4%), 18 transient tinnitus (4.6%) and 2 transient facial palsy (0.5%). All patients recovered within 15 days after surgery.

Overall mean pre-operative air conduction pure tone average (PTA) was 62.21 dB (range: 32-106; SD: ± 14 dB), whereas overall mean post-operative air conduction PTA was 36.45 dB (range: 11-70; SD: ± 12 dB). Overall mean pre-opera-

tive ABG was 33.8 dB (range: 20-61; SD: ± 9 dB), whereas overall mean post-operative ABG was 9.5 dB (range: 0-31; SD: ± 6 dB). Differences between pre- and post-operative overall PTA and ABG were statistically significant ($p = 0.003$ and $p = 0.002$ respectively). Mean post-operative ABG gain was 24.3 dB (range: 0-50; SD: ± 11 dB). ABG worsening was never reported. Overall mean pre-operative bone conduction PTA (BCPTA) was 28 dB (range: 10-66 dB; SD ± 11 dB), whereas overall mean post-operative BCP-PTA was 27 dB (range: 9-62; SD: ± 10 dB). The difference between overall pre- and post-operative mean BCPTA was not statistically significant ($p = 0.23$). Mean pre- and post-operative audiological data, stratified according to otosclerosis pattern, surgical procedure and prosthesis diameter are reported in Table II.

Otosclerosis pattern

Statistical analysis did not show significant differences between mean post-operative ABG in peripheral rim versus diffuse otosclerosis (mean post-operative ABG = 8.6 dB vs 9.9 dB respectively; $p = 0.09$). Mean post-operative ABG was significantly higher in obliterative otosclerosis (mean post-operative ABG = 14.07 dB in the latter group, $p = 0.0003$) (Fig. 1). Moreover, in peripheral rim and diffuse otosclerosis mean post-operative BCPTA increased by 2.2 and 2.1 dB, respectively, whereas it decreased by 1.2 dB in obliterative otosclerosis. The difference was not significant ($p = 0.06$). No statistically significant differences were noted in the prevalence of the surgical technique performed, while a 0.4 mm prosthesis was used in a significantly higher number of obliterative otosclerosis compared to the other techniques ($p = 0.01$) (Table III).

Table I. Patient stratification according to surgical technique and prosthesis diameter.

	0.6 mm piston	0.4 mm piston	Total
Partial stapedectomy	100 (72.9%)	37 (27%)	137
Stapedotomy	106 (45.6%)	126 (54.4%)	232
Total stapedectomy	15 (100%)	0 (0%)	15
Total	221	163	384

Table II. Multilinear regression analysis showing mean pre- and post-operative audiological data, stratified according to surgical procedure, prosthesis diameter and otosclerosis pattern.

	Surgical technique			Prosthesis diameter			Otosclerosis pattern	
	Partial stapedectomy	Stapedotomy	Total stapedectomy	0.4 mm	0.6 mm	Peripheral rim	Diffuse	Obliterative
Mean post-operative PTA (dB)	36.4 (n.s.)	36.7 (n.s.)	34 (n.s.)	38.5 (n.s.)	34.8 (n.s.)	37 (n.s.)	35.5 (n.s.)	40.9 ($p < 0.001$)
Mean post-operative ABG (dB)	9.1 (n.s.)	9.6 (n.s.)	11.2 (n.s.)	10.3 (n.s.)	8.9 (n.s.)	9.9 (n.s.)	8.6 (n.s.)	14 ($p < 0.001$)
ABG Gain (dB)	23.4 (n.s.)	25 (n.s.)	19.8 (n.s.)	23.8 (n.s.)	24.7 (n.s.)	22.2 (n.s.)	25.1 (n.s.)	25.1 (n.s.)
Post-operative mean BCPTA (dB)	27.3 (n.s.)	27 (n.s.)	22.5 (n.s.)	28.2 (n.s.)	25.9 (n.s.)	27.1 (n.s.)	26.8 (n.s.)	26.9 (n.s.)
HFBC Change (dB)	1.6 (n.s.)	2 (n.s.)	0 (n.s.)	1.5 (n.s.)	1.9 (n.s.)	2.2 (n.s.)	2.1 (n.s.)	0 (n.s.)

n.s. = not significant; PTA = pure tone audiometry; ABG = air bone gap; BCPTA = bone conduction pure tone audiometry; HFBC = high frequency bone conduction.

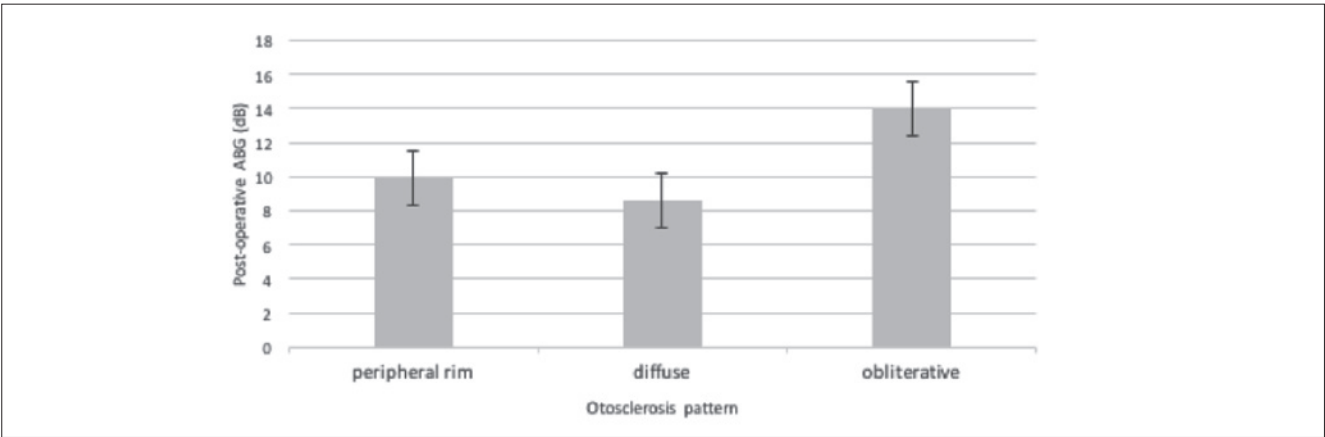


Fig. 1. Comparison of mean post-operative ABG among different otosclerosis patterns (peripheral rim, diffuse and obliterative).

Surgical technique

No significant differences were detected in terms of mean post-operative ABG according to the type of surgical technique (Fig. 2). In detail, only post-operative ABG at 0.5 kHz was significantly higher in the stapedotomy group compared to the partial stapedectomy group and the total stapedectomy group (respectively mean post-operative ABG = 11.2 dB vs

8.6 dB and 8 dB; $p = 0.003$). No significant differences were encountered in terms of mean post-operative BCPTA change according to the type of surgical technique.

Piston diameter

No significant differences were found according to the piston diameter in the overall population. Mean post-operative

Table III. Stratification of surgical procedure and diameter of the prosthesis according to the otosclerotic pattern.

	Surgical technique			Prosthesis diameter	
	Partial stapedectomy	Stapedotomy	Total stapedectomy	0.4 mm	0.6 mm
Peripheral rim (n = 186)	66 (35.4%) (n.s.)	112 (60.3%) (n.s.)	8 (4.3%) (n.s.)	73 (39.2%) (n.s.)	113 (60.8%) (n.s.)
Diffuse (n = 172)	65 (37.8%) (n.s.)	102 (59.3%) (n.s.)	5 (2.9%) (n.s.)	69 (40.1%) (n.s.)	103 (59.9%) (n.s.)
Obliterative (n = 26)	6 (23%) (n.s.)	18 (69.2%) (n.s.)	2 (7.8%) (n.s.)	21 (80.7%) ($p < 0.05$)	5 (19.3%) ($p < 0.05$)

n.s.: not significant.

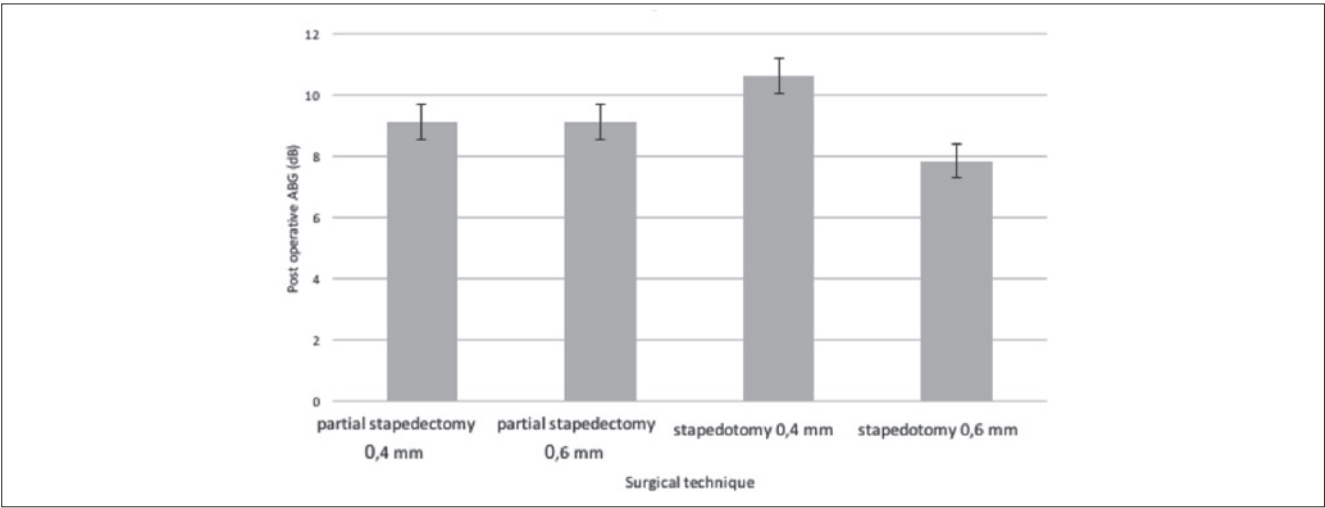


Fig. 2. Mean post-operative ABG according to surgical technique and piston diameter.

ABG was significantly higher in the 0.4 mm, compared to 0.6 mm piston group at 0.5 kHz (14 dB vs 7.5 dB respectively; $p = 0.0001$) and 1 kHz only (11.2 dB vs 9.0 dB respectively; $p = 0.015$), whereas no significant differences were found at the other frequencies ($p = 0.1$) (Fig. 3).

Moreover, in the partial stapedectomy group the mean post-operative ABG did not significantly differ between the 0.4 and 0.6 mm piston groups (9.1 dB in both), while in the stapedotomy group a significant difference was found between 0.4 and 0.6 mm piston groups in favour of the latter (respectively 10.6 vs 7.83 dB; $p = 0.04$).

Analysis of mean BCPTA change demonstrated the absence of a significant difference between the 0.4 mm and 0.6 mm-diameter groups ($p = 0.09$).

Post-operative complications

Details regarding the association between complications and surgical variables are reported in Table IV. Temporary complications (namely tinnitus, vertigo and facial palsy) were significantly higher in case of obliterative otosclerosis, 0.6 mm piston and in patients subjected to total stapedectomy ($p = 0.035$).

Discussion

The population of the present study achieved satisfactory functional results, with a mean post-operative ABG of 9.5 dB and a post-operative ABG lower than 20 dB in 93% of

cases, in agreement with our previous reports^{12,21}. Moreover, mean BCPTA improved by 1.7 dB and permanent complications were never reported.

Otosclerosis pattern

We adopted a classification based on the Portmann and Malafronte system, to synthesise both anatomical diffusion and histologic appearance. Well delimited rim and diffuse otosclerosis were associated with better hearing results compared to obliterative otosclerosis. “Blue” and “White” patterns, similar to the report by Malafronte et al., do not differ significantly on post-operative hearing function, since significant differences are reported in comparison to the “obliterative” pattern outcome only. An experienced surgeon, in fact, should be able to quickly differentiate, before removal of the superstructure, the intrinsic risk of intra-operative manipulation, according to the macroscopic appearance²². Although diffuse otosclerosis is considered as more challenging, specific competence allows to obtain comparable results in diffuse versus limited otosclerotic focus. On the other hand, the greater surgical difficulty of obliterative otosclerosis has been fully described in the literature. Daniels²³ demonstrated in a large cohort, the higher complexity in the drill-out of the oval window in the obliterative pattern, leading to a significantly lower rate of ABG closure and higher rate of sensorineural hearing loss when compared to a routine stapedectomy. Also, in our results mean post-operative ABG was significantly higher in obliterative otosclerosis, compared to other

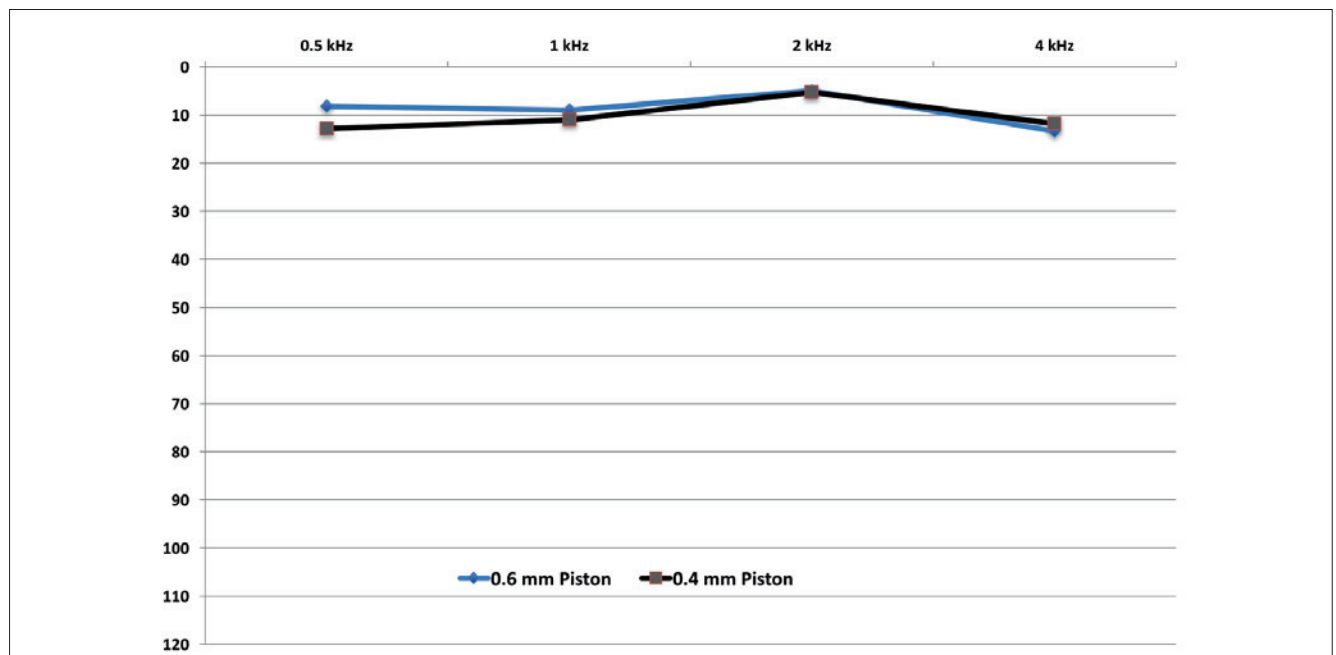


Fig. 3. Comparison of post-operative ABG between 0.4 mm and 0.6 mm-diameter piston at 0.5, 1, 2 and 4 kHz.

Table. IV. Incidence of temporary complications stratified according to the intra-operative parameters.

		Overall (n = 60)	Temporary vertigo (n = 40)	Tinnitus (n = 18)	Facial palsy (n = 2)
Surgical technique	Partial stapedectomy	26/137 (18.9%) (p < 0.05)	18/137 (13.1%) (n.s.)	7/137 (5.1%) (p < 0.05)	1/137 (0.7%) (n.s.)
	Stapedotomy	29/232 (12.5%) (p < 0.05)	19/232 (8.1%) (n.s.)	9/232 (3.8%) (p < 0.05)	1/137 (0.7%) (n.s.)
	Total stapedectomy	5/15 (33.3%) (p < 0.05)	3/15 (20%) (n.s.)	2/15 (13.3%) (p < 0.05)	0/15 (0%) (n.s.)
Prosthesis diameter	0.4 mm	15/163 (9.2%) (p < 0.05)	11/163 (6.7%) (n.s.)	3/163 (1.8%) (n.s.)	1/163 (0.6%) (n.s.)
	0.6 mm	45/221 (20.3%) (p < 0.05)	29/221 (13.1%) (n.s.)	15/221 (6.8%) (n.s.)	1/221 (0.4%) (n.s.)
Otosclerosis pattern	Peripheral rim	26/186 (13.9%) (p < 0.05)	13/186 (6.9%) (p < 0.05)	12/186 (6.4%) (n.s.)	1/186 (0.5%) (n.s.)
	Diffuse	26/172 (15.1%) (p < 0.05)	20/172 (11.6%) (p < 0.05)	5/172 (2.9%) (n.s.)	0/26 (0%) (n.s.)
	Obliterative	8/26 (30.7%) (p < 0.05)	7/26 (26.9%) (p < 0.05)	1/26 (3.8%) (n.s.)	0/26 (0%) (n.s.)

n.s.: not significant.

patterns, although mean post-operative HFBC only showed a slight decrease, which did not reach statistical significance. Moreover, no difference was found in the choice of the surgical technique in the obliterative pattern vs. the others. We found, however, that in the majority of obliterative cases a 0.4 mm-diameter prosthesis was positioned, with a significantly higher prevalence compared to the other patterns. This might be easily explained by the difficulty encountered in the extensive drill-out of a thick and friable footplate and represents a bias in the assessment of functional results obtained through different prosthesis diameters.

No patients affected by obliterative otosclerosis experienced a permanent complication. However, a significantly higher incidence of temporary complications (30.7%) was recorded compared to the other patterns. The most frequent symptom was dizziness, reported by 7/26 patients (26.9%). These results indicate that extensive drilling might cause a temporary dysfunction of sensory hair cells, leading to transient vertigo and/or tinnitus in a significantly higher percentage of patients. However, this does not translate into permanent inner ear damage, since HFBC remained stable.

Surgical technique

No functional differences were seen among the three surgical groups, since no statistically significant differences were found in mean post-operative ABG and HFBC. The significant difference in ABG at 0.5 kHz, in favour of the stapedectomy group, is consistent with reports advocating a slightly better performance obtained in the lower frequencies¹³⁻¹⁵ due to the wider surface of the oval window that is

removed. Mean post-operative HFBC change does not differ significantly, according to the surgical technique. Hair cell damage caused by the surgical trauma was similar among the three groups and the greater or smaller surface of restored footplate does not influence post-operative bone conduction^{15,24}.

Several studies were conducted regarding comparison of functional outcomes in stapedotomy versus stapedectomy, with controversial results¹²⁻¹⁵. Stapedotomies have been reported in the literature to have better hearing improvements at high frequencies¹². In other studies, stapedectomies have been advocated for higher hearing improvement at low frequencies¹³⁻¹⁵. In our previous study on 151 subjects¹², we reported that stapedotomy and partial stapedectomy have equivalent results in term of ABG closure and air conduction gain in the speech frequencies. However, stapedotomy was associated with better ABG closure at 4 kHz, ABG gain at 2, 3, and 4 kHz and greater air conduction gain in the high frequencies (4 to 8 kHz). Sakamoto et al.²⁵ demonstrated, in a 99 ear cohort, that stapedotomies were more effective on global hearing function compared to stapedectomies. Rizer²⁶ on the contrary demonstrated better results at 0.5-3 kHz with partial or total stapedectomy compared to stapedotomy. Several authors have shown overlapping hearing outcomes between stapedotomy and partial stapedectomy²⁴. The controversial results obtained in the literature in terms of the “optimal” technique may be influenced by multiple factors such as instruments used to remove the footplate (microhook, perforator, microdrill, lasers), diameter and material of the pistons, vein or connective tissue interposition and

experience of the surgeon. Moreover, intrinsic bias cannot be avoided since a significant portion of stapedotomies are converted into stapedectomy during the operation and several surgeons prefer to perform stapedotomy selectively in patients with favourable anatomic conditions, whereas stapedectomy is reserved for complicated cases.

The results of the present series show that, among morphological variables, the macroscopic otosclerosis pattern did not influence our choice. In fact, no significant difference exists in the prevalence of various patterns among the three surgical groups (see Table III). In case of total stapedectomy we used a 0.6 mm diameter prosthesis in all cases, expecting a larger prosthesis, together with a graft composed of earlobe fat and blood, to have more stability in an entirely open oval window. A tendency towards using larger diameter prosthesis is shown even in the partial stapedectomy group, compared to the stapedotomy group (Table I).

Finally, a significant increase of the risk of complications was recorded in the total stapedectomy group (33.3% of cases)²⁵. Both transient vertigo and tinnitus, due to vestibular trauma deriving from the manipulation and total removal of the footplate were reported.

Piston diameter

We systematically used a Teflon-piston prosthesis in our patients, according to the study by Durko²⁷, who considered this material as the best option. A recent review on 12 studies¹⁶ showed that the majority of those could not show a significant difference between 0.4 and 0.6 pistons. Moreover, differences that were detected were not consistently in favour of a smaller or larger-diameter piston. On the contrary, a meta-analysis by Laske et al.¹¹ reported that a 0.6-mm piston is associated with significantly better post-operative ABG at low and mid frequencies, compared to a 0.4 mm prosthesis. Bernardeschi et al.²⁸ demonstrated a significant difference in AC gain, AC threshold at 0.125 and 0.25 kHz and BC threshold at 0.25 kHz in favour of the 0.6-mm group. The latter study is one of the few to be designed as a prospective one, on consecutive cohorts, with minimum risk of bias.

According to our analysis, no significant difference was seen in mean post-operative ABG and HFBC in 0.4 mm versus 0.6 mm piston diameter, although the latter provides better ABG values at low frequencies. Although unanimous consensus has not been reached, it is reasonable to assume that an extremely narrow piston does not effectively transmit sound energy into the vestibule, producing less volume displacement especially at lower frequencies. On the contrary, a larger prosthesis has a larger surface area of transmission. The increased portion of the cochlea stimulated by the prosthesis diameter-to-footplate ratio could explain the better results of pistons with a higher diameter. Experimental

studies on temporal bones have demonstrated increased round window velocities and higher perilymphatic volume displacement^{29,30} with larger diameter prosthesis. We believe that when anatomical conditions allow a choice, a larger-diameter piston may be preferable.

Our study has some limitations due to the retrospective and non-randomised nature, heterogeneous follow-up duration and intrinsic methodological bias. Several critical procedures were in fact accidentally converted in total stapedectomies, the choice of technique and prosthesis diameter was influenced by anatomic conditions, hearing condition or size of the fenestration. Smaller-diameter pistons are usually preferred in case of unfavourable anatomic conditions (dehiscent/overhanging facial nerve, narrow oval window niche, persistent stapedial artery), affecting the association with hearing outcome. Moreover, functional outcome is influenced by other factors, besides those mentioned above, such as pre-operative threshold, cochlear function, anatomical conditions, experience of the surgeon and efficacy of prosthesis crimping.

Conclusions

A well-delimited rim and diffuse otosclerosis patterns and 0.6 mm-diameter piston can be considered as factors associated with better outcome. No functional differences were detected when comparing partial stapedectomy, total stapedectomy and stapedotomy. Obliterative otosclerosis represents an unfavourable prognostic factor, although significant sensorineural hearing loss or permanent complications were not recorded. It is not possible, at the state of our knowledge, to pre-operatively predict the extent of the otosclerotic focus, although radiologic and audiometric indicators have been proposed^{31,32}. In our opinion, the only factor considered as adequate and the less hazardous in possible intra-operative management is the experience of the surgeon.

Conflict of interest statement

None declared.

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CASE SERIES AND REPORTS

Retropharyngeal lymphatic malformations: report of two successfully treated cases and review of the literature

Malformazioni linfatiche retrofaringee:

2 casi clinici trattati con successo e revisione della letteratura

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SUMMARY

Retropharyngeal lymphatic malformations (LMs) are exceedingly rare and have rarely been reported in the literature. This condition can be life threatening, and its management is particularly challenging. Over a two-year period, two patients who presented with symptomatic (dyspnoea, snoring) retropharyngeal LMs were treated in our hospital. Both patients were treated using radiofrequency ablation of LMs through a trans-oral approach and bleomycin sclerotherapy as adjunctive treatment. No major complications occurred following surgery. During follow-up, no recurrence was noted, and both patients were asymptomatic. Our result and the review of the literature suggests that radiofrequency ablation combined with bleomycin sclerotherapy can be a safe and effective treatment.

KEY WORDS: Radiofrequency ablation • Bleomycin • Retropharyngeal • Lymphatic malformation

RIASSUNTO

Le malformazioni linfatiche (LM) retrofaringee sono un'evenienza molto rara. Tali condizioni possono mettere in pericolo la vita del paziente e la loro gestione può essere talvolta molto complicata. Negli ultimi due anni, due pazienti con LM retrofaringee, entrambi sintomatici (dispnea e russamento) sono stati trattati nel nostro ospedale. Entrambi i pazienti sono stati trattati con ablazione mediante radiofrequenze attraverso un approccio transorale e scleroterapia con bleomicina come trattamento adiuvante. Non si sono verificate complicanze dopo il trattamento. I nostri risultati e la revisione della letteratura suggeriscono che l'ablazione con radiofrequenze, in combinazione con la scleroterapia con bleomicina, può essere un trattamento efficace e sicuro.

PAROLE CHIAVE: Ablazione con radiofrequenze • Bleomicina • Malformazioni linfatiche retrofaringee

Introduction

Lymphatic malformations (LMs) are congenital vascular anomalies that result from abnormal development of lymphatic vessels, which present in the head and neck in 48% to 75% of cases, most commonly presenting as asymptomatic posterior triangle masses¹. Involvement of the upper airway is rare. The most common conditions include parapharyngeal extensions^{2,3} and tongue LMs². In addition, a few cases of LMs isolated to the larynx have been reported^{1,2}, as well as a few retropharyngeal cases⁴⁻⁶. This location is at risk of causing dyspnoea and dysphagia, and can potentially lead to acute respiratory distress in the case of rapid growth or intracystic bleeding. Removal or reduction of a lesion at this location is particularly challenging. In this study, we report on two new cases of

symptomatic retropharyngeal LMs that were successfully managed with radiofrequency ablation combined with bleomycin sclerotherapy, and a review of the literature.

Case reports

We reviewed the medical records of two children diagnosed with retropharyngeal LMs who were treated in the Department of Otolaryngology Head and Neck Surgery at Children's Hospital of Shanghai during a two-year period. Clinical charts were reviewed for demographic characteristics, presenting signs, surgical technique and outcomes. Institutional review board approval was obtained from the Shanghai Jiao Tong University Research Compliance Office. Informed consent was obtained from the parents of all children.

Diagnosis was based on radiological exam, specifically a contrast-enhanced computed tomography (CT) scan that revealed a retropharyngeal abscess, but all diagnoses were confirmed by pathological examination. All patients were assessed by the senior otolaryngologist using the same surgical procedure under general anaesthesia with orotracheal intubation. First, the Boyle-Davis mouth gag was set up to access the posterior pharyngeal wall. After the retropharyngeal LMs were properly exposed (Fig. 1a), we used a hand-held radiofrequency ablation device (EvacXtra HP, ArthroCare ENT; CA, USA) with a power setting of 7 to perform the radiofrequency ablation of the cyst wall of LMs as much as possible, sparing the surrounding structures and the mucosa. Haemostasis was simultaneously achieved using a coagulation setting of 3. Blunt dissection in areas of concern or pulsation was used to avoid disrupting the carotid sheath within this region. Frozen section pathology revealed LMs characterised by dilated spaces containing flocculated lymph and bounded by fibrous septae. After the reduction was performed (Fig. 1b), we applied bleomycin (15 mg of bleomycin dissolved in 20 ml of normal saline) into the surgical cavity. The bleomycin solution was left in situ for 3 minutes for better penetration into and reaction with the cyst wall, and then the solution was removed. After completion, the pharyngeal mucosal flaps were re-approximated and closed with 3.0 Vicryl. All

patients were extubated immediately after the procedure. All patients received an intravenous, five-day antibiotic course (ceftriaxone). During this time, the patients were given a soft diet and had no respiratory events.

Case #1

A 2-year-old boy presented with one month of snoring when sleeping. In one week, the snoring worsened, and he developed sleep apnoea. The patient was admitted to the regional hospital with inspiratory stridor. ORL examination revealed significant bulging on the posterior pharyngeal wall. Based on clinical history and laboratory tests (leukocytosis $13.5 \times 10^9/L$), a retropharyngeal abscess was suspected. Decompression by needle aspiration was performed in the local hospital. Transoral aspiration of the retropharyngeal space produced 12 ml of blood and transparent fluid. Bacteriological examination of the aspirated fluid was positive for *Streptococcus*. Five days later, breathing difficulties returned, and the boy was referred to our department. On examination, retropharyngeal bulging persisted without stridor, and the patient was noted to snore at night. The patient required sedation prior to imaging, and he was intubated to ensure airway stabilisation. In the CT scan with contrast, cystic lesions were visible (Fig. 2a and b) in the retropharyngeal space from the nasopharynx to the level of C6 (48 mm x 23 mm x 45 mm)

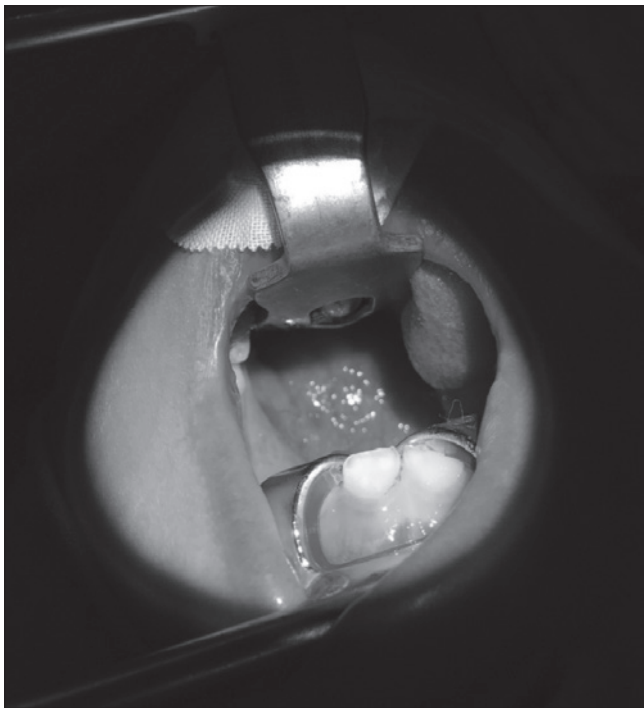


Fig. 1a. Surgical view of retropharyngeal LM, oropharyngeal mucosa overlying the left parapharyngeal space in case 1.

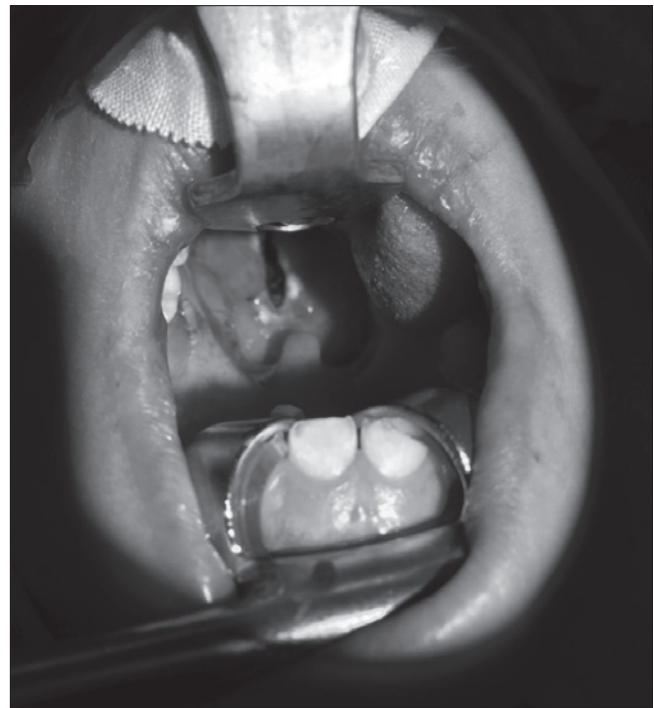


Fig. 1b. Surgical view of the reduction was made after removal of the retropharyngeal LM in case 1.

that spread to the left lateral neck. Cystic lesions were also noted around the vessels in the trigonum jugular. Surgery was performed following our protocol. Oral feeding was initiated on the first postoperative day. The patient remained in hospital for five days. Spectacular improvement of symptomatology was noted. No clinical or radiological regrowth was noted over 23 months of follow-up. No adjuvant procedure was necessary.

Case #2

A 6-year-old girl experienced snoring since birth. At four years of age, the snoring worsened, and she developed sleep apnoea. At six years of age, her dysphagia increased rapidly. On physical examination, obvious bulging was noted adjacent to the posterior wall during swallowing. Flexible endoscopy revealed a smooth mucosa-covered mass on the posterior wall of the pharynx. Contrast CT scan (Fig. 3) revealed a well-defined, low-density soft tissue mass with an enhanced rim and multiple septations. Marked anterior displacement and narrowing of the glottic and supraglottic airway were noted; the mass did not extend into the chest. A diagnosis of macrocystic lymphatic malformation was confirmed. Oral feeding was initiated on the postoperative day. No respiratory distress was noted in the following days. The duration of hospitalisation was five days. No clinical symptoms appeared during the 16-month follow-up.

Discussion and review of the literature

Lymphatic malformations are low-flow embryological vascular anomalies theorised to develop from mesenchymal progenitor cells. As a subcategory of vascular malformations, LMs can be classified morphologically as macrocystic, microcystic, or mixed. Macrocystic lesions are classically described as cystic spaces of at least 2 cm³, microcystic lesions of less than 2 cm³ and mixed lesions are associated with both macrocystic and microcystic components⁷.

Retropharyngeal locations are rarely observed, and only a few cases have been reported in the literature. Management of this location can be challenging for the otolaryngologist. Differential diagnosis of retropharyngeal lymphatic malformation includes haemangioma, vascular malformation, congenital and acquired cystic lesions, abscess and lipoma. Radiographic examination is useful not only in differentiating LMs from the other masses (haemangioma, congenital cysts, abscess and lipoma) but also in delineating the actual extent of LMs. CT scans may reveal a discrete or poorly defined water-density mass with an enhanced rim after intravenous contrast⁶.

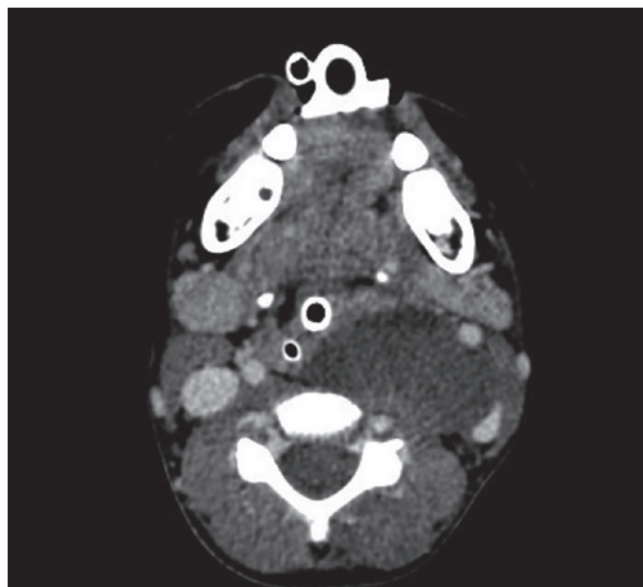


Fig. 2a. Contrast axial CT scan showing a left parapharyngeal and retropharyngeal voluminous macrocystic lymphatic malformation causing significant narrowing of the supraglottic airway.

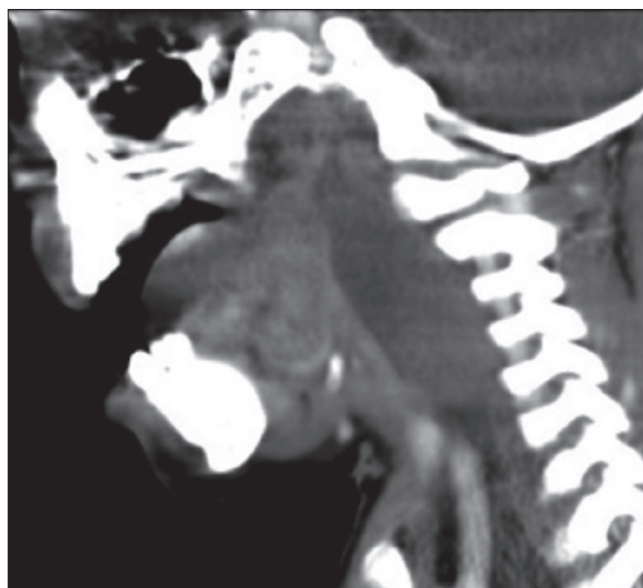


Fig. 2b. Contrast sagittal CT scan showing retropharyngeal lymphatic malformation from the nasopharynx to the level of C6.

Adams et al.⁸ systematically reviewed and reported that both surgery and sclerotherapy may be effective for treatment without any clear evidence as to which modality is superior. Bleomycin is an antitumour agent that was discovered in 1965 that can cause non-specific inflammatory reactions leading to fibrosis of cysts. Various studies have produced promising results using bleomycin sclero-

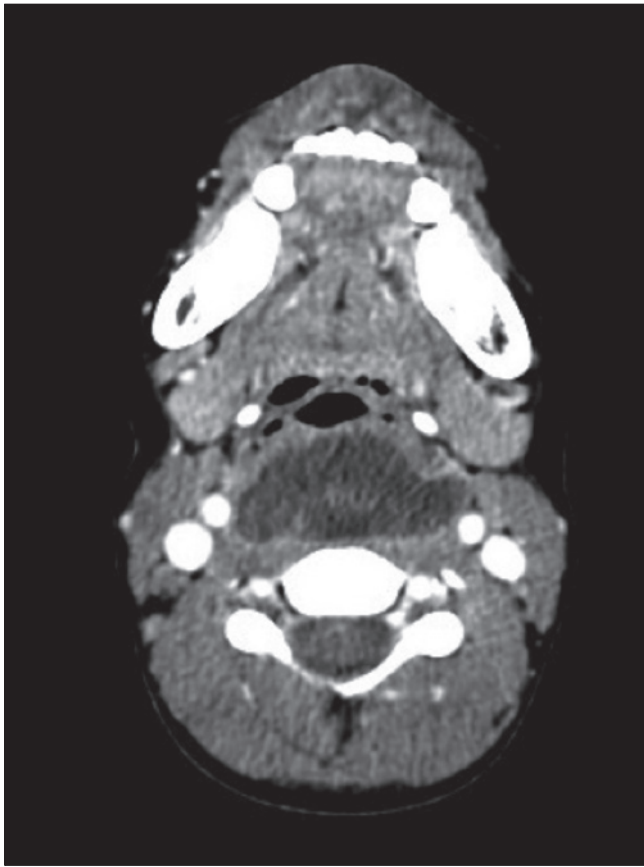


Fig. 3. Contrast axial CT scan showing a well-defined low density soft tissue mass (retropharyngeal voluminous macrocystic LM) with an enhancing rim and multiple septations, causing significant narrowing of the supraglottic airway.

therapy. Bleomycin sclerotherapy is frequently used for macrocystic disease and has become an attractive treatment option because it is less invasive, leaves minimal scarring and carries minimal risk of collateral damage to surrounding neurovascular structures^{9 10}. Olímpio et al.¹¹ reported a cross-sectional study in which the proportion of patients considered cured after the first therapeutic approach was 44% in the surgery group and 29% in the bleomycin group. Although the favourable rate was higher in the surgical group, they encountered two serious intraoperative complications and suggested that surgical excision be reserved either for the resection of remaining fibrotic tissue after sclerotherapy or as a first-line therapy for LMs localised outside the cervico-facial region, where the risk of injuring vascular structures is smaller.

In our two cases, the cystic lesions in the retropharyngeal space spread to the lateral neck were also noted around/nearby the vessels in the trigonum jugular; complete resection of the lesion is challenging in extensive lesions

because of potential complications such as carotid artery damage. Moreover, the lesion in the airway is also a particularly sensitive area, and both our patients complained of breathing difficulties when brought to our department; the voluminous masses causing significant narrowing of the supraglottic airway could be seen in CT scans. The lesion in the airway should be relieved as soon as possible. We performed surgical excision using radiofrequency ablation, and we agree that complete excision is not always possible because the cyst wall is very thin, and the lesion is often infiltrative and involves critical neurovascular structures. However, we were still able to carefully perform the procedure by radiofrequency ablation, and we tried to open up every “cell” of the lesion and remove the fluid inside. We attempted to remove as much cyst wall as possible, but when it adhered to critical structures, such as the carotid artery, we could perform marsupialisation only. In the recent literature, radiofrequency ablation has been described as a new surgical option for the removal of vascular malformations, such as LMs¹²⁻¹⁵. Radiofrequency ablation produces a controlled increase in temperature within tissue, resulting in denaturation and obliteration of the directed site. After surgical excision, we used 20 ml bleomycin aqueous solution (15 mg/20 ml) to wash the surgical cavity and induce a non-specific inflammatory reaction that would help to promote adhesion of cyst walls and fibrosis of the lesion. Following this bleomycin irrigation, all the contents were aspirated again. It has been reported that local complications of intralesional bleomycin include oedema, and major post procedure oedema in the airway cannot be tolerated. We chose bleomycin irrigation (bleomycin aqueous solution was left in situ for 3 minutes for better penetration into and reaction with the cyst wall, and then the solution was removed) instead of bleomycin injection in lesions, as we thought injection of bleomycin into the lesion might increase the risk of post-injection swelling, creating a risk of acute respiratory distress for patients with masses in retropharyngeal locations. There has been no uniformity in the dose of this drug in the reported series. In our opinion, a lower dose of bleomycin is safer for paediatric patients. Our aim is to produce the minimum effective dose of bleomycin in the retropharyngeal LMs.

As reported in our cases, we used this technique for retropharyngeal LMs, and treatment objectives include reducing symptomatology, such as dysphagia, and providing a safe airway. These patients either presented with emergency symptoms (case #1) or a long history of persistent symptoms (case #2). Our procedure allowed for fast improvement of symptomatology. As such, our result confirmed the efficacy of radiofrequency ablation com-

bined with bleomycin irrigation for retropharyngeal LMs. This improvement was confirmed over the follow-up period as no regrowth was noted in either case, and no adjuvant procedure was necessary for either patient. In addition, it is easy to achieve cavity lavage with bleomycin solution, and this procedure has the advantage of facilitating bleomycin irrigation after the contents of LMs were removed. Another advantage is the minimally invasive character of the procedure, avoiding the risk of damaging critical neurovascular structures, and thus associated with reduced morbidity. In summary, radiofrequency ablation combined with bleomycin sclerotherapy in the management of retropharyngeal lymphatic malformations is a simple and cost-effective treatment option. It allows fast recovery with minimum morbidity and a short hospital stay. Further study will be necessary to fully validate these findings and treatment indications in the long term.

Acknowledgements

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Conflict of interest statement

None declared.

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In Memoriam of Maurizio Maurizi

Prof. Maurizio Maurizi passed away on March 24, 2019. Born in Rieti on July 17, 1932 he graduated in Medicine in Perugia before moving to La Sapienza University at Rome under the guidance of Prof. Domenico Filipo. After directing the Audiology at Cagliari in 1970/1971, on 1 November 1971 he was called upon to direct the Otolaryngology Clinic at the University of Perugia where he remained until 31 October 1987. After this, he was Chair of Otorhinolaryngology at Catholic University of the Sacred Heart in Rome, a position he held until his retirement on 1 November, 2004. He was later awarded the title of Professor Emeritus. Until the day before leaving us he was always kept informed of the career developments at “his” school: we, his pupils, will always be grateful to him.

Being a leader is not easy. One must be able not only professionally and technically, but must also have a driving force to motivate their collaborators. One must know how to choose them, be lucid and fair in decisions regarding career advancements, and know how to give as well as receive, even accepting the possibility that they can become better than their teacher.

Prof. Maurizi was all this. He stimulated young people to do things and he wanted them to learn. For those who wanted to pursue a university career, he imposed the need to research and publish. He never tired of repeating that patients were at the top of the pyramid, and that it was our job to solve their problems. Under his rough skin, he was a good man, capable of unexpected gestures of affection, hard to influence and with his very specific ideas that derived from hard work, which sometimes led him to put clinical duties before his beloved wife Paola and his children Benedetta and Alessandro. One of his recognisable aspects was that he really appreciated the work of others and that he loved the substance of appearance.

His ideas on life were expressed by the many dozens of “thoughts” he loved to write with a felt-tip pen on the glass of the many paintings in his office: it would be difficult to list them all. A few examples: “We must be and not appear”, “We all need to be accepted for what we are”, “We can be better than many, but not better than everyone”, “He who knows”, “Nothing comes from nothing”, “A bad teacher is one who is not surpassed by his students” and, finally, many considerations on gratitude such as “Always do good, even if ingratitude is infinite”.

Prof. Maurizi was wrong for once, because I, we and all those who grew up with him are extremely grateful and hope to follow the path he showed us. Thanks, and rest in peace.



Gaetano Paludetti
Fabrizio Ottaviani