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HEAD AND NECK

Evaluation of three-dimensional mandibular movements after reconstruction with free fibula flap

Valutazione tridimensionale dei movimenti mandibolari dopo ricostruzione con lembo libero di fibula

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SUMMARY

Seven patients who underwent mandibular reconstruction with a fibula free flap (one on the midline, six on either right or left side) and were rehabilitated with implant supported prostheses, performed free mandibular border movements (maximal mouth opening and closing, right and left lateral excursions, protrusion) that were recorded by a non-invasive motion analyser. Temporomandibular joint (TMJ) kinematic parameters were compared to those calculated in healthy control subjects using z-scores. Maximum mouth opening was reduced in all patients, with z-scores ranging from -2.742 to -0.106, and performed with a reduced sagittal plane mandibular rotation. Interincisal point forward movement during protrusion was reduced in all but one patient. Lateral mandibular movements (displacement of the interincisal point) and bilateral condylar movements during mouth opening were very variable and sometimes asymmetrical. Mandibular rotation was also variable, with z-scores ranging from -1.265 to 1.388. Together with mandibular range of motion, we investigated biomechanical characteristics of TMJ motion that can provide further information about the joint without submitting the patient to harmful procedures, and that can be followed-up during healing. The investigation indicates those areas that need to be given special attention in preoperative planning, patient information and rehabilitation.

KEY WORDS: Fibula free flap • Temporomandibular joint • Border movements • Motion analysis

RIASSUNTO

In questo studio sono stati analizzati sette pazienti a cui è stata ricostruita la mandibola utilizzando un lembo libero di fibula. Un paziente è stato operato medialmente e gli altri sul lato destro o sinistro. I pazienti sono stati riabilitati con protesi su impianti, ed hanno eseguito una serie di movimenti limite mandibolari (massima apertura e chiusura della bocca, laterotrusioni destra e sinistra, protrusione), che sono stati registrati nelle tre dimensioni dello spazio da un sistema non invasivo di analisi del movimento. I relativi parametri cinematici dell'articolazione temporomandibolare sono stati confrontati con quelli ottenuti in un gruppo di soggetti sani di controllo utilizzando gli z-score. La massima apertura della bocca è risultata ridotta in tutti i pazienti, con z-scores compresi tra -2.742 e -0.106, ed è stata effettuata con una minore rotazione mandibolare sul piano sagittale. In tutti i pazienti salvo uno si è rilevata una riduzione del movimento del punto interincisale durante la protrusione. Nei pazienti, i movimenti del punto interincisivo in laterotrusione e i movimenti condilari durante l'apertura della bocca sono risultati molto variabili e talvolta asimmetrici. Anche la rotazione mandibolare è risultata molto variabile, con z-scores compresi tra -1.265 e - 1.388. Insieme all'ampiezza dei movimenti, sono state indagate alcune caratteristiche biomeccaniche dell'articolazione, che possono fornire informazioni relativamente ai capi articolari senza sottomettere i pazienti a procedure pericolose. Le valutazioni possono essere eseguite longitudinalmente durante il follow-up. I dati forniti da questo studio indicano quali aree facciali e quali strutture devono essere attentamente valutate durante la pianificazione preoperatoria, nell'illustrazione dei problemi al paziente e durante la riabilitazione.

PAROLE CHIAVE: *Lembo libero di fibula • Articolazione temporomandibolare • Movimenti limite • Analisi del movimento*

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Introduction

During the past decade, the free fibula flap (FFF) has become the method of choice for reconstruction of major mandibular and maxillary defects [1 2]. When compared to several microvascular transplant options, fibular bone best matches the properties of the jaws, and its ample length allows bone reconstruction after extended resections [2-4]. Skeletal and cutaneous components can be harvested as a single composite flap, thus allowing simultaneous replacement of bone and soft tissue defects [5].

Donor site morbidity has been described as mild, without a significant decrease in lower limb performance [3]. In

particular, no functional limitations during gait and stair performance has been found [6].

Oral function and postoperative facial aesthetics have a major impact on the patient's perception of outcome after ablative surgery. Numerous investigations have been carried out to assess function and quality of life after head and neck tumour resection through validated questionnaires and clinical measurements [7-14]. In general, long term follow-up studies judged facial appearance, speech, food tolerance and deglutition to be satisfactory [1 15].

In these studies, patient outcome after surgical reconstruction with a FFF was mainly evaluated according to clinician-rated observations. Objective assessments, made with actual measurements, were rarely provided. In particular, no quantitative investigations about the biomechanical characteristics of the temporomandibular joint (TMJ) have been made. Biomechanical investigations permit a closer assessment of the motional characteristics of this complex joint, dividing overall movement into its gliding and rotational components that can be measured and eventually followed-up during healing [16-18].

In our laboratory, we have devised a method for the three-dimensional detection, reconstruction and measurement of TMJ motion characteristics, and data about normal subjects, as well as surgical and dental patients, have been published [16-19]. Free mandibular movements are recorded by an optoelectronic digitiser that detects the three-dimensional position of several oral and extraoral landmarks. The instrument and measurement protocol involve minimal interference to natural jaw motion, allowing data collection in a very natural condition [16]. The only requirement is the presence of teeth in the central portion of the mandibular dental arch, where a small framework is fixed to allow detection of mandibular movements.

The aim of the current study was to quantitatively assess the kinematic characteristics of free mandibular movements in patients who underwent mandibular bone reconstruction with a FFF. These data can quantify alterations in mandibular movements after reconstruction, thus guiding the choice of the best surgical, prosthodontic and functional treatments.

Materials and methods

Patients

Between 2005 and 2014, 28 patients underwent reconstruction of the mandibular or maxillary region with FFF at the Department of Maxillo Facial Surgery at the Policlinico Hospital of Milan and Galeazzi Institute of Milan. Seven of these patients (four men, three women, age range 17-67 years, 25% of the initial group), who had a reconstruction in their mandible, agreed to participate in the present study (Table I). Follow-up time ranged from 9 to 32 months. At the time of data collection, all participants were rehabilitated with dental prostheses, and did not report major problems in mastication or mandibular movements. The remaining patients were excluded due to lack of central mandibular teeth, refusal to participate, moving from the area, or death. Four patients (F2, M1, M4, M5) underwent adjuvant radiotherapy. M1 was also submitted to adjuvant chemotherapy. Prior to surgery, M4 had a pathological fracture of the mandibular body, and M5 was in trismus; the pathology did not involve the TMJ in any case.

Table I. Anthropometric data, follow-up time and surgical data.

Patients	Age (y)	Follow-up (months)	Pathology	Soft tissue sacrifice	Neck dissection	Adjuvant therapy (RT/CT)	FFF type/ side	Reconstructed Segment	Reconstruction technique
F2	67	24	Spinocellular carcinoma recurrence	Alveolar mucosa	MRND Left	RT	OC right	Mandibular body left	Manual flap remodelling
F3	56	32	Fibroma ossificans	No	No	No	O left	Symphysis, mandibular body left	Manual flap remodelling
F4	37	9	Ameloblastoma	No	No	No	O right	Mandibular body, ramus right	Computerised virtual planning; custom made plate
M1	17	11	Osteosarcoma	No	No	CT	O left	Mandibular body, ramus left	Preplating
M2	38	12	Fibrous dysplasia	No	No	No	O right	Symphysis + canine teeth	Preplating
M4	59	32	Spinocellular carcinoma	Alveolar mucosa	SOHND right	RT	O right	Mandibular body right	Preplating
M5	58	12	Spinocellular carcinoma	Alveolar mucosa, cheek, oral pelvis	MRND right	RT	OMC left	Mandibular body, ramus right	Manual flap remodelling
Mean	47	19							
SD	17	10							

MRND: modified radical neck dissection; SOHND: supra-omohyoid neck dissection; RT: radiotherapy; CT: chemotherapy; O: bone flap, OC: osteocutaneous flap, OMC: osteomyocutaneus flap.

All patients were informed in detail about the study and signed an informed form. The patient under 18 years provided verbal consent and signed consent was provided by his parents. Approval was obtained by the local ethics committee. All procedures were non-invasive, and did not cause pain or discomfort.
Data were compared with those collected in healthy subjects, who had a complete permanent dentition, no TMJ or craniocervical disorders, no anterior or lateral reverse occlusion and no previous history of craniofacial surgery, trauma, or congenital anomalies. Some of these data have been previously published [16-19].

Surgical technique

Careful anamnesis was collected, angiography of the legs and disease staging were performed and patients were submitted to surgery in a single session. Six patients underwent only bone resection with a minimum sacrifice of soft tissue, while soft tissue resection included the retromolar trigon, floor of the mouth and gingivae in only one case (M5). No patient had condylar resections, and the TMJ capsule was respected in all cases (Table I). Three patients received neck treatment: two had a MRND III and one had a selective SOHND.
In all patients, the FFF harvests were performed with a lateral approach [20], including only minimal muscle cuff around the fibula to ensure preservation of periosteal circulation. In particular, the surgical technique devised by Baj et al. [21] was used. FFF was harvested from the left or right leg after study of the leg's vessels. Generally, the fibula ipsilateral to the facial lesion was used when only bone defects had to be reconstructed (patients F3. F4, M1, M4), while the contralateral fibula was used when osteocutaneous or osteomyocutaneous defects were present (patients F2, M3, M5). In patients with a midline defect (F1, M2), the lower limb with the most suitable vessels was used.
The fibula was osteotomised proximally and distally, preserving 6 cm of bone on either side to maintain knee and ankle stability. To preserve great toe flexion function, the flexor hallucis longus muscle was sutured to the tibialis posterior muscle and to the remaining interosseous membrane with proper tension.
A FFF was used for mandibular reconstruction in all patients, and the flaps were modelled individually as necessary [2]. In particular, in three cases a preplating technique was used to facilitate fibular modelling, while in patient F4 a computerised virtual reconstruction was made. F2, F3 and M5 had an altered mandibular contour, and manual remodelling was performed. In these patients, a preliminary intermaxillary fixation and a clinical condyle repositioning were used to permit correct occlusal relationships. For bone fixation, a custom-made plate was used in patient F4, while in the other patients 2.0 mini-plates were used.
Mandibular tumour ablations were performed taking care to preserve the facial vessels for the subsequent graft anastomoses. The pedicle length was defined by the length of the bone necessary for the reconstruction. For mandibular reconstruction, the cheek was tunnelled above the periosteum at the level of the mandibular ridge. Vascular anastomoses were made between the peroneal and facial arteries and between one of the satellite veins and facial vein.
When only bone was harvested, the skin wound of the donor site was closed primarily, while the other donor sites received split thickness skin grafts.
The donor sites with skin graft received splints with the ankle at 90° for 10 days, in the other occasions splints were not applied. At 1-2 weeks after surgery, all patients started lower limb rehabilitation with the physiotherapist, and 15 days after surgery they started rehabilitation of mandibular movements.
Two patients (M3, M4) were rehabilitated with implant support prostheses and the others had removable prostheses.

Data collection

The data collection procedure has been previously defined in our laboratory [16-19]. Free mandibular border movements (maximal mouth opening and closing, right and left lateral excursions, and protrusion) were made by patients and recorded using a motion analyser with a 60 Hz sampling rate (SMART System, BTS S.p.a., Garbagnate Milanese, Italy). Before each acquisition session, metric calibration and correction of optical and electronic distortions were made. During data collection, the patient sat on a stool without backrest, facing six high-resolution infrared sensitive charge-coupled device video cameras. The cameras define a working volume of 77 (width) cm × 66 (height) cm × 77 (depth) cm that contains the face of the patient. The cameras are coupled with a video processor, and during the execution of the movements the coordinates of the centroid of a set of passive retroreflective markers are obtained by the system, and converted to metric data. Therefore, in each frame that constituted the movement, a set of three-dimensional (XYZ) coordinates was obtained for each marker. Mean dynamic accuracy and precision indices were lower than 0.15 mm.
A set of nine 6-mm spherical markers was used: three cranial markers identified nasion, right and left frontotemporale (cranial reference plane); three mandibular markers (mandibular plane) were positioned on an extra-oral triangular framework fixed on the gingiva at midline level using surgical adhesive (Stomahesive; Convatec Inc., Deeside, United Kingdom); one marker identified the midline of the mandibular incisal edge (interincisal point), and two markers were positioned on the cutaneous projections of the right and left lateral condylar poles. The local coordinates (relative to the mandibular reference system) of the last three markers were recorded in two static acquisitions: one with open mouth, for the interincisal point; the other with closed mouth, for the condylar poles. Next, their positions during actual mandibular borders movements were virtu-

ally reconstructed relative to the cranial reference system using the movements of the mandibular plane [16-18].
Each patient performed three repetitions per movement, and mean values were computed.
The method error of mandibular movements had already been assessed, without significant differences among repeated sessions [18].

Data analysis

At first, all coordinates were referred to the cranial reference plane, thus mathematically eliminating head and neck movements. Mandibular width (unit: mm) was estimated as the distance between the right and left condylar markers after subtracting the two markers' radii; mandibular length (unit: mm) was estimated as the distance between the dental marker (interincisal point) and the midpoint of the intercondylar axis [16 18].
Mandibular movements were described by reconstructed motions of the interincisal and condylar points. In each motion frame, the rotation angles made by the mandible around the three cranial axes were calculated using Cardan angles. The range of mandibular movements (interincisal point) was assessed at maximum mouth opening, right and left lateral excursions, and protrusion (unit: mm). At maximum mouth opening, the sagittal mandibular angle was calculated (unit: degree), as well as the right and left total condylar translations, both as absolute distance (unit: mm) and relative percentage, standardised with their concomitant rotation (unit: %) [16 18].

Statistical analysis

To better assess the clinical significance of data, all right and left values (of laterality or condyle) were referred to "operated" and "not operated" side. One patient (M2) was submitted to midline surgery: conventionally, his right side was considered as "not operated".
Patient data were compared to those collected in healthy volunteers [16-19] by computing z-scores. The individual measurements obtained in the seven patients were transformed to z scores by subtracting from each value its sex reference mean value and dividing by the relevant reference standard deviation.
The z-score measures the difference between a single patient value and its reference value in terms of standard deviation: negative values indicate that the patient value is minor than the reference mean value, while positive values indicate the opposite. Z-scores comprised between -2 and 2 indicate that the patient value is within 2 SD of the reference value, while values outside this interval indicate larger deviations from the norm.
Descriptive statistics (mean and standard deviation) were computed for the values of the z-scores.

Results

No patients developed significant complications at donor or recipient sites. Mandibular movements were assessed in the patients after a mean follow-up of 19 months (SD 10). At the interview before data collection, no patient reported difficulty in performing daily activities such as talking, eating, or drinking. Additionally, no significant weight loss was observed after surgery. Only patient F2 lamented slight difficulty in speech, but reported a good mastication especially after implant rehabilitation.
All patients could perform the movements without major impairments or problems. On average, mandibular length was smaller and mandibular width larger than in reference subjects (Table II). In particular, the mandible in patients M2 and M5 was about 4 SD wider than that of reference men.
Maximum mouth opening was reduced in all patients, with z-scores ranging from -2.742 (F2) to -0.106 (F3,

Table II. Kinematic characteristics of patients during the execution of mandibular border movements compared with the healthy control group.

	Mandible		Max mouth open		Absolute translation open		Relative translation open		Maximal laterality		
Patients	Length (mm)	Width (mm)	Distance (mm)	Sagittal angle (°)	Not operated (mm)	Operated (mm)	Not operated (%)	Operated (%)	Not operated (mm)	Operated (mm)	Protrusion (mm)
F2	72.3	125.2	26.2	21.6	10.5	8.8	28	24	6.9	2.7	5.8
F3	85.1	112.7	43.6	30.6	12.3	13.1	28	27	10.1	15.9	6.1
F4	88.0	115.0	39.7	30.1	14.1	15.2	23	25	7.0	5.1	3.0
M1	70.4	118.5	33.5	23.8	8.8	9.7	23	25	5.9	4.6	4.0
M2	84.1	138.4	36.8	18.8	11.4	15.1	29	35	9.0	9.2	5.6
M4	83.7	132.6	45.8	30.0	15.1	12.4	23	22	10.8	16.0	2.5
M5	81.8	140.5	47.1	30.3	20.6	22.9	32	35	8.8	11.7	7.6
Z-scores											
Mean	-0.988	1.441	-1.230	-1.036	0.208	-0.796	0.008	0.128	0.151	0.296	-0.887
SD	1.221	2.520	1.018	0.830	1.404	3.025	1.005	1.042	0.690	2.460	0.866

Z-score values were obtained using sex-specific reference data collected in our laboratory [16-19].

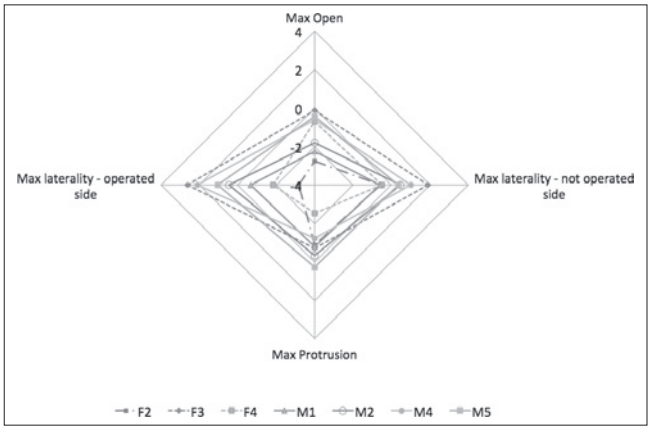

Fig. 1. Z-scores of the interincisal point excursions in each patient's maximal mandibular border movements.

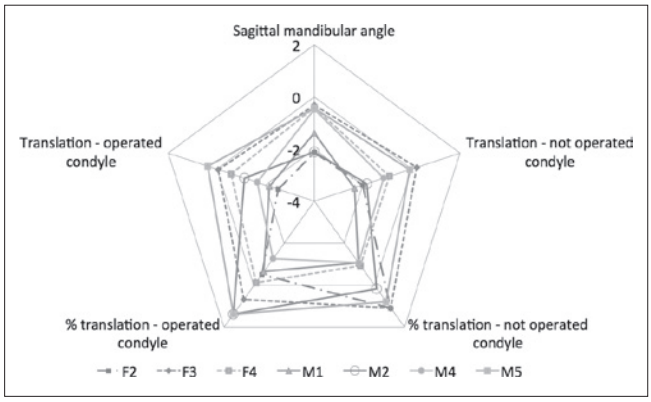

Fig. 2. Z-scores of the maximum mouth opening components in each patient. Condylar translations are reported for both operated and non-operated sides.

Fig. 1), and it was performed with a reduced sagittal plane mandibular rotation (Fig. 2). Two patients (F2, M1) had a reduction in mouth opening larger than 2 SD. In general, patients submitted to radiotherapy had a larger reduction in mouth opening.

Focusing on condylar translation during mouth opening, patients F2 and M1 had a particularly reduced absolute translation (z-scores smaller than -2). Patients M3 and M4 showed a notable asymmetry, one with a larger movement of the condyle of the side that was not operated on (M3), and the other with the opposite performance. In general, patients submitted to radiotherapy had a larger reduction in condylar translation.

Interincisal point forward movement during protrusion was reduced in all but one patient (M5). Overall, lateral mandibular movements (displacement of the interincisal point) were very variable; those towards the not operated side were somewhat reduced in three patients, and increased in the other four. Those towards the operated side had an increased movement, larger than 2 SD, in M4 and F3, and a remarkable reduction in F2 (z-score = -3.167).

Overall, if only the distance variables are considered, on average, only one patient had remarkably reduced motion than the reference subjects (F2, mean z-score for motion components -1.975), while all the other patients had mean limitations smaller than 1.5 z-scores.

Discussion

Current surgical treatment of patients with carcinoma of the oral cavity must include both the aim of complete tumour removal, and the maintenance of an acceptable quality of life through immediate and definitive reconstruction. Reconstruction should consider both function (speaking, feeding, swallowing) and aesthetics at the same time [15].

Fibular free flaps are considered the first choice for mandibular or maxillary reconstruction of extensive defects or to cover simultaneously soft-tissue defects [1 21]. The FFF possesses several favourable characteristics: the vascular pedicle, peroneal artery and its venae comitans are constant and with sufficient length and size. The bone is of exceptional quality, allowing for multiple segmental osteotomies for contouring, and it is of sufficient thickness for the subsequent positioning of dental implants. Primary insertion of osseointegrated implants can be reliably performed, but only in selected patients with benign disorders that do not need adjuvant post-surgical radiotherapy, good health and favourable prognosis [22 23]. Indeed, in the current patients oral rehabilitation was performed in a second occasion, with either mucosal-supported or implant-supported prostheses, as recently suggested [2].

The fibula, however, is usually unable to establish adequate alveolar height, especially for mandibular reconstructions. In patients in whom osseointegrated implants are planned, several manoeuvres should be considered in both jaws. The fibula should be placed about 0.5 to 1 cm above the inferior border of the native mandible, closer to the superior alveolar edge to facilitate placement of implants [22 24]. In most cases, the overlying soft tissue is able to camouflage the inferior border irregularities. A double barrel fibula can also be used [25]. Finally, vertical distraction osteogenesis of the fibular segment can be used to increase its height.

Many studies in literature have evaluated FFF donor site morbidity through questionnaires and quantitative methods such as balance tests and gait analysis [6 26]. The results achieved in these studies have been exceeding satisfactory: today, the FFF is one of the most widely performed free flaps for the reconstruction of defects in the oral cavity involving bone and soft tissue.

Moreover, several retrospective studies have been carried out to investigate the post-operative outcome of oral cavity reconstruction with FFF [27]. In these studies, assessment of the recipient site was evaluated with clinical evaluation and questionnaires.

The most common problems reported by patients after surgery are difficulty in swallowing, chewing and speech. Shpitzer et al. [1] reported that about 37% of 48 patients had problems with deglutition after FFF reconstruction, while Hidalgo and Pusic [28] described that 30% of 19 patients had problems with mastication after receiving a FFF.

Indeed, the literature lacks studies with objective, quantitative assessments for mandibular function after FFF surgery. In the current investigation, we collected free mandibular movements in a small group of patients using a three-dimensional computerised motion analyser. We applied a previously devised method that had already been employed to assess normal subjects, surgical and dental patients [16-19].

The method is non-invasive, but requires the presence of teeth in the central portion of the mandibular dental arch. This constraint limited the assessment to a restricted number of patients, and we are currently investigating novel systems to position and fix the small framework necessary for the detection of mandibular movements.

Considering the pilot nature of the current study, it is difficult to estimate differences in percentage of postoperative complications. Additionally, no information about the presurgical biomechanical characteristics of the patients' TMJ was available, and some of the post-surgical differences may be related to individual anatomical (mandibular dimensions) and functional (mandibular range of motion, TMJ biomechanics) features [18]. Also, control subjects were younger than most of the patients analysed in the current study, but no previous studies about the effect of aging on the biomechanical characteristics of the TMJ has been reported.

Nonetheless, some of the quantitative data found in the current study can be related to the clinical situation of each patient. In general, maximum mouth opening was reduced in all patients, but the worst results were reported for patient F2. Indeed, she had underwent three previous surgical treatments for squamous cell carcinoma of the oral cavity that were performed without reconstruction, as well as adjuvant radiotherapy.

Repeated surgical intervention, muscle dissection and resection, and radiotherapy provoked the formation of substantial scar tissue. Scars are a major cause of morbidity in the recipient site, and scar tissue often replaces many mandibular and lingual muscles that are cut during surgery and often sacrificed together with the tumour mass. This repair tissue leads to loss of the functional properties of muscles and reduces the elasticity of the oral mucosa [15]. Radiotherapy does not help tissue healing, favouring the formation of an inelastic tissue [29]. Fortunately, in only one patient did this complication occurred causing slight difficulties in speech.

Lateral mandibular movements (displacement of the interincisal point) and bilateral condylar movements during mouth opening were very variable and sometimes asymmetrical in the patients analysed, even in M2 who was operated on the midline. Considering that his left side was arbitrarily set as "operated", we also re-made all calculations changing the side, but no particular differences were observed (data not shown).

Together with mandibular range of motion, the current study investigated biomechanical characteristics of TMJ motion that can provide further information about the joint, and that can be followed-up during healing without submitting the patient to harmful procedures [16-18]. Indeed, the major variations in mandibular rotation were observed for patients F2 and M2. This last was operated at his symphysis, a region where no masticatory muscles insert, and that is not involved in TMJ or in its ligaments. Indeed, during surgical removal of oral cavity cancers many muscles like the mylohyoid, the digastric or the extrinsic tongue muscles are resected, or even radically dissected during a concomitant neck dissection. Anatomical reconstruction of muscle insertions should be made whenever possible; nonetheless, this destructive surgery and the subsequent scars can potentially reduce mandibular movements.

Currently, no clear clinical information is available about the medium- or long-term implications of alterations in TMJ rotation and translation characteristics. Previous studies found an increased rotation component in patients operated on for condylar fractures [18], and in patients submitted to orthognathic surgery for either skeletal Class II or III malformations [17]. Surgical intervention and modifications of the biomechanical characteristics of the facial skeleton and muscles may play a role in these alterations.

One additional limitation of the current study is the lack of chewing assessments, the actual function of the stomatognathic system that should be tested in the patients [19 30]. Indeed, in the current study, we only interviewed patients about their possible limitation for alimentation, but did not use any structured questionnaire that may help in better defining their actual situation [19 30]. Future studies should also involve the assessment of mandibular kinematics during mastication of standardised test foods.

It is clear that surgery (ablation of the tumour and reconstruction with a FFF) [31 32] is just one of the interventions that may alter TMJ function, and other aspects should be considered, starting from radiotherapy. Some differences were observed in the current group of patients, with a general increased reduction in mouth opening and condylar translation in the patients submitted to radiotherapy relative to those who did not receive this treatment. This topic should be specifically investigated in a larger number of patients. Indeed, a specifically devised rehabilitative intervention may concur to improve the follow-up efficacy of a successful surgical approach.

Conclusions

The current investigation confirms the value of using FFF in mandibular reconstruction. Valuable insight is provided into areas that need to be given special attention in preoperative planning, patient information and rehabilitation. Moreover, the functional and cosmetic dimensions of reconstruction need to be considered carefully in preoperative planning.
The small size of the current group of patients does not allow comparison of the alterations of mandibular movements with the reconstructed portion of the oral cavity: this is one of the aims of forthcoming studies. One additional target of our future investigations is the effect of concomitant treatments: in particular, the additional tissue damages caused by radiotherapy should be assessed.

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HEAD AND NECK

Human papillomavirus-associated cancers: a survey on otorhinolaryngologists' knowledge and attitudes on prevention

Carcinomi associati al papillomavirus umano: conoscenze, ruolo e attitudini dei medici otorinolaringoiatri in tema di prevenzione

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SUMMARY

Human papillomavirus (HPV) infection is a recognised causal factor associated with oropharyngeal cancers. The global burden of HPV-related oropharyngeal cancers is on the increase and is predicted to surpass the burden of cervical cancer in the near future. As evidence is accumulating on the potential effectiveness of an HPV vaccine in controlling the oropharyngeal cancer epidemic; otorhinolaryngologists assume a key role – not only in the diagnosis and treatment of HPV-related cancers – but also in educating and advocating on HPV prevention. We conducted a survey to assess Italian otorhinolaryngologists' knowledge and attitudes regarding HPV infection, HPV-related oropharyngeal diseases and cancers and available prevention measures, including vaccines. This is the first study conducted in Italy and Europe on this topic. A total of 262 Italian otorhinolaryngologists were recruited during the National Conference of the Italian Association of Otorhinolaryngologists. Our results show that Italian otorhinolaryngologists are knowledgeable regarding HPV infection and have a positive attitude towards HPV vaccine. Our findings provide a useful basis to plan, implement and evaluate targeted educational programmes and training. As we show herein, educational programmes and training specifically focusing on HPV are effective in increasing physicians' knowledge and positive attitudes towards prevention; this ultimately contributes to enhance vaccine uptake among patients and the general population. With the overall aim of controlling the burden of HPV-related cancers, resources and efforts should be devoted to promote continuing education among otorhinolaryngologists and the general medical community and to increase awareness on the role of vaccines in prevention of HPV-related cancers. In this context, there is tremendous opportunity for healthcare providers across fields to cooperate and for public health and otorhinolaryngologist communities to join forces and engage in fruitful collaboration.

KEY WORDS: Human papillomavirus • Head and Neck Neoplasms • Papillomavirus Vaccines • Knowledge • Primary prevention

RIASSUNTO

L'infezione da papillomavirus umano (HPV), in particolare HPV 16, è un riconosciuto fattore causale delle neoplasie orofaringee. L'incidenza delle neoplasie orofaringee è in aumento in diversi paesi europei, inclusa l'Italia, e negli Stai Uniti dove accurati modelli matematici hanno stimato che supererà quella del cancro alla cervice nella prossima decade. Recenti evidenze scientifiche supportano la potenziale efficacia del vaccino anti-HPV nel controllare quella che è stata definita "l'epidemia di neoplasie HPV-correlate". In questo contesto, i medici otorinolaringoiatri assumono un ruolo cruciale, non solo nella diagnosi e trattamento di questa patologia, ma anche – come è stato sottolineato dall'American Head and Neck Society – nella prevenzione. Abbiamo condotto un'indagine sulle conoscenze e le attitudini dei medici otorinolaringoiatri italiani in tema di infezione HPV, patologie correlate e prevenzione vaccinale. Si tratta della prima indagine conoscitiva in Italia e in Europa sull'argomento. 262 medici otorinolaringoiatri italiani sono stati reclutati durante il 101° Congresso Nazionale della Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale, tenutosi in maggio 2014. È stato utilizzato un questionario semi-strutturato sviluppato sulla base delle evidenze disponibili in letteratura e del parere di esperti. Le conoscenze e le attitudini sono state descritte e valutate con tecniche di analisi univariata. È stato inoltre costruito uno score composito di conoscenza. I dati dimostrano come i medici otorinolaringoiatri italiani abbiano, in media, un grado di conoscenza buono dell'infezione HPV e un'attitudine positiva nei confronti della prevenzione, in particolare della vaccinazione. I nostri risultati possono essere una utile base per pianificare, implementare e valutare programmi di educazione continua specifici sul tema della prevenzione dell'infezione da HPV. Come dimostriamo nel nostro studio, programmi di educazione continua specifici sono efficaci nell'aumentare il grado di conoscenza dei medici e l'attitudine positiva nei confronti dei programmi di prevenzione; il che contribuisce a promuovere l'adesione alla vaccinazione nei pazienti e nella popolazione generale. Con l'obiettivo generale di controllare l'epidemia di neoplasie HPV-correlate, maggiori risorse ed energie devono essere dedicate alla formazione e alla diffusione della cultura della prevenzione tra i medici otorinolaringoiatri e la comunità medica in generale. In questo contesto, identifichiamo grande potenziale nella collaborazione tra le comunità e le società scientifiche dell'otorinolaringoiatria e la sanità pubblica.

PAROLE CHIAVE: *Papillomavirus umano • Neoplasie testa-collo • Vaccini anti- papillomavirus • Grado di conoscenza • Prevenzione primaria*

Introduction

Human papillomavirus (HPV) infection is a recognised causal factor associated with head and neck cancers [1]. In particular, the International Agency for Research on Cancer (IARC) of the World Health Organization identified HPV type 16 as a carcinogenic agent responsible for oropharyngeal squamous cell carcinoma (OPSCC) in 2012 [2]. Two recent reviews published in Acta Otorhinolaryngologica Italica pooled the available evidence on the molecular mechanisms of HPV-induced carcinogenesis, on the diagnostic and clinical features of HPV-induced oropharyngeal carcinomas and their prognosis and management [3 4]. As emerged from the reviews, HPV-related OPSCCs are an independent clinico-pathological entity whose risk factors differ from HPV-unrelated cancers [3 4].
Data from the United States [5], Australia [6] and selected European countries [7-11] show that HPV-related OPSCC account for to up to 90% of all cancers diagnosed. Importantly, the share of total OPSCC related to HPV infection is increasing over time in high-income countries: in the United States, it increased by four fold from 16% to 70% in the last decades [12]; this occurred in parallel with decreasing HPV-unrelated cancer trends [10]. Such tendencies have prompted some authors to suggest that there is an *epidemic* of HPV-induced carcinomas [10 13].
Solid evidence from randomised trials demonstrated that the two available HPV vaccines prevent cervical cancers [14 15] and other non-cervical lesions and cancers [16-18]. The use of HPV vaccine to reduce the increasing burden of oropharyngeal cancers had long been hypothesised [19 20]. Preliminary findings of the first randomised controlled trial to assess HPV vaccine efficacy (VE) in the oral cavity have been recently published [21]. Bivalent HPV vaccine was reported to have a VE of 93% (95% CI = 63% to 100%) in reducing oral HPV infection at four year follow-up; this has potentially vast implications for prevention of HPV associated oropharyngeal cancer [21].
This new evidence combined with the large increase in OPSCC incidence worldwide underlines the crucial role that otorhinolaryngologists have not only in diagnosis and clinical management of HPV-associated OPSCC, but also in prevention of HPV infection. In line with that, the American Head and Neck Society (AHNS) has recently stated that head and neck surgeons share the responsibility of advocating and educating patients, the public and the general medical community on HPV vaccination [22]. Furthermore, there is evidence that healthcare providers' advice and recommendations are the most widely used source of information influencing vaccination uptake and willingness to get vaccinated [23 24]. In this context, it is important to assess otorhinolaryngologists' knowledge and attitudes with regard to HPV as this would inform the design and implementation of targeted medical education programmes with a positive impact on OPSCC prevention [25].
Limited data is available on this topic. To our knowledge, only one study is available in the literature on a sample of American Head and Neck surgeons' practices, attitudes, and knowledge regarding human papillomavirus-related cancers and vaccines [22]. No similar studies have been carried out in Europe or Italy.
The primary aim of this study was to assess Italian otorhinolaryngologists' knowledge regarding HPV infection, HPV-related oropharyngeal diseases and cancers and available prevention measures, including vaccines. The secondary objective was to assess their and attitudes, opinions and perceived benefits and barriers against oral HPV infection prevention.

Materials and methods

We conducted a survey to assess Italian otorhinolaryngologists' knowledge and attitudes regarding HPV infection, HPV-related oropharyngeal diseases and cancers and available prevention measures, including vaccines.

The questionnaire

A semi-structured questionnaire was designed on the basis of the relevant evidence available in the literature, clinical practice guidelines and input from experts in the field. The questionnaire was structured in three parts: the first explored socio-demographic characteristics as well as information about education, training and professional career; the second part investigated their knowledge on HPV infection, HPV-related oral diseases and cancers and available prevention measures, including vaccines; the last section explored opinions and attitudes towards HPV vaccination.
The questionnaire was preliminarily validated through a pilot survey administered to 30 subjects to verify its effectiveness and comprehensibility. On the basis of the feedback obtained through the pilot study, critical points were discussed and revised into the final version of the questionnaire that included 28 items (Appendix 1.A and 1.B report, respectively, the Italian version and the English version of the questionnaire - published online: www.actaitalica.it).
The questionnaire was distributed in person to all otorhinolaryngologists during the National Conference of the Italian Association of Otorhinolaryngologists held in Catania, Sicily in May 2014.

Analysis

Data extraction was independently carried out by two co-authors and an electronic database was compiled.
Descriptive analyses were performed to describe the study population. A composite HPV knowledge score was built. Seventeen HPV knowledge items were included in the score. In particular, they assessed otorhinolaryngologists' knowledge on: HPV infection transmission route,

HPV-associated diseases, carcinogenic HPV types, available HPV vaccines, recommended vaccination schedules and risk of adverse events, prevention objectives of HPV immunisation programmes and target population, national immunisation coverage targets and role of HPV vaccination in the broader context of primary and secondary prevention of HPV-related cancers.

For each correct answer, a point was added to the composite HPV knowledge score. Blank or wrong answers were given no points. The overall knowledge score was expressed as weighted percentage (%).

Differences in knowledge and attitudes by *a priori* selected relevant variables (including socio-demographic characteristics, area of residence, educational and professional profiles) were explored through univariate regression analysis. P values were derived from chi-square and t-tests. Analyses were carried out using SPSS statistical software (version 21.0).

Table I. Socio-demographic characteristics of the study population.

Characteristics	Categories	n (%)
Age (years)	≤ 35	55 (21%)
	36-50	81 (30.9%)
	51-60	92 (35.1%)
	≥ 61	30 (11.5%)
	Missing	4 (1.5%)
Gender	Male	168 (64.1%)
	Female	91 (34.7%)
	Missing	3 (1.2%)
Years of clinical practice	≥40	16 (6.1%)
	39-25	105 (40.1%)
	24-10	86 (32.8%)
	≤9	44 (16.8%)
	Missing	11 (4.2%)
Location of practice in Italy	North	120 (45.8%)
	Centre	43 (16.4%)
	South and islands	88 (33.6%)
	Missing	11 (4.2%)

Results

Socio-demographic characteristics of the study population

A total of 262 otorhinolaryngologists were included in the study (response rate 22%). Participants' socio-demographic characteristics are summarised in Table I.

The majority of respondents were male (64%, n = 168) and 66% had between 35 and 60 years (n = 173). With regards to geographical distribution, almost half were from Northern Italy (45.8%, n = 120). Overall, almost 50% (46.2%, n = 121) had more than 25 years of clinical practice experience; 71% of physicians (n = 185) reported to have participated in educational programmes and training specifically focusing on prevention of HPV infection.

Level of knowledge on HPV infection and vaccines

Overall, the average knowledge score was 64.1% (SD = 14.8), ranging from 23.5% to 88.2%. Physicians correctly identified HPV infection transmission routes: sexual (99.2%, n = 260) and cutaneous (62.6%, n = 164). However, more than half also believed that transplacental (64.5%, n = 169), haematic (67.9%, n = 178) and air (58%, n = 152) were transmission routes of HPV infection.

Moreover, 96% of physicians (n = 251) knew that HPV infection is associated with oropharyngeal cancer and 74% (n=193) knew it is associated with respiratory papillomatosis. In addition, they were aware of HPV-related diseases: genital warts (80.9%, n = 212) and cervical (99.6%, n = 261), vulvar and vaginal (79.8%, n = 209), anal (80.9%, n = 212) and penile (80.2%, n = 210) cancer. Less than 20% of respondents (17%, n = 45) identified both HPV types 16 and 18 as carcinogenic.

In addition, 48.9% of physicians (n=128) were aware of the existence both bi-valent and quadri-valent vaccines; 3.4% (n=9) thought only one vaccine is available and 47% (n = 124) ignored that any vaccine against HPV infection existed at all. Among who knew both vaccines exist, 24% (n = 31) though its administration has no risk of side effects and 56% (n = 72) were not able to answer the question.

Of interest, 77.5% (n = 203) knew that the age target for the administration of the HPV vaccine in young females is 12 years and that 12-year-old girl cohorts are actively offered free of charge the vaccine through the Italian health system. A total of 20% (n = 53) of subjects knew that three doses of vaccine were at the time recommended, while 54% (n = 141) admitted to not know it. With regard to HPV immunisation coverage rate target, only 12% (n = 31) knew the Ministry of Health set it at 95%. Lastly, 35% (n = 90) believed that immunisation against HPV did not rule out secondary prevention of HPV-related cancers.

The association between general knowledge on HPV and selected relevant variables is reported in Table II. Having participated in education programmes and training on HPV prevention was positively associated with increasing knowledge score ($p < 0.001$). When deconstructing the score and taking into consideration single items, having participated in education programmes and training remained positively associated with better knowledge on HPV transmission routes ($p < 0.001$) and availability of HPV vaccines, (although the latter was not statistically significant, $p = 0.07$). Minor differences in knowledge were reported by geographical origin of respondents. No socio-demographic characteristics were significantly associated with better knowledge on HPV (Table II).

Providers' attitudes and opinions on prevention of HPV infection

The majority of respondents believed that the main objective of HPV vaccination is primary prevention of HPV-related cancers (87%, n = 227). When asked about the perceived

Table II. Composite HPV Knowledge score and single knowledge items distribution by selected characteristics.

	Overall knowledge score (mean, SD)	*p* value*	knowledge on HPV infection transmission route (n, %)	*p* value*	Awareness of existence of both vaccines (N, %)	*p* value*
Age						
≤35	66.2 (13)	0.1	39 (24.1%)	0.13	33 (25.6%)	0.59
36-50	64 (14.4)		52 (32.1%)		39 (30.2%)	
51-60	60.5 (14.5)		58 (35.8%)		43 (33.3%)	
≥61	61.4 (15.7)		13 (8%)		14 (10.9%)	
Gender						
Male	62.1 (15)	0.26	104 (64.2%)	0.90	74 (57.4%)	0.04
Female	64.3 (13.3)		58 (35.8%)		53 (41.1%)	
missing					2 (1.6%)	
Location						
North	64.7 (13.2)	0.003	73 (45.1%)	0.004	60 (46.5%)	0.88
Centre	66.1 (9.5)		35 (21.6%)		19 (14.7%)	
South and islands	58.8 (16.6)		49 (30.2%)		45 (34.9%)	
missing			5 (3.1%)		5 (3.9%)	
HPV-specific educational programs						
Yes	66.2 (11.3)	<0.001	137 (84.6%)	<0.001	101 (78.3%)	0.07
No	58.6 (16.9)		13 (8%)		18 (14%)	
missing			12 (7.4%)		10 (7.8%)	

** p values obtained through chi-square and one-way ANOVA testing.*

usefulness of HPV vaccine, 66% of physicians (n = 173) considered HPV vaccine as a public health priority, 28% (n = 73) as a very important prevention tool, 3% (n = 9) as useful but not essential and 1% (n = 3) as absolutely useless. Respondents reported that the ideal target population to receive HPV vaccine is females before the start of sexual activity (74%, n = 191). Importantly, 22% (n = 56) thought the target population should include both males and females. More than 50% (54.2%, n = 142) reported to be asked about HPV vaccination benefits by patients as well as about vaccine side effects (12.6%, n = 33) and duration of protection (13.4%, n = 35). With regard to perceived barriers to HPV vaccination, respondents identified: inadequate information available to the general public (63.4%, n = 166), lack of vaccine benefits perception (66.8%, n = 175), parental reluctance (64.9%, n = 170) and low healthcare providers' advocacy (59.2%, n = 155). Almost all physicians (97%, n = 254) expressed their willingness to recommend HPV vaccination to patients.

Participants indicated the following as potential effective strategies to increase HPV vaccine uptake among adolescents: educational campaign through new media (60.7%, n = 159), this including websites targeting young people (29%, n = 76), school vaccination programmes (38.6%, n = 101) and counselling (40.5%, n = 106).

Discussion

The increasing key role of otorhinolaryngologists in promoting prevention of HPV-associated cancers has recently been advocated at the national and international level.

Our results show that Italian otorhinolaryngologists are knowledgeable regarding HPV infection and have a positive attitude towards HPV vaccine. These findings are of fundamental importance in light of: 1) the unfolding epidemic of HPV-related head and neck cancers [13] and 2) the mounting evidence on the efficacy of vaccine against HPV oral infection.

Overall knowledge scores exceeded 70% in almost 50% of respondents and, on specific items, it was higher compared to percentages we previously reported among general practitioners [26]. In particular, otorhinolaryngologists scored high on knowledge-based questions on HPV infection transmission and association with oral papillomatosis and oropharyngeal cancers as well as with cervical and other non-cervical cancers. More importantly, a large share of otorhinolaryngologists showed a positive attitude towards prevention of HPV-related cancers considering HPV vaccine as an effective prevention tool and a public health priority.

Some key issues that emerged from the survey merit discussion. First and of crucial significance, the large majority of respondents reported to be asked about the benefits of, side effects and duration of protection HPV vaccine, showing there is high demand for information and advice on it. Second, we report a positive correlation between having participated in educational programs and training and both high knowledge level and positive attitude to-

wards HPV prevention among physicians. This held true for overall knowledge score as well as for single knowledge items underlining the importance of continuous medical education and training to increase the delivery of preventive care [27 28].

Of note, more than a fifth of physicians thought the target population should include both males and females. This is in line with the new immunisation schedule recommended by Italian scientific societies that include both males and females as HPV vaccine target populations [29]. HPV vaccine is currently recommended to males in the United States [30] and in a few European countries [31]; however, as evidence accumulates on the effectiveness of vaccinating males to prevent HPV-related conditions in the male population as well as to enhance herd immunity in the general population [32 33], more countries are considering adhering to universal vaccination [18 34]. In particular, experts are increasingly advocating for HPV vaccination in males for the prevention of oropharyngeal cancers [33 35 36]. Lack of knowledge on specific items emerged: less than 20% of respondents correctly identified carcinogenic HPV types and almost half were not aware of the existence both bivalent and quadri-valent vaccines.

To our knowledge, this is the first study conducted in Italy and in Europe on the topic. Only one study, published on *JAMA Otolaryngology – Head & Neck Surgery,* is available in the literature on a sample of American Head and Neck surgeons' practices, attitudes and knowledge regarding HPV-related cancers and vaccines [22]. The authors reported that the respondents were relatively knowledgeable about HPV and had generally positive attitudes and beliefs about HPV education and vaccination. Although such findings are in line with our results, we argue that such knowledge is likely to be setting-specific and to vary depending on factors such as local healthcare systems, health policy strategies and medical curricula and training.

Although limited data is available on otorhinolaryngologists, several recent studies have explored knowledge of HPV among healthcare providers, including general practitioners (GPs) [37-41] and other specialists [41-43]. We have previously reported on Italian GPs' knowledge and perceived role in HPV prevention identifying some lack of knowledge on specific areas and room for improvement in communication with parents and adolescents on the topic [26]. In line with our findings, studies conducted with other specialists highlighted the importance of educating healthcare providers involved at different levels in HPV prevention [37-45].

Although those estimates come from heterogeneous studies and are likely to be influenced by the competing effect of different socio-demographic, genetic and environmental risk factors as well as HPV-testing methods and quality [46], such high percentages underlines how HPV-related OPSCC burden is a relevant clinical and public health concern and suggests that primary prevention may play a key role in reducing it.

The findings we report must be considered in light of limitations. First, the relatively low response rate limits the generalisability of our findings to the population of Italian otorhinolaryngologists. This has historically been a critical issue when conducting research among medical professionals as reported elsewhere [43]. However, the only other available study on the topic conducted in the United States had a similar sample size and response rate [22]. The small sample size might have prevented our analysis to have enough statistical power to detect specific factors associated with knowledge and attitudes toward HPV prevention. Lastly, we were not able to compare characteristics of respondents and non-respondents. Given the study design, we cannot rule out the risk of selection bias; in fact, assuming that more committed and knowledgeable physicians are more likely to complete the survey, this might have led to an overestimation of the overall knowledge on HPV infection and prevention. On the other hand – different from other similar studies which were self-administered online [22 43] – our survey was administered in person by trained staff, this limiting the risk of information bias. Finally, the questionnaire focused on primary prevention and did not explore otorhinolaryngologists' knowledge on available diagnostic tools for HPV infection, a topic of growing interest [43]. However, to increase the response rate we preferred to keep the questionnaire relatively short and we plan to explore this and other topic in future surveys.

Conclusions

The global burden of HPV-related oropharyngeal cancers is increasing and is predicted to surpass the burden of cervical cancer in the near future [12]. As evidence is accumulating on the potential effectiveness of HPV vaccine in controlling the oropharyngeal cancer epidemic [13 21], otorhinolaryngologists assume a key role – not only in the diagnosis and treatment of HPV-related cancers – but also in educating and advocating on HPV prevention [22].

To our knowledge, this is the first study conducted in the European Union to assess otorhinolaryngologists' knowledge and attitudes on HPV infection and prevention. Our results show that Italian otorhinolaryngologists are knowledgeable regarding HPV infection and have a positive attitude towards HPV vaccine. However, we identified areas of potential improvement. Our findings provide a useful basis to plan, implement and evaluate targeted educational programmes and training. As we showed herein, educational programmes and training specifically focusing on HPV are effective in increasing physician knowledge and positive attitude towards prevention [23]. In a global context of growing vaccine hesitancy, this would contributes to enhance vaccine uptake among patients and the general population [47-51]. With the overall aim of

controlling the burden of HPV-related cancers, resources and efforts should be devoted to promote continuing education among otorhinolaryngologists and the general medical community and to increase awareness on the role of vaccines in prevention of HPV-related cancers. In this context, there is tremendous opportunity for healthcare providers across fields to cooperate and for public health and otorhinolaryngologist communities to join forces and engage in fruitful collaboration.

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APPENDIX 1.A. Italian original version of the questionnaire.

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INDAGINE SULLE CONOSCENZE E SUGLI ATTEGGIAMENTI DEGLI OPERATORI SANITARI RELATIVAMENTE ALL'INFEZIONE DA HPV E ALLA VACCINAZIONE ANTI-HPV

SESSO
- o M
- o F

ETA' (anni compiuti):
- o ≤ 35 anni
- o 36 – 50 anni
- o 51 – 60 anni
- o ≥ 61 anni

PROVINCIA IN CUI SVOLGE PREVALENTEMENTE LA SUA ATTIVITA' PROFESSIONALE:_____

ANNO DI CONSEGUIMENTO DELLA LAUREA IN MEDICINA E CHIRURGIA:
_____

ANNO DI CONSEGUIMENTO DELLA SPECIALIZZAZIONE OTORINOLARINGOIATRIA: _____

EVENTUALE ALTRE SPECIALIZZAZIONI
(Specificare:.....)

AMBITO DI IMPIEGO
- o Ospedale pubblico
- o Università
- o Ospedale privato convenzionato
- o Clinica privata
- o Altro

Istruzioni per la compilazione del Questionario:

Il presente Questionario contiene 21 domande (più le sette domande della scheda socio-anagrafica sopra riportate); per alcune domande è possibile selezionare più di una risposta, mentre per altre viene richiesta una singola risposta.

QUESTIONARIO:

1. **Durante la sua carriera professionale ha partecipato a programmi di educazione sanitaria in merito alla prevenzione dell'infezione da HPV?**
   - o Sì
   - o No

2. **L'HPV si può trasmettere per via (possibile più di una risposta):**
   - o Sessuale
   - o Ematica
   - o Aerea
   - o Cutanea
   - o Transplacentare

3. **Sono patologie associate all'infezione da HPV(possibile più di una risposta):**
   - o Carcinoma della cervice uterina
   - o Condilomi genitali
   - o Papillomatosi respiratoria
   - o Carcinoma vulvo-vaginale
   - o Carcinoma anale
   - o Carcinoma orofaringeo
   - o Carcinoma penieno

4. **I tipi di HPV più frequentemente associati al carcinoma della cervice uterina sono (indicare una sola risposta):**
   - o 6 e 11
   - o 16 e 18
   - o 6, 11, 16 e 18
   - o 31, 33 e 45
   - o Non so

5. **Quale ritiene sia la percentuale di ragazze che all'età di 12 anni ha già avuto il primo rapporto sessuale? (indicare una sola risposta)**
   - o <1%
   - o 1%- 5%
   - o 6%-10%
   - o >10%
   - o Non so

6. **Quale ritiene sia il principale obiettivo della vaccinazione anti-HPV (indicare una sola risposta)?**
   - o Prevenzione dei carcinomi HPV-correlati
   - o Prevenzione del carcinoma della cervice uterina
   - o Prevenzione delle MST (Malattie Sessualmente Trasmissibili)
   - o Prevenzione dei condilomi genitali
   - o Altro (Specificare:.....)

7. La vaccinazione anti-HPV (indicare una sola risposta):
- o E' una priorità di Sanità Pubblica
- o E' un presidio di prevenzione molto importante
- o E' un presidio di prevenzione utile, ma non indispensabile
- o E' assolutamente inutile

8. Quali parametri ritiene importanti come espressione dell'efficacia di un vaccino anti-HPV(possibile più di una risposta):
- o Prevenzione delle lesioni ASCUS
- o Prevenzioni dei condilomi genitali
- o Prevenzione delle lesioni CIN2+ da HPV-16/18
- o Prevenzione delle lesioni CIN3+ da tutti gli HPV ad alto rischio oncogeno
- o Titoli anticorpali elevati

9. E' a conoscenza della disponibilità di due vaccini (Gardasil e Cervarix) anti-HPV (indicare una sola risposta)?
- o Sì, sono a conoscenza dell'esistenza di entrambi
- o Sono a conoscenza solo dell'esistenza di Gardasil
- o Sono a conoscenza solo dell'esistenza di Cervarix
- o No

10. Le dosi di vaccino anti-HPV da somministrare sono:
- o 1
- o 2
- o 3
- o 4
- o Non so

11. La vaccinazione anti-HPV può dare effetti collaterali?
- o No
- o Sì (Specificare quali sono i più frequenti:.....)
- o Non so

12. A Suo avviso, in via prioritaria, il vaccino anti-HPV dovrebbe essere somministrato (indicare una sola risposta):
- o Alle femmine prima dell'inizio dell'attività sessuale
- o Ai maschi prima dell'inizio dell'attività sessuale
- o Alle femmine e ai maschi prima dell'inizio dell'attività sessuale
- o Alle femmine sessualmente attive
- o Ai maschi sessualmente attivi
- o Alle femmine e ai maschi sessualmente attivi
- o Alle femmine e ai maschi omosessuali
- o Solo agli individui che hanno molti partner sessuali

13. Per quale classe d'età il Piano Nazionale Prevenzione Vaccinale (PNPV) 2012-2014 prevede in tutte le Regioni offerta attiva e gratuita della vaccinazione anti-HPV (indicare una sola risposta)?

- o Dodicenni
- o Tredicenni
- o Diciottenni
- o Venticinquenni
- o Altro (Specificare:.....)

14. L'obiettivo di copertura vaccinale stabilito dal PNPV 2012-2014 per la vaccinazione anti-HPV è (indicare una sola risposta):

- o 40-50%
- o 55-65%
- o 30-40% delle venticinquenni
- o ≥ 70%
- o ≥ 95%
- o Non so

15. Ritiene possano essere ostacoli alla vaccinazione anti-HPV(possibile più di una risposta):

- o Rifiuto da parte dei genitori
- o Scarso supporto/obiezione da parte degli operatori sanitari
- o Insufficiente informazione alla fascia di popolazione interessata
- o Scarsa percezione dei benefici che ne possono derivare
- o Altro (Specificare:.....)

16. Qualora Le venisse chiesta l'opinione relativamente alla vaccinazione anti-HPV di una dodicenne, Lei esprimerebbe parere:

- o FAVOREVOLE
- o SFAVOREVOLE (Specificare perché, possibile più di una risposta):
  - |_| Vaccino troppo nuovo
  - |_| Dubbi sulla sicurezza/tollerabilità
  - |_| Contrario alle vaccinazioni
  - |_| La dodicenne non è a rischio di contrarre l'HPV
  - |_| Non si conosce la durata della protezione immunitaria
  - |_| Il vaccino protegge solo da alcuni tipi di HPV
  - |_| Altro (Specificare:.....)
- o NON SO

17. Nel caso Lei sia favorevole alla vaccinazione, quale tipo di vaccino anti-HPV consiglierebbe?

- o Cervarix (Specificare perchè:……..)
- o Gardasil (Specificare perchè:……)
- o Uno o l'altro indifferentemente

18. Ritiene che la vaccinazione anti-HPV nelle adolescenti possa indurre un falso senso di protezione nei confronti del rischio di contrarre MST?

- o Sì
- o No
- o Non so

19. Che tipo di informazioni Le vengono chieste sul vaccino anti-HPV da parte delle/dei Sue/Suoi pazienti? (possibile più di una risposta)

- o Epidemiologia della malattie causate dall'HPV
- o Epidemiologia del carcinoma della cervice uterina
- o Rischio di contrarre/trasmettere l'infezione da HPV
- o Modalità di trasmissione dell'infezione da HPV
- o Benefici della vaccinazione anti-HPV
- o Durata della protezione indotta dalla vaccinazione anti-HPV
- o Possibili eventi avversi della vaccinazione anti-HPV
- o Altro (Specificare:……..)

20. Ritiene che la vaccinazione possa eliminare la necessità di screening (Pap-test) periodici nel breve periodo?

- o Sì (Specificare perché:…….)
- o No
- o Non so

21. Quali ritiene possano essere le azioni da implementare per migliorare l'adesione delle adolescenti alla vaccinazione anti-HPV? (possibile più di una risposta)

- o Campagne educazionali sui media
- o Siti web dedicati, divulgati pubblicamente
- o Creazione di uno spazio "HPV" all'interno di siti web utilizzati dai giovani (es. "Habbo Hotel")
- o Corsi di counselling per Operatori Sanitari sulla comunicazione al target "adolescenti"
- o Materiale divulgativo distribuito nei distretti vaccinali/ambulatori/farmacie
- o Vaccinazione nelle scuole
- o Altro (Specificare:……..)
- o Non so

La ringraziamo per il tempo che ha dedicata alla compilazione del Questionario; le Sue risposte saranno analizzate in modo aggregato insieme a quelle derivanti dagli altri Questionari.

APPENDIX 1.B. English translated version of the questionnaire.

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A SURVEY ON OTORHINOLARYNGOLOGISTS' KNOWLEDGE AND ATTITUDES REGARDING HPV INFECTION AND HPV-VACCINATION

GENDER:
- o M
- o F

AGE (years):
- o ≤ 35
- o 36 – 50
- o 51 – 60
- o ≥ 61

LOCATION OF PRACTISE :_____

INDICATE THE YEAR OF GRADUATION FROM MEDICAL SCHOOL: _____

INDICATE THE YEAR OF SPECIALIZATION IN OTOLARYNGOLOGY–HEAD AND NECK: _____

OTHER MEDICAL SPECIALTY (Specify:.....)

WORKING ENVIRONMENT:
- o Public hospital
- o University hospital
- o Accredited private hospital
- o Private clinic
- o Other

Instructions for the compilation of the questionnaire:

The present questionnaire includes 21 items (plus the 7 items of the socio-demographic section above); for some of the items it is possible to choose more than one answer, for others only one answer is acceptable.

QUESTIONNAIRE:

1.During your professional career, have you participated in educational programs and training on HPV prevention?
- o Yes
- o No

2. HPV can be transmitted (more than one answer is acceptable):
- o Sexually
- o By blood
- o Airborne transmission
- o Skin-to-skin contact
- o Transplacentar infection

3. HPV infection is often associated with (more than one answer is acceptable):
- o Cervical cancer
- o Genital warts
- o Respiratory papillomatosis
- o Vulvar and vaginal cancer
- o Anal cancer
- o Oropharyngeal cancer
- o Penile cancer

4. HPV types which are most frequently associated with cervical cancer (only one answer is acceptable):
- o 6 and 11
- o 16 and 18
- o 6, 11, 16 and 18
- o 31, 33 and 45
- o I don't know

5. What is in your opinion the percentage of young girls aged 12 who have already had a first sexual experience? (only one answer is acceptable)
- o <1%
- o 1%- 5%
- o 6%-10%
- o >10%
- o I don't know

6. What is the main objective of HPV vaccination? (only one answer is acceptable)
- o Primary prevention of HPV-related cancer
- o Prevention of HPV-related cervical cancer
- o Prevention of STD (Sexually Transmitted Diseases)
- o Prevention of genital warts
- o Other (Specify:.....)

7. HPV vaccination is considered (only one answer is acceptable):
- o Public Health priority
- o Very important prevention tool
- o Useful but not essential prevention tool
- o Absolutely useless

8. What are, in your opinion, the most important parameters of HPV vaccine effectiveness (more than one answer is acceptable) :
- o Prevention of ASCUS lesions
- o Prevention of genital warts
- o Prevention of CIN2+ HPV 16/18-related lesions
- o Prevention of CIN3+ lesions related to infection with high risk type HPV
- o High levels of Ab-anti HPV

9. Are you aware of the existence of two types of HPV vaccines (Gardasil and Cervarix) (only one answer is acceptable) ?
- o Yes, I am aware of the existence of both vaccines
- o I know only Gardasil
- o I know only Cervarix
- o No

10.How many doses of HPV vaccine should be administered?
- o 1
- o 2
- o 3
- o 4
- o I don't know

11. Does (the administration of) HPV vaccine have side effects?
- o No
- o Yes (Specify the most frequent ones:.....)
- o I don't know

12. To whom, in your opinion, should HPV vaccine be administrated as a priority? (only one answer is acceptable):
- o Female population before the start of sexual activity
- o Male population before the start of sexual activity
- o Both female and male population before the start of sexual activity
- o Sexually active female population
- o Sexually active male population
- o Both female and male population sexually active
- o Both female and male homosexual population
- o Only subjects who have different sexual partners

13. With regard to the National Vaccination Prevention Plan 2012-2014 (Piano Nazionale Prevenzione Vaccinale, PNPV 2012-2014), what is the age target for free-of-charge HPV immunization in all Italian Regions (only one answer is acceptable)?

- o 12-year-olds
- o 13-year-olds
- o 18-year-olds
- o 25-year-olds
- o Other (Specify:.....)

14. With regard to PNPV 2012-2014, what is the HPV immunization coverage rate target (only one answer is acceptable)?

- o 40-50%
- o 55-65%
- o 30-40% of 25-year-olds
- o ≥ 70%
- o ≥ 95%
- o I don't know

15. In your opinion, what could be the possible barriers to HPV vaccination? (more than one answer is correct):

- o Parental reluctance to vaccination
- o Poor support by healthcare providers
- o Inadequate information to the vaccine target population
- o Poor perception of vaccine benefits
- o Other (Specify:.....)

16. If asked about immunization of 12-year-old (female) with HPV vaccine, you would:

- o Express your willingness to recommend HPV vaccination
- o Be unwilling to recommend HPV vaccination (Specify why, more than one option is acceptable):
  - |_| HPV vaccine is too recent to recommend it
  - |_| Uncertainty about vaccine safety and tolerability
  - |_| I am against vaccination
  - |_| The 12-year-old does not risk the HPV infection
  - |_| Not enough information about duration of HPV protection
  - |_| Vaccine gives protection only against some types of HPV
  - |_| Other (Specify:.....)
- o I don't know

17. In case you have expressed your willingness to recommend HPV vaccination, what type of vaccine would you recommend?

- o Cervarix (Specify why:……..)
- o Gardasil (Specify why:……)
- o Either Gardasil or Cervarix

18. Do you think that HPV vaccination could give a false sense of protection against STD (Sexually Transmitted Diseases) in young people?

- o Yes
- o No
- o I don't know

19. What are the most frequent questions regarding HPV vaccination that your patients ask you about? (more than one answer is correct)

- o Epidemiology of HPV-related diseases
- o Epidemiology of cervical cancer
- o Risk factors related to HPV infection-transmission
- o How HPV is transmitted
- o Health benefits of HPV vaccination
- o Duration of HPV protection after vaccination
- o Possible HPV vaccine side effects
- o Other (Specify:……..)

20. Do you believe that immunization against HPV could soon rule out secondary prevention of HPV-related diseases (Pap-test screening program)?

- o Yes (Specify why:…….)
- o No
- o I don't know

21. What could be potential effective strategies to increase HPV vaccine uptake among adolescents? (more than one answer is acceptable)

- o Educational campaigns through new media
- o Dedicated websites divulged publicly
- o Creation of HPV advertising space on websites targeting young people (ex. "Habbo Hotel")
- o Counselling/training programs for healthcare providers on communication targeting young people
- o Distribution of information material among health districts/clinics/ pharmacies
- o HPV vaccination in schools/ School vaccination programs
- o Other (Specify:…….)
- o I don't know

Thank you for the time dedicated to complete this Questionnaire; your answers will be analyzed together with other questionnaires.

ACTA OTORHINOLARYNGOLOGICA ITALICA 2015;35:386-393; DOI: 10.14639/0392-100X-919

HEAD AND NECK

Impact of microvascular free flap reconstruction in oral cavity cancer: our experience in 130 cases

L'impatto della ricostruzione mediante lembo microvascolare nei tumori del cavo orale: la nostra esperienza su 130 casi

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SUMMARY

The aim of this study was to investigate the oncological outcomes in patients affected by oral carcinoma treated with radical compartmental surgery followed by microvascular flap reconstruction. We conducted a retrospective analysis on a cohort of 130 patients. All patients underwent ablative tumour resection (compartmental surgery) followed by immediate reconstruction with free flaps and adjuvant chemoradiotherapy, when necessary according to our tumour board and international guidelines. Disease-specific survival (DSS) curves were obtained using the Kaplan-Meier method. Log-rank test and generalised Wilcoxon test were used to investigate the most important prognostic factors on 5-year DSS. A Cox proportional hazards model was constructed to provide hazard ratios or relative risks for individual variables. 88.5% of patients were affected by SCC. There were 46 (35.4%) women and 84 (64.6%) men in the sample with a mean age of 58.5 years. At the end of the follow-up period, 36 (27.7%) patients died, only 3 of which for other causes. The 5-year DSS rate was 67.8% (S.E. 4.9%). In univariate Kaplan-Meier analysis and in multivariate Cox regression model, seven variables were found to have a significant relationship with DSS: T (p = 0.026) and N (p = 0.0001) status, clinical stage (according to the UICC TNM Sixth Edition) (p = 0.007), margins of resection (p = 0.001), extracapsular spread (p = 0.005), recurrence of disease (p = 0.00002) and treatment modality (evaluated as surgery alone or surgery + RT/CHT) (p = 0.004). Our results confirmed findings already reported in the literature, and allowed us to conclude that compartmental surgery combined with free flap reconstruction can increase survival in oral cancer patients.

KEY WORDS: Oral cavity cancer • Microvascular free flaps • Survival • Compartmental surgery

RIASSUNTO

Obiettivo del presente studio è stato valutare i risultati oncologici della nostra casistica di pazienti affetti da tumore del cavo orale trattati mediante chirurgia compartimentale radicale seguita da ricostruzione mediante lembo microvascolare. Abbiamo condotto un'analisi retrospettiva su 130 casi. Tutti i pazienti sono stati sottoposti ad una resezione chirurgica della neoformazione seguita da una ricostruzione immediata mediante lembo libero e, quando necessario, in accordo con la valutazione espressa dal nostro tumor board e con le linee guida internazionali, ad un trattamento chemioradioterapico adjuvante. Le curve di sopravvivenza specifica per malattia (DSS) sono state ottenute mediante il metodo di Kaplan-Meier. Il test Long Rank e il Wilcoxon sono stati utilizzati per investigare i più importanti fattori influenzanti la sopravvivenza specifica per malattia a 5 anni. Per calcolare l'HR e il RR per le singole variabili è stato utilizzato un modello di Cox. L'88,5% dei pazienti è risultato affetto da una neoplasia a istologia squamocellulare. Il campione è risultato essere composto da 46 (35,4%) donne e 84 (64,6%) uomini con un età media di 58,5 anni. Al termine del periodo di follow up, 36 pazienti (27,7%) erano deceduti, 3 dei quali per altre cause. Il DSS è stato del 67,8% (S.E. = 4,9%). All'analisi univariata secondo Kaplan-Meier ed alla analisi multivariata con regressione di Cox sono state individuate sette differenti variabili aventi una relazione significativa con il DSS: T (p = 0,026) ed N (p = 0,0001), lo staging clinico (UICC TNM Sixth Edition) (p = 0,007), i margini di resezione (p = 0,001), l'extracapsular spread (p = 0.005), la recidiva di malattia (p = 0,00002) e la modalità di trattamento (sola chirurgia o chirurgia + RT/CHT) (p = 0,004). In nostri risultati sono risultati in linea con le osservazioni in letteratura, e ci permettono di sottolineare come la chirurgia ricostruttiva mediante lembo libero microvascolare possa incrementare la sopravvivenza nei pazienti con tumore del cavo orale.

PAROLE CHIAVE: *Tumori del cavo orale • Lembi liberi microvascolari • Sopravvivenza • Chirurgia compartimentale*

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Introduction

Oral cancer is the 8th most common neoplasm worldwide with 300,000 cases annually [1]. It presents extensive variability in terms of incidence between different regions and is highest in southeast Asia. In Italy, about 4/100,000 new cases per year are documented and it is most common in areas where voluptuary habits such alcohol consumption and tobacco smoking are more diffuse [2].

Surgery is considered the gold standard to achieve tumour control, but the diagnosis is usually late when the disease has already reached an advanced stage, for this reason, in the majority of cases, neoplasm dimensions, combined with the necessity of clear margins at least 1 cm around the tumour, lead to large resections requiring reconstructive surgery with important functional implications. Today this aim can be achieved through the use of microvascular free flaps that have replaced classical local and regional flaps to ensure oncologic radicality on one hand, better functional and aesthetic results on the other [3].

In fact, quality of life has gained great interest in the last years, and has become a secondary endpoint of care, while survival is the main outcome for these patients [4-8].

Starting from this observation, we focused on disease-specific survival (DSS), because the relatively advanced age and comorbidities of patients can create several problems when basing outcome only on overall survival [9]. We analysed a cohort of 130 patients treated with reconstructive surgery affected by oral cancer from 2005 to 2013 and correlated survival to clinical and pathological parameters.

Materials and methods

Patients

The retrospective cohort consisted of 130 patients affected by oral cancer; all underwent surgical treatment between 2005 and 2013 at the Department of Head and Neck Surgery - Otolaryngology/Department of Plastic and Reconstructive Surgery, Catholic University of Sacred Heart. 88% of the patients were affected by oral squamous cell carcinoma (OSCC). The main clinical characteristics of our patients are shown in Table I. Preoperative head and neck CT and MRI (to establish clinical staging and therapeutic planning), total body PET-CT (in case of relapse/persistence of disease), colour Doppler ultrasound of neck vessels and free-flap donor vessels (to evaluate anatomy and calibre of vessels and perforator anatomy in case of perforator flaps) were performed for each patient.

The type of oncologic resection and reconstruction, as well as length of stay in the intensive care unit and recipient/donor site postoperative complications were also recorded.

All patients underwent radical compartmental surgery followed by immediate microvascular flap reconstruction. Because of the correlation between the thickness of the primary tumour and the risk of nodal metastasis [10], we performed selective bilateral neck dissection in all patients who presented a depth of tumour invasion > 3 mm, or a locally advanced stage (T3-T4) with N+ at presentation. Adjuvant radiotherapy was performed in case of positive margins, T4 status, N status >1 and extracapsular spread. Following the NCCN guidelines, we respected the ≤6 week interval between resection and post-operative RT and used a typical regimen based on a three field method including bilateral parallel opposed fields to the primary site and upper neck. We generally administered 60-66 Gy (2 Gy daily fraction 5 days per week) for irradiation of the primary site and neck in case of involved nodal stations, and 44-64 Gy (1.6-2.0 Gy daily fraction 5 days per week) for the neck in case of uninvolved nodal stations.

Recurrence was evaluated as local (if involving only the oral cavity relative to the primary tumour), regional (if involving only the neck) and loco-regional (if involving both the primary site and neck). To confirm recurrences, we used biopsy, CT or MRI and generally PET-CT.

Statistical analysis

Data were analysed with statistical software (SPSS 21.0 for Windows; SPSS, Inc., Chicago, IL). DSS curves were obtained using the Kaplan-Meier method. Log-rank test and generalised Wilcoxon test were used to investigate the most important prognostic factors on 5-year DSS. A Cox proportional hazards model was constructed to provide hazard ratios for individual variables. A P value <0.05 was considered statistically significant.

Results

There were 46 (35.4%) women and 84 (64.6%) men in the sample with a mean age of 58.5 years ± 12.04 (range 26 to 83 years). On a total 130 patients, 119 received primary surgery in our department; 13 received salvage surgery for persistence/recurrence of disease; 11 underwent primary surgery in different hospitals and were referred to us for treatment of recurrence with reconstructive surgery. As shown in Table I, 58 patients (44.6%) received an ALT flap, 28 (21.5%) a fibula flap, 18 (13.9%) a FFR flap, 14 (10.8%) a DIEP flap, 6 (4.6%) a TRAM flap and 1 (0.8%) a VRAM flap reconstruction. Five patients (3.8%) underwent reconstruction with a chimeric flap, defined as a combined composite flap used in special cases in which we had the need to reconstruct, in addition to a bone defect, an extensive cutaneous or mucosal defect.

At the end of the follow-up period, on June 2013, (average 33.4; range 2 to 205 months) 36 patients had died, 33 for the disease and 3 for other causes. We observed a 5-year DSS of 67.8% (± 4.9% SE) (Fig. 1). Univariate Kaplan-Meier analysis revealed statistically significant relationships between DSS and T (p = 0.026) and N (p = 0.0001) status, clinical stage (p = 0.007), margins of resection (p = 0.001), extracapsular spread (p = 0.005), recurrence of disease (p = 0.00002) and treatment modality (p = 0.004). Results are shown in Table II. Kaplan-Meier survival curves by different variables are shown in Figure 2.

On multivariate Cox regression analysis, the same variables showed a significant relationship with DSS, and in particular N stage (HR 2.2; p = 0.0001), margins of resec-

Table I. Clinical features.

Characteristics	No. patients (%)
Gender	
Male	84 (64.6%)
Female	46 (35.4%)
Age	
Mean	58.5 (±1.05 S.E.)
<50	36 (27.7%)
≥50	94 (72.3%)
Primary site	
Tongue	56 (50%)
Floor of mouth	29 (22.3%)
Retromolar trigone	12 (9.2%)
Gum	8 (6.2%)
Buccal mucosa	3 (2.3%)
Palate	7 (5.4%)
Mandible	3 (2.3%)
Lip	3 (2.3%)
Histology	
Squamous cell carcinoma (SCC)	115 (88.4)
Adenoid cystic carcinoma	7 (5.4)
Other	8 (6.2)
T status	
T1	10 (7.7%)
T2	45 (34.6%)
T3	30 (23.1%)
T4	45 (34.6%)
N status	
N0	52 (40%)
N1	31 (23.9%)
N2	45 (34.6%)
N3	2 (1.5%)
Clinical Stage*	
I	5 (3.8%)
II	20 (15.4%)
III	33 (25.4%)
IV	72 (55.4%)
Type of flap	
ALT**	58 (44.6%)
Fibula	28 (21.5%)
FFRF**	18 (13.9%)
DIEP**	14 (10.8%)
TRAM**	6 (4.6%)
Chimeric Flap**	5 (3.8%)
VRAM**	1 (0.8%)
Margin	
Positive	19 (14.6%)
Close	14 (10.8%)
Negative	97 (74.6%)
Extracapsular spread	
Yes	98 (75.4%)
No	32 (24.6%)
Perineural invasion	
Yes	118 (90.8%)
No	12 (9.2%)
Mandible/Maxilla involvement	
Yes	48 (36.9%)
No	82 (63.1%)
Recurrence	
Yes	47 (36.1%)
No	83 (63.9%)
Treatment modality	
Surgery alone	46 (35.4%)
Surgery + RT/CT	84 (64.6%)
Lymph node dissection	
Unilateral	14 (10.8%)
Bilateral	114 (87.7%)
No	2 (1.5%)
Clinical status at end of follow-up	
No evidence of disease (NED)	79 (60.8%)
Alive with disease (AWD)	15 (11.5%)
Dead of disease (DOD)	36 (27.7%)

**According to UICC TNM Sixth Edition.*

***ALT: Anterolateral Thigh Perforator flap; FFR: Free Forearm Radial Flap; DIEP: Deep Inferior Epigastric Perforator flap; TRAM: Transverse Rectus Abdominis Myocutaneous flap; VRAM: Vertical Rectus Abdominis Myocutaneous flap; Chimeric flap: combination of two microvascular flaps.*

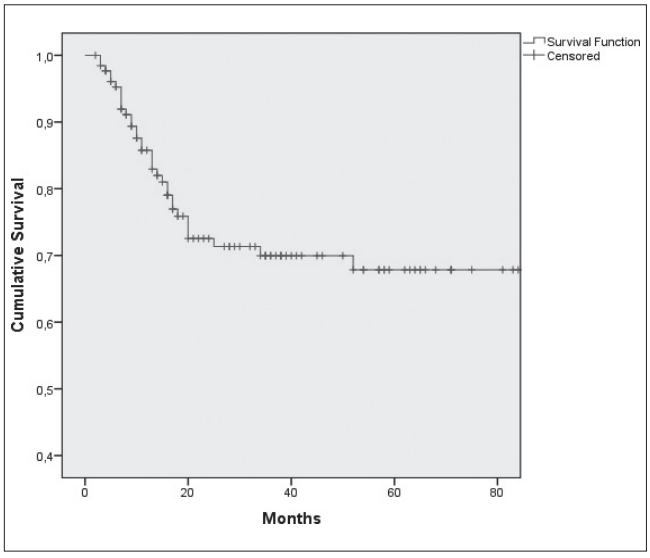

Fig. 1. Cumulative disease-specific survival.

tion (HR 2; p = 0.0001) and recurrence of disease (HR 5.3; p = 0.00001). Results are summarised in Table III.

Flap complications

Nine patients experienced major complications after sur-

Table II. Kaplan-Meier analysis: relationship between variables and survival.

Variables	No. patients (%)	5 year DSS (±S.E.)	Mean survival time (mo) (95% CI)	p value
Gender				0.20
Male	84 (64.6%)	63.9% (5.9%)	75.9 (64-87)	
Female	46 (35.4%)	75.4% (8.4%)	159.7 (130-188)	
Age				0.88
Mean	58.5 (±1.05 S.E.)			
<50	36 (27.7%)	62.3% (9.6%)	76.7 (60-93)	
≥50	94 (72.3%)	68.1% (5.4%)	148.8 (128-269)	
Primary site				0.62
Tongue	56 (50%)	73% (6.1%)		
Floor of mouth	29 (22.3%)	68.5% (9.5%)		
Retromolar trigone	12 (9.2%)	56.6% (17%)		
Gum	8 (6.2%)	37.5% (17.1%)		
Buccal mucosa	3 (2.3%)	50% (34%)		
Palate	7 (5.4%)	53.3% (24.8)		
Mandible	3 (2.3%)			
Lip	3 (2.3%)	66.7% (27.2%)		
Histology				0.36
Squamous cell carcinoma (SCC)	115 (88.4)	65.2% (5.3%)		
Adenoid cystic carcinoma	7 (5.4)	100%		
Other	8 (6.2)	83.3% (15.2%)		
T status				0.026
T1	10 (7.7%)	100%		
T2	45 (34.6%)	84.9% (5.7%)		
T3	30 (23.1%)	64.7% (10.6%)		
T4	45 (34.6%)	47.5% (9.2%)		
N status				0.0001
N0	52 (40%)	87% (5.7%)	98.8 (88-108)	
N1	31 (23.9%)	66.2% (10.2%)	66.9 (53-80)	
N2	45 (34.6%)	54% (8.1%)	115.6 (85-146)	
N3	2 (1.5%)	0%	11.5 (0-28)	
Clinical Stage*				0.007
I	5 (3.8%)	100%		
II	20 (15.4%)	93.3% (6.4%)		
III	33 (25.4%)	80.1% (8.3%)		
IV	72 (55.4%)	54.2 (6.9%)		
Type of flap				0.055
ALT	58 (44.6%)	77.4% (6.1%)		
Fibula	28 (21.5%)	68.3% (10.4%)		
FFRF	18 (13.9%)	73.3% (17.6%)		
DIEP	14 (10.8%)	30.6% (15.7%)		
TRAM	6 (4.6%)	66.7% (19.2%)		
Chimeric Flap	5 (3.8%)	30% (23.9%)		
VRAM	1 (0.8%)	100%		
Margin				0.001
Positive	19 (14.6%)	24.2% (10.5%)	35.3 (17-52)	
Close	14 (10.8%)	77% (11.5%)	71.4 (52-89)	
Negative	97 (74.6%)	76.5 % (5.5%)	161 (141-180)	
Extracapsular spread				0.005
Yes	98 (75.4%)	46.7% (9.6%)	102.7 (66-138)	
No	32 (24.6%)	75.6% (5.4%)	88.3 (78-97)	

Variables	No. patients (%)	5 year DSS (±S.E.)	Mean survival time (mo) (95% CI)	p value
Perineural invasion				0.22
Yes	118 (90.8%)	58.3% (17%)	38.8 (23-54)	
No	12 (9.2%)	68.9% (5.1%)	146.3 (127-164)	
Mandible/Maxilla involvement				0.75
Yes	48 (36.9%)	60.5% (9%)	68.4 (55-81)	
No	82 (63.1%)	72.4% (5.5%)	151.7 (130-172)	
Recurrence				0.00002
Yes	47 (36.1%)	86.9% (4.1%)	97.9 (89-105)	
No	83 (63.9%)	38.4% (8.7%)	89.2 (58-120)	
Treatment modality				0.004
Surgery alone	46 (35.4%)	90.1% (4.7%)	101 (91-110)	
Surgery + RT/CT	84 (64.6%)	56.6% (6.4%)	122.9 (99-146)	
Lymph node dissection				0.63
Unilateral	14 (10.8%)	57.9% (19.9%)		
Bilateral	114 (87.7%)	67.5% (5.2%)		
No	2 (1.5%)	100%		

**According to UICC's TNM Sixth Edition.*

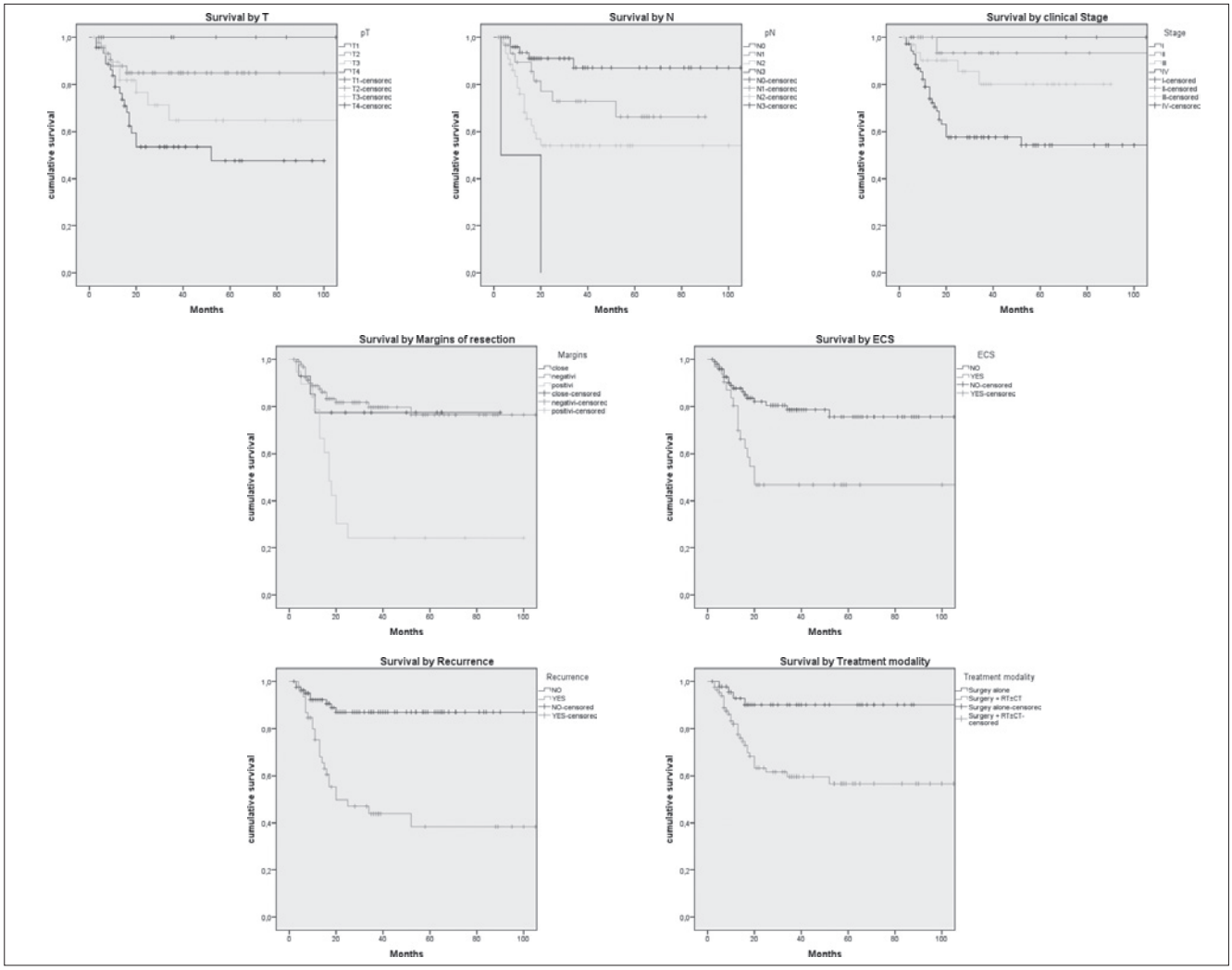

Fig. 2. Kaplan-Meier survival curves by: A, Tumour size (p = 0.026); B, N status (p = < 0.0005); C, Clinical Stage (p = 0.007); D, Margins of resection (p = 0.001); E, Extracapsular spread (p = 0.005); F, Recurrence (p = < 0.0005); G, Treatment modality (p = 0.004).

Table III. Cox regression analysis.

Variables	χ^2	SE	Exp(B)	95% confidence interval		p value
				Inferior	Superior	
Gender	1.8	0.40	0.58	0.26	1.28	0.18
Age	0.1	0.37	1.15	0.55	2.38	0.7
Primary site	1.1	0.08	1.09	0.92	1.29	0.28
Histology	1.3	0.58	0.51	0.16	1.64	0.26
T status	11.6	0.21	1.98	1.31	3.01	0.001
N status	15.5	0.21	2.24	1.46	3.43	0.0001
Clinical stage*	11.4	0.35	3	1.49	6.03	0.002
Type of flap	4.8	0.09	1.24	1.02	1.50	0.03
Margins	15.7	0.19	2.04	1.40	2.97	0.0001
Extracapsular spread	9.2	0.35	2.77	1.39	5.52	0.004
Perineural invasion	1.1	0.53	0.56	0.19	1.60	0.28
Mandible/Maxilla involvement	0.4	0.35	1.26	0.63	2.51	0.5
Recurrence	23	0.39	5.35	2.48	11.54	0.00001
Treatment modality	9.5	0.53	4.50	1.58	12.82	0.005
Lymph node dissection	0.4	0.53	0.68	0.24	1.96	0.48

**According to UICC TNM Sixth Edition.*

gery (9/130; 6.9%). Five patients had total flap failure for venous thrombosis (5/130; 3.8%); one of these was saved after vascular re-exploration, and the other four required a second flap. Three patients had exposure of osteoplastic plates and one patient had salivary fistula. The majority of these complications occurred when a fibula flap was used for reconstruction (6 cases) and 2 of 8 complications occurred when using other types of flaps.

Discussion

Oral carcinoma still remains a neoplasm with poor prognosis, especially for advanced stage tumours. The local control rate extends from 95% of T1-T2 lip carcinoma to 20% of T4 tongue and retromolar trigone cancer [11 12].

In the past 20 years, the contribution of plastic and reconstructive surgery has resulted in a breakthrough in the treatment of these tumours, and in particular for reconstruction of large and complex tissue defects [13-25]. As demonstrated by De Vicente et al. [26], free flap surgery leads to a trend toward better survival than loco-regional flap, primary closure or skin grafts; this is because the chance to re-establish anatomical and functional continuity guarantees genuine oncological radicality, improving, on the other hand, quality of life. The study by Marchetti et al. [27] showed an overall 5-year survival rate of 41.9% in a cohort of 42 oral cancer patients treated by microvascular flap reconstruction, while De Vicente et al[26] reported a 5-year survival rate of 58.6% in the "free flap group" (49 patients) [28]. The best results were achieved by Rogers et al. [9]; with an overall 5-year survival of 51% (2% SE), they obtained a 5-year DSS of 70% (3% SE). In our experience, we obtained a DSS of 67.8% (4.9% S.E.). Results from statistical analysis highlight the role that some of the variables we considered play in influencing prognosis. Some of these, such as tumour size (expressed by pT stage), presence of lymph node metastasis, extracapsular spread and recurrence of disease are well known prognostic indicators for survival of oral cancer patients [29-31], and our results are in agreement with the findings in the literature. Other variables which, in our series, were shown to influence the survival are treatment modality and involved margins of resection. Moreover, the relationship between these prognostic indicators and DSS was statistically significant. These findings are not surprising: in fact, patients needing adjuvant radio/chemotherapy are usually affected by advanced stage disease (T4 stage, lymph node metastasis > N1, presence of extracapsular spread or involved margins of resection) or a particularly aggressive neoplasm (in fact, only 10% of patients suffering a relapse of disease underwent surgery alone), and in our opinion this is the reason for the poor prognosis. Our study sample included a large percentage of patients affected by stage III-IV disease; 14.6% and 10.8%, respectively, had involved and close margins of resection. Analysing the corresponding Kaplan-Meier curve, it is possible to appreciate that patients with negative and close margins showed approximately the same trend of survival, in contrast to those with positive margins, which are characterised by a much more unfavourable prognosis.

Microvascular flap surgery could ideally lead to better control of disease, because the possibility of bridging extended tissue defects can push surgeons to perform more aggressive resections to achieve a truly oncological radical result, especially in light of the close correlation between prognosis and disease-free resection margins.

This hypothesis has already been advanced by Hanasono [32] and reinforced by the data of De Vicente [26]. As previously noted, in our series 19/130 patients (14.6%) had involved margins and 47/130 patients (36.1%) suffered recurrence of disease. Multivariate Cox backward logistic regression model demonstrated an influence of these two variables on patient survival (HR = 1.75 for margins of resection and HR = 4.63 for recurrence of disease; p = 0.003 and 0.0001 respectively). This result unfortunately deviates from those obtained by the authors mentioned above whom found positive margins in 7% and 8.2% of microvascular group patients, respectively [32 26].

To explain this finding, we have to underline that the majority of patients with positive resection margins underwent microvascular flap surgery during the first years after the introduction of this technique in our surgical practice. Over the following years, the trend has shown a marked improvement, and in our opinion this result could be explained by looking on one hand at the enhancement of our reconstructive technique, and on the other at the increased confidence of highly aggressive surgery dismissing the mentality of a resection "cut on reconstruction", in favour of an ablation which aims only to achieve oncological radicality [33 34].

Furthermore, during tumour resection not only of the tongue, but also in other sites of the oral cavity, we adopted the principles of compartmental surgery which advocate removal of compartments (anatomo-functional units) containing the primary tumour, eliminating the disease and potential muscular, vascular, glandular and lymphatic pathways of spread and recurrence [35]. This could also explain the improvement of DSS observed in our series even if we had a large number of patients with advanced stages of disease.

Finally, the progressively increasing use of the anterolateral thigh perforator flap and the DIEAP-polygonal flap, which have become workhorses for head and neck soft tissue reconstruction, are associated with better results in terms of disease-free margins of resection, also because their use as an "on-site tailoring" flap instead of a "premarked" flap allows to tailor the flap at the end of the oncologic resection [36].

Conclusions

In conclusion, in our experience, reconstruction of oral cavity defects with microvascular flaps combined with compartmental surgery confirms that it can play an important role in increasing survival in oral cancer patients.

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HEAD AND NECK

Osteoperiosteal free fibula flap as an effective preprosthetic reconstructive option in severe jaw atrophy and oncological resection

Il lembo libero osteoperiosteo di fibula come opzione ricostruttiva preprotesica nelle atrofie severe e nei difetti post oncologici dei mascellari

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SUMMARY

The gold standard in modern surgical treatment of patients with severe maxillo-mandibular atrophy must include the aim to achieve restoration of function and aesthetics with immediate reconstruction of the oro-mandibular defects. The medical records of 14 patients who were treated in a 5-year period (2010-2014) at our department with severe maxillary and mandibular atrophy, and reconstructed by vascularised free fibula flap were reviewed. Among the former, a total of 14 patients underwent maxillary and mandibular reconstruction using the osteoperiosteal fibula free flap. No major complications were reported. The main advantage of this technique is that it allows the formation of keratinised gengiva, which provides the best implantological options. The only disadvantage of the technique is that the wounds have to heal for second intention, and for this reason patients have to undergo strict follow-up for the first months after the operation. The aim of this article is to evaluate the efficiency of the technique in bone reconstruction after jaw resection or severe atrophy.

KEY WORDS: Fibula free flap • Oncological reconstruction • Head and neck tumours • Jaw atrophy • Jaws rehabilitation

RIASSUNTO

Il gold standard nella ricostruzione dei mascellari nelle atrofie severe, siano esse di natura idiopatica o iatrogena, come nei casi di chirurgia resettiva oncologica, deve essere incentrato verso tecniche di ricostruzione immediata che consentano un veloce recupero funzionale ed estetico. I pazienti considerati in questo studio sono stati trattati durante un periodo di 5 anni (2010-2014) con ricostruzione immediata del deficit dei mascellari, eseguito per mezzo di lembo libero di fibula osteo-periosteo. Sono stati pertanto selezionati 14 pazienti sottoposti a ricostruzione con tale tecnica, senza riportare complicanze a medio e lungo termine. Il principale vantaggio di questo tipo di ricostruzione va ricercato nella formazione di gengiva cheratinizzata sovrastante il lembo libero che consente la migliori condizione possibile per una ricostruzione implantoprotesica. L'unico svantaggio di questa tecnica è da imputare alla necessità di lasciare che la ferita chirurgica intraorale guarisca per seconda intenzione in modo da promuovere la formazione di gengiva cheratinizzata dai bordi della ferita stessa, per tale ragione però il pazente necessita di un rigido follow up per il primo mese dopo l'intervento. Lo scopo di questo lavoro è valutare l'efficacia di tale tecnica nelle ricostruzioni ossee dei mascellari.

PAROLE CHIAVE: *Lembo libero fibula • Ricostruzioni oncologiche • Tumori testa collo • Atrofie dei mascellari • Riabilitazione implantoprotesica*

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Introduction

The gold standard in modern surgical treatment of patients with severe maxillo-mandibular atrophy and post oncological resections must include the aim to achieve restoration of function and aesthetics with an immediate reconstruction of the oro-mandibular defects [1]. Several techniques have been described to rehabilitate the atrophy of bone and the lack of mucosa, skin and muscles in the orofacial region. Bone splitting of narrow ridges [2], alveolar distraction osteogenesis [3], zygoma implants [4], guided bone regeneration [5] and Le Fort I osteotomy with interpositional bone grafts [6] are used.

The current gold standard is represented by the reconstruction with autogenous bone grafts taken from intraoral or extraoral sites, in case of larger defects, which require a greater amount of bone which is not possible with the aforementioned techniques, the use of free flaps becomes mandatory. Vascularised rib, iliac crest, scapula, fibula and radius free flap have routinely been employed as donor sites to reconstruct the defect.

Specifically, as the longest bone segment in the body, the free vascularised fibula flap has selectively been used for extensive oromandibular reconstructions [7]. A fibula graft has been indicated to have several advantages such as ide-

al length, which facilitates numerous osteotomies, good bone height and width for implants rehabilitation, low donor site morbidity, good vascularisation, and a location of the donor site that allows two contemporary surgical approaches [8].

Commonly the fibula flap [9] is harvested as osteocutaneous flap, so that a skin paddle is harvested with the fibula bone graft. This is associated with a notable series of limitations: thickness, fat patients hair-bearing surface, desquamation, difficult insetting into complex maxillary defects and unideal surface for dental prosthesis rehabilitation [10]. Different techniques have been described in literature to avoid these drawbacks [11 12], although in tumours infiltrating soft tissues The disadvantage of the osteo-periosteal flap of the fibula is that it is not applicable in all patients. In fact, in the case of malignant tumours in which resection of large areas of soft tissue and mucosa is required, the use of a skin paddle becomes inevitable. The approach of our unit aims to obtain with a single surgical phase a suitable preprosthetic tissue to harvest a osteo-periosteal fibula flap.

Materials and methods

The medical records of 14 patients who were treated in a 5-year period (2010-2014) at the maxillo-facial department of the Complesso Integrato Columbus (Catholic University of Saved Heart, Rome, Italy) with severe maxillary and mandibular atrophy and reconstructed by vascularised osteo-periosteal free fibula flap were reviewed. The study was conducted by adhering to the guidelines of the Declaration of Helsinki. Inclusion criteria were: no general comorbidities and no need for radiotherapy.

In 5 patients, the atrophy concerned the maxillary bone and in the remaining 9 patients the atrophy involved the mandibular bone. The atrophy was caused in 8 cases by maxillary and mandibular secondary to resection for ameloblastoma and in 6 cases by progressive atrophy in edentulous patients. None of the patients had comorbidities, and all were educated to maintain good oral hygiene. No patient had to undergo to radiotherapy after surgical resection.

Patients treated for ameloblastoma underwent a resection phase and reconstructive phase as a one-stage surgery, and the periostium was removed when the overlying mucosa was involved by the tumour.

The surgery procedures were performed in all patients under general anaesthesia with naso-tracheal intubation. The osteo-periosteal graft used in our technique is similar to the surgery described by Smith et al. (2012) for mandibular and maxillary reconstruction. The patient is placed in a supine position and the proximal and distal fibula are marked and the axis of the bone is drawn. The incision is made down to the fascial level, exposing the lateral compartment; the periosteum is left attacked to the fibular bone as the surgeon proceeds with the dissection. Once the osteotomies are made, bone clamps are placed at the superior and inferior ends of the bone to provide traction on the intraosseous membrane. When the membrane is divided, the peroneal artery and the accompanying veins can be seen, their distal aspects are ligated and divided and the flap can be raised superiorly on the vascular pedicle.

Once harvested, the fibular bone segment is modelled by osteotomies to match the defect morphology and fixated to the residual bone with osteosynthesis plates and screws. It is mandatory to sculpt bone segments more than 2 cm in length in order to lessen the risk of their devascularisation. For the same reason, it is necessary to reduce damage to the periosteum during flap shaping, especially in case of multiple osteotomies. We fix the periosteum and mucosa with tight Donati's stitches using Vicryl 3/0, taking care to spare the vascular pedicle from injuries. After flap insertion, microvascular anastomoses are performed to the facial or lingual artery and to the internal jugular, lingual or facial vein (Fig. 1a-b).

The bone is left covered only by its periosteum without any coverage by cutaneous or subcutaneous paddles as protective layer. It means that the periosteum itself is left exposed in the oral cavity. In our hands, this is not a risky procedure as it mucotises in a few days. Thus, the graft is left to heal by second intention, requiring daily care.

All patients were administered 2.2 gm of amoxicillin iv every 12 hours, starting at the time of general anaesthesia induction and continuing for six days after surgery. A nasogastric tube was maintained for one week. Post-operative instructions included an appropriate oral hygiene by teeth brushing and mouth rinse with 0.2% chlorhexidine. Sutures were removed 14 days post-operatively. A soft diet was suggested for the first post-operative month.

Histological samples from the newly formed mucosa were obtained randomly from 7 patients at the moment of implant placement.

Results

A total of 14 patients underwent maxillary and mandibular reconstruction using the osteo-periosteal fibula free flap.

The mean hospital stay after the reconstructive procedure was 7 days (range 5-13 days). During this time, patients received daily medication of the reconstructed and donor site. They were followed weekly in the first month and monthly in the first year post-surgery. In all patients the fibula demonstrated a good post-operative perfusion of all segments. The time to complete epitelialisation of the osteo-periosteal surface ranged from 6 to 8 weeks. All patients were able to tolerate a soft diet postoperatively after removal of the nasogastric tube. Four of the 14 patients required prolonged hospitalisation for difficulties

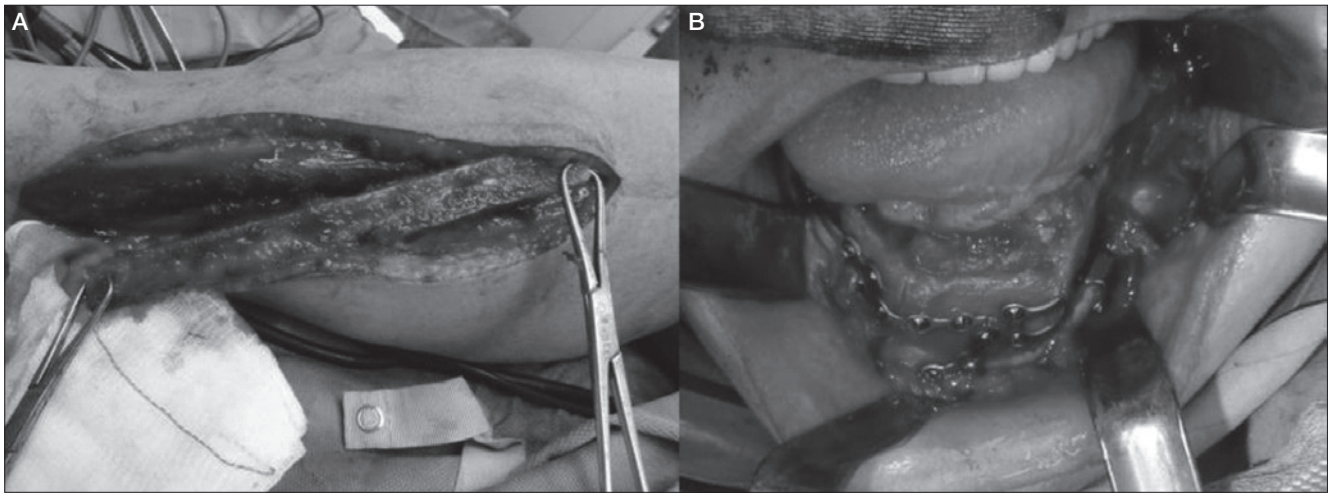

Fig. 1. (a, b) Surgical phases: modelled fibula flap, fixation of fibula flap.

in eating and swallowing. Three of the 14 patients had complications during healing: they had exposure of the bone graft and were treated with weekly courettage of the reconstructed site. However, none of these patients lost the flap. Donor-site complications included patients with minimal epidermolysis at the lower portion of the leg incision that healed spontaneously and one patient who developed a hypertrophic scar at the donor site.

In all cases a layer of newly formed mucosa over the flap covering the bone was adherent. Thus, a second preprosthetic surgery to prepare the soft tissues for future implant rehabilitation was not necessary.

A total of 72 implants were placed after a mean of 6 months (range 4-8 months) in all patients; implants ad a mean width of 4.2 mm and length of 11.5 mm. During the same surgery, in 8 patients the osteosynthesis previously used for fibula stabilisation was removed. The remaining 6 patients refused to remove the osteosynthesis due to the increased invasiveness of surgery (Figs. 2ab, 3, 4).

In the 7 patients in whom histological samples were obtained, microscopical findings showed the formation of orthokeratinised mucosa, with no difference compared to normal gingival mucosa (Fig. 5).

The mean follow-up time after reconstruction was 25 months (range 12-50 months): two of the 14 patients experienced the loss, respectively, of one and two implants about a year after prosthetic loading; the other 69 implants showed no complications.

Discussion

The target of maxillo-mandibular reconstruction in patients with severe atrophy of the oral cavity is achieved with integration of the osseous flap and when bone and oral mucosa are able to load osteointegrated implants [13 14]. Several vascularised bone grafts have been used for reconstruction of oral cavity defects, including the radius, rib, scapula, iliac crest and fibula. The vascularised fibula

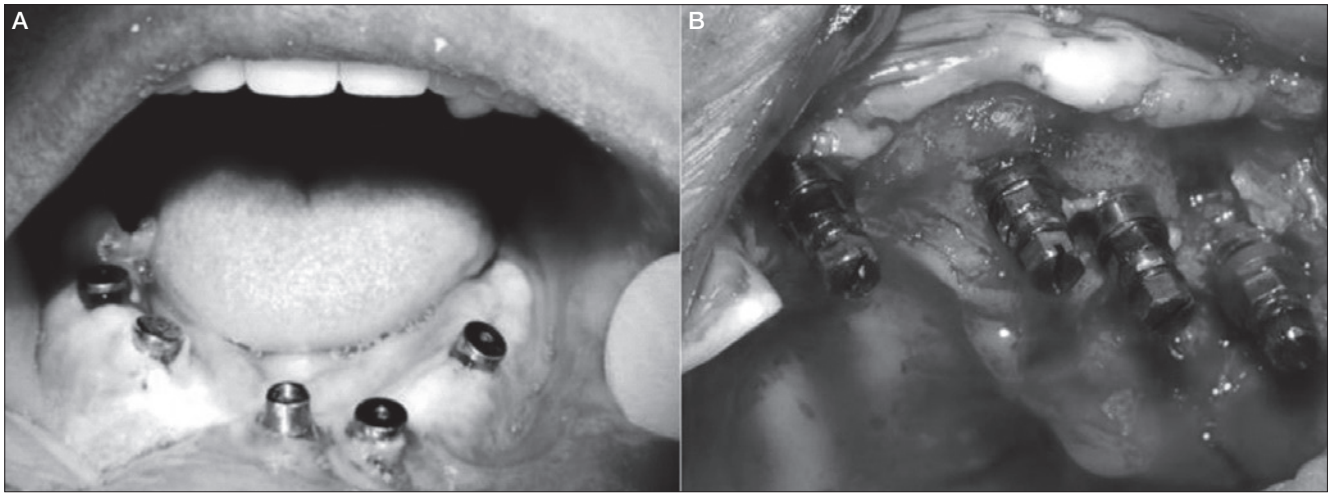

Fig. 2. (a, b) Implant insertion.

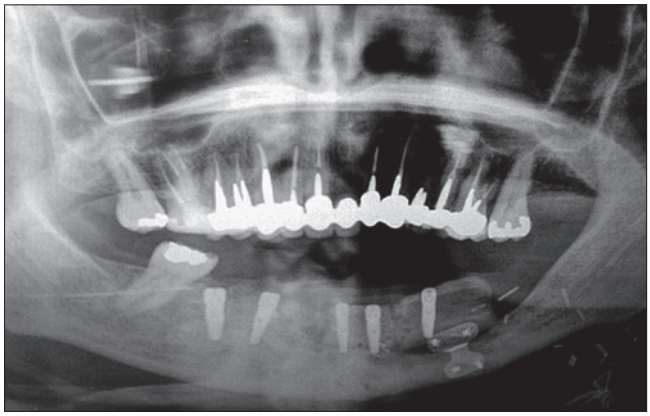

Fig. 3. Rx orthopanoramic image after implant positioning.

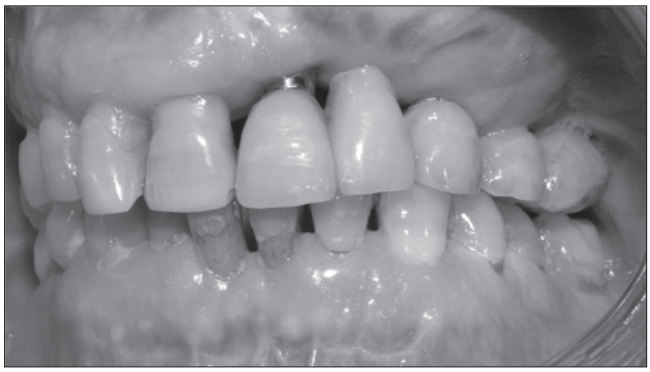

Fig. 4. Prosthetic rehabilitation.

flap is the widely most used in reconstructive maxillo-mandibular surgery because of its advantages compared to others such as length and shape of the bone, good blood supply and low donor site morbidity [15 16]. The biggest problem with this free flap consists in obtaining adequate soft tissue including keratinised mucosa to allow optimal pre-prosthetic rehabilitation [17]. No existing flap can reproduce the physiology of the oral mucosa better than the oral mucosa itself. Smaller mucosal defects can be repaired by local mucosa flaps or by prelaminated fascio-mucosal free flaps [18]. For larger defects, skin grafted fascia, muscle flaps or fasciocutaneous flaps have been used [19 20]. Among these, skin grafts are still used frequently in oral cavity reconstruction. However, their many disadvantages include hair growth, fistula, stone formation and significant contraction deformity [10 11].

Even when skin grafts are used, the subcutaneous tissue is always different in terms of quality and thickness compared to the submucosal tissue. The attached gingiva is a peculiarity of the oral mucosa and is very difficult to get this new formation [21]. Only a regeneration of the gum itself by second intention can ensure appropriate peri-implant tissue and, therefore, may increase the survival of long-term implants [22].

In our study, clinical findings of keratinised mucosa were supported by histological findings on randomly obtained histological samples from 7 patients.

The absence of an adequate keratinised mucosa around implants was associated with higher plaque accumulation, gingival inflammation, bleeding on probing and mucosal recession. This occurs because is very difficult to achieve good oral hygiene around dental restorations without the protection of a band of gingival tissue [23]. In patients exercising good oral hygiene and receiving regular implant maintenance therapy, implants with a reduced width of < 2 mm of peri-implant keratinised mucosa were more prone to lingual plaque accumulation and bleeding as well as the buccal soft-tissue recession over a period of 5 years [24].

Skin flaps also result in bulky reconstruction and excessive mobility of the skin. The subcutaneous tissue with a conventional free fibula flap is always too thick, and sev-

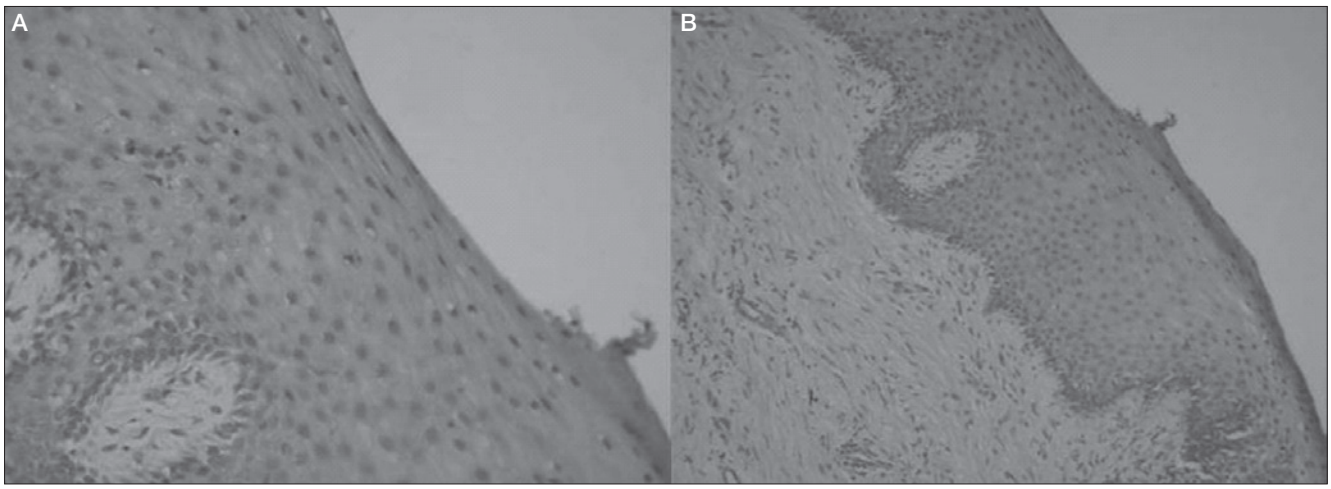

Fig. 5. (a, b) Histological appearance of samples of the newly formed gingiva of the flap showing a parakeratosic appearance, typical of keratinised mucosa.

eral pre-prosthetic procedures are needed to obtain a suitable site for implant placement [25 26].

The osteo-periosteal fibula flap used in this protocol seems to avoid these drawbacks. Unlike other procedures, the skin paddle is not used; therefore, despite the healing for secondary intention, this flap begins to provide thin and foldable tissues for a very effective implant rehabilitation by osteointegrated implants and prosthetic devices in a few weeks.

The disadvantage of the osteo-periosteal flap of the fibula is that it is not applicable in all patients. In fact, in the case of malignant tumours in whom resection of large areas of soft tissue and mucosa is needed, the skin paddle becomes inevitable [27-29]. However, in some situations, as in the case of rehabilitation for atrophies important or in the case of removal of tumours confined to the bone tissue with preservation of the mucosa, the technique described is revealed of considerable utility in our experience. Only with revascularised flaps, since they have more intrinsic vascularity than bone grafts, is it possible to leave the bone covered by its periosteum only without the risk of necrosis. The exposure of the bone, in these cases, individually heals by secondary intention or curettage, without phenomena of avascular necrosis following exposure in the oral cavity. In fact, compared to a more frequent need for care in the period of healing by second intention, the quality of the mucosa formed after the new formation of epithelium is excellent and compatible with a good soft tissue peri-implant integration.

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Laryngology

Pharyngocutaneous fistula following total laryngectomy: analysis of risk factors, prognosis and treatment modalities

Fistola faringocutanea dopo laringectomia totale: analisi dei fattori di rischio, della prognosi e delle modalità di trattamento.

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SUMMARY

The aim of this study was to establish the incidence, risk factors, and the management of pharyngocutaneous fistula (PCF) after primary and salvage total laryngectomy. A retrospective, match-paired analysis of 86 patients who developed fistula after total laryngectomy was carried out and compared with a control group of 86 patients without fistula, randomly selected from a pool of 352 total laryngectomies, performed between January 1999 to October 2014. The overall incidence of PCF in the series was 24.4%; we recorded rates of 19.0%, 28.6% and 30.3% following primary total laryngectomy (PTL), salvage laryngectomy post-radiotherapy (RT-STL) and salvage laryngectomy post-chemoradiotherapy (CRT-STL), respectively. Multivariate analysis revealed that the relative risk of fistula was respectively 2.47, 3.09 and 7.69 for hypoalbuminaemia ≤3.5 g/dL, RT-STL and CRT-STL. An early onset of PCF within 10 postoperative days was recorded in case of salvage total laryngectomy. The management of PCF significantly differed between PTL, RT-STL and CTRT-STL, with exclusive conservative treatment for PTL (93.55%), while in the CRT-STL group surgical closure with regional flaps (58.82%) prevailed. Conservative management, adjuvant hyperbaric oxygen therapy and surgical closure were equally distributed in the RT-STL group. Thorough knowledge of patient-related risk factors and its prognostic value, allows the surgeon to better evaluate preventive strategies with the aim of minimising fistula formation, hospitalisation times and related costs.

KEY WORDS: Pharyngocutaneous fistula • Salvage total laryngectomy • Risk factors • Chemoradiotherapy

RIASSUNTO

In questo studio sono state valutate l'incidenza, i fattori di rischio e le modalità di trattamento in pazienti con fistola faringocutanea dopo laringectomia totale primaria e di salvataggio. Nel periodo compreso tra gennaio 1999 e ottobre 2014, 352 pazienti affetti da carcinoma squamocellulare della laringe sono stati sottoposti a laringectomia totale. Il decosro postoperatorio di 86 pazienti è stato complicato dall'insorgenza di fistola fainrogcutanea. Questi sono stati comparati in uno studio caso-controllo con 86 pazienti selezionati tramite software, fra quelli che non avevano sviluppato la fistola salivare. L'incidenza globale di fistola dopo laringectomia totale è stata del 24,4%, rispettivamente abbiamo registrato incidenze del 19,0%, del 28,6% e del 30,3% dopo laringectomia totale primaria, dopo radioterapia e dopo radiochemioterapia. L'analisi multivariata ha rivelato che per ipoalbuminemia ≤3,5 g/dL, per pregressa radioterapia e radiochemioterapia il rischio relativo di sviluppo di fistola è stato rispettivamente 2,47, 3,09 e 7,69. In caso di laringectomia totale di salvataggio abbiamo registrato una comparsa precoce della fistola entro i primi 10 giorni postoperatori. Le modalità di trattamento della fistola faringocutanea sono risultate essere significativamente differenti in caso di laringectomia totale primaria, dopo radioterapia e dopo radiochemioterapia. Infatti, mentre nel primo caso è stato sufficiente un trattamento di tipo conservativo (93,55%), dopo chemioradioterapia ha prevalso il ricorso a tecniche chirurgiche ricostruttive con lembi regionali (58,82%). Nel caso dei pazienti radiotrattati, le opzioni terapeutiche della fistola sono risultate essere equamente distribuite tra quella medica, eventualmente con l'aggiunta dell'ossigenoterapia iperbarica, e quella chirurgica ricostruttiva. La conoscenza dei fattori di rischio soggettivi e il loro valore prognostico, permettono al chirurgo di pianificare le strategie preventive al fine di ridurre il rischio di formazione della complicanza e, conseguentemente, dei tempi di degenza e dei relativi costi.

PAROLE CHIAVE: *Fistola faringocutanea • Laringectomia totale di salvataggio • Fattori di rischio • Radiochemioterapia*

Acta Otorhinolaryngol Ital 2015;35:400-405

Introduction

The development of a pharyngocutaneous fistula represents a complication of total laryngectomy that is usually self-limiting. Its management is thus mainly based on careful conservative treatment; however, at times, this complication can carry potentially devastating sequelae, and further surgery is required.

The incidence of pharyngocutaneous fistula has been reported to be 14.3% (95% CI 11-7-17.0) after primary total laryngectomy, increasing significantly to 22.8% (95% CI 18.3-27.4) and 34.1% (95% CI 22.6-45.6) in case of previous radiotherapy or previous chemoradiotherapy [1].

Numerous risk factors, such as pre-existing comorbidities, smoke and alcohol abuse, pre- and postoperative haemoglobin and albumin values, tumour site and stage, concurrent neck dissection etc., have been implicated in fistula formation [2-13], although, the actual impact of these remains debatable.

In this retrospective study, we analysed potential risk factors for the development of postoperative pharyngocutaneous fistula after total laryngectomy and describe our systematic approach in the management of this complication.

Materials and methods

Between January 1999 and October 2014, 352 consecutive total laryngectomies for laryngeal squamous cell carcinoma were performed at the Otolaryngology Clinic of the Department of Surgery and Translational Medicine of the University of Florence. The search was restricted to laryngeal SCC and to total laryngectomies without flap reconstruction.

One hundred and sixty-three patients (46.3%) underwent primary total laryngectomy (PTL), 133 (37.8%) underwent salvage total laryngectomy after radiotherapy (RT-STL), and 56 (15.9%) received salvage total laryngectomy after chemoradiotherapy (CRT-STL). In 31 patients, the procedure was extended to the pharynx (piriform sinus and/or base of tongue), and in PTL we also included salvage procedures after previous transoral laser or previous partial laryngectomy.

Institutional Review Board permission was obtained by the local committee.

Pretreatment staging was corrected using the (UICC) TNM 7th edition based on the clinical charts [14].

The postoperative course of 86 patients was complicated by the onset of a pharyngocutaneous fistula; this group was matched and compared with a control cohort group of 86 patients without PCF, randomly selected within our series. Groups were homogeneous for age and gender.

Between groups we matched and compared risk factors for PCF, including smoke and alcohol habits, comorbidities, previous radiotherapy and chemoradiotherapy, pre- and postoperative haemoglobin (≤ 12.5 mg/dL) and albumin (≤ 3.5 g/dL), tumour site and T stage (T1-3 vs. T4a), N stage (N0 vs. N+), uni- or bilateral neck dissection and type of neck dissection [selective neck dissection (SND), modified radical neck dissection (mRND), radical neck dissection (RND)], neck level VI dissection.

The surgical technique was standardised among all surgeons. Laryngectomy included standard removal of the hyoid bone and infrahyoid muscles, pharyngeal closure was always performed in a single layer, with a "T" shaped suture line, using Vicryl (polyglactin 910) 3/4-0 sutures. Two suction drains were applied and generally removed when producing less than 15 cc in 24 hours. Antibiotic therapy with amoxicillin/clavulanate was generally started one day before surgery and continued for the following seven days. Skin sutures were removed on postoperative day 9. Enteral feeding through the nasogastric tube was started on the third postoperative day, and oral feeding was started on postoperative day 14 if contrast radiographic study showed no signs of fistula.

Statistical analysis

Randomisation was carried out with the Intel® Digital Random Number Generator. A chi-square test was used to compare discrete variables. A p value < 0.05 was considered statistically significant. Analysis was conducted using Graph Pad software (Graph Pad, San Diego, CA). A logistic regression model was used on the significant risk factors to estimate the relative impact of fistula formation. McNemar's test was used to assess time interval significance between variables within a cut-off time (10 days after intervention). Data regarding fistula treatment were also collected and an ANOVA test was employed to compare different treatment modalities in the three patient groups (PTL, RT-STL, and CRT-STL). These tests were all conducted using STATA (Stata Corporation, College Station, TX).

Results

In this series, the incidence of PCF was 19% among patients receiving primary total laryngectomy, while it increased to 28.6% and 30.3% for patients receiving salvage total laryngectomy after radiotherapy and chemoradiotherapy.

The match-paired analysis for factors predisposing to PCF formation showed a statistical significant difference regarding comorbidities, salvage laryngectomy and postoperative albumin values in the two groups (Tab. I).

Furthermore, pre- and postoperative haemoglobin values below 12.5 mg/dL and bilateral neck dissection with inclusion of level VI showed a trend towards statistical significance.

The assessment of the relative impact of independent variables was established using logistic regression analysis on the most relevant risk factors: odds ratios for PCF development were 2.478 for postoperative albumin val-

Table I. Patient, disease, treatment and pathology specimen-related factors predisposing to PCF formation.

Variables	Fistula Group (n = 86)	Control Group (n = 86)	p value
Smoke			
No	18	27	p = ns
Yes	68	59	p = ns
Alcohol			
No	50	47	p = ns
Yes	36	39	p = ns
Alcohol+Smoke	34	29	p = ns
Comorbidities	**42**	**28**	**p = 0.0433**
Previous RT	**38**	**22**	**p = 0.0161**
Previous CRT	**17**	**4**	**p = 0.0042**
Pharyngolaryngectomy	4	3	p = ns
Neck dissection (type)	46	43	p = ns
RND	7	4	p = ns
mRND	18	15	p = ns
SND	21	24	p = ns
Neck dissection (side)			
Monolateral	29	31	p = ns
Bilateral	17	12	p = ns
Neck dissection+ VI level			
Monolateral	10	8	p = ns
Bilateral	7	1	p = 0.0640
Preoperative haemoglobin ≤12.5 mg/dL	34	22	p = 0.0730
Postoperative haemoglobin ≤12.5 mg/dL	58	46	p = 0.0859
Preoperative albumin ≤3.5 g/dL	21	25	p = ns
Postoperative albumin ≤3.5 g/dL	**28**	**14**	**p = 0.0204**
T Stage II,III	55	48	p = ns
T Stage IV	31	38	p = ns
N Stage			
N0	42	37	p = ns
N+	44	49	p = ns
T site			
Supraglottic	30	26	p = ns
Pharyngolarynx	4	6	p = ns
Glottic	44	51	p = ns
Transglottic	3	2	p = ns
Subglottic	5	1	p = ns

ns; not significant.

ues below 3.5g/dL (p=0.023), 3.072 for salvage TL after radiotherapy (p=0.002) and 7.694 for salvage TL after chemoradiotherapy (p=0.001) (Tab. II).

Mean hospitalisation time for fistula group and control group was respectively 51.6 (19-250) and 19.8 (15-22) days, (p=0.0034). The mean time interval between total laryngectomy and fistula formation was 18.33 (3-180) days; patients submitted to primary total laryngectomy showed a mean time of PCF formation of 21.43 days, while for those who developed PCF after salvage procedures was 15.19 days. Risk factors that showed significance at multivariate analysis were analysed with a McNemar test for early PCF formation, with a cut-off time of 10 days after surgery, radiotherapy and chemoradiotherapy tested positive for early fistula formation (Tab. III).

Fifty-four fistula patients (62.8%) were treated conservatively (neck dressing, antibiotic therapy, PPI etc.), 15 patients (27.7%) received hyperbaric oxygen therapy and 32 patients (37.2%) needed further surgery: of these, in 17 cases (53%) surgical revision and primary closure was sufficient, while in the remaining 15 patients (47%) surgical repair was performed using pectoralis major myofascial or myocutaneous flap transposition. Figure 1 displays our flowchart in the management of PCF.

Conservative treatment for PCF was the most frequent option for patients after PTL, CRT-STL patients were mostly treated with pectoralis major flap transposition, RT-STL patients were equally treated either with conservative treatment or conservative treatment plus hyperbaric oxygen therapy and surgical revision.

Discussion

With the evolution of non-surgical organ preservation protocols for treatment of laryngeal and hypopharyngeal squamous cell carcinomas, total laryngectomy is increasingly performed as salvage procedure. Wound complications and pharyngocutaneous fistula have become an increasing concern. Wound healing complications can have a multi-factorial origin including previous chemoradiotherapy, hypoalbuminaemia, hypohemoglobinaemia, neck dissection, tumour stage and site [2-13].

Our study showed that postoperative albumin level below 3.5 g/dL, previous radiotherapy and chemoradiotherapy were significantly correlated with PCF formation. Because of the retrospective setting, we were unable to assess the impact of nutritional status in multivariate analysis. In fact, the albumin level in itself is an insufficient parameter, and the prognostic nutritional index, which is a combination of biochemical factors (serum albumin, transferrin), immune competence (total lymphocyte count, hypersensitivity skin tests) and anthropometric measurements (BMI, arm muscle circumference, and skin fold thickness), would be more

Table II. Multivariate analysis of PCF risk factors.

Risk factors	p value	Odds ratio (95% CI)
Comorbidities	0.191	1.584 (0.794-3.158)
Postoperative albumin ≤3.5 g/dL	0.023	2.478 (1.131-5.428)
Previous RT	0.002	3.072 (1.485-6.353)
Previous CRT	0.001	7.694 (2.338-25.323)

Table III. McNemar test for the risk factors related time interval impact on PCF formation.

Risk factors	Exact McNemar significance probability	Odds ratio	95% CI
Postoperative albumin ≤3.5 g/dL	0.7283	0.8333	0.3909-1.7509
Radiotherapy	0.0008	3.0909	1.5292-6.7626
Radiochemotherapy	0.00004	9.8	3.9260-31.5173

appropriate. Moreover, in head and neck carcinoma, nutritional status deteriorates during chemoradiotherapy or hyperfractionated RT [15] and this has been shown to have a negative effect on morbidity, mortality and survival [16 17].
It is likely that the increased morbidity of surgery in patients receiving CRT-STL compared with patients of comparable T classification receiving PTL is due to impaired nutritional status as well as the direct toxic effects of chemoradiation on tissue healing.
The role of radiotherapy in the genesis of pharyngocutaneous fistula has been extensively described, and some authors report that there is no significant associations [18-22]. In a recent meta-analysis, Paydarfar et al. [23] showed that, although preoperative radiotherapy represented a significant relative risk (RR) of PCF formation, there was also heterogeneity of effects among studies; in fact, other radiotherapy-associated variables such as radiotherapy dose and time frame between the end of radiation and surgery, did not demonstrate an increased RR. At multivariate analysis, the odds ratio for PCF formation after radiation was 3.072 (p=0.002), and fistula seemed to occur early (OR=3.0909; within 10 days).
Similar results have been reported by a small number of authors [19 24]. Chemoradiotherapy showed an odds ratio of 7.694 for fistula formation (p=0.001) with a high OR=9.8 for early onset.
Assessment of fistula formation was proven by X-ray swallow study, after two weeks postoperatively (Fig. 1). Some authors advocate the scintigraphic analysis as an objective and non-invasive tool to precisely identify the presence of pharyngocutaneous fistula and location of its internal orifice and to monitor its spontaneous closure [25].
Our study is in agreement with the findings from the meta-analysis of Sayles et al., where chemoradiotherapy seems to increase the risk of major wound complications more than radiotherapy alone. Furthermore, concurrent chemoradiotherapy protocols offers superior locoregional control at the expense of more frequent wound complications in the event of salvage surgery than induction chemotherapy followed by radiotherapy [1]. Newman reported similar rates of PCF between patients receiving RT alone or more intensive therapy with either sequential or concomitant chemoradiotherapy [26]. Aires et al. found no significant differences between PTL and CRT-STL in terms of PCF development [27].
Regarding PCF treatment, the results from our observational study pointed out that in PTL patients conservative therapy is almost exclusive, while pectoralis major flap transposition prevails in CRT-STL patients who develop fistula. In our series, the management of PCF in RT-STL was equally distributed among conservative treatment +/- hyperbaric oxygen therapy and revision surgery (Tab. IV). Hyperbaric oxygen therapy improves wound healing, although the data do not suggest that it promotes short-term growth of cancer [28], and thus its use remains controversial. We believe that for salvage patients who cannot receive further adjuvant radiotherapy its use is well justified and highly effective since in all cases it eventually promotes complete healing.
Early revision surgery with pectoralis major flap transposition was employed in case of major wound breakdown with vessel exposure and in case of evidence of fistula progression in CRT-STL patients, otherwise surgical revision with or without flap transposition was undertaken after persistence of the fistula despite 3 weeks of conservative therapy**.** The pectoralis major flap can be harvested as a myofascial or myocutaneous flap [29 30]. In general, at re-exploration, the pharyngeal mucosa is oedematous and fragile so that

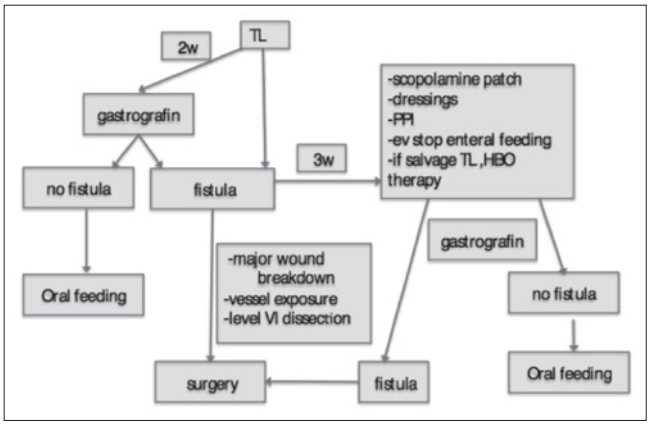

Fig. 1. Fistula treatment flow-chart.

Table IV. ANOVA for fistula treatments in PTL, RT-STL and CRT-STL groups. Fisher's exact= 0.000.

	Med	Med+HbO	Surgical revision	PM flap	Total
PTL	29	1	1	0	31
%	93.55	3.23	3.23	0.00	100.00
STL-RT	7	14	12	5	38
%	18.42	36.84	31.58	13.16	100.00
STL-CTRT	2	1	4	10	17
%	11.76	5.88	23.53	58.82	100.00
Total	38	16	17	15	86
%	44.19	18.60	19.77	17.44	100.00

MED = medication, HbO = Hyperbaric Oxygen, PM = pectoralis major

primary closure is feasible and wise only when the defect is minimal and direct suture will not produce excessive tension. In all other cases, the myofascial transposition of the flap is the preferred method, and the muscle is sutured inlay around the defect ensuring a tight closure. The myocutaneous transposition is used only in rare cases of large pharyngeal breakdown with major tissue loss/necrosis of the pharyngeal mucosa. In these cases, the skin paddle, sutured inlay, will prevent pharyngeal stenosis that could occur more easily with a large myofascial inlay placement. If the necrosis also involves the central portion of the skin of the neck, we recommend to address the pharyngeal closure as described above and to provide outer skin reconstruction using a split thickness skin graft over the pectoralis major muscle that will be sutured inlay to the outer skin defect. In our opinion, pectoralis major flap transposition is the most efficient option since it is easy and quick to harvest and rotate, and has been demonstrated to be reliable even in hostile recipient sites [31 32]. Furthermore, it does not require postoperative monitoring [33] and is cost effective [29].

One minor disadvantage is the morbidity associated with loss of the pectoralis major muscle function especially in case of concomitant shoulder dysfunction following neck dissection [30 34-36].

Based on our retrospective analysis, the incidence of PCF after previous RT or CRT was 29.1% (55 of 189), and the incidence of salvage laryngectomies requiring a flap transposition was 7.9% (15 of 189). We do not suggest to routinely harvest flaps in case of salvage total laryngectomies, although this seems reasonable after previous chemoradiation in patients with comorbidities and low preoperative albumin values. In these cases, we would recommend a myofascial transposition of the pectoralis major flap overlay that is placed over the suture line of the primary pharyngeal closure to protect the suture and overlying skin of the neck. Some authors recently described the use of the myofascial infrahyoid flap for defects following total laryngectomy [37], despite our enthusiastic experience with this reconstructive method [38-42], we always remove the infrahyoid muscles during total laryngectomy for oncologic reasons. Furthermore, we do not believe that this flap can represent a valid solution in the standard management of PCF because of the relative contraindication represented by previous radiotherapy, and because this flap always needs to be harvested during ablative surgery and not when PCF appears in the postoperative course.

Unfortunately, there is no evidence that mechanical stapler pharyngeal closure might reduce fistula formation in high risk cases [43].

We currently continue to assess serum albumin, transferrin, total lymphocyte count and BMI and we are testing other anthropometric parameters to better establish the time for surgery and identify easy-to-obtain parameters during follow-up consultations. We are also trying to improve the preoperative nutritional status by integrating with Oral Impact® (Nestlé, Vevey, Switzerland) 1000 ml (1000 kcal) per day plus usual diet for 5-7 days prior to surgery, as suggested by our nutritionists. However, we have data in this regard at the time of writing.

The limitations of this study are mainly represented by its retrospective setting. Even if the cohort of patients with PCF is relatively small (86 cases), this represents a single institution experience over the last 15 years. Using software, we tried to avoid other biases by random assignment of patients to the control group.

Conclusions

This study confirms that postoperative albumin values below 3.5 g/dL, previous radiotherapy and chemoradiotherapy are significant predictors of PCF. Conservative treatment is advisable for PCF developing in non-(chemo) radiated patients, hyperbaric oxygen therapy is effective as adjuvant treatment after previous radiotherapy, and most PCF developing in chemoradiated patients tend to progress and need flap coverage to avoid devastating outcomes.

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Salivary glands

Use of the SMAS flap for reconstruction of the parotid lodge

L'utilizzo del lembo di SMAS per ricostruzioni della loggia parotidea

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SUMMARY

The purpose of our study was to evaluate the benefits of the SMAS flap in patients with benign tumours of the parotid gland treated by superficial parotidectomy. We carried out a retrospective chart review on 123 patients suffering from benign tumours of the parotid gland admitted to our Institution between March 1997 and March 2010. A superficial parotidectomy was performed in all the cases reported. Our sample was divided in two groups basing SMAS flap reconstruction done (Group 2) or not (Group 1) after superficial parotidectomy. Reconstruction using SMAS flap was accomplished in 64 patients. Chi-square test was used to assess statistical difference between the two groups. The level of statistical significance was $P < 0.05$. No significant differences concerning hematoma, wound infection and facial paralysis were observed between the first and second group (3.38 vs 1.56% [$P > 0.05$], 8.47% vs 4.68% [$P > 0.05$], 5.08% vs 0.00% [$P > 0.05$]). Transient facial nerve weakness, fistula, dip skin and Frey's syndrome were significantly more frequent without SMAS flap reconstruction (10.16% vs 3.125% [$P < 0.05$], 13.55% vs 3.125% [$P < 0.05$], 13.55% vs 3.125% [$P < 0.05$], 20.33% vs 0% [$P < 0.05$] respectively). The use of the SMAS flap is able to reduce the cosmetic and functional complications that occur after the removal of a benign tumour of the parotid through the superficial parotidectomy technique, above all, it reduces the occurrence of Frey's syndrome.

KEY WORDS: SMAS flap • Parotidectomy • Frey syndrome • Facial nerve palsy

RIASSUNTO

Lo scopo dello studio è stato quello di valutare i benefici della ricostruzione con lembo di SMAS nei pazienti affetti da neoplasie benigne della parotide e sottoposti a parotidectomia superficiale. Abbiamo condotto uno studio retrospettivo su 123 pazienti affetti da neoplasie benigne della ghiandola parotide ricoverati presso il Nostro istituto tra il Marzo 1997 e Marzo 2010. Tutti i pazienti arruolati sono stati sottoposti a parotidectomia superficiale. Il Nostro campione è stato diviso in due gruppi in base alla esecuzione (Gruppo 2) o no (Gruppo 1) di ricostruzione con lembo di SMAS dopo la parotidectomia superficiale. La ricostruzione con lembo di SMAS è stata eseguita in 64 pazienti. Un test chi quadro è stato utilizzato per valutare le differenze statistiche tra i due gruppi. Il livello di significatività statistica scelto è stato di $p<0,05$. Non è stata rilevata differenza statisticamente significativa tra i 2 gruppi per quanto riguarda l' insorgenza di ematoma, infezione della ferita e paralisi del faciale (3,38 vs 1,56% [$P > 0,05$] , 8,47% vs 4,68% [$P > 0,05$, 5,08% vs 0,00%). La paralisi transitoria del facciale, la fistola, la depressione della cute e la sindrome di Frey sono significativamente più frequenti nei pazienti non ricostruiti con lembo di SMAS (10,16% vs 3,125% [$P < 0,05$], 13,55% vs 3,125% [$P < 0,05$] , 13,55% vs 3,125% [$P < 0,05$], 20,33% vs 0% [$P < 0,05$], rispettivamente). Il lembo di SMAS è capace di ridurre le complicanze funzionali ed estetiche che si verificano dopo la rimozione di un tumore benigno della parotide mediante parotidectomia superficiale, tra queste, riduce il verificarsi della sindrome di Frey.

PAROLE CHIAVE: *Lembo di SMAS • Parotidectomia • Sindrome di Frey • Paralisi del nervo facciale*

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Introduction

Benign tumours of the parotid gland account for 70% of all salivary glands tumours [1]. The literature shows that usually about 8 out of 10 salivary gland tumours are benign. The treatment of choice in the case of benign parotid tumours with a diameter greater than 3 cm located in the superficial portion of the parotid gland is superficial parotidectomy [2]. This technique is also used in the case of tumour recurrence because it allows maintaining safety margins. Superficial parotidectomy is not free from complications; we report depression of the skin, salivary fistula, transient or persistent facial nerve paralysis, cap-

sular rupture and Frey's syndrome [3-6]. Frey syndrome or auriculotemporal nerve syndrome was described for the first time by Lucy Frey in 1923 [7] and is characterised by the appearance of redness, pain, sweating and heat in the parotid region following by gustatory stimulus. It is caused by an aberrant regeneration of injured postganglionic secretomotory parasympathetic nerve fibres of the auriculotemporal nerve after parotidectomy [8 9]. Thanks to the face-lift incision introduced by Appiani and Delfino [10] (1984) and the use of superficial muscoloaponeurotic system (SMAS) flap introduced by Rapaport and Allison in 1985 [11], there has been reduction of cosmetic and functional post-parotidectomy complications [12]. The SMAS flap is a biological barrier capable of filling the cavity that is formed after removal of the tumour. The withdrawal of the SMAS flap is contextual to parotidectomy and increases surgical times very little (about 15 min) [13]. The aim of our study was to compare postoperative outcomes after superficial parotidectomy in patients who receive or not parotid lodge reconstruction with SMAS flap.

Materials and methods

We carried out a retrospective chart review of 123 patients suffering from benign tumours of the parotid gland admitted to our Institution between March 1997 and March 2010. Patients had to meet the following inclusion criteria:
- diagnosis of benign parotid tumour (pleomorphic adenoma or cystadenolymphoma);
- indication for superficial parotidectomy;
- possible reconstruction with SMAS flap;
- modified face-lift incision.

Our cohort was divided in two groups:
- Group 1 = 59 patients treated with superficial parotidectomy. In these cases, no flap reconstruction of the parotid lodge was used;
- Group 2 = 64 patients treated with superficial parotidectomy and reconstructed with SMAS flap.

The decision of whether to use a SMAS flap or not was made individually by the surgeon who operated on each patient.

All patients underwent pre-operative diagnosis of parotid disease through colour Doppler ultrasonography, magnetic resonance or contrast-enhanced computed tomography, and fine needle aspiration cytology (FNAC) [14].

Patients had a minimum follow-up of 48 months and maximum of 120 months; mean of 84 months. All patients were screened for scarring and facial nerve functionality (Fig. 1). We also verified the presence of Frey's syndrome using the minor starch iodine test [15]. One month after surgery each patient was administered a questionnaire to measure the degree of postoperative satisfaction on a visual analogue scale from 1 to 10. Values ranges from 1 to 3 showed a poor result, from 4 to 7 a good result and from 8 to 10 an excellent result.

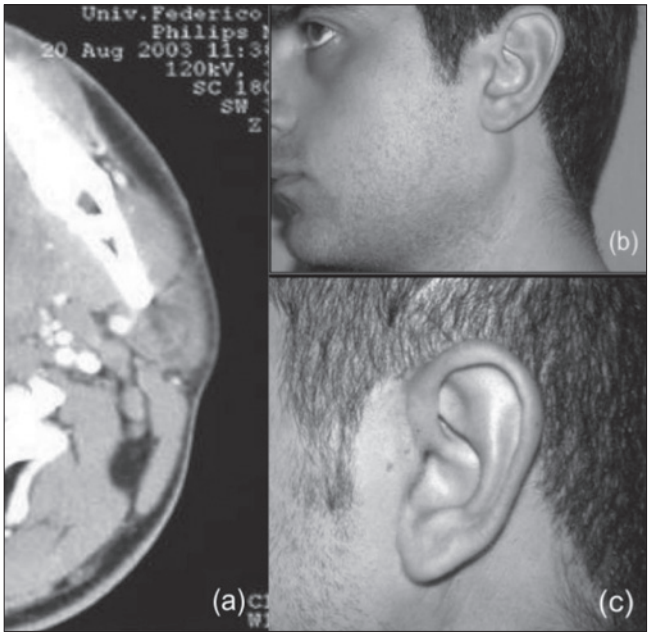

Fig. 1. (a) Pre-operative axial CT scan showing a left parotid lesion; (b) pre-operative patient appearance showing swelling on the left parotid region; (c) scar at 6 months follow-up.

Statistical calculations were performed with the Statistical Package for Social Sciences (version 17.0; SPSS, Chicago, IL). The difference between groups regarding evaluated recurrence rate and complications was measured with a χ^2 test. The level of statistical significance was $P < 0.05$.

SMAS flap

The SMAS is a layer of muscle fibre and connective tissue located just under the skin and over the parotid fascia. Its function is to transmit, distribute and amplify the activity of all facial muscles [13].

The SMAS continues anteriorly in the mid-cheek area with the zygomatic muscles; above with the temporoparietal fascia and below with the platysma muscle.

On the upper side, the preparation of the SMAS flap consists of a horizontal incision 1 cm below the zygomatic arch reaching the malar eminence, and a vertical incision in the preauricular region along the posterior portion of the platysma muscle that continues until finding a point placed 5-6 cm from the bottom of the mandibula [1 16].

The dissection is done very carefully to avoid any damage to the branches of the facial nerve. Once the flap is established it is possible to proceed with superficial parotidectomy. After the procedure is completed, reconstruction was accomplished by suturing the SMAS on the zygomatic periosteum and parotid-masseteric fascia [13] (Fig. 2).

Results

A total of 123 patients were enrolled, 56 women and 67 men (average age 51 years); 98 adenomas and 25 cystad-

enolynphomas were diagnosed on the histopathological report. Superficial parotidectomy was performed in all the cases reported. We performed reconstruction with SMAS flap in 64 patients. In Group 1, we found 6 cases of transient paralysis of the facial nerve, 1 case of facial paralysis, 12 Frey's syndrome, 8 skin depressions, 8 salivary fistulas, 2 wound infections and 5 haematoma. In Group 2, there were no cases of Frey's syndrome. We encountered 2 cases of transient paralysis of the facial nerve, 2 cases of salivary fistula, 2 cases of skin depression, 1 wound infection, no facial paralysis and 3 haematomas. We also evaluated the satisfaction in patients with and without SMAS flaps reconstruction; 53 of 64 patients operated with SMAS flap (Group 2) achieved an excellent result, and 11 patients had a good result. In patients without SMAS flap reconstruction (Group 1), the degree of satisfaction was much more variable; 15 patients reported a poor result, 18 patients an excellent result and 26 patients a good result.
Table I shows outcome results of χ^2 test comparing the first and the second group: except for wound infections and haematomas, which have a similar incidence, the complication rate was higher in Group 1 patients. Furthermore, the rate occurrence of Frey's syndrome was 20.33% in Group 1 and 0% in Group 2 [P<0.05]. Transient facial nerve weakness was significantly more frequent in Group 1 (10.16%) than in Group 2 (3.125%) [P<0.05]. The presence of fistulas, dip skin and accessory spinal nerve injury was significantly more frequent in Group 1 [P<0.05].

Discussion

In 1903 for first Gutierrez described the parotidectomy approach for benign parotid neoplasm removal. Then Patey [17], and Patey and Thackeray [18] described the concept of superficial parotidectomy for benign tumours of the parotid gland. This technique is used when faced with tumours greater than 4 cm in diameter, located in the deep portion of the gland and in recurrences [19]. Parotidectomy is used in these tumours because excision of the tumour would be incomplete using extracapsular dissection techniques. Foresta et al. [20], in a recent review and ensuing meta-analysis based on 123 studies over the last 65 years, compared the two techniques and found fewer complications and recurrences in the extracapsular dissection. They concluded that in patients with unilateral pleomorphic adenoma, located in the superficial lobe, sized less than 4 cm and with no clinical involvement of cranial nerve VII, extracapsular dissection represents a viable alternative option to superficial parotidectomy in terms of successful outcome, convenience and ease of performance. According to Foresta et al., in our study, we perform 123 superificial parotidectomy related to exeresis of disease recurrences, tumours located in the deep portion of the parotid gland or larger than 4 cm. Superficial parotidectomy, however, is not free from complications. We can include, for example, the presence of an unsightly scar especially in women and other functional complications such as Frey's syndrome, facial paralysis, haematoma and fistula. For this reason, the introduction of the face-lift by Appiani and Delfino in 1984 [10] produces less skin scarring. This surgical approach alone, however, cannot eliminate the depression of the skin after the removal of a tumour. Actually, the removal of the tumour leaves a cavity which results in a facial asymmetry with unpleasant aesthetic outcome. Furthermore, the lack of interface between the muscle-aponeurotic residual parenchyma and skin predisposes to the onset of salivary fistula and Frey Syndrome.
Frey's syndrome or *auriculotemporal nerve syndrome* was described for the first time by Lucy Frey in 1923 [7] and is characterised by the appearance of redness, pain, sweating and heat in the parotid region following gustatory stimulus. This is caused by an abnormal post-parotidectomy reinnervation of the *auriculotemporal nerve* that eventually causes improper innervation to the sweat glands of the skin. To prevent this type of syndrome, a barrier must be formed between the postganglionic parasympathetic nerve fibres and sweat glands of skin flap, thereby preventing this type of connection [8 9 12 21-28]. The percentage of this syndrome in the literature varies widely. This could be due to the fact that most of the time there is a late onset of this syndrome compared to the short-term post-operative follow-up reported. Bremerich, for example, analysed the occurrence of Frey's syndrome in 372 patients who had a benign tumour of the parotid gland removed. In this study,

Table I. Results of χ^2 test of group 1 vs group 2.

	Group 1	Group 2	p value
n	59	64	
Frey's syndrome	12 (20.33%)	0 (0.0%)	< 0.05
Transient facial nerve weakness	6 (10.16%)	2 (3.125%)	< 0.05
Fistula	8 (13.55%)	2 (3.125%)	< 0.05
Dip skin	8 (13.55%)	2 (3.125%)	< 0.05
Wound infection	2 (3.38%)	1 (1.56%)	> 0.05
Haematoma	5 (8.47%)	3 (4.68%)	> 0.05
Facial paralysis	1 (1.69%)	0 (0.00%)	> 0.05

we can verify that while about 50% of Frey's syndrome developed within 12 months after surgery, approximately 20% patients developed it after 24 months [29]. Precisely for this reason, we believe that our study, which has a mean follow up of 84 months, makes a valid contribution to the literature and achieves very good results regarding the occurrence of this syndrome. To remedy functional and aesthetic complications, various possible treatments are described, such as radiotherapy, oral medication and botulinum toxin or surgical techniques. If symptoms are of low intensity, however, they do not require any type of treatment [17-22]. The use of non-biological materials such as acellular dermis may decrease the incidence of Frey's syndrome, but greatly increases the incidence of salivary fistula [30]. Some authors suggest the use of the temporoparietal fascia flap in case of surgical gaps larger than 3 cm, in spite of significant decreases in the rate of Frey's syndrome, and it can cause other types of functional complications such as paralysis of the facial nerve, haematoma and aesthetic complications such as alopecia and extension of the surgical scar in the temporal region. In addition, compared to other surgical flaps, the time of duration greatly increases [31-33].

The SCM flap is another flap described in the literature that can lower the onset of the Frey's syndrome. It is easy to set up, but has a greater risk of complications such as spinal accessory nerve injury, neck pain and cranial haematoma [34-37]. In addition, Sanabria [38] in a recent study found that it greatly lowers the onset of Frey's syndrome. Indeed, we are accustomed to using this type of technique only in the case of recurrences that require a second surgery.

Precisely for the type of complications described for other reconstructive techniques, we believe that the SMAS flap is effective for resurfacing the surgical cavity after parotid surgery. It may, in fact, prevent Frey's syndrome, fill the depression and preserve facial symmetry. The withdrawal of the SMAS flap is very simple because the initial surgical incision is followed, the flap from the parotid fascia is separated and prepared to rebuild the cavity [39 40]. Certainly the use of the SMAS flap to improve post-parotidectomy defects is not new. The first to use this type of flap was reported by Rappaport and Allison [11] who studied 112 patients and found only 2 cases of Frey's syndrome. The same flap was used by Casler et al. in 1991 [41] who found no cases of of Frey's syndrome and by Bonanno and Casson in 1992 [42] with excellent results. Cesteleyn et al., in 2002 [31], also showed that with the SMAS flap the timing of the recovery of the facial nerve decreases from 3 to 1.5 months. Honig in 2005 [16] and Meningaud in 2006 [43] continued to propose this type of post-parotidectomy flap. Curry et al. in two studies [44 45] explained how the SMAS flap together with fat grafting can improve facial asymmetry and prevent Frey's syndrome. Wille-Bischofberger et al. [46] in their study analysed the effectiveness of SMAS flap reconstruction compared to a group where the flap had not been used. The same flap was used by Zhao et al. [47] and by Arden et al. [48] with excellent results. The effectiveness of this type of flap has also been reported by Durgut et al. [49] and by Barbera et al. [50] in two very interesting publications. Both explain that the use of the SMAS flap prevents Frey's syndrome and provides very satisfactory aesthetic results. The use of this flap, however, is not recommended in the case of malignant tumours, because the SMAS flap extends into the superficial capsular layers of the parotid gland, and in patients with thin subcutaneous tissue [51 52]. The use of reconstruction technique in our study was associated with a substantial decrease in Frey's syndrome in Group 1 patients (20.33%) compared to Group 2 (0.00%) and in deep skin in Group 1 patients (13.55%) compared to Group 2 (.125%).

Conclusions

In conclusion, the results of this study reveal that there was a statistically significant difference in functional and aesthetic post-parotidectomy complications between Group 1 and Group 2. The onset of Frey's syndrome decreased in the case of reconstruction with SMAS flap. Moreover, thanks to a specific questionnaire on patient satisfaction, in aesthetic terms reconstruction with SMAS flap gave a higher level of satisfaction.

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Voice

Post-laryngectomy voice rehabilitation with voice prosthesis: 15 years experience of the ENT Clinic of University of Catania. Retrospective data analysis and literature review

Riabilitazione vocale post laringectomia con voce protesica: 15 anni di esperienza della Clinica Otorinolaringoiatrica dell'Università di Catania. Analisi retrospettiva dei dati e revisione della letteratura

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SUMMARY

This study reports our 15-year experience, in Sicily, with the use of voice prostheses, analysing the different variables that have influenced the success or failure of speech rehabilitation. The retrospective clinical analysis was carried out by reviewing the clinical histories of 95 patients with laryngeal cancer, in whom a voice prosthesis had been placed by trachea-oesophageal puncture between 1998 and 2013. Age, type of tumour, type of surgery, use of prior radiation therapy, type of puncture, prosthesis used and its duration, number of replacements, complications and causes for prosthetic success or failure were analysed. The results showed a mean of Harrison-Robillard-Schultz (HRS) TEP rating scale of 11.8 in primary TEP and 12.6 in secondary TEP (P =0.613). PORT did not affect overall rehabilitation success. In these patients, the mean HRS rating scale was 11.2, with long-term success of 85% (P =0.582). In patients over 70 years old, long-term success was 82.5%, with 78% in primary and 86% in secondary TEP, the mean HRS was 11.2 in primary and 12 in secondary TEP (P =0.648). In total, long-term success was 87.5%, with 84% in primary and 91% in secondary TEP. The results obtained by retrospective analysis of 15 years of prosthetic rehabilitation in the Sicilian territory highlighted standard rehabilitation, in terms of intra and postoperative complications, fistula related pathology and overall success.

KEY WORDS: Laryngectomy • Alaryngeal voice • Tracheoesophageal puncture • Vocal prosthesis • PORT

RIASSUNTO

L'obiettivo dello studio è stato quello di riportare 15 anni di esperienza, nel territorio Siciliano, con l'utilizzo della voce protesica (VP), analizzando le differenti variabili che hanno influenzato il successo o il fallimento riabilitativo vocale. L'analisi clinica retrospettiva è stata condotta revisionando le storie cliniche di 95 pazienti affetti da carcinoma laringeo, nei quali una protesi vocale era stata posizionata a mezzo di una puntura tracheoesofagea tra il 1998 e il 2013. Età, tipologia neoplastica, tipo di chirurgia, utilizzo di radioterapia, complicanze e cause di successo o fallimento protesico riabilitativo erano analizzate. I risultati hanno mostrato una Harrison-Robillard-Schultz (HRS) TEP rating scale media di 11,8 in TEP primaria e di 12,6 in TEP secondaria (P =0,613). PORT non ha influito sul successo riabilitativo globale. In questi pazienti l'HRS media è stata di 11.2 in primaria e 12 in TEP secondaria (P =0,648). Complessivamente, il successo a lungo termine è stato 87,5%, con 84% in primaria e 91% in TEP secondaria. I risultati ottenuti dall'analisi retrospettiva su 15 anni di attività protesico riabilitativa condotta nel territorio siciliano hanno evidenziato un elevato standard riabilitativo, in termini di complicanze intra e postoperatorie, patologia fistolo correlata e successo riabilitativo globale.

PAROLE CHIAVE: *Laringectomia • Voce alaringea • Puntura tracheoesofagea • Protesi vocale • Radioterapia postoperatoria*

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Introduction

Voice rehabilitation is commonly achieved by oesophageal speech, an artificial larynx, or the creation of a trachea-oesophageal fistula with insertion of vocal prosthesis. As is known, the advantages of prosthetic speech are immediate phonation, simple training, longer phonation time, greater volume and better intelligibility. The disadvantages of trachea-oesophageal speech include finger utilisation required to occlude the tracheostoma, dependence on the physician for change of prosthesis and a second intervention if the patient is undergoing a secondary insertion [1].

Since the introduction of the trachea-oesophageal puncture (TEP) method coupled with insertion of voice prosthesis (VP) by Singer and Blom in 1980, the success of restoring vocal communication in laryngectomies has improved significantly. At the beginning caution was indicated, however trachea-oesophageal speech (TES) soon became widely accepted. Nowadays, the method is generally recognised as a routine procedure for speech restoration after laryngectomy [2].

Technological advancements have been such that today the indwelling prostheses are designed to meet the criteria of low airflow resistance, optimal retention in the trachea-oesophageal party wall, prolonged device lifetime, simple maintenance by patient and comfortable outpatient replacement.

Indwelling low-resistance voice prostheses have become the valves of choice in patients with TEP, reporting success rates from 40 to 90% with excellent voice quality [3 4 5 6].

In Sicily, trachea-oesophageal voice rehabilitation has improved significantly only during last decade. This finding is justified mainly by steady progress of care towards patients with laryngectomies, who until a few years ago, made use of electrolarynx almost exclusively for voice recovery, significantly limiting both psychosocial and working aspects.

This geographical area, marked until recently by a large negligence of the population, especially in more rural areas, towards neoplastic risk factors and the possibility of early diagnosis for conservative or reconstructive surgery, is characterised by a high number of laryngectomees, whose tracheo-oesophageal speech recovery occurred only in the last 15 years.

This effort, however, has been wide spread in our area, placing for over a decade the gold standard rehabilitation over other vocal rehabilitative methods.

The objective of this study is to report our 15-year experience, in Sicily, with the use of voice prostheses following total laryngectomy, analysing the variables that have influenced the success or failure of speech rehabilitation.

Materials and methods

In a tertiary care centre, ENT Clinic of the Department of Medical Sciences, Surgical and Advanced Technologies, University of Catania, a retrospective study was carried out by examining the clinical outcomes of 15 years of experience (1998-2013) in trachea-oesophageal voice rehabilitation, during which period 95 patients with laryngeal cancer were subjected to TEP with vocal prosthesis.

The following variables were analysed: age, type of tumour, type of surgery, use of prior radiation therapy, type of puncture, prosthesis used and its duration, number of replacements, complications and causes for prosthetic success or failure.

In particular, 95 subjects were included, 78 males and 17 females with a mean age at the time of intervention of 61 years (range 42-80).

The indications for total laryngectomy (TL) or total pharyngolaryngectomy (TPL) were primary laryngeal squamous cell carcinoma (n = 57), pharyngeal squamous cell carcinoma (n = 8), recurrent laryngeal or pharyngeal squamous cell carcinoma (n = 27), persistent and severe aspirations after partial laryngectomy (n = 2) and adenoid cystic carcinoma (n = 1).

Patients with a previously untreated pharyngeal or laryngeal squamous cell carcinoma were staged according to the 2002 *American Joint Committee on Cancer* (AJCC) staging system. Patients whose surgical margins were involved by tumour, with perineural invasion, extralaryngeal extension, neck metastasis or extracapsular extension of metastasis were subjected to adjuvant radiation or chemoradiation.

Considering disease control: 58 patients underwent TL and neck dissection (ND), 13 patients underwent TL, 14 patients underwent TL and ND and postoperative radiotherapy (PORT) and 10 patients underwent TL and partial hypopharyngectomy with pharyngoesophageal reconstruction and ND and PORT, the latter in 3 cases (Tab. I).

In particular, a phonatory fistula between trachea and oesophagus with prosthesis positioning by means of a primary puncture (primary TEP) was carried out in 43 cases and a secondary puncture (secondary TEP) was performed in 52 cases (Tab. I); all TEPs were performed after appropriate assessment of motivations, local oncological conditions, comorbidities and psychic and physical fitness, both local and systemic.

Procedures for primary and secondary TEP were carried out according to those described by other authors [5 7 8]. All patients were rehabilitated with indwelling Provox voice prostheses (Atos Medical AB, Hörby, Sweden). The local institutional review board approved the study protocol and informed consent was obtained from the patients.

In all patients, a surgical refinement was performed at the time of TL for prevention of hypertonicity of the neoglottis, microstoma or deep stoma and pseudo-vallecula formation. In particular, a short cricopharyngeal myotomy

Table I. Study group.

Surgery group	Number of patients	Primary TEP	Secondary TEP
TL	13	9	4
TL+ND	58	30	28
TL+ND+PORT	14	4	10
TPL+ND	7	0	7
TPL+ND+PORT	3	0	3
TOTAL	95	43	52

TL = Total laryngectomy; TPL = Total laryngectomy + partial hypopharyngectomy; ND = Neck dissection; PORT = Postoperative radiotherapy

and tracheostoma construction was performed by suturing the skin flap as far back as possible to the lateral-posterior tracheal cartilage and sectioning of the sternal head of the sternocleidomastoid muscles, and pharyngeal reconstruction by closure in T-shape and constrictor muscle closure across the midline and to the base of the tongue muscles.
In secondary TEP, presurgical evaluation of pharyngoesophageal segment (PES) tonicity was carried out by an insufflation test as described by Blom et al [9]. Swallowing videofluoroscopy was performed to rule out hypertonicity or spasm of the PES. Patients with hypertonicity or spasm of the PES did not undergo voice prosthesis insertion and were excluded from the examination group. In 15-years experience of prosthetic rehabilitation, this finding was fortunately infrequent, involving <5% of patients annually submitted to TL.
We also excluded patients who presented cancer recurrence or metastases at the time of evaluation or a new primary head and/or neck tumour.
The results were obtained analysing complications and problems during and after surgery, the long-term overall success, which was evaluated no sooner than one year after surgical procedures, according to the parameters *use, quality* and *care* as they are stated by the Harrison-Robillard-Schultz (HRS) TEP rating scale [10]. A total overall score ≥11 was established as the cut-off for successful voice prosthesis rehabilitation. Because the Provox voice prosthesis was not to be self-removed and inserted by most patients, the maximum reachable score of subscale parameter *care* in these patients was only 4 instead of 5 points.
The rate of speech restoration was analysed using a non-parametric Mann-Whitney's-test, which was used to assess differences between categories. In all cases, P values <0.05 were considered statistically significant.

Results

The rate of postoperative laryngectomy complications was 13%, and the most common were pharyngocutaneous fistulas in 90% of cases, followed by bleeding in 5% and medical complications in another 5%. The presence of postoperative complications did not have an overall significant impact on failure of TEP (*P*=0.716).
Primary trachea-oesophageal punctures with immediate insertion of the vocal prosthesis at the time of total laryngectomy were performed in 43 patients. In this group, no major complications during or after surgery were observed. However, in seven cases, instability of tracheostomy diameter was seen that prevented cannula removal and needed adequate management a fenestrated LaryTube use, making counselling for trachea-oesophageal voice learning particularly difficult and mildly reducing vocal intelligibility. In four other cases, a reduction of vocal intelligibility with strained voice was observed, unsuitable for functional use during conversation caused by a residual hypertonicity of the PE segment (Tab. II).

Table II. Intra and postoperative problems.

Group	Major Surgical Complications	Hypertonicity of PES	Tracheostome Instability
Primary TEP	0	4	7
Secondary TEP	3	1	0
TOTAL	3	5	7
Overall percentage	3.1%	5.2%	7.3%

PES=Pharyngo-oesophageal segment; TEP=Tracheo-oesophageal puncture-

In 52 cases, who underwent secondary TEP, the mean interval between laryngectomy and prosthesis implant was 22.2 months, with a range of 6.3 to 38.1 months. In this group, two cases of TEP tract infection were recorded with cellulitis of soft perifistula tissue that made it necessary to immediately remove the prosthesis; specific antibiotic therapy was started that led to the subsequent healing of trachea-oesophageal tissue. Moreover, another case of mediastinitis was observed due to a small lesion of the posterior wall of the oesophagus during rigid esophagoscopy. In secondary TEP, only one patient had an unsatisfactory voice prosthesis (Tab. III).
Moreover, in this group, 10 cases were subjected to a partial hypopharyngectomy with pharyngoesophageal reconstruction. In these patients, the pharyngeal defect was repaired by a direct mucosal suture for small defects or by using a pectoralis major myocutaneous flap for more extensive non-circular defects. In the same patients, TEP was performed less than 8 months after reconstruction only in patients free of complications and major comorbid diseases. No intraoperative and/or postoperative complications were observed, nor problems of vocal intelligibility, and there were no differences in TEP complications between the standard TL and the reconstructed TL group (*P*=0.782)
Prosthetic replacement is generally performed in the absence of prosthetic or fistula related disease in 75% of cases. In such circumstances, the substitution occurred, on average, not later than the fifth month, mainly to reduce the risk of fistula related disease. The anterograde procedure was used in 90% of cases. All patients performed regular cleaning of the valve including oral antifungal drops at least twice a week.
The reason for this was that prosthetic replacement was necessary before the specified intervals, involving 25%

Table III. Fistula related pathology.

TEP	TE Granuloma	Periprosthetic Leakage	Fistula Migration	Overall Percentage
Primary TEP	4	4	1	5.2%
Secondary TEP	7	3	2	12.6%
TOTAL	11	7	3	22%

TEP=Tracheo-oesophageal puncture; TE Granuloma= Tracheo-oesophageal granuloma.

of patients mainly due to abnormal colonisation of mycobacterial biofilms with leakage through the prosthesis. We report, hereinafter, the median device lives of different types of indwelling voice prosthesis used in 15 years of prosthetic clinical practice, considering that, in view of the significant longer device life of the first prosthesis, some authors suggest to not include the first device in calculation of the mean and/or median device life of indwelling voice prostheses [11].

The median device lifetimes were 150 days (from 120 to 180 days) for the first generation of prosthetic valves (Provox I - 95 patients) and 125 days (from 95 to 155 days) for the second generation of prosthetic valves (Provox II - 73 patients) and 140 days (from 125 to 165 days) for the third generation (Provox Vega - 22 patients). In patients with PORT, the mean device lifetime was generally shorter, often due to major early fungal colonisation, but this difference was not significant (*P=0.*573). In such cases, the replacement procedure was observed following the above cited criterion.

Regarding fistula-related pathologies, this occurred in 22% of cases. Tracheo-oesophageal granuloma was most frequently observed and occurred in 11 patients (12%) (Fig. 1); periprosthetic leakage occurred in 7 patients (7%) (Fig. 2), severe atrophy of the fistula party wall was recorded in two cases presenting persistent and incoercible leakage and fistula migration was seen in 3 patients (3%) (Fig. 3).

The surgical closure of the fistula was recorded in 8 cases. The main causes leading to the closure were: five patients for ineffective voice production (four in primary and one in secondary TEP), one case due to progressive downward fistula migration and another two patients due to giant tracheoesophageal granuloma, which necessitated the closure of the fistula and surgical removal of the granuloma. In these latter two patients, a new fistula in secondary technique was repackaged after six months.

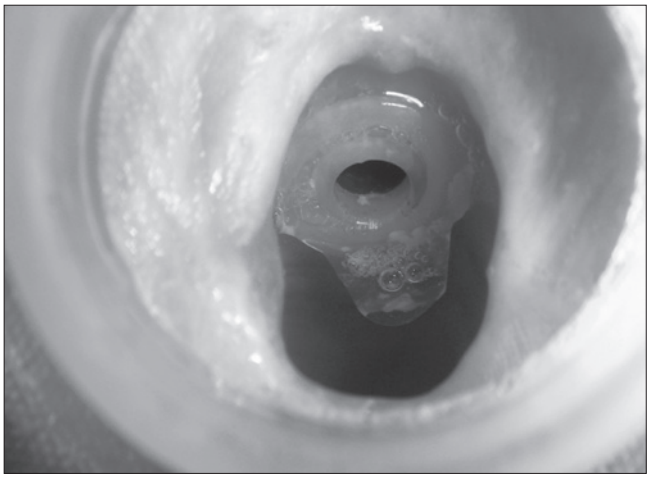

Fig. 2. Periprosthetic leakage.

As far as long-term success is concerned, the parameters taken into consideration were *use*, *quality* and *care* as stated by the HRS TEP Rating Scale [10]. The mean HRS rating scale was 11.8 in patients with primary TEP and 12.6 in patients with secondary TEP (*P*=0.613). PORT did not affect overall rehabilitation success. The mean HRS rating scale of patients who underwent PORT was 11.2 points, with long-term success of 85% (*P*=0.582). In patients over 70 years old, the long-term success was 82.5%, with 78% in primary TEP and 86% in secondary TEP. The

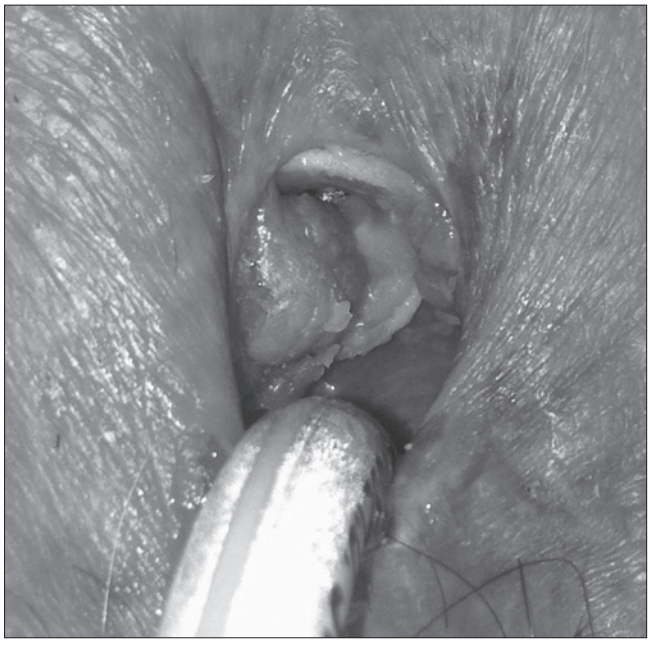

Fig. 1. Tracheoesophageal granuloma.

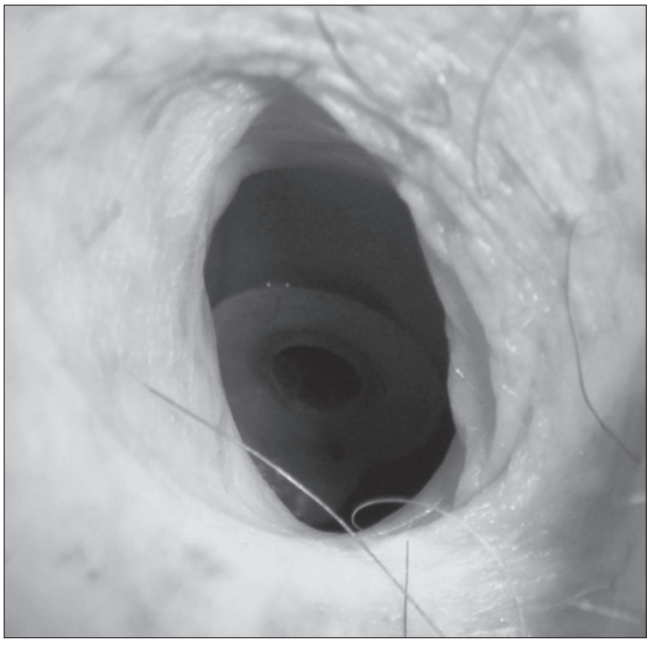

Fig. 3. Fistula migration.

mean HRS rating scale was 11.2 in patients with primary TEP and 12 in patients with secondary TEP (*P*=0.648) (Tab. IV). In total, long-term success (HRS overall score ≥11) was 87.5%, with 84% in primary TEP and 91% in secondary TEP (Tab. V).

Table V. Long-term success.

Group	Without PORT (n=81)	With PORT (n=14)	Elderly (n=40)
Primary TEP	84%	83%	78%
Secondary TEP	91%	87%	86%
TOTAL	87.5%	85%	82.5%

TEP=Tracheo-oesophageal puncture; PORT= Postoperative radiotherapy.

Discussion

Progress in voice rehabilitation following TL over the last 30 years has made an enormous difference in the concept of management of laryngeal cancers. As is well known, there are currently several options available for these patients and the choice varies from patient to patient.

Data concerning the tracheoesophageal overall success rehabilitation in Sicilians in patients over 70 years were registered in a recent retrospective study, which assessed advantages and drawbacks of this method of vocal recovery in 40 subjects, underwent a primary puncture in 18 cases and a secondary puncture in 22 cases. The results from these patients were compared with data obtained from a group of 39 patients, less than 70 years of age, which thus represented the control group. The results showed the absence of a statistically significant difference in incidence of complications, during and after surgery (p>0.9) as well as the overall success ratio of prosthesis implants between the two groups (p>0.7) [12]. In this context, the ability of the larynx of the elderly to functional recovery after partial laryngectomy is widely known [13].

TEP can be performed primarily or secondarily. This approach provides serviceable and satisfactory vocal function after laryngectomy in the vast majority of patients, with an overall success rate that ranges between 80% and 92% [3 4 14].

Essentially, the benefits of primary TEP consist in avoiding a second procedure and immediate good voice restoration with a remarkable psychological boost to patients. According to the literature, intra- and/or postoperative complications may occur during a secondary puncture with an incidence varying from 15 to 25%, and include para-oesophageal abscess cellulitis, aspiration of the prosthesis, enlarged fistula, oesophageal perforation, oesophageal stenosis, death from aspiration pneumonia, fracture of the cervical spine, osteomyelitis, subcutaneous emphysema, and wound infection [15-17].

Our series showed a much lower rate of complications than sometimes reported in the literature. The surgical problems and immediate postoperative complications that we encountered were rarely serious and unusual only in 2.5% of cases (*P*=0.695). The routine use of prophylactic broad-spectrum antibiotics was a regular practice, especially in potentially high-risk patients. This would include diabetic patients, those with severe chronic obstructive lung disease, malnourished individuals and immunosuppressed patients.

A retrospective multicentre study, conducted to record the complications of trachea-oesophageal voice restoration involving 95 patients, found complications that ranged from mild to severe, and included problems with predictive values obtained during insufflation, fistula retention, TEF angulation shifts, fungal colonisation of the prosthesis, valve retention problems, difficulty with digital occlusion, pressure necrosis, post radiation necrosis, dysphagia, phonatory gagging, emesis, gastric distention, pouching, stenosis, infection, hypertrophy, shunt insufficiency, persistent spasm, myotomy, inadvertent fistula closure and aspiration of the prosthesis [18].

With few exceptions [19 20], primary and secondary TEP have been shown to be equally successful in voice rehabilitation with reported success rates of 65-85% and 69-83%, respectively [5 21-23]. This range can depend on the criteria used to select candidates to TEP and on the method to assess the success of post-TEP voice. Brown et al. found that patients with TEP described a high degree of satisfaction with no difference between patients undergoing primary or secondary TEP [24].

Based on our experience, the overall success was almost the same in the two methods, but we preferred to use secondary insertion of vocal prosthesis, and mainly to test the real motivations of the patient to trachea-oesophageal

Table IV. HRS score*.

Group	HRS <11	HRS >11	HRS mean without PORT	HRS mean with PORT	HRS mean Elderly pt
Primary TEP (n)	11	32	11.8	11	11.2
Secondary TEP (n)	6	46	12.6	11.4	12
TOTAL (n)	17	78	12.2	11.2	11.6
p value	-	-	0.613	0.582	0.648

HRS = Harrison-Robillard-Schultz; TEP = Tracheo-oesophageal puncture.

**In accord with TEP Rating Scale[8].*

voice and his/her decisions toward a more acceptable vocal recovery, assessing accurately the pattern of response of the pharyngo-oesophageal segment (PE segment), predictive of a good and satisfactory voice quality.
As is known, the characteristics of the trachea-oesophageal voice production are determined by aerodynamic factors of the prosthesis, but primarily by the characteristics of the PE segment.
In terms of clinical management of the vocal valve, the time between the placement of the prosthesis and the first replacement varies between 3 and 6 months (mean 4.5 months). During the learning curve of both the patient and the medical services, visits to the hospital are more frequent; however, at present, the replacement procedure is so simple and the mean duration of the vocal prosthesis practically eliminates the burden for these patients.
The replacement of the prosthesis is not complicated, especially with improved devices for trans-tracheostomal application and retrograde method, which requires only local anaesthesia. The retrograde means with guide wire was considered uncomfortable in 80%, in our series, for the following reasons: gagging, coughing, pain and/or anticipatory anxiety. The data for the anterograde method were much more favourable.
In the majority of the patients leakage through the prosthesis was the reason for valve replacement (75%), which was mostly secondary to myco-bacterial biofilm colonisation of the prosthetic valve, despite regular cleaning of the prosthesis with the appropriate original brushes and antimitotic solution for the prevention.
In spite of how traditionally performed in the past, prosthetic management should include a process of replacement no longer performed in necessity but programmatically to reduce the risk of the onset of fistula related problems. In addition to traditional data, reported by Op de Coul et al. [6] (89 days), de Carpentier et al. [25] (137 days), and Laccourreye et al. [26] (216 days) on the median device lifetime, variables in relation to the case series and to the type of prosthesis, we report our data in relation to the prosthetic generation: 125 days for first, 140 days for second and 165 days for third generation.
Fistula related pathologies were seen in 22% of cases in our series. In agreement with some authors, we believe that gastro-oesophageal reflux and its treatment currently is a central and determining role in the onset of the two main fistula related diseases, namely leakage around the prosthesis and trachea-oesophageal granulomas, which represent the causes that may lead to potential rehabilitation failure [27-30].
Recently, Lorenz KJ et al. reported data on the correlation between severity of reflux and trachea-oesophageal fistula problems before and after anti-reflux therapy with proton pump inhibitors (PPI), performing a simple biopsy from the region of the fistula and a subsequent molecular examination [31].
In this context, a retrospective study recorded the therapeutic outcomes in patients with trachea-oesophageal granulations, unsatisfactory vocal results and frequent prosthesis replacement, within a 3-month period, due to abnormal biofilm development, using a therapeutic protocol characterised by full-dose PPI treatment given twice daily for 2 months and a maintenance-dose PPI treatment for 1 month, with the addition of alginate at the maximum dose three times daily for 3 months and correct diet indications. The introduction of a specific therapeutic protocol improved the quality of prosthesis (QoP) in 22 of the 43 patients [32].
In our series, the rate of fistula enlargement and periprosthetic leakage was 7%, comparable with what is reported in the literature, about 10% [33 34]. Some authors, however, associate this problem with a number of risk factors, including radiotherapy, malnourishment, diabetes, smoking, oesophageal stricture, hypothyroidism, VP diameter, timing of TEP placement and flap reconstruction [34]. According to other authors, the increasing use of radiotherapy as a primary treatment modality for laryngeal cancers and the subsequent challenge of salvage surgery may contribute to an increasing incidence of this problem [33 34].
In our series, these patients, after failure with aggressive anti-reflux treatment (2/7), were generally managed by downsizing the prosthesis, and/or by permanent augmentation of the party wall with a non-degradable collagen or Bioplastique® (silicone product) injected around the fistula, with long-term success in all cases.
The effect of radiotherapy on VP restoration remains controversial. Radiation therapy may cause lack of wound healing because of tissue necrosis, scar formation, and vascular impairment and may deteriorate the pliability of the pharyngo-oesophageal mucosa [36-41], but considering long-term speech success, no significant influence of postoperative radiotherapy and primary or secondary VP rehabilitation was found on speech quality; in this context, many retrospective studies have reported the absence of consequences on quality of voice or complication rates [4 5 37]. In addition, a report suggested that neck dissection in conjunction with postoperative radiotherapy does not adversely affect short-term speech success in VP rehabilitation patients [38].
In our series, no data were found to support the influence of prior radiation therapy on the rate of surgical complications, voice problems, or HRS score. Instead, we believe that voice prosthesis patients who have undergone radiotherapy may be particularly sensitive to the reflux effect without the protective and neutralising action of saliva. This phenomenon seems to play a significant role in the development of fistula pathology, in which its incidence and relapsing character can drastically reduce therapeutic control of reflux for successful voice recovery in patients.
In this context, a recent study has analysed the association of radiotherapy (PORT) with gastro-oesophageal re-

flux as a determinant of fistula-related pathology in voice prosthesis patients. The authors observed a higher rate of failure of speech rehabilitation in laryngectomy patients with gastro-oesophageal reflux: this occurred when there was a history of postoperative radiotherapy (45%) or not (17%) (P<0.05), although all patients were treated with PPIs. The results seem to confirm the importance of the association between PORT and gastro-oesophageal reflux in fistula-related problems [39].

Elving et al. reported that radiation on the primary tumour site with a dose ≥60 Gy was correlated with a limited lifetime of voice prosthesis [11]. Voice failure after prolonged speech therapy may be due either to fistula or prosthesis related complications or may be due to poor patient motivation. In our series, trachea-oesophageal voice failure was recorded in 6% of cases. In these subjects, surgical closure of the fistula was performed. The causes were essentially fistula-related pathologies with persistent leakage around the prosthesis (2%), giant trachea-oesophageal granuloma (2%) and downward fistula migration (1%). Only one patient with persistent poor vocal quality preferred prosthesis removal.

In the surgical procedure of closure there is no standard reconstructive procedure and a tailored approach is always required. It was performed by separating the trachea-oesophageal party wall, 2-layer closure of the oesophagus and 1-layer closure of the trachea with the use of a fascia graft interposition to reinforce the oesophageal and tracheal suture lines. No failure was recorded.

The overall success was 87.5%, 84% in primary TEP and 91% in secondary TEP, which appeared to be very satisfactory and similar to previously reported results, which show comparable overall success rates [36-40].

Conclusions

Tracheo-oesophageal speech using VP has revolutionised vocal rehabilitation following TL and, today, must be considered as the gold standard for voice rehabilitation in Sicily. This data have demonstrated the benefits of a focused therapeutic protocol from time of cancer diagnosis to recovery time of trachea-oesophageal voice. Retrospective analysis of 15 years of prosthetic rehabilitation in the Sicilian territory highlighted standard rehabilitation almost identical to those found in the recent literature in terms of intra-and postoperative complications, fistula-related pathologies and overall success.

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OSAS

Oxidative stress in patients with obstructive sleep apnoea syndrome

Stress ossidativo nei pazienti con diagnosi di sindrome delle apnee ostruttive notturne

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SUMMARY

Obstructive sleep apnoea syndrome (OSAS) is a disorder that leads to metabolic abnormalities and increased cardiovascular risk. The aim of this study was to identify early laboratory markers of cardiovascular disease through analysis of oxidative stress in normal subjects and patients with OSAS. A prospective study was designed to compare outcomes of oxidative stress laboratory tests in 20 adult patients with OSAS and a control group of 20 normal subjects. Laboratory techniques for detecting and quantifying free radical damage must be targeted to assess the pro-oxidant component and the antioxidant in order to obtain an overall picture of oxidative balance. No statistical differences in age, sex distribution, or BMI were found between the two groups ($p>0.05$). There were significant differences in the apnoea/hypopnoea index (AHI) between OSAS patients and the control group ($p<0.05$). Statistically significant differences in isoprostane, advanced oxidation protein products (AOPP) and non-protein bound iron (NPBI) levels were found between the study and control groups. No significant difference in the levels of thiol biomarkers was found between the two groups. The main finding of the present study was increased production of oxidative stress biomarkers in OSAS patients. The major difference between thiols and other oxidative stress biomarkers is that thiols are antioxidants, while the others are expressions of oxidative damage. The findings of the present study indicate that biomarkers of oxidative stress in OSAS may be used as a marker of upper airway obstructive episodes due to mechanical trauma, as well as a marker of hypoxaemia causing local oropharyngeal inflammation.

KEY WORDS: Obstructive Sleep Apnoea Syndrome • Oxidative damage • Biomarkers of oxidative stress • Polysomnography

RIASSUNTO

La Sindrome delle Apnee Ostruttive Notturne (OSAS) è una patologia caratterizzata da alterazioni metaboliche e da un elevato rischio di sviluppo di patologie cardiovascolari. Lo scopo dello studio è stato quello di identificare dei markers precoci predittivi di rischio cardiovascolare con la valutazione dello stress ossidativo misurato attraverso esami di laboratorio in soggetti normali e pazienti con diagnosi di sindrome delle apnee ostruttive notturne. È stato effettuato uno studio prospettico per confrontare i risultati di laboratorio ottenuti dalla valutazione dei biomarkers dello stress ossidativo in 20 pazienti adulti con OSAS e 20 soggetti sani. Le tecniche di analisi utilizzate avevano l'obiettivo di identificare e quantificare i danni dei radicali liberi attraverso la misurazione di anti-ossidanti e pro-ossidanti in modo da valutare l'equilibrio ossidativo presente nei due gruppi di studio. I due gruppi di pazienti sono risultati omogeni per sesso, età ed indice di massa corporea ($p < 0,05$). Una differenza statisticamente significativa è stata individuata tra i livelli di indice di apnea-ipopnea valutata alla polisonnografia e di isoprostani, produzione di proteine di ossidazione e proteine non legate al ferro nei due gruppi in esame. Nessuna differenza significativa è stata trovata nel livello dei tioli tra i soggetti sani e i pazienti con sindrome delle apnee ostruttive. I tioli, a differenza degli altri markers, sono molecole anti-ossidanti, i restanti sono invece espressione di danno ossidativo. I risultati dello studio indicano che i biomarkers potrebbero essere utilizzati come indici di ostruzione delle vie aeree superiori (VAS) e come marcatori precoci di ipossiemia causando processi flogistici ricorrenti e danno locale da radicali liberi a carico delle VAS.

PAROLE CHIAVE: *Sindrome delle apnee ostruttive notturne • Danno ossidativo • Biomarkers dello stress ossidativo • Polisonnografia*

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a disorder that leads to metabolic abnormalities and increased cardiovascular risk [1]. It is characterised by obstruction of the upper airways with repetitive pauses in breathing during sleep and daytime sleepiness, despite efforts made to breath, and is usually associated with a reduction in blood oxygen saturation. Patients with OSAS are usually unaware of this sleep disruption, but changes in sleep patterns contribute significantly to the prominent symptom of chronic daytime sleepiness typical of these patients.

OSAS has many organic sequelae. Excessive daytime sleepiness impairs quality of life, cognitive performance and social activity [2]. Cardiovascular consequences, such as systemic arterial hypertension, coronary artery disease, heart failure and stroke, are the greatest risks [3-9]. The mechanisms hypothesised to explain the association between OSAS and cardiovascular disease are varied and probably interconnected. In fact, repeated episodes of airway occlusion during sleep determine hypoxaemia, hypercapnia and rapid recurrent changes in intrathoracic pressure, triggering a wide variety of autonomic and haemodynamic responses [4 5]. During episodes of OSAS, intermittent hypoxia determines an increase in oxidative stress that may be involved in the development of cardiovascular disease, vascular injury and endothelial dysfunction. There is much evidence that inflammatory markers, such as oxidative stress, play important roles in atherogenesis and arterial thrombus formation. Patients with OSAS are subject to oxidative stress, due for example to elevated production of reactive oxygen species correlated with high levels of soluble circulating inflammatory factors, such as adhesion molecules [6]. Intermittent apnoea-related hypoxia and post-apnoeic reoxygenation probably contribute to production of reactive oxygen species and inflammatory mediators, triggering upper airway and systemic inflammation. Upper airway inflammation, aggravated by mechanical injury caused by repeated pharyngeal collapse, increases airway obstruction. The systemic inflammatory process also increases release of oxygen-free radicals beyond physiological antioxidant capacity, generating oxidative stress. Various diseases and/or anatomical conditions of the upper airways play a significant role in the ethiopathogenesis of OSAS [7-11]. The diagnostic technique of Sleep Endoscopy represents the gold standard for the diagnosis of the anatomical sites involved in the pathogenesis of OSAS [10]. The treatment of these particular conditions rely to some extent on surgical interventions [12-16].

The adverse effects of obstructive apnoea on the cardiovascular system are not limited to sleep. Daytime sympathetic nervous activity and systemic blood pressure also increase in these patients. Although the mechanism is uncertain, intermittent apnoea-related hypoxia may be involved, since hypoxia causes sympathetic activation and blood pressure elevations that persists after removal of the hypoxic stimulus. The aim of this study was to identify early laboratory markers of cardiovascular disease through analysis of oxidative stress in subjects without pathological obstruction of the upper airways and patients diagnosed with OSAS.

Materials and methods

A prospective study was designed to compare outcomes of oxidative stress laboratory tests in 20 adult patients with OSAS and a control group of 20 normal subjects. The inclusion criteria for the study group were: a) age 18-60 years; b) no previous treatment for OSAS; c) polysomnogram AHI (Apnoea-Hypopnoea Index) > 30. The exclusion criteria were: a) smoking; b) no comorbidities that increase oxidative stress (diabetes, obesity, asthma, nasal polyposis and hypertension). All subjects underwent in the same day: ENT (Ear, Nose and Throat) examination with endoscopy, polysomnography, BMI (Body Mass Index) assessment and evaluation of oxidative stress in plasma sample from fasting venous blood and in urine's exam. Evaluation of oxidative stress in healthy subjects and patients on pharmacotherapy is indispensable to exclude tissue damage and monitor response to treatment in all conditions involving reactive oxygen species. Laboratory techniques for detecting and quantifying free radical damage must be targeted to assess the pro-oxidant component and the antioxidant in order to obtain an overall picture of oxidative balance. Oxidative stress is now recognised to be involved in the pathogenesis of at least 100 different diseases, including atherosclerosis, emphysema/bronchitis, Parkinson's disease, muscular dystrophies, preeclampsia, cervical cancer, alcoholic liver damage, diabetes, nephropathy with renal impairment, Down's syndrome, aging, retrolental fibroplasia, cerebrovascular disorders, ischaemia-reperfusion damage and rheumatoid arthritis.

Pro-oxidant and antioxidant assays were performed at the Oxidative Stress laboratory of the Neonatal Unit of Siena Hospital.

NPBI (non-protein bound iron)

Iron is a versatile and highly reactive element. Having two valencies, iron (II) (ferrous) and iron (III) (ferric), it has access to a wide range of redox potentials spanning the standard redox potential range from +300 to -500 mV. Normally, iron is safely sequestered in transport proteins such as transferrin and lactoferrin and stored in proteins such as ferritin and haemosiderin. As iron ions cannot exist in plasma, the term "free iron" was introduced to indicate a low molecular mass iron form without high-affinity binding to transferrin. A lowering of plasma pH, as occurs during ischaemia (a frequent event in preterm newborns), releases iron, producing free radicals [17-22],which release even more iron by mobilising zinc from ferritin. The resulting cascade of iron release and free radical production may cause extensive cell damage.

The method of detection of NPBI in small samples of biological fluids and tissues [23] is based on preferential chelation of NPBI by a large excess of NTA (nitrilotriacetic acid, low affinity ligand). NTA captures all iron bound to low molecular weight proteins and non-specifically bound to serum proteins. It does not remove iron bound to transferrin or ferritin. A two-step filtration procedure was used to separate NPBI: 1) filtration with a 100 kDa MWCO (Molecular Weight Cut-Off) Vecta-Spin Micro-

Whatman ultracentrifuge filter; 2) filtration with a 20 kDa MWCO Vecta Spin Micro-Whatman ultracentrifuge filter at RCF 16.1 and 4°C. The filtrate was injected directly into an isocratic reverse-phase liquid chromatograph after precolumn derivatisation with the high affinity iron ligand 3-hydroxy-1,2-dymethyl-4(1H)pyridone. All glassware and plastic ware was treated to ensure minimum iron contamination.

Protein carbonyls are formed by a variety of oxidative mechanisms and are sensitive indices of oxidative injury. Reactive oxygen species (ROS) cause cell damage, such as oxidation of amino acid residues on proteins to protein carbonyls, leading to alterations in protein structure and amino acid sequence, formation of protein-protein cross-linking and fragmentation of the protein backbone. Carbonyl groups form during normal aging, as well as in neonates receiving oxygen ventilation, and are increased by oxidative stress. Protein carbonyl groups are formed by oxidation of the side chains of lysine, proline, arginine and threonine residues; they are produced as a consequence of oxidative cleavage of the peptide backbone via the amidation pathway or by cleavage associated with oxidation of glutamyl residues. Carbonyl groups can also be formed as a result of secondary reactions of certain amino acid side chains with lipid oxidation products, such as 4-hydroxy-2-nonenal (HNE) or with reducing sugars or their oxidation products.

The quantity of protein carbonyls in a protein sample can be determined by derivatising with dinitrophenylhydrazine (DNP) and measuring protein-bound DNP with an anti-DNP antibody. Protein carbonyl concentrations were determined by enzyme-linked immunosorbent assay (ELISA), by which carbonyls can be quantified with microgram quantities of protein. The assay was set up so that about 1 mg of derivatised protein was applied to each well of the ELISA plate.

Isoprostanes are a series of prostaglandin-like compounds formed by direct ROS attack on arachidonic acid (AA), an unsaturated fatty acid component of cell membranes. Unlike prostaglandins, which are enzymatic products of this fatty acid, isoprostanes are initially formed in situ in cell membranes, from which they are subsequently cleaved by phospholipase [24]. The different pathways for the formation of F2-isoprostanes during oxidation of AA lead to four series of regioisomers (5, 8, 12 and 15 series), which can comprise eight racemic diasteromers. An isoP, 8-iso-$PGF_{2\alpha}$, is formed in abundance in vivo in human diseases correlated with free radical production [25 26].

Samples for evaluation of oxidative stress were collected with butylated hydroxytoluene (BHT) to prevent oxidation during processing, centrifuged at 1000 rpm and the supernatant was stored at a temperature of -80°C. F2-isoprostanes in plasma and urine were quantified after purification and derivatisation using the method of Morrow [27]; the method used was selected ion monitoring gas chromatography/negative ion chemical ionisation-mass spectrometry (GC/NICI-MS) employing 2H4] 8-iso-prostaglandin F2α as internal standard. 1 ng of deuterated 15-F2t-IsoP was added to the sample as an internal standard. The sample was then acidified to pH 3 with 1 M HCl and diluted to 3 ml with H_2O. The mixture was vortexed and applied to a C18 Sep-Pak column preconditioned with 5 ml methanol and 5 ml water (pH 3). The column was then washed sequentially with 10 ml water (pH 3) and 10 ml heptane. Samples were eluted with 10 ml ethyl acetate/heptane (50:50, v/v). The ethyl acetate/heptane eluate from the C18 Sep-Pak was then dried in a stream of nitrogen and applied to a silica Sep-Pak. The cartridge was washed with 5 ml ethyl acetate and samples were eluted with 5 ml ethyl acetate/methanol (50:50, v/v). The ethyl acetate/methanol eluate was evaporated under a stream of nitrogen. Ssamples were then converted to pentafluorobenzyl ester with a mixture of 40 µl 10% pentafluorobenzyl bromide in acetonitrile and 20 µl 10% *N,N*-diisopropylethylamine in acetonitrile at 37°C for 30 min**.** The reagents were dried under nitrogen and the residue eluted on TLC with 50 µl methanol. Compounds migrating in the region of the methyl ester of PGF2a (Rf 0.22) and the adjacent area 1.1 cm above were scraped and extracted from the silica gel with ethyl acetate. The ethyl acetate was dried under nitrogen and the isoprostanes converted to a trimethylsilyl ether derivative by adding 20 µl BSTFA (N,O-bis trimethylsilyl trifluoroacetamide) and 10 µl dimethylformamide, and incubating at 37°C for 20 min. The reagents were dried under nitrogen and the isoprostanes redissolved in 20 µl undecane for analysis by GC/MS (Gas chromatography–mass spectrometry). For quantification purposes, we compared the height of the peak containing the derivatised 15-F2t-IsoP (m/Z 569) with the height of the deuterated internal standard peak.

Thiol production was measured with the -SHp test (Diacron International, Italy) [28 29]. Thiols are a qualitatively significant component of the antioxidant plasma barrier. Indeed, thiol groups (-SH) of plasma compounds (e.g. proteins, P-SH) oppose the propagation step of radical chain reactions by inactivating alkoxyl radicals (RO*), according to the reaction:

2 P-SH + 2 RO* → 2 PS* + 2 ROH → P-S-S-P + 2 ROH

They also neutralise the tissue-damaging action of hydroxyl radicals (HO*), according to the reaction:

2 P-SH + 2 HO* → 2 PS* + 2 H_2O → P-S-S-P + 2 H_2O

From a merely stoichiometric point of view, a pair of thiol groups reduces a pair of alkoxyl (RO*) or hydroxyl (*OH) radicals by exchanging two electrons (as hydrogen atoms), inactivating the radicals. Indeed, alkoxyl and hydroxyl radicals are transformed to alcohol and water, respectively, while the thiol groups, now oxidised, react among themselves, forming disulphide bonds. The -SHp test is based on the ability of thiol groups in a biological sample to develop a photometrically-detectable coloured

Table I. Demographic and clinical data of the study and control groups.

	Study group	Control group	p value
Number of subjects	20	20	
Age	47.3 ± 10.44	39 ± 12.12	p > 0.05
Sex (Male/Female)	14/6	12/8	p > 0.05
BMI (Body Mass Index)	25.11 ± 3.01	23.22 ± 2.39	p > 0.05
AHI (Apnoea – Hypopnoea Index)	35.89 ± 16.27	1.3 ± 1.53	p < 0.0001

complex (maximum peak of absorbance, 405 nm) in an adequately buffered solution (R_1 reagent of the kit) by reacting with 5,5-dithiobis-2-nitrobenzoic acid (DTNB), which is dissolved as a chromogenic mixture (R_2 reagent of the kit). The intensity of photometrically-detected colour is directly proportional to the concentration (or title) of thiols, according to the Lambert-Beer law. Continuous variables were analysed using a Student's t test. All tests were two-tailed, and p values of <0.05 were taken as statistically significant. Data is presented as mean ± standard deviation or as mean/median with range, as appropriate.

Ethical standards

The present study was approved by the Ethics Committee of the University of Siena and were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments. All persons gave their informed consent prior to inclusion in the study.

Results

Demographic and clinical data of the study population and control group are shown in Table I. No statistical differences in age, sex distribution, or BMI were found between the two groups (p > 0.05). There were significant differences in AHI between OSAS patients and the control group (p < 0.05). Statistically significant differences in isoprostane levels were found between the study and control groups (67.35±40.02 vs 21.195±14.71, p < 0.0001; Fig. 1). AOPP (Advanced Oxidation Protein Products) levels were significantly higher in the OSAS group (111.97±24.44 vs 19.53 ±6.85, p < 0.0001; Fig. 2). Statistical differences in NPBI were found between the two groups of patients (3.01±2.21 vs 0.69±0.83, p = 0.0014; Fig. 3). No significant difference in the levels of thiol biomarkers was found between the two groups (488.80 ±65.27 vs 489.1±58.15, p = 0.6733; Fig. 4). Significantly higher urine isoprostane levels were found in OSAS group (216.78±244.22 vs 1.13±0.12, p < 0.0001; Fig. 5).

Discussion

OSAS is a major risk factor for cardiovascular and cerebrovascular disease. The mechanisms involved in the pathogenesis of OSAS include oxidative stress, systemic inflammation and endothelial dysfunction. The main finding of

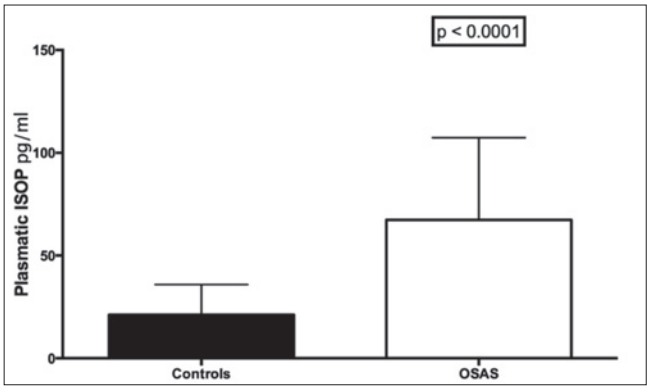

Fig. 1. Isoprostane levels in the two study groups.

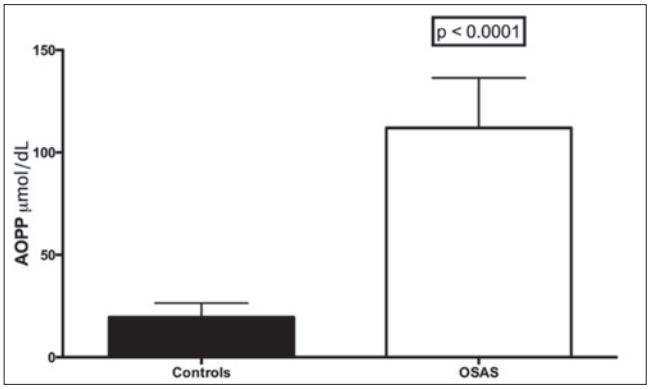

Fig. 2. AOPP levels in OSAS patients and the control group.

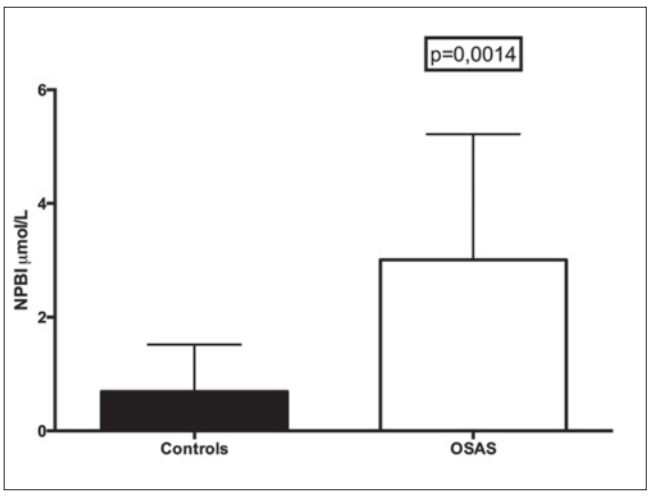

Fig. 3. NPBI levels in the two study groups.

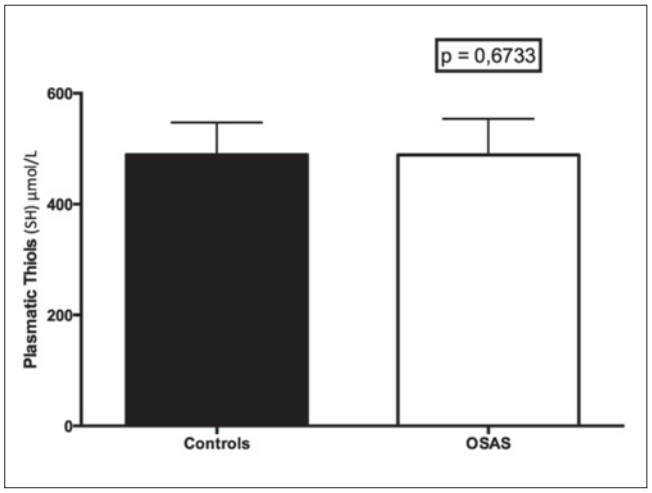

Fig. 4. Levels of thiol biomarkers in the two study groups.

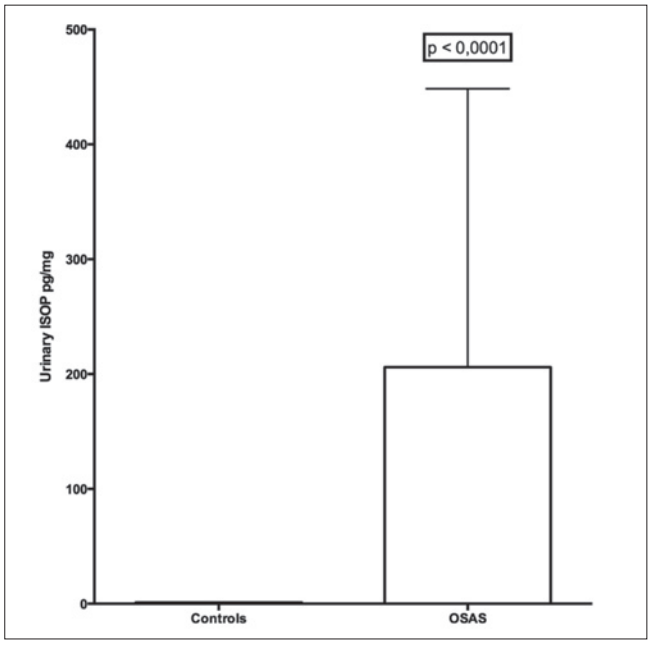

Fig. 5. Urine isoprostane levels in OSAS patients.

the present study was increased production of oxidative stress biomarkers in OSAS patients. Since biomarkers are inflammatory markers, this finding is in line with previous studies showing inflammation of the pharynx, uvula, soft palate and oral cavity of OSAS patients [30 31].

Various studies have outlined the role of inflammation markers as indirect markers of upper airway obstructive episodes. A correlation has been demonstrated between oral nitric oxide and OSAS severity due to local oropharyngeal inflammation caused by mechanical trauma and hypoxaemia. Oral inflammation in OSAS is thought to originate in the upper airways, where repetitive closing and opening during apnoeic episodes leads to increased production of inflammatory cytokines. Oral inflammation in OSAS may also be a consequence of intermittent hypoxia and reperfusion. The increased levels of oxidative stress biomarkers may arise from the recurrent episodes of hypoxia, while subsequent inflammatory status and reperfusion damage are cofactors that may lead to a further increase in these biomarkers.

Our results showed significant differences in the levels of the biomarkers studied in the two groups of patients, apart from thiols, which did not show any difference between patients and controls. The main difference between thiols and the other oxidative stress biomarkers is that thiols are antioxidants, while the others are expressions of oxidative damage. Thiols are a qualitatively significant component of the antioxidant plasma barrier. Indeed, thiol groups of plasma compounds (e.g. proteins, P-SH) oppose the propagation of radical chain reactions by inactivating alkoxyl radicals. The similar levels of thiols found in the two groups confirm the homogeneity of the two study populations, since no patient was taking antioxidant drugs or had manifest cardiovascular disease that may have led to reduced expression of antioxidants. Furthermore, thiol levels may be a late rather than an early marker of oxidative stress.

The results showed 100% specificity for all biomarkers analysed, and 100% and 95% sensitivity for protein carbonyl and urine isoprostanes, respectively (Tab. II). Plasma isoprostanes and NPBI showed 60-70% sensitivity. In conclusion, the findings of the present study indicate that biomarkers of oxidative stress in OSAS may be used as a precursor marker of upper airway obstructive episodes due to mechanical trauma, as well as a marker of hypoxaemia causing local oropharyngeal inflammation. Increased oxidative stress may have important clinical implications in OSAS patients in terms of diagnostic, therapeutic and prognostic aspects. The aim of the present study was to evaluate the levels of oxidative stress indicators in OSAS patients and a control group. It will be important investigate whether the levels and activities of these markers are correlated with demographic, biochemical, metabolic and polysomnographic parameters. By amplifying oxidative and nitrosative stress, oxidative biomarkers may have a pathogenic role in OSAS.

Conclusions

The findings of the present study indicate that biomark-

Table II. Sensitivity and specificity of oxidative stress biomarkers in OSAS subjects.

	Sensitivity	Specificity
Plasma isoprostanes	70%	100%
Protein carbonyls	100%	100%
NPBI (non-protein bound iron)	60%	100%
Thiols	0%	100%
Urine isoprostanes	95%	100%

ers of oxidative stress in OSAS may be used as a marker of upper airway obstructive episodes due to mechanical trauma, as well as a marker of hypoxemia causing local oropharyngeal inflammation.

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OSAS

Drug-induced sleep endoscopy as a selection tool for mandibular advancement therapy by oral device in patients with mild to moderate obstructive sleep apnoea

Ruolo della sleep endoscopy nella selezione dei pazienti affetti da sindrome delle apnee ostruttive durante il sonno di grado lieve moderato candidati a terapia ortodontica con dispositivo di avanzamento mandibolare

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SUMMARY

Nowadays oral appliance therapy is recognised as an effective therapy for many patients with primary snoring and mild to moderate obstructive sleep apnoea (OSA), as well as those with more severe OSA who cannot tolerate positive airway pressure (PAP) therapies. For this reason, it is important to focus on objective criteria to indicate which subjects may benefit from treatment with a mandibular advancement device (MAD). Various anthropometric and polysomnographic predictors have been described in the literature, whereas there are still controversies about the role of drug-induced sleep endoscopy (DISE) and advancement bimanual manoeuvre as predictor factors of treatment outcome by oral device. Herein, we report our experience in treatment of mild moderate OSA by oral appliance selected by DISE. We performed a single institution, longitudinal prospective evaluation of a consecutive group of mild moderate patients with obstructive sleep apnoea syndrome who underwent DISE. During sleep endoscopy, gentle manoeuvre of mandibular advancement less than 5 mm was performed. In 30 of 65 patients (46.2%) we obtained an unsuccessful improvement of airway patency whereas in 35 of 65 patients (53.8%) the improvement was successful and patients were considered suitable for oral device application. Because 7 of 35 patients were excluded due to conditions interfering with oral appliance therapy, we finally treated 28 patients. After 3 months of treatment, we observed a significant improvement in the Epworth medium index [(7.35 ± 2.8 versus 4.1 ± 2.2 ($p < 0.05$)], in mean AHI [(21.4 ± 6 events per hour versus 8.85 ± 6.9 ($p < 0.05$)] and in mean ODI [(18.6 ± 8 events per hour to 7 ± 5.8 ($p < 0.05$)]. We observed that the apnoea/hypopnoea index (AHI) improved by up to 50% from baseline in 71.4% of patients selected after DISE for MAD therapy. In the current study, mandibular advancement splint therapy was successfully prescribed on the basis not only of severity of disease, as determined by the subject's initial AHI, but also by DISE findings combined with results of gentle mandibular advancement manoeuvre allowing direct view of the effects of mandibular protrusion on breathing spaces in obstruction sites, and showing good optimisation of selection of patients for oral device treatment.

KEY WORDS: Obstructive sleep apnoea syndrome • Mandibular advancement device • Drug-induced sleep endoscopy • AHI • BMI

RIASSUNTO

Il trattamento con dispositivi di avanzamento mandibolare (MAD) rappresenta un'efficace alternativa terapeutica per i pazienti affetti da roncopatia semplice, OSAS di grado lieve/moderato e in casi selezionati di OSAS grave con scarsa tollerabilità alla terapia ventilatoria con C-PAP. Pertanto è importante identificare dei criteri oggettivi per selezionare i pazienti che possono beneficiare del trattamento con i sistemi di avanzamento mandibolare (MAD). In letteratura sono stati descritti vari fattori predittivi sia antropometrici che polisonnografici, mentre esistono ancora controversie circa il ruolo della Sleep Endoscopy e della manovra di avanzamento mandibolare bimanuale durante lo stesso esame come fattori predittivi del successo terapeutico con MAD. In questo studio descriviamo la nostra esperienza nel management di pazienti affetti da OSAS lieve/moderata trattati con MAD e selezionati mediante "sleep endoscopy". Abbiamo eseguito una valutazione prospettica longitudinale di una serie consecutiva di pazienti giunti alla nostra osservazione con diagnosi di OSAS lieve/moderata e sottoposti a sleep-endoscopy. Durante il sonno indotto farmacologicamente è stata eseguita una delicata manovra di avanzamento mandibolare con escursione inferiore ai 5 mm e abbiamo riscontrato che in 30 dei 65 pazienti (46,2%) lo spazio respiratorio non migliorava in modo significativo a livello dei siti di ostruzione osservati, mentre in 35 dei 65 pazienti (53,8%) si osservava un miglioramento significativo tale da poter indicare terapia con MAD. In 7 dei 35 pazienti venivano riscontrate condizioni che ostacolavano l'applicazione del MAD per cui 28 dei 35 pazienti sono stati sottoposti a terapia con MAD. Dopo 3 mesi di trattamento abbiamo documentato un miglioramento significativo dell'indice di Epworth medio [(7,35 ± 2,8 vs 4,1 ± 2,2 ($p < 0.05$)], dell'AHI medio [(21.4 ± 6 eventi per ora verso 8,85 ± 6,9 ($p < 0.05$)] e dell'ODI medio [(18.6 ± 8 eventi per ora versus 7 ± 5.8 ($p < 0.05$)]. Abbiamo inoltre osservato che l'AHI migliorava di almeno il 50% rispetto al basale nel 71.4% dei pazienti selezionati mediante sleep endoscopy. In questo studio, la terapia con i dispositivi di avanzamento mandibolare è stata prescritta con successo sulla base non soltanto dell'indice di apnea/ipopnea, ma anche dei reperti della sleep endoscopy e della manovra di avanzamento mandibolare, ottenendo una visione diretta degli effetti della protrusione mandibolare sullo spazio respiratorio in corrispondenza dei siti di ostruzione, e ottenendo una buona ottimizzazione della selezione dei pazienti per il trattamento con MAD.

PAROLE CHIAVE: *Sindrome delle apnee ostruttive durante il sonno • Dispositivo di avanzamento mandibolare • Endoscopia durante il sonno indotto farmacologicamente • AHI • BMI*

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterised by recurrent episodes of apnoea and hypopnoea during sleep caused by repetitive upper airway (UA) collapse and often resulting in decreased oxygen blood levels and arousal from sleep [1]. It is also associated with excessive daytime sleepiness and an increased risk of cardiovascular and cerebrovascular complications [2-4] and metabolic comorbidities [5 6]. Its prevalence in the general population is around 3%. However, its distribution varies widely according to gender, age and race. The incidence in men increases with a direct proportion to age from 40 to 65 years [7 8] and it is considered an important and independent risk factor for several systemic diseases such as hypertension, obesity and diabetes [6-9]. The aetiological role of OSAS in severe hemodynamic or pulmonary function disorders is now recognised [10].

Treatment of sleep-disordered breathing (i.e. snoring, upper airway resistance syndrome, sleep apnoea syndrome) may include lifestyle modification, i.e. weight loss, cessation of evening alcohol ingestion, sleep position training, upper airway surgery, oral appliances and continuous positive airway pressure (CPAP). The latter is the most widely suggested method because it provides the most reliable therapeutic modality, especially in severe OSAS. Nevertheless, there is poor compliance of patients who often consider it a cumbersome therapy that is difficult to tolerate and unacceptable. For these reasons, several surgical [11-13] and non-surgical procedures have been proposed as an alternative, particularly in young non-apnoeic snorers, mild to moderate OSAS and in selected patients with severe OSAS. Among non-surgical techniques, good results have been obtained with the use of oral appliances [14 15], which are intended to protrude and stabilize the mandible maintaining a patent airway during sleep and producing favourable results within a short time [15 16].

Herein, we report our experience in treatment of mild moderate OSAS by oral appliance selected by drug induced sleep endoscopy (DISE) focusing on the following outcomes: sleep apnoea [i.e. reduction in the apnoea/hypopnoea index (AHI) or respiratory disturbance index], ability of oral appliances to reduce snoring and effect on daytime function which are predictive parameters of good efficacy of the device.

Materials and methods

From September 2014 to February 2015 we evaluated 65 patients who underwent sleep endoscopy at our institution (Department of Head and Neck Surgery, Institute of Otorhinolaryngology "A. Gemelli Hospital", Catholic University School of Medicine and Surgery, Rome), and polysomnographically diagnosed as mild-to-moderate OSAS (AHI ≥ 5 to ≤ 30/h of sleep), 55 males and 10 females, aged between 22 and 68 years (mean age 44.26 years). BMI ranged from 22.6 to 30.4 kg/m^2 (mean BMI 27.2±3.04). Mean Epworth index was 9.8±2.75. Study design: single institution, longitudinal prospective evaluation of a consecutive group of mild moderate OSAS patients who underwent DISE. All patients were willing to participate and consented to their inclusion.

All patients successfully underwent DISE. The procedure was performed in the operating theatre under the presence of an anaesthesiologist, neuroelectrophysiology technician and otolaryngologist. All patients, already prepared for polygraphic intraoperative recording, received sedation with administration of increasing doses of propofol (3 mg/kg/h). The mean duration of the procedure was 25±18 min. The degree of sedation was under continuous monitoring by bispectral index (BIS) monitoring (Apect Medical Systems, Newton, MA). When BIS was between 50 and 70, generally during snoring, we introduced a 3.4 mm flexible nasopharyngoscope into the nasal cavity to visualise and record the pattern and degree of obstruction (nasopharynx, oropharynx, hypopharynx and larynx). During DISE, the level (palate, oropharynx, tongue base, hypopharynx/epiglottis), the direction (anteroposterior [AP], concentric, lateral) and degree of upper airway collapse (none, partial, or complete) were scored in a standard fashion [17]. Finally, we evaluated the degree of enlargement of the space in the sites of respiratory obstruction through a bimanual mandibular advancement manoeuvre. The mandible was gently advanced 4 to 5 mm by the anaesthetist and its effect on airway obstruction and snoring were noted. Subjects were considered eligible to utilise an oral appliance and were referred to the orthodontic department of our hospital in case of successful mandibular advancement manoeuvre. (Definition of success: obstructive events better or absent for at least 3 min, associated with endoscopic evidence of improved airway patency at one or more sites of obstruction by at least 50%). Within 30 days of the indication, the SomnoDent (Somnomed ® Ltd, Australia), a customised mandibular advancement device made of a rigid material Bflex, was applied.

All treated patients were evaluated at baseline and after an acclimatisation period of 3 months. We used the Epworth sleepiness scale to assess the severity of daytime symptoms, and the Berlin Questionnaire [18] to assess the degree and frequency of snoring, impact on daytime activities and degree of sleepiness. All subjects underwent polysomnography (Somntè, Compumedics Australia) before and after 3 months from application of device. We collected the main reference parameters of number and degree of pathological respiratory events: apnoea hypopnea index (AHI), oxygen desaturation index (ODI) and oxyhaemoglobin saturation performance (mean SpO2, minimal SpO2 and mean desaturation).

The data were analysed using Microsoft Excel and the SSPS statistical software package. Qualitative data were

compared using Wilcoxon signed rank and T-tests. We considered an AHI value < 5 or a reduction of AHI ≥ 50% from baseline as criteria for successful treatment. Differences were considered statistically significant if the p value was less than 0.05. Results were presented as means and standard deviations.

Results

During DISE, 30 of 65 patients (46.2%) had a unsuccessful mandibular advancement manoeuvre, and were considered as "not suitable" for treatment with an oral device and other treatment options could be offered. On the other hand, 35 of 65 (53.8%) patients had a successful manoeuvre and were considered suitable for oral device application. Nevertheless, 7 of 35 patients were excluded because of a condition interfering with an oral appliance (edentulous or an insufficient number of healthy teeth in one or both dental arches, evidence or history of temporomandibular joint disease, inability to tolerate the device throughout the night, choking sensations, dry mouth, claustrophobia during MAD wear) and were referred for surgical procedures. Finally, 28 patients (6 females, 22 males) of 35 were recommended for an oral device.

An overview of the distribution of the levels of upper airway collapse at baseline for patients treated with an oral appliance based on DISE scoring is shown in Table I. The majority of patients had multilevel collapse [26/28 (92.8%)], predominantly at the palatal and tongue base levels and rarely at the oropharyngeal and hypopharynx/epiglottis levels. The most common upper airway collapse patterns noted were AP collapse at the levels of the palate [28/28 patients (100%)] and the tongue base [20/28 (71.4%)]. In none of the locations considered was a latero-lateral closing pattern observed. In agreement with literature data, most of our mild/moderate OSAS patients were without serious comorbidities [hypertension was seen in 10/28 patients (35.7%); no patient had diabetes, ischaemic heart disease, cerebrovascular disease, or atrial fibrillation)].

The results for each question of the Berlin questionnaire before and after therapy are shown in Table II. Clustering the Berlin questionnaire answers by category, we observed a positive category 1 in 28/28 (100%) and a positive category 2 in 18/28 (64.2%) before treatment. After treatment, both were significantly reduced to 8/28 (28.6%) and 0/28 (0%), respectively. Answers related to category 3 were always negative.

In treated patients, the Epworth medium index [19] significantly decreased after application of an oral device from 7.35 ± 2.8 to 4.1 ± 2.2 ($p < 0.05$). The distribution of Epworth scores in treated patients are shown in Figure 1. The mean AHI decreased significantly from 21.4 ± 6 events per hour at baseline to 8.85±6.9 events per hour ($p < 0.05$) after 12 weeks of treatment. In addition, the mean ODI decreased significantly from 18.6 ± 8 events per hour at baseline to 7 ± 5.8 ($p < 0.05$), as shown in Figures 2 and 3. We did not observe a significant variation of the mean values of desaturation maximum (respectively 85% versus 84.5%), desaturation average (91% versus 90.4%) and average saturation (94% versus 93.5%) before and after treatment. None of the treated patients referred complications with the oral device.

Analysing the success rate of treatment at baseline 4 out of 28 (14.3%) patients showed polysomnography AHI > 5 and < 15 and 24 out of 28 (85.7%) patients showed an AHI > 15 and < 30. After treatment, 6 out of 28 (21.4%) patients achieved an AHI < 5, whereas in 18 out of 28 (57.1%) cases AHI values decreased by ≥ 50%. In Table III the distribution of patients according to the degree of OSAS before and after treatment is presented.

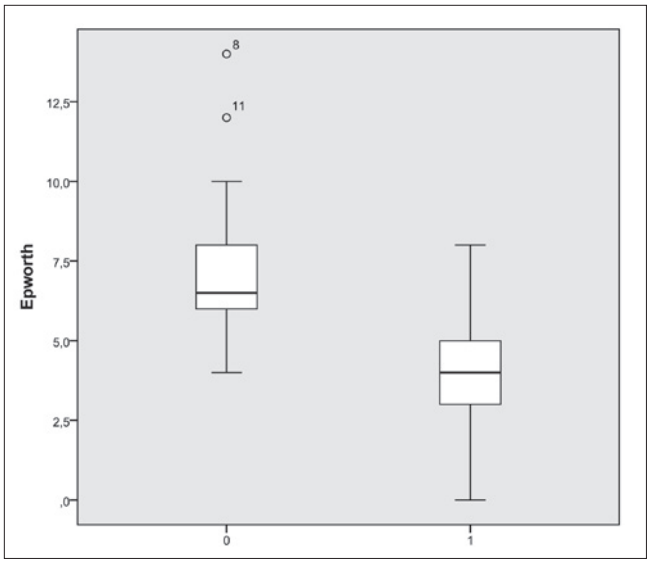

Fig. 1. Epworth score distribution at baseline and after three months of treatment with an oral device (0: pre; 1: post). The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.

Table I. Distribution of the levels of upper airway collapse including the corresponding direction of upper airway collapse based on DISE scoring in the 28 treated patients.

	Palate	Tongue base	Oropharynx	Larynx
Anterior-posterior	14/28 (50%)	18/20 (90%)	8/10 (80%)	2/2 (100%)
Concentric	14/28 (50%)	2/20 (10%)	2/10 (20%)	0/2 (0%)
Latero-lateral	0/28 (0%)	0/20 (0%)	0/10 (0%)	0/2 (0%)

Table II. Berlin questionnaire results before and after treatment.

	Pre-treatment	Post-treatment
CATEGORY 1		
Do you snore?		
a. Yes	28/28 (100%)	8/28 (28.6%)
b. No	0/28 (0%)	15/28 (53.5%)
c. Don't know	0/28 (0%)	5/28 (17.9%)
Your snoring is:		
a. Slightly louder than breathing	0/28 (0%)	20/28 (71.4%)
b. As loud as talking	0/28 (0%)	8/28 (28.6%)
c. Louder than talking	14/28 (50%)	0/28 (0%)
d. Very loud. Can be heard in adjacent rooms.	14/28 (50%)	0/28 (0%)
How often do you snore?		
a. Almost every day	26/28 (92.86%)	0/28 (0%)
b. 3-4 times per week	2/28 (7.14%)	8/28 (28.6%)
c. 1-2 times per week	0/28 (0%)	14/28 (50%)
d. 1-2 times per month	0/28 (0%)	2/28 (7.14%)
e. Rarely or never	0/28 (0%)	4/28 (14.3%)
Has your snoring ever bothered other people?		
a. Yes	15/28 (53.5%)	4/28 (14.3%)
b. No	3/28 (10.9%)	8/28 (28.6%)
c. Don't know	10/28 (35.6%)	16/28 (57.1%)
Has anyone noticed that you stop breathing during your sleep?		
a. Almost every day	16/28 (57.1%)	0/28 (0%)
b. 3-4 times per week	8/28 (28.6%)	0/28 (0%)
c. 1-2 times per week	4/28 (14.3%)	0/28 (0%)
d. 1-2 times per month	0/28 (0%)	25/28 (89.3%)
e. Rarely or never	0/28 (0%)	3/28 (10.7%)
CATEGORY 2		
How often do you feel tired or fatigued after your sleep?		
a. Almost every day	10/28 (35.6%)	0/28 (0%)
b. 3-4 times per week	8/28 (28.6%)	0/28 (0%)
c. 1-2 times per week	4/28 (14.3%)	10/28 (35.6%)
d. 1-2 times per month	2/28 (7.14%)	10/28 (35.6%)
e. Rarely or never	4/28 (14.3%)	8/28 (28.6%)
During your waking time, do you feel tired, fatigued or not up to par?		
a. Almost every day	10/28 (35.6%)	0/28 (0%)
b. 3-4 times per week	8/28 (28.6%)	0/28 (0%)
c. 1-2 times per week	4/28 (14.3%)	10/28 (35.6%)
d. 1-2 times per month	2/28 (7.14%)	10/28 (35.6%)
e. Rarely or never	4/28 (14.3%)	8/28 (28.6%)
Have you ever nodded off or fallen asleep while driving a vehicle?		
a. Yes	4/28 (14.3%)	0/28 (0%)
b. No	24/28 (85.7%)	28/28 (100%)
How often does this occur?		
a. Almost every day	0/4 (0%)	0 (0%)
b. 3-4 times per week	1/4 (25%)	0 (0%)
c. 1-2 times per week	2/4 (50%)	0 (0%)
d. 1-2 times per month	1/4 (25%)	0 (0%)
e. Rarely or never	0/4 (0%)	0 (0%)
CATEGORY 3		
Do you have high blood pressure?		
a. Yes	10/28 (35.6%)	10/28 (35.6%)
b. No	18/28 (64.3%)	18/28 (64.3%)
c. Don't know	0/28 (0%)	0/28 (0%)
BMI	always <30	always <30

Scoring Questions: *Any answer in bold is a positive response;* ***Scoring categories: Category 1*** *is positive with 2 or more positive responses to questions 1-5.* ***Category 2*** *is positive with 2 or more positive responses to questions 6-9.* ***Category 3*** *is positive with 1 positive response and/or a BMI > 30.*

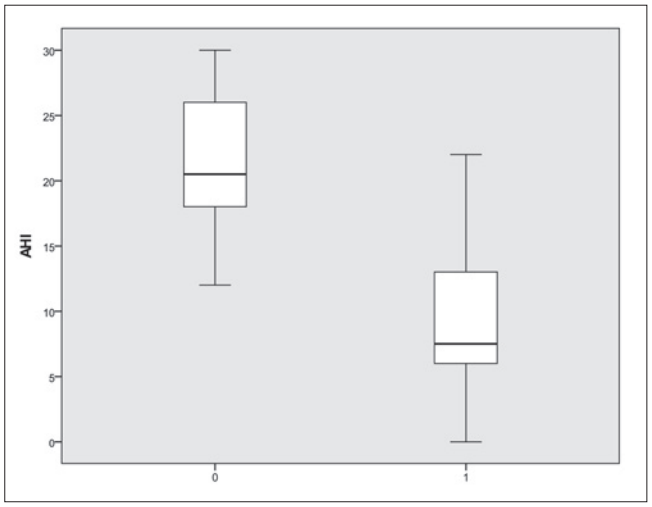

Fig. 2. AHI distribution at baseline and after three months of treatment with an oral device (0: pre; 1: post). The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.

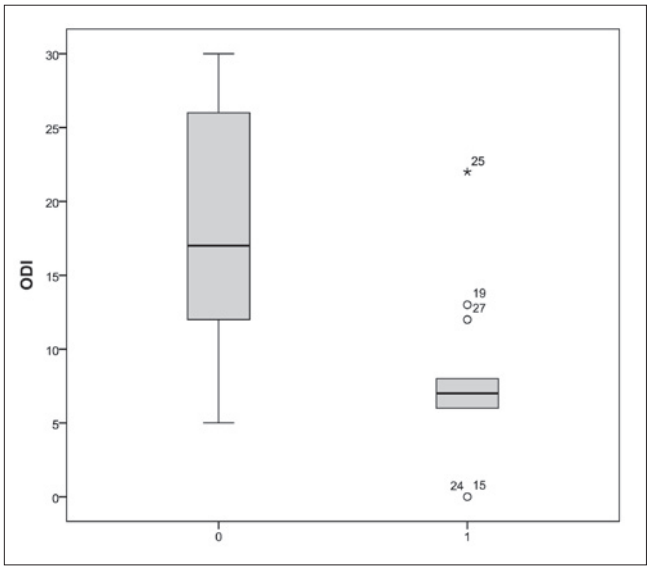

Fig. 3. ODI distribution at baseline and after three months of treatment with an oral device (0: pre; 1: post). The box plots show the median and inter-quartile range and the error bars show the 5th and 95th percentiles.

Table III. Distribution of patients according to the degree of OSAS before and after treatment.

AHI	Pre	Post	p value
AHI<5	0/28 (0%)	6/28 (21.4%)	<0.005
5<AHI<15	4/28 (14.3%)	16/28 (57.1%)	<0.005
15<AHI<30	24/28 (85.7%)	6/28 (21.4%)	<0.005

Discussion

Nowadays oral appliance therapy (OAT) [20] is recognised as an effective therapy for many patients with primary snoring and mild to moderate OSAS, as well as those with more severe OSAS who cannot tolerate positive airway pressure (PAP) therapies [21]. It has been presumed that OAT may prevent upper airway collapse and increase the cross-sectional airway dimensions, thereby reduce snoring and obstructive sleep apnoeas [22]. Advancement devices (MADs) are currently the most common class of oral appliances used to treat OSAS, and custom-made MADs are preferred and recommended over prefabricated devices [23]. Bearing in mind the wide use of mandibular advancement appliances in the management of sleep-related breathing disorders, it is very important to focus on objective criteria to indicate which subjects may benefit from such treatment by trying to look for predictors of treatment outcome and selecting patients for MAD treatment [24].

Various anthropometric and polysomnographic predictors have been described in the literature, including lower AHI, lower BMI, lower age, female gender and supine-dependent OSA [25], whereas there are still controversies about the role of DISE and in particular about mandibular advancement bimanual manoeuvre during OSA as predictor factors of treatment outcome by an oral device. In the literature, the effect of a mandibular protrusion less than 5 mm was suggested to improve patient selection for MAD treatment [26]. Johal et al. [27] suggested that DISE with concomitant gently mandibular advancement manoeuvre to mimic the treatment effect may be of prognostic value in determining the likelihood of successful mandibular advancement splint therapy in subjects with sleep-related breathing disorders. In the literature, other authors have supported the concept of DISE with the addition of a simulation bite [28]. Vroegop et al. [29] demonstrated that patients in whom upper airway patency improved substantially with the presence of the simulation bite in maximal comfortable protrusion during DISE are more likely to be treated successfully with MAD treatment. Furthermore, the author concluded that a manoeuvre of hyperprotrusion/maximal protrusion of the mandible had no predictive value on oral device therapy outcomes. The authors suggested that the chin-lift manoeuvre in maximal protrusion may be clinically less relevant for therapeutic decision-making than simulated advancement because each oral appliance inherently causes a certain amount of vertical mouth opening and the manoeuvre is not reproducible in terms of the degree of mandibular advancement. Finally, manoeuvres can be disturbing stimuli during DISE, potentially provoking arousal by awakening of the patient during the procedure.

In the current study, mandibular advancement splint therapy was prescribed on the basis not only of severity of disease, as determined from the subject's initial AHI, but also by DISE findings and results of the gentle mandibular advancement manoeuvre during DISE allowing a direct view of effects of mandibular protrusion on breathing spaces in obstruction sites [30 31]. All data were considered

and subjects who demonstrated improved airway patency and/or reduced snoring as a result of a gentle mandibular advancement manoeuvre were referred for splint therapy. In treated patients, a significant improvement of Epworth index [(7.35 ± 2.8 versus 4.1 ± 2.2 ($p < 0.05$)], mean AHI [(21.4 ± 6 events per hour versus 8.85 ± 6.9 ($p < 0.05$)] and mean ODI [(18.6 ± 8 events per hour to 7±5.8 ($p < 0.05$)]. Furthermore, the results of this study indicate that the presence of antero-posterior pattern of closure and absence of the latero-lateral one at the level of the palate as documented during pre-treatment DISE are associated with therapeutic success in mild/moderate OSA patients treated with custom-made MADs.

The results of our study suggest that the mandibular advancement manoeuvre during DISE could help to optimise the selection of patients for oral device treatment. In fact, we observed that AHI improved up to 50% from baseline in 71.4% of patients selected after DISE for MAD therapy. This result is consistent with data reported in the literature. In 2013, Doff MJ et al. [32], by comparing the results obtained with MAD vs. CPAP in two groups homogeneous for age, sex, BMI, degree of OSAS and symptoms, confirmed the efficacy of MAD in mild/moderate diseases (64% of success at one year) and CPAP in patients with severe disease. Other studies have already indicated such a trend [33 34]. Finally, Vanderveken V et al. [35], using a simulation byte, demonstrated that the successful rate may increase to 83.3%.

We believe that several factors may affect the interpretation of data about mandibular advancement manoeuvre during DISE including: subjective nature of the observations during DISE, DISE scoring system used, grade of protrusion (hyper or gentle protrusion), criterion adopted for successful manoeuvre (complete resolution of snoring and obstructive breathing events) and complete or partial resolution of apnoeic events > 50% from baseline); extent that upper airway patency needs to change in order to counteract upper airway collapse effectively. Further studies should help to clarify these points. We believe that it is also very important to look for predictive factors of tolerability of the MADs [36] based on the grade of mandibular protrusion during DISE.

Based on our data, we believe that even though the best setting should be obtained using a simulation costumed - byte during DISE, if it is not available gentle manoeuvre of mandibular advancement should be performed because it may optimise selection of patients for MAD therapy. Since it has been recently demonstrated that DISE, completed with a jaw thrust manoeuvre, has a relevant influence on the location of treatment recommendations, especially when considering MAD treatment [37 38], future studied should focus on the most simple and reliable procedure with the best cost effectiveness ratio that should be applied during sleep endoscopy to predict the best outcomes with oral appliance therapy.

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Otology

Factors affecting residual hearing preservation in cochlear implantation

Fattori influenzanti la conservazione dei residui uditivi negli impianti cocleari

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SUMMARY

The likelihood of residual hearing preservation in cochlear implantation (CI) is related to surgical factors such as type of cochleostomy (trans-fenestral vs. promontorial), use of lubricants and protective drugs, and device-related factors such as shape, length and flexibility of the array. We investigated the impact of these factors on the hearing preservation rate in adults and children with conventional audiological indications to CI. Eighty-two children aged 1-9 years and 73 adults (16-79 years) received a CI in the right (59%) or left ear (41%). An anterior-inferior promontorial cochleostomy was performed in 143 ears (92%); a trans-fenestral approach was used in 12 (8%). A perimodiolar electrode was implanted in 144 ears (93%), and a straight electrode in the remaining 11 (7%). Overall, some post-operative hearing was retained in 39% of ears. The rate of preservation was higher at the low than at the high frequencies. When correlated with age, side of implant, implant model and type of cochleostomy, the mean threshold variations did not reach statistical significance for any of these variables. A slight trend in favour of better residual hearing preservation in children vs. adults was seen, especially at lower frequencies.

KEY WORDS: Cochlear implant • Residual hearing • Insertion technique • Cochleostomy • Array • Electrode

RIASSUNTO

La possibilità di conservazione dei residui uditivi è stata correlata a fattori chirurgici quali il tipo di cocleostomia (transfenestrale vs. promontoriale), l'uso di lubrificanti e farmaci otoprotettivi, e a fattori legati all'impianto quali la forma, la lunghezza e la flessibilità dell'elettrodo. Abbiamo studiato l'impatto di questi fattori sul tasso di conservazione dell'udito residuo in adulti e bambini con indicazioni audiologiche convenzionali all'impianto cocleare. Ottantadue bambini di età compresa tra 1 e 9 anni e 73 adulti (tra 16 e 79 anni) hanno ricevuto un IC monolaterale, nell'orecchio destro (59%) o sinistro (41%). Una cocleostomia promontoriale antero-inferiore è stata impiegata in 143 orecchi (92%), e un approccio a trans-fenestrale in 12 (8%). Un elettrodo perimodiolare è stato impiantato in 144 orecchi (93%); un elettrodo "straight" è stato utilizzato nei rimanenti 11 (7%). Complessivamente, un residuo uditivo post-operatorio è stato mantenuto nel 39% dei casi. Il tasso di conservazione è stato superiore alle frequenze gravi rispetto alle acute. Quando correlato all'età, al lato dell'impianto, al modello di elettrodo e al tipo di cocleostomia, le variazioni medie di soglia uditiva acustica non sono risultate statisticamente significative per alcuna di queste variabili. Un lieve trend in favore di una migliore conservazione uditiva si è osservato nei bambini rispetto agli adulti, specialmente alle frequenze gravi.

PAROLE CHIAVE: *Impianti cocleari • Udito residuo • Tecnica d'inserzione • Cocleostomia • Elettrodi*

Acta Otorhinolaryngol Ital 2015;35:433-441

Introduction

Cochlear implantation has been always viewed as a destructive inner ear procedure. For a long time, surgeons believed that the patient's residual hearing would be compromised by surgical trauma, even when great care was taken, during the insertion of the electrode array, and patients were counselled accordingly.

At the end of the 1990s, some clinical studies hypothesised the feasibility of successful hearing preservation with cochlear implants, and thereafter many studies addressed the issue and confirmed the initial observations [1-9]. This has radically changed the approach to CIs and widely expanded the audiological indications [6 10].

Previous "soft surgery" techniques [11] have been further refined [5 12-17], and specially designed electrodes have been developed by most producers for this purpose [18-20]. The rate of preservation of hearing residuals in CI recipients is related mainly to surgical factors:

– type and dimension of array (perimodiolar vs. straight; rounded vs. smoothened tip; short vs. regular; with or without stylet);
– type of cochleostomy (round window or fenestral, promontorial);

– type of insertion (soft surgery with advance-off-stylet [AOS] vs. standard);
– use of lubricants or drugs in the cochlea (e.g. intrascalar corticosteroids) [21 22].

In addition, anatomical factors such as diameter, shape and length of scala tympani, audiological criteria (preoperative amount of residual pure tone hearing and speech perception abilities) [23 24] and demographic factors (age, side of implantation, gender) have been demonstrated to be relevant to hearing preservation in CIs. The objective of this study was to correlate some of these factors with the hearing preservation rate in our initial personal experience in adults and children with conventional indications for CI.

Materials and methods

This study is a retrospective analysis conducted on a group of adult and paediatric CI recipients who were operated upon by the first author at the Otorhinolaryngology Department of the University of Brescia, Italy, between January 2002 and July 2010, with surgical techniques aimed at preservation of residual hearing.

All patients underwent the same mini-invasive surgical approach under general anaesthesia. A linear incision about 3 cm long was made in the retroauricular skin, 1.5 cm from the sulcus, at or just behind the hairline (Fig. 1A). A subperiosteal pocket is dissected at 45° angle to the Frankfurt line, tailored to the dimensions of the receiver/stimulator of the implant that will be used. In situ trials with the silicone dummies provided by the factories helped to adjust the size of the pocket. A minimal mastoidectomy with sharp edges is drilled and the usual landmarks are identified (lateral semicircular canal, short process of incus); the posterior bony canal wall is thinned (Fig. 1B). An enlarged posterior tympanotomy is drilled between the chorda tympani and the mastoid segment of the Fallopian canal (Fig. 1C). The round window (RW) niche is exposed and, if necessary, its prominent anterior or superior bony lip is removed by a low-speed drill-out under constant irrigation. An appropriate well for the receiver/stimulator is drilled in the subperiosteal pocket and connected to the mastoidectomy with a semi-channel. The device is inserted in the pocket and fitted to the well (Fig. 1D). The ground electrode is recessed under the temporalis muscle. A promontorial cochleostomy (at the anterior-inferior edge of the RW niche) is achieved (Fig. 1E). When the RW exposure allows it, a trans-fenestral approach with direct piercing of the RW membrane is preferred.

Dexamethasone (4 mg/ml) solution is gently flushed into the middle ear cavity and the cochleostomy; hyaluronic acid gel is then placed to temporarily seal the latter in order to prevent bone dust or blood to enter the cochlear lumen. The electrode array is slowly inserted into the scala tympani, with the standard technique or the AOS technique described by Roland et al. [13] (Fig. 1F). The cochleostomy site is then sealed with autologous connec-

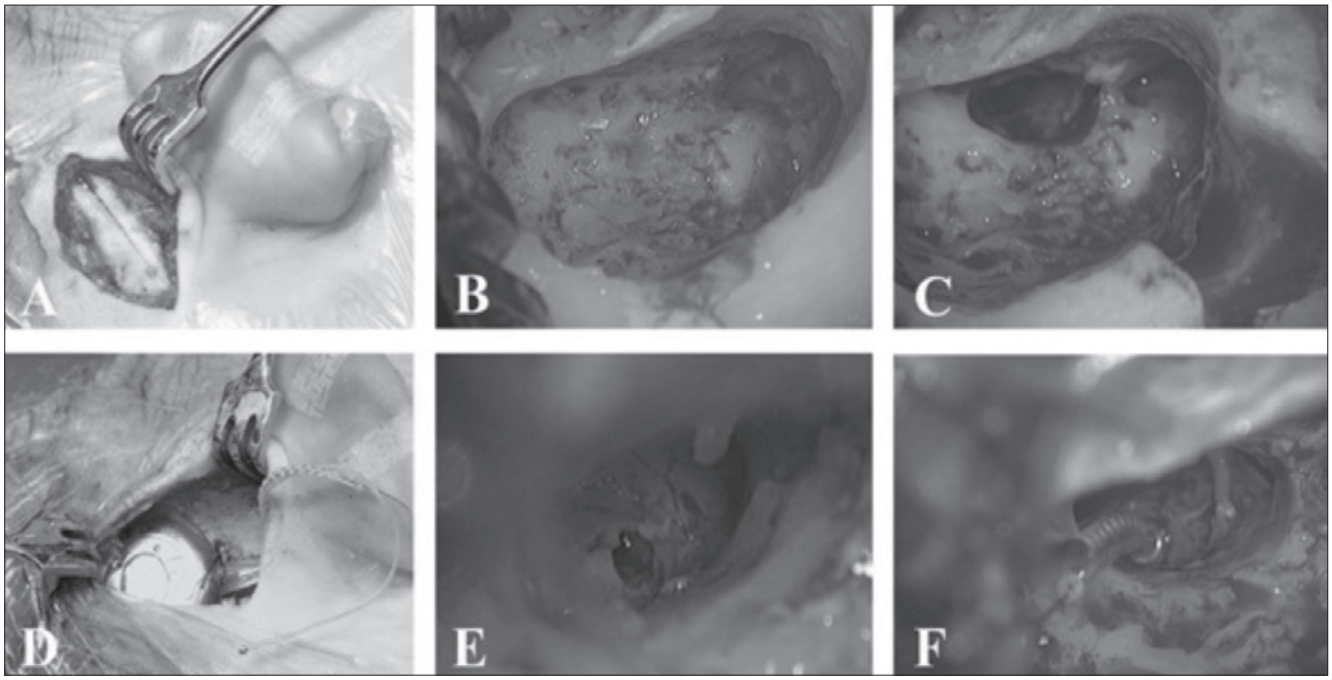

Fig. 1. Intraoperative images of the surgical procedure. A: retroauricolar incision and subperiosteal dissection; B: "minimal" mastoidectomy; C: posterior tympanotomy; D: insertion of receiver/stimulator in subperiosteal pocket after drilling of a well; E: iuxtafenestral cochleostomy; F: insertion of electrode array.

tive tissue, as well as the posterior tympanotomy, and the rest of the array is laid in the mastoidectomy cavity and the connecting semi-channel.

The study population was extracted from a pool of CI patients operated consecutively. Those who showed some residual hearing at any frequency before implantation were included; ears with no measurable threshold (anacusis) were excluded. Ears with middle or inner ear anomalies and cholesteatoma, which have a higher risk of cochlear damage or other complications during surgery [25 26], were also excluded from the analysis to make the cohort more homogeneous.

All patients suffered from severe to profound bilateral hearing loss, with less than 50% dissyllabic word recognition abilities in the best aided condition. Children showed poor aided speech perception abilities by age appropriate behavioural and electrophysiological measures. Thus, all patients were "regular" CI candidates by conventional standards of practice.

All patients were fitted with a postauricular speech processor.

In all patients the pre- vs. post-operative variations of air-conducted (AC) thresholds were recorded at each frequency (0.5, 1, 2, 4 kHz) in the ear to be implanted with an insert probe. Personnel exclusively dedicated to paediatric audiology performed all audiometric tests in children.

Post-operative thresholds were measured between one and two months after the operation to exclude a possible residual conductive component of hearing loss.

All pure tone tests were performed with a calibrated audiometer whose maximal output was 120 dB HL. For tabulation purposes, an arbitrary value of 125 dB HL was recorded in case of absent response at maximal signal intensity.

We considered the hearing residuals to be preserved when any measurable response was obtainable at low frequencies (0.5-1-2 kHz). In our study, we decided to extend the measurement to 4 kHz. Patient age, cause of hearing loss, side of implantation, cochleostomy site (fenestral vs. promontorial) and electrode model according to insertion technique were the categorical variables considered for statistical analysis.

The aims of the study were: 1) to evaluate the post-operative threshold variations at different frequencies; 2) to correlate the overall hearing preservation rates with the selected variables.

The long-term outcomes of preserved residual hearing and the correlation with speech perception outcomes is outside the scope of this paper and will be presented in a future study.

Statistical analysis was performed using the Mann-Whitney U-test to evaluate median differences of hearing deterioration between groups; the Kruskall-Wallis method was applied to test the significance of 3 different parameters; the chi-square test was used to compare categorical variables between groups. A p value < 0.05 was considered statistically significant. Results are expressed as medians and interquartile ranges (IQR).

Results

Pre-operatively, 155 patients met inclusion criteria and had a measurable hearing threshold at 500 Hz; at 1 kHz 6 of 155 had no sensation (4%), as well as 11 patients at 2 kHz (7%) and 19 at 4 kHz (12%).

The median IQR, minimum and maximum pre-operative thresholds of the entire group of patients included in the study were 100 dB (95-110) at 0.5 kHz, 110 dB (100-120) at 1 kHz, 115 dB (105-120) at 2 kHz and 120 dB (110-120) at 4 kHz, and are plotted in Figure 2.

They were 82 children (53%) and 73 adults (47%). Children's ages at implantation ranged between 1 and 16 years (median 4, IQR 2-8 years); adults ranged between 18 and 79 years (median 53, IQR 39-65 years).

The cause of hearing loss was genetic in 33 ears (26 non-syndromic, 7 syndromic), whereas in 53 ears is was related to diverse aetiologies (otosclerosis, 11; non-cholesteatomatous otitis media, 8; prenatal infections, 7; acoustic trauma, 6; meningitis, 6; sudden hearing loss, 5; Meniere disease, 4; other causes, 6). In 69 ears the cause of hearing loss remained undetermined.

The right ear was implanted in 92 cases (59%) and the left in 63 (41%).

An anterior-inferior promontorial cochleostomy was performed in 143 ears (92%); a trans-fenestral approach was preferred in 12 (8%). The implants had a straight electrode in 11 cases (7%) and a peri-modiolar electrode in 144 (93%); a standard technique of electrode insertion was used in 37 cases (24%), while the AOS technique was used in 118 (76%).

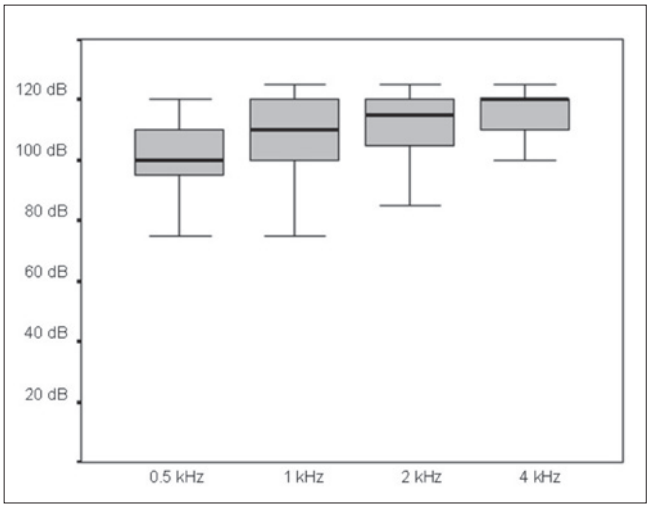

Fig. 2. Median, IQR, minimum and maximum pre-operative thresholds of the entire group of patients included in the study.

Table I. Comparison of retained residuals after surgery between analysed variables.

Variable		p value
Age		0.04
Children	46% (38/82)	
Adults	30% (22/73)	
Aetiology		0.007
Genetic	54% (18/33)	
Non-genetic	23% (12/53)	
Idiopathic	43% (30/69)	
Side		0.4
Right	36% (33/92)	
Left	43% (27/63)	
Cochleostomy		0.7
Promontorial	33% (4/12)	
Round window	39% (56/143)	
Electrode		0.2
Perimodiolar with AOS	35% (41/118)	
Perimodiolar	50% (13/26)	
Straight	54% (6/11)	

Overall, some residual hearing was preserved post-surgery in 60 of the 155 CI recipients (39%). Children and genetic hearing loss had a higher probability of retaining residual hearing (Tab. I). When matching these two variables, significant difference for aetiology was present only in children (probability of preserving residual hearing: idiopathic 46%, genetic 58%, other 10%; p = 0.03).

The rates of hearing threshold preservation at different frequencies in the whole sample is shown in Figure 3. It is evident that the preservation rate progressively decreased from the low to the high frequencies.

The median (IQR) difference between the pre- and post-operative hearing threshold (without the implant) was 12.5 dB (6.25-20): it was 15 dB (10-30) at 0.5 kHz, 10 dB (5-20) at 1 kHz, 10 dB (5-20) at 2 kHz and 5 dB (5-15) at 4 kHz.

The median threshold variation values were correlated with age (Tab. II), aetiology of hearing loss (Tab. III), side of implant (Tab. IV), type of cochleostomy (Tab. V) and electrode model according to insertion technique (Tab. VI). None of the abovementioned variables showed a statistically significant difference in terms of residual hearing preservation scores at any of the investigated frequencies. A slight trend towards lesser hearing deterioration for some variables was seen, but this did not reach statistical significance in any case; furthermore, the size of some of the subgroups is very limited, hindering comparison.

The post-operative pure tone thresholds obtained with the CI in free-field were satisfactory for all patients. The median (IQR) scores are reported in Table VII. At each frequency, the thresholds were slightly better in recipients who retained residual hearing: the difference was not significant (Tab. VII).

Table II. Correlation of differences between post- and pre-operative hearing thresholds and age of the subject at implantation (Median, IQR).

Frequency	Children (n = 82)	Adults (n = 73)	p value
Average	12 (6-20)	12 (6-20)	0.6
0.5 kHz	15 (5-25)	20 (10-30)	0.2
1 kHz	15 (5-25)	10 (5-20)	0.6
2 kHz	10 (5-20)	10 (5-15)	1
4 kHz	5 (5-20)	5 (5-10)	0.5

Table III. Correlation of differences between post- and pre-operative hearing thresholds and aetiology. (Median, IQR).

Frequency	Genetic (n = 33)	Other (n = 53)	Idiopathic (n = 69)	p value
Average	11 (6-16)	11 (5-21)	14 (6-21)	0.5
0.5 kHz	15 (5-25)	15 (5-25)	20 (10-30)	0.4
1 kHz	15 (5-15)	10 (5-20)	15 (5-25)	0.3
2 kHz	5 (5-15)	10 (5-20)	10 (5-20)	0.5
4 kHz	5 (5-10)	5 (5-20)	5 (5-15)	0.3

Table IV. Correlation of differences between post- and pre operative hearing thresholds and side of implantation (Median, IQR).

Frequency	Right (n = 92)	Left (n = 63)	p value
Average	11 (6-19)	14 (6-20)	0.6
0.5 kHz	15 (5-27)	20 (10-30)	0.9
1 kHz	10 (5-20)	15 (5-20)	0.3
2 kHz	5 (5-15)	15 (5-20)	0.3
4 kHz	5 (5-15)	5 (5-15)	0.7

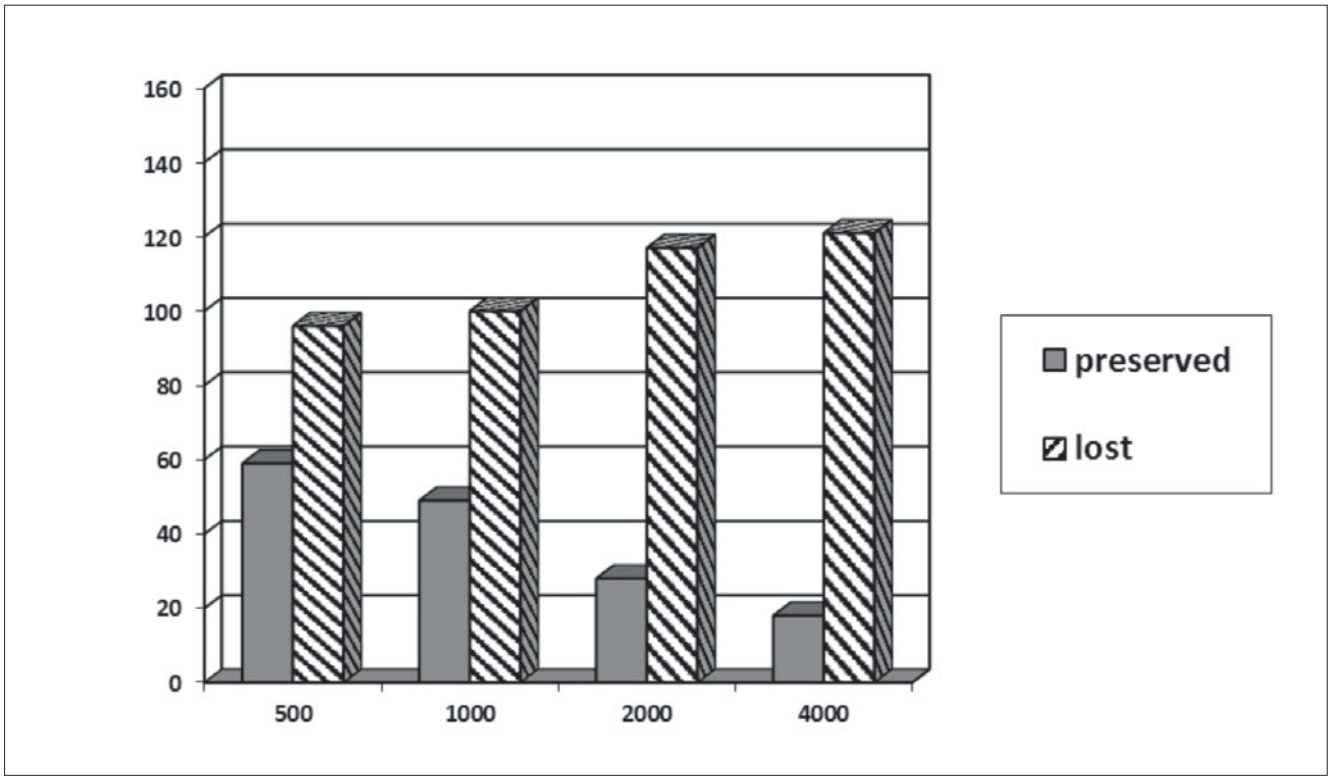

Fig. 3. Rate of threshold preservation at different frequencies for the entire sample.

Table V. Correlation of differences between post- and pre-operative hearing thresholds and type of cochleostomy (Median, IQR).

Frequency	Fenestral (n=12)	Promontorial (n=143)	p value
Average	11 (7-18)	12 (6-20)	1
0.5 kHz	20 (12-27)	15 (7-30)	0.5
1 kHz	10 (5-20)	10 (5-20)	0.7
2 kHz	5 (0-22)	10 (5-20)	0.5
4 kHz	5 (0-12)	5 (5-15)	0.3

Table VI. Correlation of differences between post- and pre-operative hearing thresholds and electrode model according to insertion technique (Median, IQR).

Frequency	Straight (n=11)	Perimodiolar (n=26)	Perimodiolar AOS (n=118)	p value
Average	14 (7-17)	12 (7-24)	11 (6-20)	0.7
0.5 kHz	20 (15-27)	20 (10-30)	15 (5-25)	0.6
1 kHz	5 (0-12)	15 (5-20)	12 (5-20)	0.1
2 kHz	15 (2-15)	10 (5-15)	10 (5-20)	1
4 kHz	5 (5-17)	5 (5-20)	5 (5-15)	0.7

Table VII. Correlation of differences in free-field hearing thresholds with CI between lost or preserved residual hearing (Median, IQR).

Frequency	Loss	Preserved	p value
Average	34 (27-40)	30 (26-41)	0.3
0.5 kHz	35 (30-40)	30 (25-40)	0.2
1 kHz	35 (30-40)	30 (25-40)	0.1
2 kHz	30 (25-40)	30 (25-40)	0.3
4 kHz	35 (25-40)	30 (25-40)	0.8

Discussion

Reasons for preserved hearing are several-fold: the conservation of the anatomical integrity of the cochlear duct, i.e. spiral lamina and ligament, organ of Corti and stria vascularis, favours the modulation of activity of spiral ganglion cells, supports the survival of neural elements and allows integration of spectral and temporal features of the stimulus, through a better CI-neural tissue interface [27-30]. This leads to improved perceptive performances, possible delivery of protective drugs, rescuing agents and/or regenerating factors, and opens new scenarios for possible future intracochlear interventions.

Reviewing the literature, it is evident that the loss of residual hearing is mainly related to insertion of the electrode array [31 32]. The inevitable surgical trauma due to the electrode insertion can be minimised by strictly adhering to the rules of "soft surgery" proposed by Lenhardt in 1993 [11]. Following other experiences in the literature [13 14 16 33], these rules have been further refined and we strictly apply them, as described in the previous section, even to patients who are not candidates for hearing preservation. Notwithstanding, the meticulous application of soft surgery techniques in all patients, our overall residual hearing preservation results did not exceed 40% of CI recipients.

In the literature a high variability of results is reported: hearing preservation scores range between 18% and 100% [2 5-9 31 34-36]; 60% of the variability is due to surgical factors [37].

According to Roland et al. [13], the cochlear damage that can result from placement of the array can be condensed in 2 large groups of aetiopathogenetic factors: 1) trauma related to the cochleostomy, including 1a - complete or partial loss of perilymph fluid, 1b - bone dust penetration into the scala tympani and delayed neo-osteogenesis, or 1c - reactive fibrous tissue formation around the array; 2) Insertion trauma: 2a - damage to the organ of Corti through breakdown of basilar membrane or 2b - osseous spiral lamina or 2c lateral wall.

Other phenomena that can lead to a delayed loss of residual hearing are: 1) related with surgical trauma: 1a - middle ear lesion (effusion, TM perforation, ossicular disruption); 1b - cochleostomy (drilling, perilymph suction, ionic homeostasis disruption, bone dust); 1c - electrode insertion (perilymph outflow, direct inner ear damage); 2) reactive (delayed): 2a - inner ear toxicity (blood, irrigation fluids, bone dust, device material); 2b - primary disease progression; 2c - inflammation (infection, fibrosis, effusion).

In our group of patients there was the opportunity to analyse the impact of several variables on residual hearing preservation after cochlear implantation.

Age at implantation

There are few reports on hearing preservation surgery in children. Skarzinski et al. [38] initially reported the feasibility of conservation of low frequency hearing in 8 of 9 children implanted for partial, down-sloping sensorineural hearing loss. The preservation was total in 44.5% and partial in 55.5%. In our experience, children seem to benefit more than adults from hearing preservation techniques (Tab. I). To our knowledge, this effect has not been reproduced in other studies [39].

Aetiology of deafness

Some considerations about the aetiology of deafness and hearing preservation have been reported in the literature [39]. Congenital hearing loss has better hearing preservation outcomes and is attributed to the possibility that subjects with congenital hearing loss have more stable auditory systems that can tolerate the CI procedure better [39]. Our experience can support this hypothesis for genetic hearing loss in children due to the small subgroup of adults with this type of deafness.

Side of implant

Even if our results are below the level of statistical significance, the left ear seems to be advantaged, but in terms of residual preservation scores right ear had lower median variations. This might be related to the right-handedness of surgeons or to a more favourable anatomy, although these remain only speculative hypotheses. We could not find significant data in the literature supporting or refuting our findings; no definitive conclusions can be drawn on this subject, and further studies are required.

Type of cochleostomy

Some authors claim the superiority of the trans-fenestral (RW) approach in terms of hearing preservation [39 40]. In the study by Skarzynski et al. [16] hearing preservation was achieved in the majority of their implanted patients through RW insertion; on that basis, the authors proposed to proceed to a CI even in cases with partial deafness, i.e. with profound sensorineural hearing loss limited to the frequencies equal or higher than 2000 Hz.

Conversely, recent experimental studies in guinea pigs [17] has shown that the type of cochleostomy is only marginally relevant to inner ear damage, while it is tightly related with the features of the selected array. Berrettini et al. [41] were able to preserve residual hearing in 81.8% of patients implanted with a perimodiolar electrode using the AOS technique by an anterior inferior cochleostomy. They observed that this combination of device and technique reduced the trauma to the lateral wall of the cochlea during electrode insertion.

In agreement with our results, the majority of the clinical studies report no significant differences between the two types of cochleostomies [42-44]. A systematic review on the topic [45] confirmed that the percentage of patients with postoperative complete hearing preservation ranged from 0% to 40% for the cochleostomy group and from

13% to 59% in the RW group. Unfortunately, no double-blind prospective studies have directly compared the two cochleostomy approaches, which deserve to be addressed more specifically.

Electrode array model and insertion technique

Shortened arrays have been designed with the purpose of preserving the low-frequency residual hearing by limiting the penetration of the electrode to the basal and mid-portion of the middle cochlear turn.

An initial FDA trial with a hybrid 10 mm electrode with 87 patients showed that over time 30% of patients partially or totally lost their low-frequency residual hearing [18].

Preliminary outcomes of a European multicentre clinical trial [46] demonstrated the ability to preserve residual hearing within 15dB in 68% of subjects implanted with a 16 mm long hybrid electrode, with results that were stable over time.

Another multicentre study [47] investigated a different type of array; similar to the 16 mm long hybrid model, this electrode showed a 68% hearing preservation score, with 16% of patients unfortunately losing residual hearing over 6 months after the CI.

Perimodiolar CIs have been related to a higher risk of intracochlear traumatisation compared to free-fitting arrays [15]. A perimodiolar model has been proven to be traumatic to inner ear structures when inserted through the RW in 50% of patients in the case series in Melbourne and 33% of those in Dallas [48]. However, some clinical studies offer evidence for atraumatic implantation and preservation of residual hearing even with perimodiolar arrays [7 49 50], provided that promontorial cochleostomy is selected. In agreement with our present findings, no significant differences were found by Di Nardo et al. [51] in terms of hearing preservation between electrode arrays bearing a stylet or not.

In a study comparing two electrodes designed for hearing preservation purposes (slim straight electrode vs. hybrid electrode), in a large cohort of consecutive CI patients with substantial residuals at the low frequencies, Jurawitz et al. [52] found that the median hearing loss of patients with the first model (n = 97) was 10 dB at initial fitting and 15 dB after 24 months. For those with the second electrode (n = 100), the median loss was 14.4-dB at activation and 30 dB at 2 years. The first model recipients exhibited greater threshold stability and lesser hearing loss over time than those with the second model.

The main criticism to the use of shorter electrodes regards their inability to stimulate sufficient extension of the acoustic nerve endings toward the cochlear apex in the case the residual hearing is lost after implantation.

However, in the most recent meta-analysis on the subject [32] the use of longer length electrode arrays with deeper insertion or contoured vs. straight-electrode arrays was not found to endanger hearing preservation.

To date, no single array design achieves all three objectives of deep insertion, proximity to modiolus and atraumatic introduction of the array. Long, flexible and progressively thinner electrodes (from base to apex) should be the aim of production of new devices by manufacturers [35 36].

Conclusions

In our experience with 155 "conventional" CI recipients (82 children and 73 adults), who were all operated upon by a refined soft surgery technique, the overall likelihood of preservation of residual hearing was 39%. The threshold conservation rate was higher at lower than at higher frequencies.

When correlated with age, aetiology of deafness, side of implant, type of cochleostomy, implant model and insertion technique, a significant rate of hearing preservation was observed for children with genetic hearing loss, whereas the median differences in threshold variation did not reach statistical significance for any of these variables. A slight trend in favour of better residual median hearing preservation for children, left side, perimodiolar electrodes inserted with AOS through fenestral cochleostomy was observed. The post-operative pure tone thresholds obtained with the CI in free-field were slightly better for individuals with preserved residuals. Due to the limited power of the study, no definitive conclusions can be drawn, and further studies are required.

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AUDIOLOGY

Role of bimodal stimulation for auditory-perceptual skills development in children with a unilateral cochlear implant

Ruolo della stimolazione bimodale nello sviluppo delle abilità percettivo-uditive nei bambini con impianto cocleare monolaterale

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SUMMARY

This is a prospective randomised study that evaluated the differences arising from a bimodal stimulation compared to a monaural electrical stimulation in deaf children, particularly in terms of auditory-perceptual skills development. We enrolled 39 children aged 12 to 36 months, suffering from severe-to-profound bilateral sensorineural hearing loss with residual hearing on at least one side. All were unilaterally implanted: 21 wore only the cochlear implant (CI) (unilateral CI group), while the other 18 used the CI and a contralateral hearing aid at the same time (bimodal group). They were assessed with a test battery designed to appraise preverbal and verbal auditory-perceptual skills immediately before and 6 and 12 months after implantation. No statistically significant differences were observed between groups at time 0, while at 6 and 12 months children in the bimodal group had better scores in each test than peers in the unilateral CI group. Therefore, although unilateral deafness/hearing does not undermine hearing acuity in normal listening, the simultaneous use of a CI and a contralateral hearing aid (binaural hearing through a bimodal stimulation) provides an advantage in terms of acquisition of auditory-perceptual skills, allowing children to achieve the basic milestones of auditory perception faster and in greater number than children with only one CI. Thus, "keeping awake" the contralateral auditory pathway, albeit not crucial in determining auditory acuity, guarantees benefits compared with the use of the implant alone. These findings provide initial evidence to establish shared guidelines for better rehabilitation of patients undergoing unilateral cochlear implantation, and add more evidence regarding the correct indications for bilateral cochlear implantation.

KEY WORDS: Cochlear implant • Bimodal stimulation • Deaf children • Auditory-perceptual skills

RIASSUNTO

Il presente studio prospettico randomizzato ha lo scopo di valutare le differenze che emergono tra una stimolazione bimodale e una elettrica monolaterale nei bambini sordi, in particolare in termini di sviluppo delle abilità percettivo-uditive. Sono stati arruolati 39 bambini di età compresa tra i 12 e 36 mesi di vita, affetti da ipoacusia neurosensoriale bilaterale severo-profonda con residui uditivi in almeno un orecchio. Tutti i pazienti sono stati sottoposti a impianto cocleare monolaterale: 21 di questi indossavano solo l'impianto (stimolazione elettrica monolaterale, Gruppo 1) mentre i restanti 18 utilizzavano l'impianto da una parte e la protesi acustica controlaterale dall'altra (stimolazione bimodale, Gruppo 2). Ciascuno di questi pazienti è stato sottoposto a una batteria di test progettata per valutare le abilità percettivo-uditive preverbali e verbali immediatamente prima e a distanza di 6 e 12 mesi dall'intervento di impianto cocleare. Non si è apprezzata una differenza statisticamente significativa tra i gruppi al tempo 0, mentre a 6 e 12 mesi dall'impianto i pazienti con stimolazione bimodale ottenevano in ogni test somministrato prestazioni migliori del gruppo con sola stimolazione elettrica monolaterale. Di conseguenza, nonostante la sordità/udito monolaterale non infici l'acuità uditiva in situazioni d'ascolto semplici, l'uso contemporaneo dell'impianto e della protesi (udito binaurale attraverso una stimolazione bimodale) garantisce un vantaggio nella acquisizione delle abilità percettivo-uditive, consistente nel raggiungimento delle tappe dello sviluppo percettivo più velocemente e in maggiore quantità rispetto ai bambini con solo un impianto cocleare. Perciò, mantenere attiva la rete nervosa uditiva controlaterale, anche se non dominante nel determinare l'acuità uditiva, garantisce dei benefici rispetto al non uso del dispositivo. Queste informazioni possono rappresentare un'evidenza iniziale per stabilire linee guida condivise per la migliore gestione riabilitativa dei pazienti sottoposti a intervento di impianto cocleare, e possibilmente fornire un'evidenza scientifica solida al fine di una indicazione certa all'impianto cocleare bilaterale.

PAROLE CHIAVE: *Impianto cocleare • Stimolazione bimodale • Sordità infantile • Abilità percettivo-uditive*

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Introduction

Cochlear implants (CI), together with the introduction of universal newborn hearing screening programs, have represented a revolution in the treatment of paediatric severe-to-profound sensorineural hearing loss. In fact, children who receive an early diagnosis of deafness, proper speech

rehabilitation and undergo early cochlear implantation are able to develop auditory and linguistic skills at par with their hearing peers [1-11].

In Italy, the current shared guidelines state that cochlear implantation is recommended in children older than 12 months with bilateral profound sensorineural hearing loss who do not get significant benefit from conventional hearing aids [12]. Little further information is given about bilateral cochlear implantation, other than its recommendation in selected cases, such as in deaf-blind subjects and in case of deafness from meningitis, where there is a substantial risk of rapid cochlear ossification [13 14].

Next to these two hearing solutions (unilateral and binaural electrical hearing), there is actually a third option, namely the chance to stimulate the ear opposite to the implanted side using a conventional hearing aid (binaural hearing though a bimodal stimulation). Surprisingly, in normal clinical practice (NCP) no stimulation of the contralateral ear is recommended in patients undergoing unilateral cochlear implantation. The decision to not stimulate the contralateral ear with a conventional hearing aid is due to multiple factors: in some cases, the monaurally implanted child refuses to wear the hearing aid on the other side, given the little perceived benefit compared with the electrically stimulated side; in others, parents themselves disregard the application of the contralateral hearing aid, considering it unnecessary after cochlear implant surgery; finally, the absence of scientific evidence about the effective benefit of a contralateral acoustic stimulation authorises the clinician, as well as parents, to minimise this aspect and maintain the belief that restoration of a monaural hearing through a CI is sufficient to ensure a proper development of perceptual-language skills. This belief is also supported by the treatment given to patients who, following trauma or infection, lose their hearing in only one ear (acquired unilateral deafness) and who, in NCP, receive no indications for the application of a conventional hearing aid.

However, several recent studies have demonstrated that restoration of a binaural hearing facilitates sound localisation and improves speech comprehension in noisy environments compared to monaural stimulation alone [15-18]. According to these findings, the ideal goal would be to restore binaural hearing in every circumstance [19]. Therefore, patients undergoing unilateral CI might achieve acceptable binaural processing by bimodal stimulation rather than or before receiving a second implant in the contralateral ear, whose cost/benefit ratio is yet to be fully demonstrated [20]. Some studies have shown that bimodal stimulation improves the auditory-perceptual abilities of adults with usable residual hearing in the non-implanted ear [17]. However, little is known about the comparison between auditory-perceptual performances of prelingually deaf children (0-3 years) with a unilateral CI and those of age-matched peers who benefit from a bimodal stimulation [21].

In this scenario, our work aims to evaluate the differences arising from a bimodal stimulation compared to a monaural stimulation in children. The main outcome measure is auditory-perceptual skills development, which represent the basic and essential prerequisites to development of language. The secondary outcomes are pure tone thresholds in free field and basic perceptive milestone achievement. It is expected that patients with bimodal stimulation develop preverbal and verbal auditory-perceptual skills faster than patients with only a CI and no contralateral stimulation. Finding an advantage for bimodal stimulation would be an important reference for the management of postoperative rehabilitation of children receiving one CI, as well as the basis for investigating the potential benefits of the binaural development of acoustic networks in order to achieve adequate perceptual and communication skills in children with pre-lingual hearing loss.

Materials and methods

Population

The entire protocol was reviewed and approved by the Ethics Committee of the institution (protocol code 811/2014) and in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient's parents.

We enrolled patients aged 12 to 36 months with similar demographic and audiological characteristics. All suffered from idiopathic or genetic severe-to-profound bilateral sensorineural hearing loss with some residual hearing, i.e. an unamplified pure tone threshold ≥70 and ≤90 dB HL for frequencies 0.25-0.5 kHz; subjects with an unamplified pure tone threshold ≥90 dB HL for frequencies 0.25-0.5 kHz were excluded from the study. Each patient had already been included in a speech and language rehabilitation programme. Other exclusion criteria were indication for simultaneous bilateral cochlear implantation (e.g. meningitis, deaf-blind children), presence of a concomitant cognitive delay, cochlear malformation, hypo-aplasia of the acoustic nerve and the impossibility to return for follow-up visits.

We enrolled 39 children, among those attending our Centre of Audiology and Otology and waiting for a CI (mean age 23.60 ± 6.24 months; 21 males and 18 females). Each patient underwent unilateral cochlear implantation, all with a perimodiolar array (Cochlear® CI512 electrode or Nucleus Freedom). Children were then divided by means of a simple randomisation into two groups using a Excel® Random Numbers Generator function: those who received and wore only a CI (unilateral CI Group, or Group 1: 21 patients; 11 males and 10 females; mean age at implantation 23.01 ± 5.96 months), and those who were instructed to use both the implant and a conventional hearing aid in the contralateral ear (Bimodal Group, or Group 2: 18 pa-

tients; 10 males and 8 females; mean age at implantation 24.28 ± 6.65 months). All children used bilaterally digital hearing aids prior to implantation; after being assigned to Group 1, subjects had to interrupt the use of the hearing aid in the non-implanted ear as a result of randomisation. Patients in Group 2 used a powerful digital hearing aid, optimised to its best fitting thanks to periodic adjustments by a hearing healthcare professional with extensive experience in paediatric audiology. Since guidelines about specific bimodal fitting protocols are yet to be provided, in Group 2 the hearing aid was regularly fitted by their HA provider, whereas CI fitting was provided by trained professionals within the CI Centre.

Test battery

Patients were assessed with a test battery designed to appraise preverbal and verbal auditory-perceptual skills. The entire battery was administered at time 0 (T0, i.e. before unilateral cochlear implantation), and after 6 (T1) and 12 months (T2) of CI use (±contralateral hearing aid, where required).

– *Auditory gain/benefit testing*: the auditory gain/benefit of the CI with or without the contralateral hearing aid was evaluated in terms of free-field hearing threshold in, i.e. the average threshold for the frequency range 0.5- 3 kHz (PTA 0.5-3 kHz), according to the Committee on Hearing and Equilibrium guidelines of the American Academy of Otorhinolaryngology, Head & Neck Surgery [22]. Each child underwent 2 to 5 play audiometry sessions and electrophysiological testing (Auditory Brainstem Responses, ABR) to obtain the best pre-implant pure tone threshold possible, given the cohort's young age.
– *Auditory perception testing*, which includes:
  • *Infant-Toddler Meaningful Auditory Integration Scale* (IT-MAIS) [23]: a structured interview schedule designed to assess the child's spontaneous responses to sound in his/her everyday environment. The assessment is based upon information provided by the child's parent(s) in response to 10 probes, assessing three main areas: 1) vocalisation behaviour, 2) alerting to sounds; and 3) deriving meaning from sound;
  • *Infant Listening Progress Profile* (ILIP) [1]: a profile specifically devised to monitor changes in early auditory performance of young implanted children. The profile covers a range of abilities from first response to environmental sounds, through discrimination of environmental sounds and voice, to identification of own names. As the IT-MAIS, the ILIP also investigates where and when children use their CIs or hearing aids in everyday life;
  • *Categories of Auditory Performance* (CAP) [1]: comprises a hierarchical scale of auditory-perceptual abilities, the lowest level describing no awareness of environmental sounds, through awareness and discrimination of speech sounds, and the highest level being represented by the ability to use a telephone with a known speaker;
  • *Ling Six Sound Test* (SST) [24]: explores the ability to detect six sounds (/m/, /a/, /u/, /i/, /s/, /ʃ/) whose spectrographic characteristics provide an estimate of proper auditory perception throughout the whole speech frequency range.

The assessment of auditory-perceptual skills was obtained by a speech therapist in auditory-verbal mode, in a silent environment and in the presence of the patient's parents.

Through administration of this test battery the so-called *Basic Perceptual Milestones Achievement* (BPMA) was identified [25]. According to these authors, the BPMA is defined as the acquisition of certain auditory skills to obtain a "minimum" score in each of the aforementioned tests at the same time: 22 points of 40 for the IT-MAIS, 12 of 16 for the ILIP, 4 of 7 for the CAP and 6 of 6 for the SST. This set of scores, in the whole, is the minimum and indispensable auditory prerequisite needed to be acquired to develop proper oral language. Conversely, a failure to achieve one of these skills after at least one year of continuous CI use is almost invariably associated with delayed language skills, even after correcting performances for auditory age.

Statistical analysis was conducted using the EpiInfo software [26]. Each outcome variable was compared across groups using a parametric statistic test (Student's t-test); alpha error was set at 0.05.

Results

In the unaided condition, Group 1 children showed a PTA 0.25-0.5 kHz = 89.41 ± 2.19 dB and click-evoked auditory brainstem responses ≥107 dBHL, while Group 2 patients had a PTA 0.25-0.5 kHz = 88.41 ± 2.87 dB ($p = 0.18$), again having click-evoked auditory brainstem responses ≥ 107 dBHL.

At time 0 (pre-implant evaluation), there were no statistically significant differences ($p > 0.05$) between groups compared to the scores obtained for IT-MAIS (3.38 ± 0.76 vs. 4.67 ± 0.76 for Group 1 and 2, respectively; $p = 0.24$), ILIP (3.29 ± 0.73 vs 5.28 ± 0.73, respectively; $p = 0.06$), SST (1.10 ± 0.32 vs. 1.89 ± 0.38, respectively; $p = 0.12$) and CAP (0.67 ± 0.19 vs. 1.17 ± 0.19, respectively; $p = 0.06$).

At time 1 (6 months after unilateral cochlear implantation), scores were statistically different between groups for all but one test: IT-MAIS (17.14 ± 2.04 for Group 1 vs 21.67 ± 1.48 for Group 2; $p = 0.08$), ILIP (10.38 ± 0.91 vs. 13.44 ± 0.44 for Group 1 and 2, respectively; $p = 0.005$), SST (4.52 ± 0.41 vs. 5.78 ± 0.13, respectively; $p = 0.007$) and CAP (2.29 ± 0.28 for Group 1 vs. 3.39 ± 0.22 for Group 2; $p = 0.003$). On the other hand, the free field hearing gain did not differ between groups (PTA 0.5-3 kHz

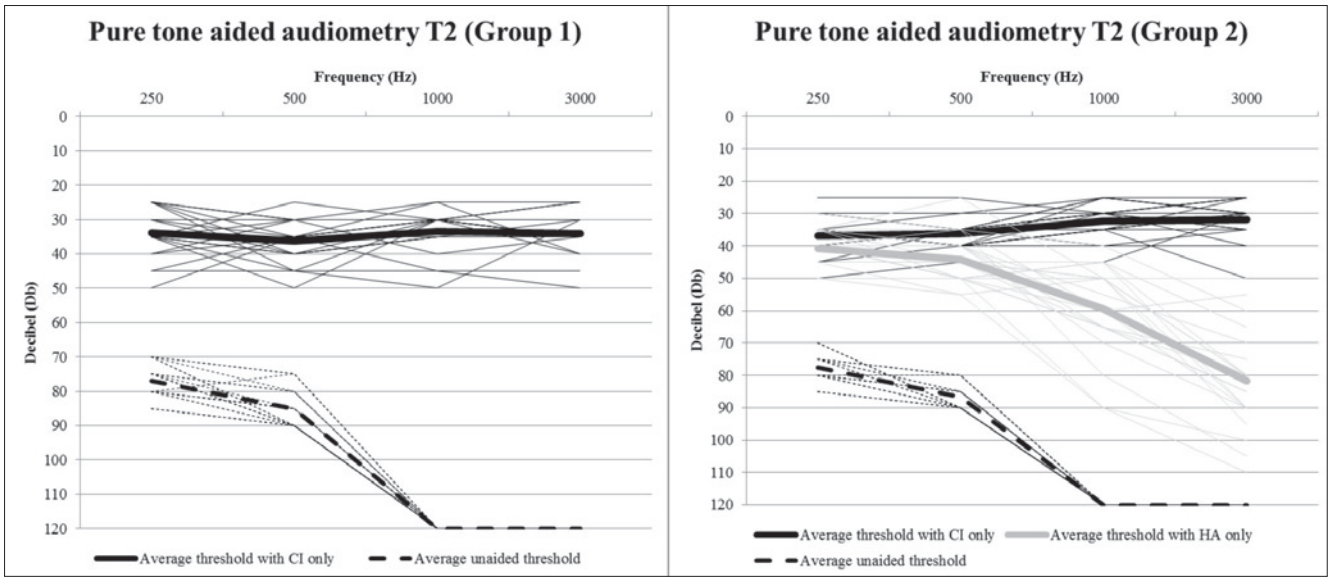

Fig. 1. Pure tone audiograms at T2 for each study participant in aided conditions; bold bars represent average thresholds.

= 38.81 ± 1.63 dB for Group 1 and PTA 0.5-3 kHz = 40.56 ± 1.19 dB for Group 2; p = 0.39).

At final evaluation, 1 year after cochlear implantation (time 2), there was still a statistically significant difference, although less powerful, between groups for two of four tests. Monaurally implanted children's auditory-perceptive skills were similar to or worse than those achieved by Group 2 children: IT-MAIS (25.71 ± 2.21 vs. 29.44 ± 1.71 for Group 1 and 2, respectively; p = 0.19), IL-IP (13.76 ± 0.65 vs. 15.39 ± 0.27, respectively; p = 0.02), SST (5.62 ± 0.2 vs 6.00 ± 0.00, respectively; p = 0.07) and CAP (3.67 ± 0.33 vs. 4.44 ± 0.17, respectively; p = 0.04). Again, the hearing gain was not statistically different between groups (PTA 0.5-3 kHz = 35.52 ± 1.37 dB for Group 1 and PTA 0.5-3kHz = 34.39 ± 1.29 dB for Group 2; p = 0.55). Figure 1 shows pure tone audiometry for each group in aided conditions at T2. Figure 2 shows the results obtained for each test/questionnaire at time 0, 6 and 12 months after cochlear implantation.

The BPMA was also evaluated. In Group 1, 6 of 21 children (28.57%) reached BPMA after 6 months of CI use, while another 10 patients (47.63%, total 72.20%) reached the BPMA after 1 year from the hook up; the remaining 5 children (23.80%) did not obtain the scores required for each of the tests even at T2. In Group 2, 9 of 18 children (50%) showed a BPMA at T1, the other 8 (44.45%, total 94.45%) at T2 and only 1 patient (5.55%) did not get the scores required for the BPMA (Fig. 3).

Discussion

Auditory-perceptual skills represent a cornerstone for language development in children. These are essential for auditory feedback, proper voice self-monitoring and the subsequent acquisition of oral language. In the hearing impaired child, the auditory-perceptual skills need to be reset/acquired through CIs and/or hearing aid use and activated by speech therapy and rehabilitation training to families.

Given the burgeoning interest of the scientific community for the auditory-perceptual skills related to language development in children [27 28] in this prospective randomised study we sought for a "springboard", namely the acquisition of a minimum level of skills such as to expect verbal language to develop in cochlear implant patients. The first milestone is the detection of all of Ling Six Sounds, thus confirming the access to all speech frequencies. Continued use of the implant and the inclusion of the child in a stimulating sound environment (as assessed by the IT-MAIS and ILIP) allow proper exposure to the world of sounds, which is crucial for verbal language learning; the same applies to the ability to discriminate among different environmental sounds (explored by the CAP) which enable acquiring the auditory prerequisites necessary for language development. In our clinical practice, we considered that the BPMA, that is the simultaneous achievement of certain scores in each of the test from our battery, represents the starting point to develop a proper verbal language.

Until a few years ago, the scientific literature unanimously agreed in considering only one ear to be completely sufficient for the acquisition of auditory-perceptual skills and the subsequent development of language in children with preverbal hearing loss. Thus, it did not seem worth the effort to have guidelines based on solid scientific evidence about the management of the ear contralateral to the implant. However, this lack of evidence has created great heterogeneity in the postoperative management of unilaterally implanted children: in most cases, the issue is still assigned to the clinical orientation of each tertiary care centre or left to the initiative of the parents of the

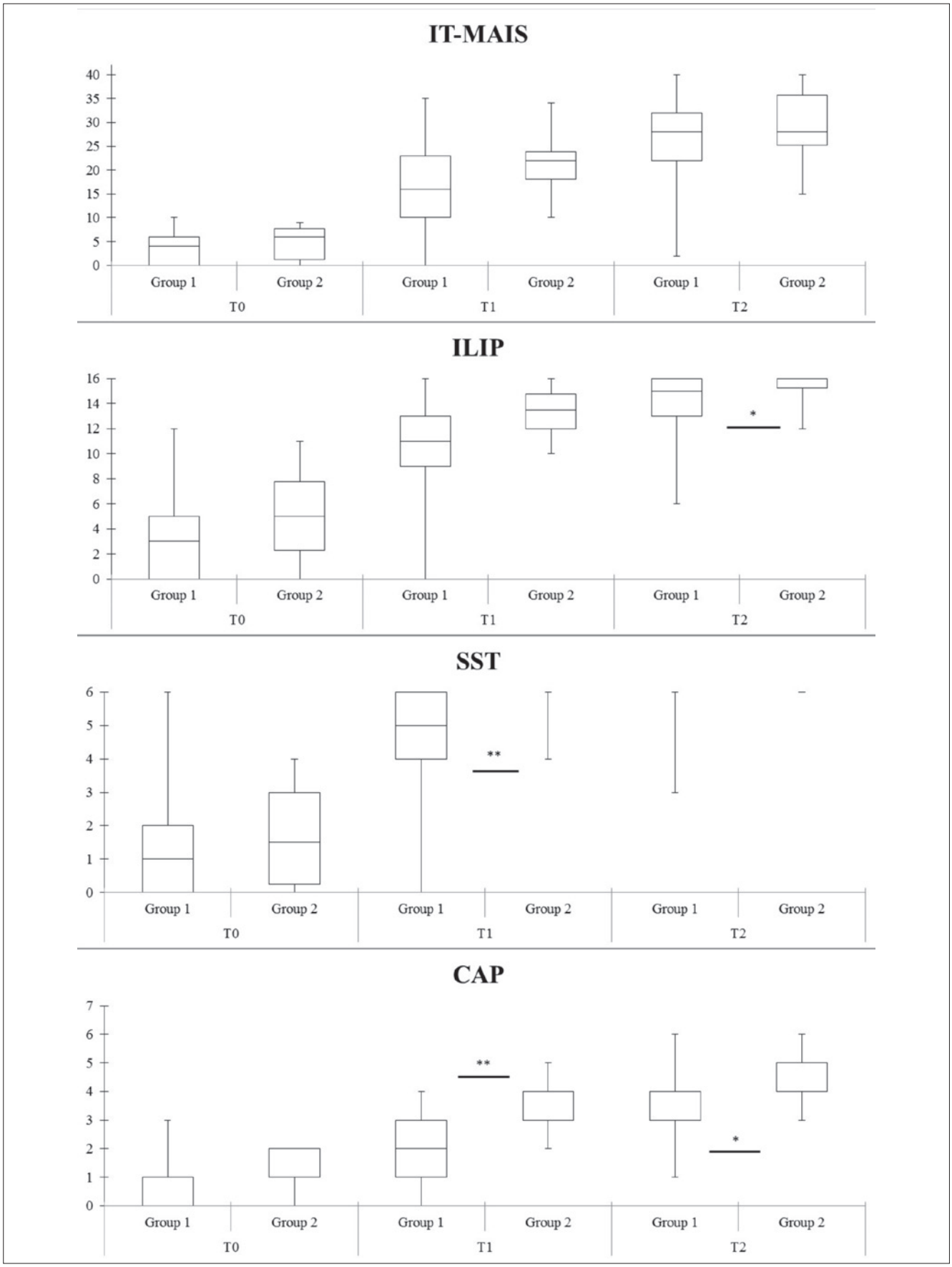

Fig. 2. Box and whisker plots for each of the two groups for each test/questionnaire administered. Statistically significant differences are represented by * ($p < 0.05$) and ** ($p < 0.01$).

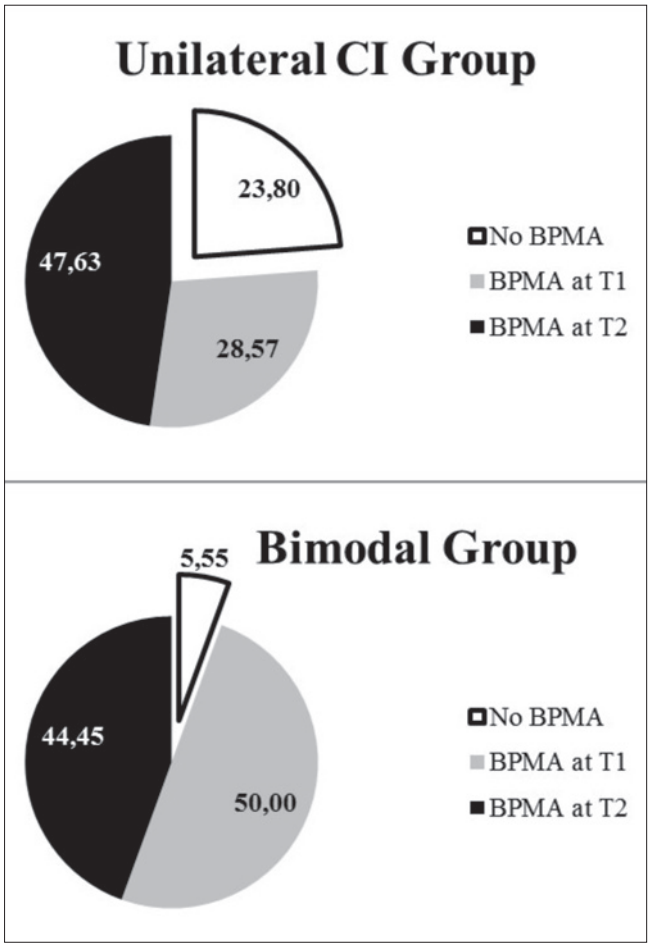

Fig. 3. The pie charts show the percentage of children who reach BPMA after 6 (grey area) and 12 months (black area) of CI use, and those who do not reach BPMA even after 1 year of CI experience (white area) across groups.

child, but there are still many in the field who do not encourage bimodal stimulation, believing it may be even confusing, for the two different strategies of stimulation of the acoustic nerve (electric vs. acoustic).

In fact, it is known from the literature that unilateral deafness does not undermine hearing acuity in normal listening, having no influence on the tonal threshold in free field conditions in a quiet environment. This is consistent with our results, since free field hearing thresholds between the two study groups did not differ significantly in spite of contralateral hearing aid use. However, when a residual hearing is present, a conventional acoustical amplification provides an advantage in terms of signal processing, since starting from an initial assessment (which did not differ significantly between groups, confirming the enrollment of two homogeneous cohorts of patients) T1 and T2 evaluations documented significantly better scores in Group 2.

One possible explanation could be that binaural stimulation of the auditory system through bimodal stimulation promotes the central integration of the stimulus and supports the acquisition of auditory perceptual skills. Thus, "keeping awake" the contralateral auditory pathway, though not crucial in determining auditory acuity, guarantees perceptual benefits compared with no use of the device [29]. The difference between the two groups in the percentage of children who reached the BPMA 12 months after the initial assessment compared to the evaluation at time 1 is reduced, probably because of a phenomenon of test saturation, as a "ceiling effect".

Analysing the individual data of children who did not reach the BPMA 12 months after the initial assessment, poor adaptation to the cochlear implant, defined as a discontinuous use or limited to a few hours a day, was observed in all cases. An interesting consideration is the fact that most of these children belonged to Group 1. In this scenario, we assume that the parents might play a role: if family members are convinced of the potential benefits of binaural stimulation of the auditory system, they presumably encourage the use of both devices, and counter the reluctance of their children, helping increase the compliance for a continuous use of both the implant and the hearing aid to a greater extent than parents of children with only one implant. Hence, it confirms the importance of raising awareness as well as informing and involving families about the rehabilitation process of their children.

Conclusions

This study provides preliminary yet convincing data about the benefits arising from the use of contralateral hearing aid in patients with unilateral cochlear implant, consisting of faster and more numerous BPMA than children with only one CI.

These findings could represent the initial evidence to establish shared guidelines for better rehabilitation management of patients undergoing cochlear implantation, and possibly provide increasingly credible evidence for bilateral cochlear implantation.

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CLINICAL TECHNIQUES AND TECHNOLOGY

The GOCCLES® medical device is effective in detecting oral cancer and dysplasia in dental clinical setting. Results from a multicentre clinical trial

Il dispositivo medico GOCCLES® è in grado di individuare displasie e cancro orale se impiegato nel setting odontoiatrico. Risultati da uno studio multicentrico

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SUMMARY

The purpose of this study is to demonstrate that the GOCCLES® medical device allows proper autofluorescence examination of the oral mucosa in a dental care setting. This is a non-randomised multicentre clinical trial on consecutive patients at risk for oral cancer. Patients underwent a classical naked eye inspection of the oral cavity followed by autofluorescence examination wearing the GOCCLES® spectacles while the light from a dental curing light irradiated the oral mucosa. Lesions were defined as visible potentially malignant lesions and/or fluorescence loss areas. All persisting lesions underwent excisional or incisional biopsy. Sixty-one patients were enrolled. Data from 64 biopsies were analysed. Of the 62 lesions identified by the device, 31 were true positives. The device identified 31 of 32 true positive lesions. One lesion (an invasive carcinoma) was not visible to the naked eye. The device identified all lesions classified as moderate dysplasia to invasive cancer. In 56.7% of cases, true positive lesions showed greater extension when observed through the device. The GOCCLES® medical device allowed the direct visualisation of fluorescence loss in patients suffering from mild to severe dysplasia and in situ to invasive oral cancer. It allowed autofluorescence examination with each source of light used during the study. These results suggest that the role of the autofluorescence visualisation is that of a complementary inspection following naked eye examination when dealing with patients at risk for oral cancer. The device allows detection of otherwise invisible lesions and otherwise impossible complete resections.

KEY WORDS: Oral cancer • Early Detection of Cancer • Dentistry • Fluorescence • Curing Lights • Dental

RIASSUNTO

Scopo di questo studio è dimostrare che il dispositivo medico GOCCLES® permette di condurre l'esame dell'autofluorescenza del cavo orale nel setting odontoiatrico. Si tratta di uno studio multicentrico non randomizzato su pazienti consecutivi a rischio di cancro orale. I pazienti sono stati sottoposti ad ispezione del cavo orale ad occhio nudo seguita dall'esame dell'autofluorescenza condotto indossando gli occhiali GOCCLES® mentre una lampada fotopolimerizzante illuminava la mucosa orale. Le lesioni sono state definite come qualunque lesione precancerosa del cavo orale visibile ad occhio nudo o area di perdita di fluorescenza visibile con GOCCLES®. Tutte le lesioni persistenti sono state sottoposte a biopsia escissionale o incisionale. Sono stati reclutati 61 pazienti e analizzati i dati da 64 lesioni. Delle 62 lesioni identificate dal dispositivo, 31 erano veramente positive. Il dispositivo ha identificato 31 delle 32 lesioni veramente positive. Una lesione (un carcinoma invasivo) non era visibile ad occhio nudo. Tutte le lesioni classificate come displasia tra moderata e severa e ogni carcinoma sono stati correttamente identificati dal dispositivo. Nel Il 56,7% delle lesioni identificate dal dispositivo mostrava margini più ampi rispetto a quelli visibili ad occhio nudo. Il dispositivo medico GOCCLES® permette di osservare il fenomeno della perdita di fluorescenza in pazienti affetti da displasia o cancro del cavo orale. Ha permesso di effettuare l'esame dell'autofluorescenza con ciascuna lampada fotopolimerizzante testata. I risultati suggeriscono di impiegare GOCCLES® come esame complementare rispetto all'ispezione ad occhio nudo del cavo orale su pazienti a rischio per cancro orale. Il dispositivo permette di identificare lesioni altrimenti visibili o i cui margini sono sottostimati dall'ispezione ad occhio nudo.

PAROLE CHIAVE: *Cancro orale • Diagnosi precoce del cancro • Odontoiatria • Fluorescenza • Lampade fotopolimerizzanti*

Introduction

No oral cancer screening test on large populations is currently recommended for oral cancer. However, studies on low-cost oral cancer diagnostic techniques are currently ongoing [1]. The autofluorescence examination is among these techniques.

Autofluorescence of the oral mucosa consists of a dim light coming from oxidised flavin adenine dinucleotide (FAD) and other fluorophores when excited by blue-violet and ultra-violet (UV) light [2]. Healthy tissues produce a 515 nm (green) light. Conversely, tissues with disorders of cell metabolism (such as dysplastic mucosa) appear as dark spots on a green background [2]. The disruption of the extracellular matrix, hyperemia and neo-angiogenesis also contribute to reduce fluorescence emission [2].

Persistent areas of decreased fluorescence can therefore be a sign of dysplasia or cancer and should be treated accordingly. Today, it is commonly accepted that potentially malignant lesions of the oral cavity must be treated if they persist for more than 2 weeks, and many researchers are trying to find a role for autofluorescence not only in the early detection, but also in the complete surgical resection of cancerous or pre-cancerous lesions [3].

The GOCCLES® (Glasses for Oral Cancer – Curing Light Exposed – Screening) medical device was created in order to provide comfortable, easy and low cost direct visualisation of abnormalities of the oral cavity tissue fluorescence.

This device has already been tested in a clinical trial, with promising results [4]. However, that study suffered from several limitations, and was a pilot study on just 32 patients. Two-thirds of enrolled patients were in follow-up after the surgical resection of an oral cancer, and therefore at high risk of showing dysplastic tissues at histological examination regardless of the results of autofluorescence examination because of disease relapse or incomplete resection. Moreover, during this trial only a prototype of the device was studied, and it was tested with only one dental curing light (an Elipar 2500 3M ESPE). Furthermore, the study was conducted only by the research team responsible for the creation of the device, with obvious conflicts of interest.

In order to demonstrate the capability of the GOCCLES® medical device to allow proper autofluorescence examination of the oral mucosa, which is the aim of this multicentre trial, it is therefore necessary to involve more patients, multiple research groups and curing lights, and to test the final model of the device.

Materials and methods

The GOCCLES® device (Pierrel S.p.A, Italy) consists of a pair of glasses equipped with filters (Fig. 1) that highlight autofluorescence when the oral mucosa is illuminated by the light emitted by any dental curing light.

Fig. 1. The GOCCLES (Glasses for Oral Cancer – Curing Light Exposed – Screening) medical device.

The device was studied in a non-randomised multicentre clinical trial in which eligible consecutive patients underwent oral examination with GOCCLES®.

Subjects above the age of 17 years were eligible for the study if showing potentially malignant lesions of the oral mucosa or if they were in follow-up after surgical resection for oral cancer. Patients who underwent radiotherapy for oral or head and neck cancer in the previous three months were excluded from the study.

All eligible subjects were informed in detail on the study protocol and participants joined the study voluntarily after signing an informed consent form. All eligible subjects showing lesions at naked eye oral inspection or on autofluorescence analysis were asked to participate in the study. For ethical reasons, subjects with totally negative naked eye and autofluorescence examinations did not undergo biopsy of the oral mucosa and were excluded.

Enrollment took place at the following six Centers: Unit of Maxillofacial Surgery, C.I. Columbus, Università Cattolica del Sacro Cuore (Rome); Department of Reconstructive and Diagnostic Surgical Sciences, Unit of Oral Pathology and Medicine and Complex Unit of Maxillofacial Surgery, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan (Milan); Department of Integrated Activities Head-Neck, Unit of Maxillofacial Surgery and Unit of Oral Medicine, Università di Napoli Federico II (Naples); Unit of Maxillofacial Surgery, Nuovo Ospedale San Giovanni Battista (Foligno). Enrollment lasted one year and started in September 2013.

Patients underwent a naked eye classical inspection of the oral cavity followed by the autofluorescence examination wearing the GOCCLES® medical device while the light from a dental curing light irradiated the oral mucosa. All examinations were performed by skilled physicians and surgeons with patients lying in a dental chair in a setting similar to that of the dental practice. All operators were asked to hold the light at 20-40 cm

distance from the oral mucosa and to direct the light perpendicularly to the inspected area. The naked eye inspection and the autofluorescence examination had to be performed by the same operator. All fluorescence loss areas were regarded as potentially malignant lesions of the oral mucosa. The following dental curing lights were used during the study: Elipar S10 3M ESPE (used by the Units of Milan); Led.B Carlo de Giorgi (Units of Rome and Foligno); Optilux 501 Kerr Corporation (Units of Naples). After examinations, all lesions persisting for at least two weeks (detected by at least one between the naked eye inspection and the autofluorescence examination) underwent excisional biopsy. If the excisional biopsy was not feasible, patients underwent incisional biopsy. All biopsies were properly oriented and showed the margins detected by both examinations. If an incisional biopsy including both identified margins was not feasible, two incisional biopsies of the same lesion on different margins were allowed. Different incisional biopsies of the same lesion were considered as a single biopsy. All biopsies underwent histological examination. No blinding on pathologist assessment or data analysts was planned.

For each lesion the following data were recorded: if visible to the naked eye and/or on autofluorescence analysis; which examination showed the greater extension if results were non-overlapping; which margins identified by the two techniques were infiltrated; the histological report. True positive lesions were defined as any dysplasia or cancer of the oral cavity. False positive lesions included negative histological findings and any other disorder of the oral mucosa not related to cancer.

Primary outcomes of the study were: proportion of visible lesions; proportion of infiltrated margins; proportion of true positive, false positive and false negative lesions. Given the study design, it was not possible to assess true negative lesions (no proper follow-up was planned).

The study protocol was approved by the respective ethics committees of the Institutions involved in the study.

Statistical analysis

Differences in terms of diagnostic performance between the autofluorescence analysis and naked eye inspection of the oral mucosa were assessed using the two-tailed McNemar test. Data analysis was performed with the IBM SPSS 22 Statistics Software for Windows. Statistical significance was set at $p = 0.05$.

Sample size calculation was based on the results of the previous study [4]. Assuming that the examination of autofluorescence showed larger margins compared to the naked eye in 25% of the lesions and that the opposite occurs in about 5% of cases, a sample of 100 patients was set in order to observe a significant difference between the two examinations with a probability of 95% (accepting a probability of type I error of 5%).

An interim analysis was planned at one year. After analysis of the first results the study was discontinued given the low probability of achieving more conclusive results with the preset sample of 100 patients.

Results

Sixty-one patients were enrolled and all underwent both naked eye inspection and autofluorescence examination of oral cavity mucosa. Data from all 61 patients entered the analysis. Main characteristics of the patients are summarised in Table I.

Autofluorescence of the oral mucosa was analysed using a Led.B curing light on 29 patients (47.6% of the sample), an Elipar S10 on 21 patients (34.4%) and an Optilux 501 on 11 patients (18.0%).

Naked eye inspection of the oral cavity detected 60 suspect lesions, while autofluorescence examination with the GOCCLES® device detected 62 suspect lesions. A total of 65 lesions were detected: in 59 cases (90.8% of observed suspected lesions) they were visible to both naked eye and autofluorescence, while 2 suspected lesions (3.1%) were only visible during the naked eye inspection and 4 (6.2%) were only visible on the autofluorescence examination. No significant differences in terms of detected suspect lesions were observed between the naked eye inspection

Table I. Main demographic and clinical characteristics of the patients enrolled in the GOCCLES study, by center

		Rome	Milan	Naples	Foligno	TOTAL
Patients [N]		14	21	11	15	61
Age [mean, (SD)]		67 (14)	66 (16)	66 (13)	63 (11)	66 (14)
Gender [N, (%)]	Female	8 (57.1)	15 (71.4)	8 (72.7)	7 (46.7)	39 (63.9)
Group [N, (%)]	A*	11 (78.6)	16 (76.2)	11 (100)	14 (93.3)	52 (85.2)
	B†	3 (21.4)	5 (23.8)	0 (0)	1 (6.7)	9 (14.8)
Biopsies/patient	1	14 (100)	21 (100)	10 (90.9)	13 (86.6)	58 (95.1)
[N, (%)]	2	0 (0)	0 (0)	1 (9.1)	1 (6.7)	2 (3.3)
	3	0 (0)	0 (0)	0 (0)	1 (6.7)	1 (1.6)

** Patients suffering from suspected dysplastic lesions of the oral mucosa.*

† Patients in follow-up after surgical resection of oral cancer.

Table II. Autofluorescence examination.

Lesion description	Detected by naked eye inspection only	Detected by both techniques	Detected by AF examination only	TOTAL*
False positive† [N (%)]	1 (3.1)	28 (87.5)	3 (9.4)	32 (50.0)
True positive [N (%)]	1 (3.1)	30 (93.8)	1 (3.1)	32 (50.0)
Of which:				
Mild dysplasia [N (%)]	1 (9.1)	10 (90.9)	0 (0)	11 (17.2)
Moderate dysplasia [N (%)]	0 (0)	4 (100)	0 (0)	4 (6.3)
Severe dysplasia [N (%)]	0 (0)	3 (100)	0 (0)	3 (4.7)
Carcinoma in situ [N (%)]	0 (0)	2 (100)	0 (0)	2 (3.1)
Invasive cancer [N (%)]	0 (0)	11 (91.7)	1 (8.3)	12 (18.8)
TOTAL [N (%)]	2 (3.1)	58 (90.6)	4 (6.3)	64 (100)

** The percentages under the "total" column relate to the whole sample. † Includes other non-precancerous and non-cancerous disorders of the oral mucosa. Definitive diagnoses are based on histological findings. No patients were negative for both naked eye and autofluorescence analysis because no subject with totally negative physical examination underwent biopsy of the oral mucosa.*

and autofluorescence examination of oral mucosa (McNemar test $p = 0.687$).

Sixty-five biopsies of the oral mucosa were thus taken. Fifty-eight patients underwent one oral mucosa biopsy, while two underwent two biopsies and another patient underwent three biopsies because of multiple lesions. An invalid sample was excluded from statistical analyses and data from 64 of 65 biopsies (98.5% of all biopsies) were analysed. Thirty-two of 64 samples (50.0% of the valid samples) were classified as false positives. Of the 32 truly positive samples, 11 (17.2% of the valid samples) were classified as mild dysplasia, 4 (6.3%) as moderate dysplasia, 3 (4.7%) as severe dysplasia, 2 (3.1%) as carcinoma in situ and 12 (18.8%) as invasive cancer.

Of the 60 suspected lesions detected by naked eye inspection of the oral cavity, 31 were true positive lesions (51.6%), while of the 62 lesions identified on autofluorescence examination, 31 (50.0%) were true positives. In particular, autofluorescence examination identified all the lesions classified as moderate to severe dysplasia and all lesions classified as cancer. Main results of the study are summarised in Table II. Both techniques identified 31 of 32 (96.9%) actual lesions. One lesion (a carcinoma) was not visible to the naked eye, while one lesion (a mild dysplasia) was not visible on the autofluorescence examination. No significant differences in terms of diagnostic performance were observed between the two techniques (McNemar test $p = 1.000$).

Thirty true positive lesions were visible by both classical inspection and autofluorescence analysis. In 17 cases (56.7% of the 30 true positive lesions), extension of the lesion detected on the autofluorescence examination was greater than that observed at naked eye inspection, while in two cases (6.7%) the margins overlapped and in nine cases (30.0%) autofluorescence examination showed a smaller lesion. In two cases (6.7%), the operator was unsure whether the margins were overlapping or not.

The resection margins identified during the naked eye inspection were infiltrated in 21 cases (67.7% of the 31 lesions identified). Of the 31 true positive lesions identified by autofluorescence examination, 24 (77.4%) showed infiltrated margins. No significant differences were observed between the two techniques in terms of free resection margins (McNemar test $p = 0.754$, see Tab. III).

No statistically significant differences were observed in the performance of the autofluorescence test using different curing lights (Tab. IV).

Discussion

The GOCCLES® medical device allowed visualisation of fluorescence loss in patients suffering from mild to severe dysplasia and oral cancer (Fig. 2). The device worked

Table III. Proportions of free and infiltrated margins of the lesions identified during naked eye inspection of the oral cavity and on autofluorescence examination.

	Not visible to AF	AF margins not infiltrated	AF margins infiltrated	TOTAL
Not visible to the NE	-	0 (0%)	1 (3.1%)	1 (3.1%)
NE margins not infiltrated	1 (3.1%)	3 (9.4%)	6 (18.8%)	10 (31.3%)
NE margins infiltrated	0 (0%)	4 (12.5%)	17 (53.1%)	21 (65.6%)
TOTAL	1 (3.1%)	7 (21.9)	24 (75.0%)	32 (100%)

NE: naked eye inspection; AF: auto fluorescence examination.
No patients showed lesions invisible to both techniques because no subject with totally negative physical examination underwent the biopsy of the oral mucosa.

Table IV. Comparison of the performance of the GOCCLES device with different curing lights.

	Auto fluorescence examination results				Lesion margin detection		
	TP lesion	FP lesion	Not detected	p value*	Free margins	Infiltrated margins	p value*
Led.B [N (%)]	15 (46.9)	16 (50.0)	1 (3.1)	0.488	4 (26.7)	11 (73.3)	0.174
Elipar S10 [N (%)]	8 (38.1)	13 (61.9)	0 (0)		0 (0)	8 (100)	
Optilux 501 [N (%)]	8 (72.7)	3 (27.3)	0 (0)		3 (37.5)	5 (62.5)	

*TP: true positive; FP: false positive. * Chi square test.*

properly with each source of light used in this study, which have different technical characteristics reproducing the variety of available dental curing lights. The Led.B is a LED lamp with a wavelength of 440-490 nm and an intensity of 1,000-1,200 mW/cm^2; the Elipar S10 LED lamp has a 430-480 nm wavelength and an intensity of 1,000 mW/cm^2; the Optilux 501 is a halogen lamp with a wavelength of 400-505 nm and an intensity of 850-1,000 mW/cm^2. The GOCCLES® device was also previously successfully tested with another halogen lamp with different characteristics (400-500 nm wavelength and 600 mW/cm^2 intensity).

The study was performed with patients lying in dental chairs in order to reproduce the settings of common dental practice. The intended purpose of the device was to allow any dentist equipped with a curing light to perform low-cost autofluorescence examination. According to the scientific literature, autofluorescence examination shows otherwise invisible characteristics of the oral mucosa that are associated with oral cancer [2 4]. However, the current evidence suggests that the role of the autofluorescence examination is that of a complementary inspection following the naked eye examination, which should not be replaced by any screening test. Moreover, given the high risk of false positive findings (50% in this study), it is recommended that every dentist equipped with the device is properly trained before using it and that only patients at risk for oral cancer or showing potentially malignant lesions undergo examination with GOCCLES®. Remarkably, however, in one case GOCCLES® allowed the detection of an otherwise invisible lesion, and in four cases it allowed otherwise impossible complete resections of lesions with infiltrated margins.

We hope that the availability of additional low cost screening techniques encourages more careful and more frequent inspections of the oral cavity among dentists, and further promotes a much needed culture of oral cancer prevention: naked eye inspection of the oral cavity alone could, in fact, save about 37,000 lives worldwide each year [5].

Furthermore, data on its diagnostic performance are lacking because of the small sample size and study de-

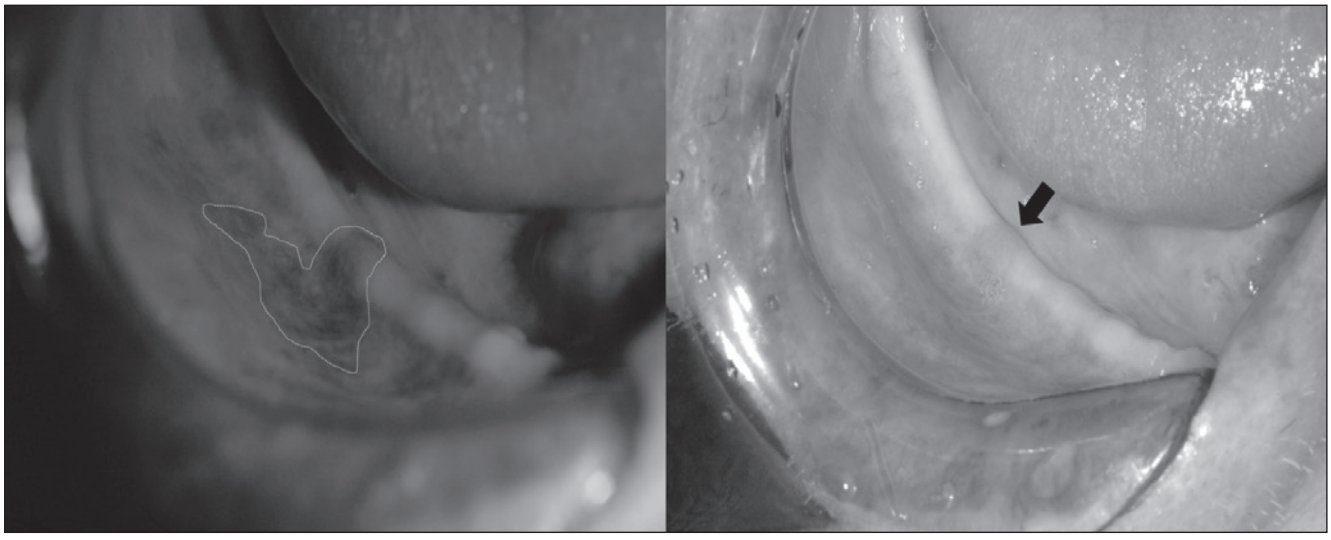

Fig. 2. Oral cancer in an edentulous patient in follow-up after surgical resection of a malignant lesion. Autofluorescence examination (on the left) vs. conventional visual examination (on the right). The lesion is barely visible if the oral examination is performed with superficiality. Loss of fluorescence increased contrast making it easier to see the tumour. Also visible in this figure is a clear difference in the extension of the margins of the lesion: fluorescence loss extended beyond the margins, which were visible to the naked eye. The arrow points to the main lesion. The margins of the lesion (as visible on the autofluorescence examination) are also highlighted.

sign (it was impossible to assess the proportion of false negatives in this study as no follow-up of negative patients was planned). Further studies on much larger samples (possibly randomised clinical trials comparing the device with other techniques) are needed to define its diagnostic performance. The previous pilot study (in which patients underwent a follow-up of one year) showed 100% sensitivity, 95% specificity, 93% positive predictive value and 100% negative predictive value. However, the device was studied on patients at very high risk, and most had a history of oral cancer. It is likely that the diagnostic performance is heavily affected by the population tested, being poorer in the general population and improving greatly when dealing (as appropriate) with subjects at risk.

Conflict of interests

This study was funded by Pierrel S.p.A., owner of the rights on the GOCCLES medical device. Three researchers involved in this study (SP, AM, FDN) have royalty percentages on the sales of the device.

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CASE SERIES AND REPORTS

Sinonasal and rhinopharyngeal solitary fibrous tumour: a case report and review of the literature

Tumore fibroso solitario nasosinusale e rinofaringeo: un caso clinico e una revisione della letteratura

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SUMMARY

Solitary fibrous tumours are rare neoplasms that arise mostly from the pleura. Much more rarely they can also be found in extrapleural sites, including the head and neck. We report a rare case of a sinonasal and rhinopharyngeal solitary fibrous tumour. The tumour, measuring 67 x 28 x 55 mm, was first embolised and then successfully removed through endonasal endoscopic surgery. Histopathologic analysis confirmed the nature of the lesion, which was positive for CD34 and vimentin. A post-operative CT scan and endoscopic follow-up demonstrated total resection and absence of recurrence after 13 months.

KEY WORDS: Solitary fibrous tumour • Extrapleural solitary fibrous tumour • Endoscopic resection • Sinonasal tumour • Rhinopharyngeal tumour • Case report

RIASSUNTO

I tumori fibrosi solitari sono neoplasie rare, che si sviluppano principalmente a livello pleurico. Molto più raramente possono comunque coinvolgere sedi extrapleuriche tra cui la testa e il collo.Riportiamo un raro caso di tumore fibroso solitario extrapleurico nasosinusale e rinofaringeo. La neoplasia, di 67 x 28 x 55 mm, è stata prima embolizzata e poi asportato con successo per via endoscopica transnasale. L'esame istologico ha confermato la natura della lesione, che si è dimostrata positiva alla CD34 e alla Vimentina. Una TC post-operatoria e uno stretto programma di follow-up endoscopico hanno dimostrato l'assenza di persistenze e o recidive di malattia dopo 13 mesi.

PAROLE CHIAVE: *Tumore fibroso solitario • Tumore fibroso solitario extrapleurico • Tumore naso-sinusale • Tumore rinofaringeo • Caso clinico*

Acta Otorhinolaryngol Ital 2015;35:455-458

Introduction

Solitary fibrous tumours (SFTs) are rare neoplasms arising in the majority of the cases from the pleura. Extrapleural forms are much more rare, especially in the head and neck. To our knowledge, no more than 31 cases involving nasal cavities and paranasal sinuses have been described. We present an additional case of a sinonasal and rhinopharingeal SFT.

Case report

A case of massive sinonasal and rhinopharyngeal extrapleural SFT has been treated at Santa Maria Hospital of Terni, Italy. The patient, a 26-year-old man, came to our attention complaining of nasal obstruction, muco-purulent rhinorrhea and frequent epistaxis. He was also affected by a right temporo-mandibular joint ankylosis as the result of a previous trauma. Endoscopic evaluation showed a reddish mass, completely obliterating the left nasal cav-

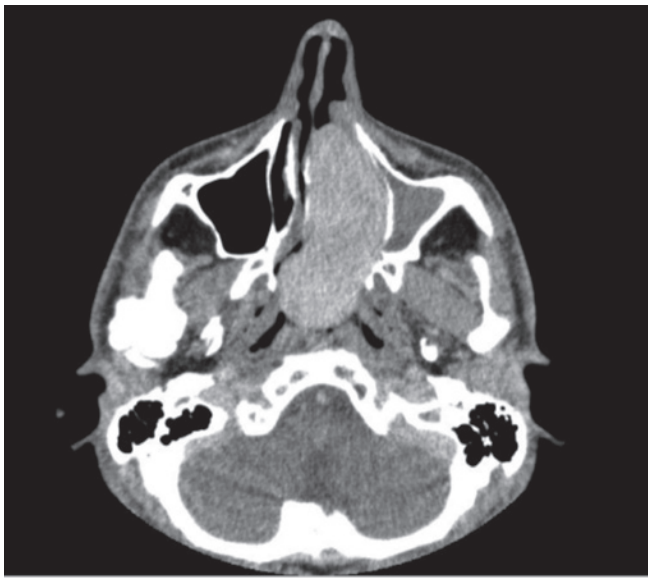

Fig. 1. Sinonasal and rhinopharyngeal solitary fibrous tumour. CT image axial section.

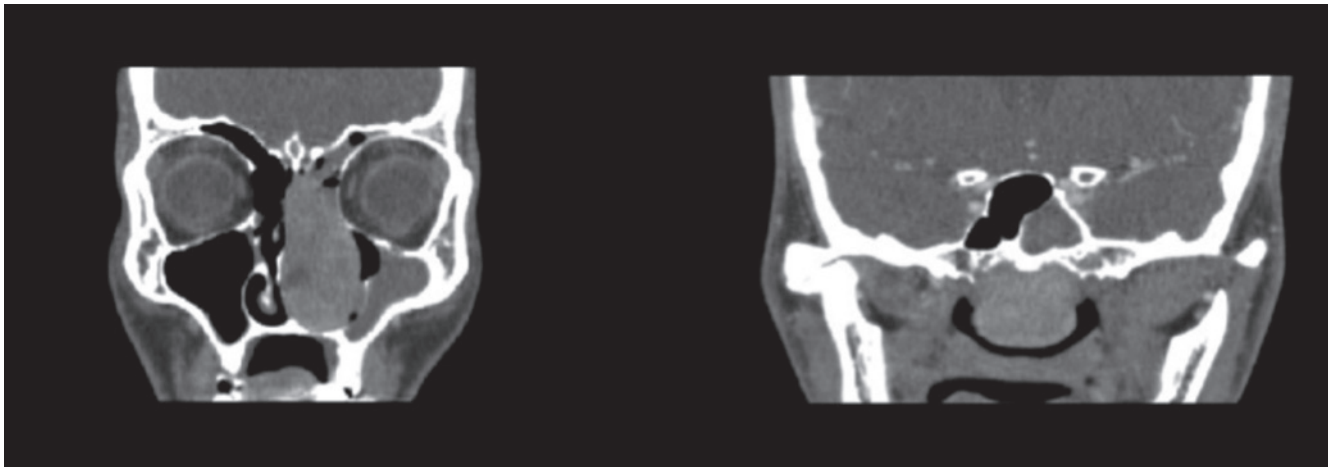

Fig. 2. Same patient. CT coronal sections.

ity and rhinopharynx. A CT scan (Figs. 1, 2) revealed an isodense, solid, neoplasm with mild and homogeneous contrast enhancement, of 67 x 28 x 55 mm, involving rhinopharynx, left nasal cavity, ethmoid cells and sphenoid sinus up to the level of the optic nerve.

We performed embolisation of the mass and subsequent surgical resection. A tracheotomy under local anaesthesia was necessary since it was impossible to introduce the endotracheal tube through the mouth because of the temporo-mandibular joint disease. After tracheotomy, total anaesthesia was obtained and we performed an endoscopic piecemeal resection of the mass with subsequent elevation and resection of the periosteum of the bones that the tumor contacted. Haemostasis was obtained by electrocautery and nasal packing. The packing was removed after five days, and no complications were noted.

Histological examination confirmed the lesion to be an extrapleural SFT with positivity for CD34 and vimentin (Fig. 3). After one month, the surgical cavity was clear and well-epithelialised. Follow-up CT confirmed total resection of the neoplasm (Fig. 4). The patient is still disease free after 13 months and is following our endoscopic follow-up programme (Fig. 5).

Discussion

Solitary fibrous tumours (SFTs) are rare neoplasms of mesenchymal origin first described by Klemperer and Rabin in 1931, and classified in pleural SFTs and extrapleural SFTs. Extrapleural forms, much more rare, can be found in several anatomical sites, including the head and neck. In the head and neck, SFTs have been described at the level of external ear canal, lacrimal sac, larynx, thy-

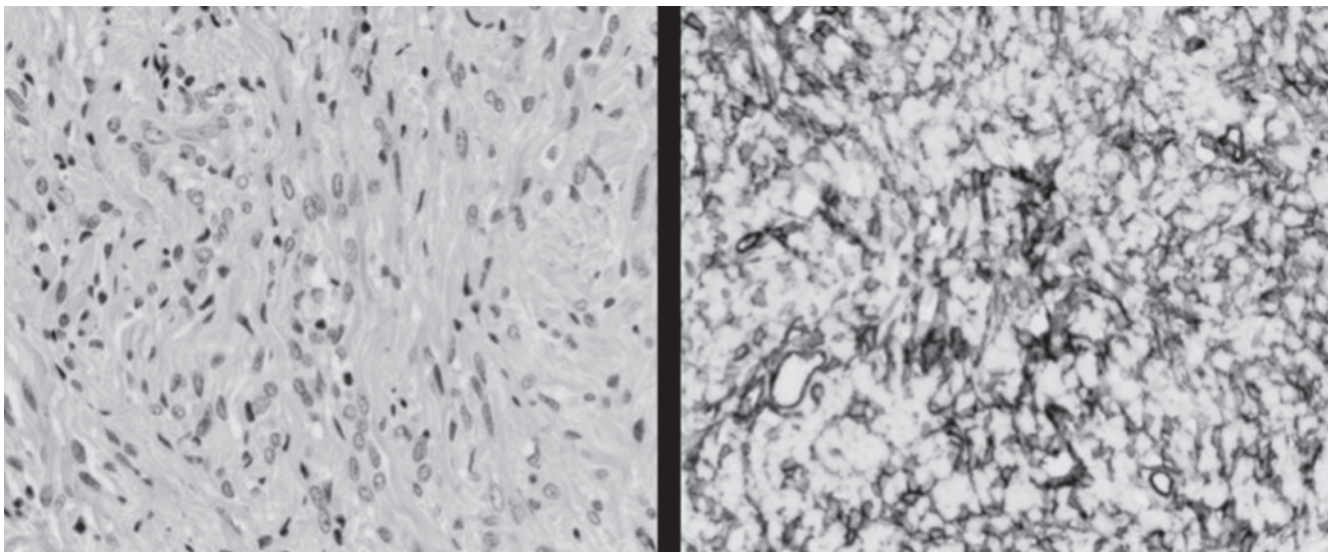

Fig. 3. Solitary fibrous tumour. Original magnification 20x. On H&E staining the tumour has a monotonous appearance and is composed of rounded-to-spindle cells with vesicular nuclei. On CD34 staining, the strong positivity of cells is evident.

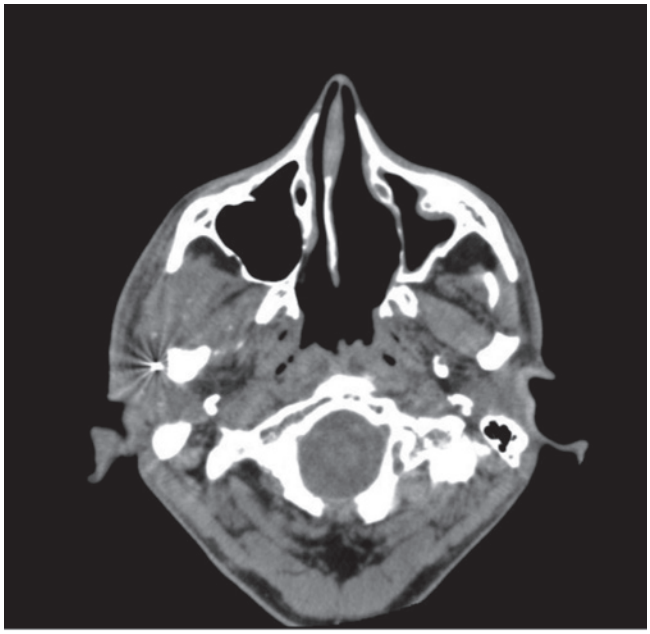

Fig. 4. Post-operative result.

roid gland, major salivary glands, parapharyngeal space, nasal cavity, orbit and rhinopharynx. These tumours usually show a benign behaviour and present themselves as space-occupying masses, which compress neighbour structures and determine a certain degree of bone resorption. In the sinonasal tract, they lead to nasal obstruction, more commonly unilateral, as well as nasal discharge, epistaxis and headache.

Malignant forms, with local aggressiveness and metastatic potential, albeit described, are exceptional, amounting for less than 5-10% of extrapleural SFTs. A markedly increased cellularity, nuclear atypia, intensive mitotic activity (> 4 mitoses/10 high power fields) and necrotic areas are to be considered as malignant criteria.

From a histological point of view, these neoplasms are capsulated tumours, constituted of fibrous tissue and capillaries surrounded by round or spindle cells with vesicular nuclei, without a well-defined growth pattern and with some combinations of different patterns.

By immunohistochemical analysis, cells are positive for CD34, vimentin and frequently bcl-2, and negative for keratin, desmin and S100 protein.

In our opinion, for sinonasal forms, CT is the best imaging modality for diagnosis since it allows precise knowledge of tumour extension and the amount of bone resorption. CT findings are a well-demarcated isodense mass with heterogeneous contrast enhancement. MRI should be considered as a second step examination reserved for cases with orbit or endocranial extension. At MRI, the tumor appears as hypo- or isointense on T1-weighted images and hypo- or, more commonly, hyperintense on T2-weighted images, with heterogeneous contrast enhancement after gadolinium infusion.

Treatment of choice is surgical resection with negative margins. Although not amenable to en bloc resection, endoscopic sinus surgery with piecemeal resection and subsequent elevation and resection of the periosteum of the tumour-contacting bone has been demonstrated to be a good option since it allows complete clearance of the tumour by a mini invasive procedure. We also embolised the tumour before the operation to decrease bleeding, but other authors have intervened without any additional treatment and report no particular bleeding complications during the procedure or in the post-operative period.

Alternative treatment modalities, such as radiotherapy or embolisation, even if described in literature, cannot be considered as effective.

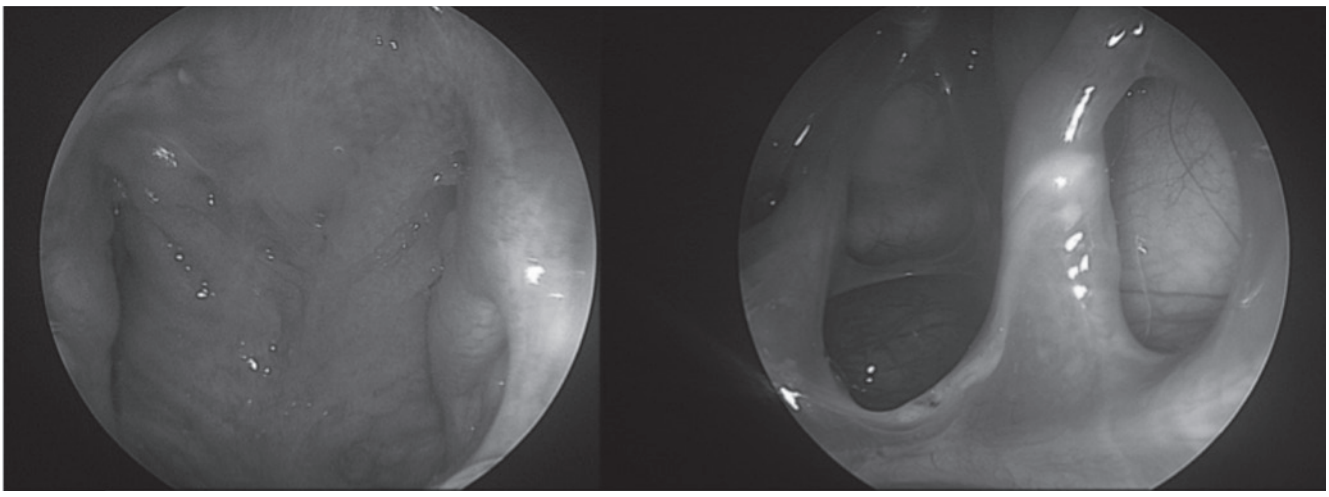

Fig. 5. Endoscopic outcome at one year post-surgery.

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Calendar of events – Italian and International Meetings and Courses

Acta Otorhinolaryngol Ital 2015;35:459

Information, following the style of the present list, should be submitted to the Editorial Secretariat of Acta Otorhinolaryngologica Italica (actaitalicaorl@rm.unicatt.it).
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JANUARY-DECEMBER 2016

CORSO DI DISSEZIONE OTOLOGICA, OTONEUROLOGICA e IMPLANTOLOGIA UDITIVA
January 5-7, 2016 • Paris – France

Course Directors: Olivier Sterkers, Daniele Bernardeschi. Info: daniele.bernardeschi@aphp.fr

INFLAMMATION – WINTER SYMPOSIUM • *January 24-27, 2016 • Miami – USA*

Directors: Sylvia Daunert, Angelo Azzi, Joseph Kissil, Stephen Nimer, Claes Wahlestedt, William J. Whelan – Website: www.miamiwintersymposium.com

6° CONGRESSO NAZIONALE CO.R.TE. • *March 10-12, 2016 • Rome – Italy*

President: Nicolò Scuderi – Tel. +39 06 35497114 – E-mail: corte@jaka.it

VI INTERNATIONAL WORKSHOP ON ENDOSCOPIC EAR SURGERY
April 7-9, 2016 • Modena and Verona – Italy

Course Directors: Livio Presutti and Daniele Marchioni – E-mail: Italy-ear-surgery@hotmail.com – Website: www.nordestcongressi.it

7th INTERNATIONAL SYMPOSIUM ON SENTINEL NODE BIOPSY IN HEAD AND NECK CANCER
April 8-9, 2016 • Rome - Italy

Organised by: M.G. Vigili and G. Tartaglione – Website: www.seventhsnb.com

15th INTERNATIONAL MEETING OF THE MEDITERRANEAN SOCIETY OF OTOLOGY AND AUDIOLOGY
April 28-30, 2016 • Cappadocia – Turkey

President: S. Armagan Incesulu – Website: www.msoa2016.org

ENDOCHICAGO 7th WORLD CONGRESS FOR ENDOSCOPIC SURGERY OF THE SKULL BASE AND BRAIN • *May 15-18, 2016 • Chicago (IL) – USA*

Course Directors: Amin B. Kassam, Martin Corsten, Ricardo L. Carrau, Daniel M. Prevedello, Vijay Anand, Theodore H. Schwartz – Website: www.endoworld.org/d-1_7TH_WORLD_CONGRESS

103° CONGRESSO NAZIONALE SIO SOCIETA ITALIANA DI OTORINOLARINGOLOGIA E CHIRURGIA CERVICO-FACCIALE • *May 25-28, 2016 • Rome – Italy*

President: Roberto Filipo – Website: www.sioechcf.it

HEAL (HEARING ACROSS THE LIFESPAN): "EARLY INTERVENTION: THE KEY TO BETTER HEARING CARE" • *June 2-4, 2016 • Lake Como – Italy*

Website: www.heal2016.org – E-mail: meet@meetandwork.com – Tel. +39 049 8601818 – Fax +39 0498602389

CORSO PRATICO DI ANATOMIA CHIRURGICA E DISSEZIONE SPERIMENTALE OTOLOGICA 2° LIVELLO - XXVII EDIZIONE • *June 6-10, 2016 • Sanremo (IM) – Italy*

A cura di: A. Tombolini, F. Baricalla – Coordinato da: A. Tombolini

26th CONGRESS OF THE EUROPEAN RHINOLOGIC AND THE 35TH INTERNATIONAL SYMPOSIUM OF INFECTION AND ALLERGY OF THE NOSE & 17th CONGRESS OF THE INTERNATIONAL RHINOLOGIC SOCIETY (ERS 2016) • *July 3-7, 2016 • Stockholm – Sweden*

President: Pär Stjärne – Website: www.ers-isian2016.com

INSTRUCTIONAL WORKSHOP EUROPEAN ACADEMY OF OTOLOGY AND NEURO-OTOLOGY
September 28 - October 1, 2016 • İzmir, Turkey

President: O. Nuri Ozgirgin – Website: www.eaono.org

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Acta Otorhinolaryngol Ital 2015;35:460-461

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