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Review

Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir

Papillomatosi respiratoria ricorrente da HPV: revisione della letteratura e aggiornamento sull'uso del cidofovir

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SUMMARY

Recurrent respiratory papillomatosis is a viral induced disease characterised by exophytic epithelial lesions affecting the larynx. The problem with its treatment is the high recurrence of papilloma growth after surgical removal. The aim of our review is to analyse the actual use of cidofovir, an agent used in adjuvant therapy. We have reviewed 6 manuscripts that included a total of 118 patients. The parameters taken into account were: concentration of infiltrated cidofovir (mg/ml), therapeutic response, relapse-free time (months), side effects, genotypes (HPV-6/11/18) and evolution of dysplasia. Cidofovir was injected at concentrations from 2.5 to 15 mg/ml, therapeutic response was from 56.25% to 82.3% and relapse-free time was from 10.05 to 49 months. There were 2 cases of dysplasia during therapy. Ten patients had been infected by HPV-6, 4 patients by HPV-11 and 10 patients by HPV-6 and HPV-11. The purposes of our review include the following: to stress that the juvenile form is more aggressive than other forms, to demonstrate than the drug has good adjuvant action although it does not significantly change the final response to the disease, to show that side effects are modest and, finally, to disprove the hypothesis that cidofovir may promote evolution towards dysplasia. In conclusion, combination of surgical removal and injection of cidofovir is associated with good response in recurrent respiratory papillomatosis.

KEY WORDS: Cidofovir • Recurrent respiratory papillomatosis • Larynx

RIASSUNTO

La papillomatosi respiratoria ricorrente è una malattia di origine virale caratterizzata da lesione esofitiche della laringe. Il problema del trattamento è l'alta frequenza con cui si riforma la lesione dopo l'asportazione chirurgica. Lo scopo della nostra review è valutare l'efficacia del cidofovir attualmente utilizzato come terapia adiuvante. Abbiamo analizzato 6 manoscritti, per un totale 118 pazienti. Sono stati considerati i seguenti parametri di valutazione: concentrazione cidofovir infiltrato (mg/ml); risposta terapeutica; tempo libero da ricadute (mesi); effetti indesiderati; genotipo (HPV-16,-18/HPV-6,-11) e evoluzione displasia. L'infiltrazione del cidofovir è variata da 2,5 mg/ml a 15 mg/ml, con una risposta terapeutica tra il 56,25% e l'82,3% e un tempo libero da ricadute dai 10,05 ai 49 mesi. In corso di terapia si sono avuti due casi di displasia. 10 pazienti erano stati infettati da HPV-6, 4 da HPV-11, 10 da entrambi i genotipi HPV-6 e 11. Dai nostri dati è emersa la conferma che la forma giovanile è maggiormente aggressiva, il farmaco ha una buona azione adiuvante ma non incide in modo significativo sulla risposta finale alla malattia, modesti sono gli effetti collaterali ed infine si smentisce l'ipotesi che il cidofovir possa favorire l'evoluzione verso la displasia. In conclusione la combinazione dell'ablazione chirurgica e cidofovir ha una buona azione adiuvante nella papillomatosi respiratoria ricorrente.

PAROLE CHIAVE: *Cidofovir • Papillomatosi respiratoria ricorrente • Laringe*

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Introduction

Recurrent respiratory papillomatosis (RRP) is primarily caused by human papilloma virus (HPV). It is a benign and rare disease of the larynx, but rarely involves an extra laryngeal extension especially in childhood forms, with tracheal and bronchial involvement that is life-threatening [1 2]. Treatment includes surgical removal of the epithelial lesion in order to maintain airway patency and phonation. Occasionally, surgical therapy is not sufficient and specific antiviral medical therapy is ineffective. One of the most important types of adjuvant therapy is the injection of intralesional cidofovir (Vistide) [3]. Herein, we review published studies that enrolled patients with RRP. All patients were treated by surgically removing laryngeal papillomas in combination with laryngeal injections of cidofovir.

Aetiology, epidemiology, clinical presentation and pathophysiology

Aetiology

HPV is a small non-enveloped virus, approximately 55 nm in diameter that belongs to the papillomaviridae family and has 72 capsomers. Its DNA genome is a double-stranded circular structure and encodes 8-10 genes. The mechanism involved infection of the host cell is unclear. Analysis of HPV has revealed more than 180 different genotypes. In the larynx affected by mucosal HPV, viral types are classified as low risk (HPV-6, HPV-11 responsible for approximately 90% of patients with RRP) [4] and high risk (HPV-16, HPV-18) in reference to the potential malignant transformation that occurs in less than 1% of cases [5 6].

The virus initially infects the basal layer of epithelia through minor abrasions. In the upper layers of squamous epithelia virions are produced, which are freed through normal desquamation processes, causing inflammation. E6 and E7 proteins, expressed by the virus, inactivate interferon regulatory factor allowing HPV infection to remain persistent and asymptomatic. Viral genomes can replicate in an episomal or integrated manner. When viral genomes replicate episomally, they show relatively low levels of E6 and E7 gene expression, and, in most cases, resolve spontaneously by an effective immune response. However, when viral DNA is introduced into the host genome, in most cases, it often displays a strong expression of E6 and E7 genes. In these cases, carcinogenic transformation progresses rapidly. The E7 protein promotes cell division by binding pRb, while virus protein E6 binds and inhibits p53 protein which is active in repressing the cell cycle in case of DNA damage. E6 protein also activates cellular telomerase that synthesise telomere repeat sequences. HPV types 6 and 11 replicate episomally, and as such are not usually carcinogenic.

Epidemiology

HPV tends to induce widespread latent infection due to the interference with host immune function. The anogenital site is the primary reservoir of HPV. It is widely accepted that HPV may be transmitted from the mother's anogenital site to the infant's respiratory tract during and even before delivery through infected placenta and amniotic fluid, resulting in juvenile-onset RRP after months or years, while in adults it may be transmitted through oral-genital sexual contact. Approximately 0.7% of infants, with maternal anogenital warts during pregnancy, have a 231-fold higher risk of illness than others. These facts suggest maternal anogenital warts during pregnancy may be a primary risk factor for the juvenile-onset of RRP. In adults, RRP may be caused by high risk factors such as sexual activity and/or oral sex with multiple partners. Additionally, extra-oesophageal acid reflux disease is a high risk factor for RRP. Iatrogenic transmission also deserves attention since HPV can survive on cryoprobe, in liquid nitrogen and in the plume generated by laser ablation or electrocautery [7].

Rabah et al. found that HPV-11 infection confers a more aggressive course to RRP than HPV-6. HPV-11 is more common among the Afro-American patients than among Caucasians. Patients with HPV-11 are diagnosed at a younger age (36.2 *vs.* 48.2 months) and are more likely to have active disease. They tend to have longer periods of disease activity (8 years *vs.* 5 years), require more surgical procedures (42 procedures/patient *vs.* 13.6), and more procedures per patient per year (2.9 *vs.* 5.3). Three patients infected with HPV-11 developed invasive papillomatosis and bronchogenic squamous cell carcinoma, and 2 of these died of disease [8]. The most reliable data regarding the Norwegian population where the incidence is 0.17 per 100,000 individuals in young people with an average age of 4 years, and 0.54 per 100,000 person-years in adults with an average age of 34 years; disease is more frequent in men.

RRP may arise anywhere in the respiratory tract with a preference for the so-called transformation area where squamous epithelia and ciliated columnar epithelia meet. The incidence of lower respiratory tract or pulmonary infection is low. High risk factors for spread of RRP towards the lower respiratory tract include HPV-11 infection, age below 3 years and tracheotomy preformed to avoid airway obstruction [9].

RRP arising in the trachea without laryngeal involvement has been reported in only a few cases [10].

Under some conditions such as smoking, irradiation, cytotoxic drugs, p53 mutation, HPV-11 infection, high severity score or high activity of 2'-5'-oligoadenylate synthetase, RRP lesions may undergo malignant transformation [11 12].

Clinical presentation and pathophysiology

Common clinical RRP symptoms include hoarseness, cough, wheezing, voice change, chronic dyspnoea, choking, syncope, etc. Stridor or respiratory harshness is possibly audible on chest auscultation. Chest x-rays are usually unremarkable. Due to its non specific clinical manifestations, RRP is easily mistaken for asthma, acute laryngitis, upper respiratory infection, or bronchitis. However, asthma therapies and anti-infective treatments are inefficacious.

Endoscopy, which is the most reliable method used to reach definite diagnosis, should be performed as soon as possible in patients with persistence of symptoms in order to favour early and correct diagnosis. Multiple cauliflower-like neoplasms with smooth and neat surface and without necrosis can be observed on endoscopy.

Detection of HPV DNA by PCR with consensus primers and subsequent restriction mapping or hybridisation methods using probes for each HPV type are available for specific HPV genotyping [7].

What is the aim of treatment?

Treatment involves surgical removal of the epithelial lesion in order to maintain airway patency and phonation. In many cases, the patient must undergo several surgeries, and sometimes surgical therapy is not sufficient; specific antiviral medical therapy may also be ineffective. The papillomatous lesion never exceeds the basal membrane, involvement of underlying tissues is considered iatrogenic damage, often inevitable, and therefore surgical techniques have evolved to reduce damage to healthy tissue.

Surgical techniques

According to many authors, CO_2 laser is convenient and precise, and represents one of the best options in the management of RRP. Lasers offer surgeons the advantage of unobstructed vision of the surgical field with minimal tissue manipulation and a longer working distance. Decreased risk of postoperative bleeding, increased sterility, minimal surrounding tissue damage, better intraoperative haemostasis, fewer surgeries and complications such as tracheostomy are among the potential benefits of laser surgery (Table I) [13-16]. However, microdebriders with cold instruments are still in use.

Lasers are useful in surgical procedures due to their production of high energy. Laser-tissue interaction is characterised by the conversion of laser energy absorbed by the cells into heat energy. This heat energy can cut, vaporise or coagulate the affected tissue.

Laser energy is delivered to tissue and can be reflected, transmitted, scattered or absorbed. If the light is reflected by or transmitted through the tissue, no heating occurs, while if the light is scattered, it will increase the amount of tissue over which the laser energy is distributed, thus increasing thermal damage to surrounding tissues. The efficiency by which the energy is transferred to the tissue depends on the wavelength of the laser. Lasers that have less depth penetration and cause less damage to surrounding tissues are, in order, erbium:Yag, CO_2 and holmium:Yag, and in these lasers the energy is absorbed largely by water. For flat lesions such leukoplakia, papillomas, or verrucous carcinoma, these lasers are preferred due to their precision. In fact, damage to the submucosa and fibromuscular regions in the larynx is life-threatening for the patient since scarring causes dysphonia and decreases airway patency.

Continuous laser is preferred due to its coagulative and haemostatic properties. Despite the notable benefits, laser surgery does have some disadvantages. Laser heat can increase scarring and cause damage to adjacent tissue. Laser treatment may also cause endotracheal explosion, mucosal burns, vocal fold webs, stenosis, and glottic incompetence [17].

Recent improvements of the CO_2 laser have increased its applicability and efficacy. Remacle et al. tested the reliability and efficacy of the new AcuPulse 40WG CO_2 laser with the FiberLase Xexible waveguide (CO_2 LWG) on patients treated with transoral laser surgery (TLS) [18]. Two patients with laryngeal papillomatosis were tested with this new device.

Burns et al. presented good results with regression of papillomatosis using a 532 nm pulsed potassium-titanyl-phosphate laser (KTP) with short-term follow-up [19]. Although anterior-commissure disease was present in 93% cases, no new webbing/synechia occurred. All patients reported that their vocal function improved after treatment.

According to Carney et al. radiofrequency coblation appears to be an attractive alternative to CO_2 laser in surgical treatment of laryngotracheal papillomatosis [20]. In that study, 6 patients were treated by CO_2 laser vaporisation with or without intralesional cidofovir for at least 2 years. All 6 patients subsequently underwent treatment with radiofrequency coblation with or without intralesional cidofovir. Coblation resulted in longer periods between surgical interventions compared to CO_2 laser.

Treatment with adjuvant drugs

The most used adjuvant drugs are interferon, various virostatics (acyclovir, valacyclovir and cidofovir), indole-3-carbinol [21], and unsedated office-based photoangiolytic laser surgery (UOLS) [22].

cidofovir is an antiviral agent indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Since 1998, cidofovir has been used to treat patients with

Table I. Surgical complications.

Authors	Patients	Complications
Preuss SF et al. [16]	194	9% of patients after laser surgery and 5% after conventional surgery required tracheotomy. 6% of patients after laser surgery and 20% after conventional surgery had postoperative glottic webs and scar formations
Dikkers FG et al. [14]	9	None of the patients had local complications.
Wierzbicka M et al. [13]	32	None of the patients had local complications.
Pudszuhn A et al. [15]	10	1 patient required tracheotomy + temporary PEG.

RRP [3]. Its mechanism of action involves decreasing the efficiency of DNA transcription following incorporation into the growing DNA chain [23].
This review evaluates the therapeutic efficacy of cidofovir in the adjuvant treatment of laryngeal papillomatosis.

Materials and methods

We have selected articles written in English from 1998 up to now on the use of cidofovir as adjuvant therapy in laryngeal papillomatosis treated with CO_2 laser or cold instruments. All articles were found on PubMed by searching with the keywords "recurrent respiratory papillomatosis" and "cidofovir laryngeal papillomatosis". Some data were derived from studies published by members of the panel of the Committee of European Laryngological Society (ELS) dedicated to "Recurrent Respiratory Papillomatosis". We reviewed 6 manuscripts that enrolled a total of 82 patients with "adult onset recurrent respiratory papillomatosis" (AORRP) and 36 patients under 12 years of age with "juvenile onset recurrent respiratory papillomatosis" (JORRP). We excluded manuscript by Chhetri et al. due to the small number of cases enrolled. Our review evaluated the following evaluation parameters: concentration of infiltrated cidofovir (mg/ml); therapeutic response (CR: complete response, PR: partial response, NR: no response); relapse-free time (months); side effects, most common genotype (HPV-6/11/18) and progression to dysplasia. (Table II).

Results

Infiltrated cidofovir concentrations ranged from 2.5 mg/ml to 7.5 mg/ml. As an exception, Friedrich et al. used 15 mg/ml [24]. The best results were reported by Snoeck et al. (82.3%), and worst by Wierzbicka et al. (56.25%). JORRP had worse prognosis (RC mean = 53.8%) than AORRP (RC mean = 72.6%). The best relapse-free times were obtained by Friedrich et al. (mean = 49 months), while the worst by Wierzbicka et al. (mean = 10.05 months). Among the 6 manuscripts examined, Snoeck et al. were the only authors who did not present data on the possible evolution of laryngeal lesions to dysplasia. Only 2/101 patients developed dysplasia during therapy: 1 developed severe dysplasia/carcinoma in situ after 5 treatments (Neumann et al.) and 1 after 6 treatments (Dikkers G). Observation continued for 3-96 months (mean 26.1). Only 4 authors reported, often in an incomplete manner, HPV genotype for a total of 25 patients (21.1%): 10 were infected by HPV-6 (Froehlich P, Neumann K, Dikkers G, Snoeck R); 4 were infected by HPV-11 (Froehlich P, Neumann K); and 10 by genotypes HPV-6 and 11 (Dikkers G, Snoeck R). No authors reported any side effects. Correlation between cidofovir concentrations and relapse-free times are shown in Fig. 1, and there was no correlation between cidofovir concentrations and CR (Fig. 2; Table II).

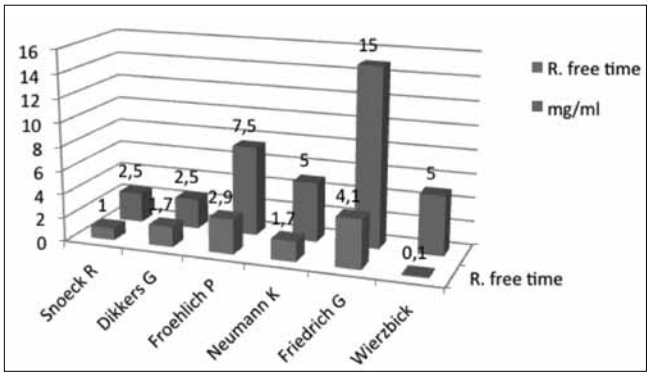

Fig. 1. Correlation between relapse-free time and dose of cidofovir.

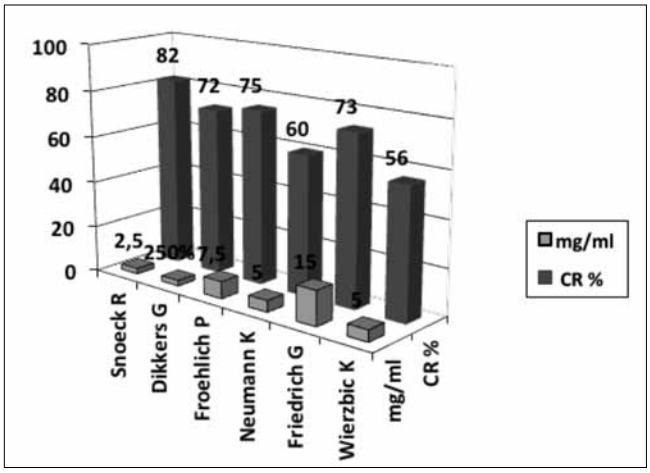

Fig. 2. Correlation between dose of cidofovir and complete response.

Technical and clinical success of treatment options

The study highlighted the good correlation between infiltrated dose and relapse-free times, so although the optimal drug concentration remains unclear, it seems that higher doses are in fact better [13-15 24 26 27]. There is no correlation between infiltrated doses and CR, cidofovir does not significantly change the final disease response. This supports the mechanism of action of the drug which reduces, without stopping, the efficiency of DNA transcription following incorporation into the growing DNA chain [23]. In addition, it seems that JORRP is more aggressive than AORRP, confirming literature data [13 15 24 28].
The use of cidofovir in the treatment of CMV retinitis limits of safety the intralesional injection to 3 mg/kg [29], and higher doses during RRP are off label. In 2011, concerning news was announced by Gilead, the manufacturer of cidofovir, regarding off label use. The warning included reports on cases of nephrotoxicity, neutropenia, oncogenesis and even deaths. However, a recent retrospective international study of 635 RRP patients, including 275 treated with cidofovir from 16 hospitals in 11 countries worldwide showed no statistically significant differences in the incidence of neutropenia or renal dys-

Table II. Use of cidofovir in published reports.

Author	AORRP/ JORRP	Cidofovir concentration	Response	Relapse-free time (months)	Side effects	Genotype HPV	Dysplasia
Wierzbicka M et al. [13]	26 AORRP 6 JORRP Total = 32	5 mg/ml	CR = 56.25% (18 = 2 JORRP + 16 AORRP); PR = 40.6% (13 = 3 JORRP + 10 AORRP); NR = 3,12% (1 JORRP)	10.05 (3-21)	3 patients. 1/3 had weakness and diarrhoea for about 4 days. 2/3 had ALT and AST levels increased.	Not specified	None
Friedrich G. et al. [24] (2013)	26 AORRP 8 JORRP Total = 34	From 7.5 mg/ml to 15 mg/ml during the study (single dose)	CR = 73.5% (25 = 5 JORRP + 18 AORRP); CR after laser = 5.8% (2 JORRP); PR = 17.6% (6 AORRP + 1 JORRP) (2.9%)	49 (12-96)	None	Not specified	None
Froehlich P. et al. [26] (2006)	16 JORRP	From 5 mg/ml to 7.5 mg/ml	CR = 75% (12 JORRP); PR = 25% (4 JORRP)	33.6 (12-76)	None	8 HPV 6; 3 HPV 11; 5 not specified	None
Neumann K. et al. [15] (2007)	7 AORRP 3 JORRP Total = 10	5 mg/ml	CR = 60% (6 = 5 AORRP + 1 JORRP); PR = 20% (2 JORRP); 2 AORRP stopped therapy (one developed dysplasia and another had accidental trauma)	19 (8-30)	None	1 HPV 11; 1 HPV 51; 1 HPV 6; 7 not specified	1 Severe dysplasia / carcinoma in situ. follow-up = 19 months
Dikkers G. [14]	9 AORRP	2.5 mg/ml	CR = 77.7% (7 AORRP); PR = 22.3% (2 AORRP)	19 (6-36)	None	1 HPV 6, 8 HPV 6 and 11	1 dysplasia
Snoeck R. et al. [25] (1998)	14 AORRP 3 JORRP Total = 17	2.5 mg/ml	CR = 82,3% (14 = 2 JORRP + 12 AORRP); PR = 11,7% (2 = 1 JORRP + 1 AORRP); 1 AORRP lost in follow-up	12 (2-27)	None	2 HPV 6 and 11; 15 not specified	Not specified

AORRP: adult onset recurrent respiratory papillomatosis; JORRP: juvenile onset recurrent respiratory papillomatosis; CR: complete response; PR: partial response; NR: No response.

function after administration of cidofovir, and no significant difference in the incidence of upper airway and tracheal malignancies between cidofovir and non-cidofovir groups [30]. Four of the 6 studies evaluated exceeded the recommended limit and in 118 cases there were no side effects except for a few patients who had mild changes in laboratory parameters (neutropenia, Gilbert's syndrome, an increase in AST and ALT). The therapeutic results and side effects excessive doses of cidofovir in patients with RRP and HPV is one of the most discussed topics in the European Laryngological Society (ELS) and has prompted a multicentre retrospective study to provide reliable data on the safety and efficacy of cidofovir in RRP [3]. Preliminary results, presented at the 9th Congress of the ELS, confirm our observation of the low incidence of side effects. Only 25/118 patients enrolled underwent genotypic analysis, so that this information is just an indication. Twenty-four of the 25 patients who underwent genotypic analyses had been infected by HPV-6, HPV-11, or both; HPV-6 and HPV-11 are classified as low risk for neoplastic transformation, which coincides with the only 2 cases of dysplasia reported. Several studies have reported that HPV-11 and HPV-6 can promote bronchogenic and laryngeal squamous cell carcinoma [31-35]. The aim of our review is to confirm the low probability (2.02%) that RRP lesions treated with cidofovir infiltration evolve towards dysplastic lesions. We thus confirm that use of cidofovir does not seem to induce dysplastic changes in HPV-infected laryngeal epithelium. Broekema et al. reported only 5/188 cases (2.7%) that evolved into dysplastic lesions [36]. Hoffman performed biopsies before and after cidofovir injections and dysplastic changes in HPV-infected laryngeal epithelium did not appear to develop. Sajan et al. affirmed that JORRP is rarely associated with laryngeal epithelial dysplasia [37]. Hall et al. affirmed the natural progression of dysplasia into RRP if patients are not treated with adjuvant therapy. In that study, 27/54 adult patients (50%) had dysplasia, and 9 cases (16.7%) developed a higher dysplastic grade during treatment. One of 54 patients (2%) developed squamous cell carcinoma [38]. This review shows that cidofovir does not seem to induce dysplastic changes in HPV-infected laryngeal epithelium, and its use has shown promising results in treatment of RRP. Nevertheless, there is still insufficient information regarding the natural progression of dysplasia in RRP [39].

Conclusions

Treatment involving surgical removal, especially with digital scanning CO_2 and cidofovir, has a good adjuvant action in RRP. The drug shows a high efficiency by increasing the relapse-free time and decreasing the number of surgeries required. Cidofovir has no side effects even after high cumulative doses. However, further research is necessary to define the most adequate doses, frequency of administration and duration of therapy.

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HEAD AND NECK

Salvage surgery for locoregional recurrences of advanced pharyngolaryngeal squamous cell carcinoma after organ preservation failure

Chirurgia di salvataggio nelle recidive locoregionali dei carcinomi squamocellulari faringolaringei avanzati dopo fallimento di preservazione d'organo

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SUMMARY

Organ preservation treatment for advanced head and neck squamous cell carcinoma is associated with poor outcomes due to locoregional recurrences. Salvage surgery is the main therapeutic option for some of these patients. The aim of this study was to analyse the results of salvage surgery for advanced pharyngolaryngeal squamous cell carcinoma previously treated with radiochemotherapy. We performed a retrospective study on 38 patients (36 men, 2 women). The median age at diagnosis was 60 years with a mean follow-up period of 49.8 months. Recurrences were diagnosed at a mean of 395 days after finalising organ preservation treatment. Patients went under different salvage surgeries, including 22 total laryngectomies, 6 partial laryngectomies (3 transoral laser surgeries and 3 opened surgeries), 8 functional neck dissections and 2 tongue base surgeries. Nineteen patients had no postoperative complications after a mean hospital stay of 2 weeks. However, 5 patients died of significant recurrent bleedings. There were 4 salivary fistulas that responded to conservative management, while 7 patients had important pharyngostomas that required reconstruction with either regional or free flaps. The mean hospital stay was of 61.60 days for all patients. Five-year overall survival from diagnosis, overall survival after salvage surgery and survival after salvage surgery were 44.20, 37.90 and 45.70%, respectively. In summary, we conclude that salvage surgery is an optimal treatment for pharyngolaryngeal and regional recurrences and provides improvement in locoregional control and survival, despite the severe complications.

KEY WORDS: Salvage surgery • Pharyngocutaneous fistula • Organ preservation • Total laryngectomy

RIASSUNTO

Il trattamento con protocollo di preservazione d'organo per i carcinomi squamocellulari avanzati del distretto testa-collo è associato a una bassa sopravvivenza a causa delle recidive locoregionali. Per alcuni di questi pazienti la chirurgia di salvataggio è la principale opzione terapeutica. L'obiettivo di questo studio è stato quello di analizzare i risultati della chirurgia di salvataggio per i carcinomi faringolaringei a cellule squamose trattati in precedenza con radio-chemioterapia. Abbiamo effettuato uno studio retrospettivo su 38 pazienti (36 uomini, 2 donne). L'età mediana alla diagnosi è stata di 60 anni, con un periodo di follow-up medio di 49,8 mesi. Le recidive sono state diagnosticate dopo una media di 395 giorni dal trattamento con preservazione d'organo. I pazienti sono stati sottoposti a diversi tipi di chirurgia di salvataggio, fra i quali 22 laringectomie totali, 6 laringectomie parziali (3 con chirurgia laser transorale e 3 con chirurgia open), 8 svuotamenti laterocervicali funzionali e 2 interventi sulla base della lingua. Dopo una permanenza media in ospedale di 2 settimane, 19 pazienti non hanno avuto complicanze postoperatorie. Tuttavia 5 pazienti sono deceduti per importanti sanguinamenti nel postoperatorio, 4 hanno presentato fistole salivari che hanno risposto positivamente ad una gestione conservativa, mentre 7 pazienti hanno avuto delle importanti fistole faringee che hanno richiesto ricostruzioni con lembi regionali o liberi. La permanenza media in ospedale è stata di 61,60 giorni. L'overall survival a 5 anni dalla diagnosi, l'overall survival dopo chirurgia di salvataggio e il disease specific survival dopo chirurgia di salvataggio sono stati rispettivamente del 44,2, 37,9 e 45,7%. Possiamo concludere che la chirurgia di salvataggio risulta un trattamento ottimale per le recidive faringolaringee e regionali e determina un miglioramento nel controllo regionale e nella sopravvivenza, nonostante le gravi complicanze associate.

PAROLE CHIAVE: *Chirurgia di salvataggio • Fistola faringocutanea • Preservazione d'organo • Laringectomia totale*

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Introduction

In 2012, 299,264 new cases of pharyngolaryngeal cancers were diagnosed worldwide with an estimated 179,466 deaths [1]. Squamous cell carcinomas are the most frequent neoplasms of the head and neck, and 60% are in an advanced stage (stage III-IV) at initial diagnosis [2 3]. Treatment of advanced pharyngolaryngeal squamous cell carcinomas has undergone substantial changes in the last two

decades. Concurrent chemoradiotherapy (CCRT) has become the standard of care for nonsurgical organ preservation after two landmark trials, the VA study in 1991 [4] and RTOG 91-11 in 2003 [5]. For patients with unresectable disease, the current standard of treatment is concurrent cisplatin-based chemoradiation. This is also the standard for patients with resectable disease when nonsurgical organ preservation is desired and, as adjuvant treatment, for patients with high-risk pathological findings at surgical resection. Lefebvre et al. reported the 10-year results of the EORTC trial 24,891 which compared a larynx-preserving approach to immediate surgery in hypopharynx and lateral epilarynx squamous cell carcinoma. Their results did not compromise disease control or survival (which remained poor) and allowed more than half of survivors to retain their larynx [6]. Despite such an approach, the majority of patients develop local and/or regional recurrences, and distant metastases occur in 20-30% of patients [3]. Depending on the site, recurrence rates range from 25 to 50% and patients with advanced-stage disease may expect only a 30 to 60% cure rate [7]. Hoffman et al. attribute the decrease in survival in patients with laryngeal cancer during the past 2 decades in the United States to the increase in nonsurgical treatment [8]. Kerry Olsen critically analysed the studies of the VA and RTOG, concluding that their results cannot be easily transferred to a normal population of patients that does not conform to the selection markers in a study setting [9]. According to American statistics, the global survival for laryngeal cancer has significantly decreased from 66 to 63% in the last years [10]. However, a significant increase in the global survival rates for cancer of the oral cavity and pharynx has been described, up to 65%, compared to 54% in prior decades. In addition, the European statistics for pharyngolaryngeal cancers have not shown such a decrease in survival of these patients. In fact, an important improvement in survival has been described in the latest statistics [11 12]. The favourable trends in cancer mortality can be largely attributed to changes in exposure to specific environmental and lifestyle risk factors. Alcohol and tobacco consumption has been steadily declining over the last decades in southern Europe, with a consequent favourable impact on oral, pharyngeal, esophageal and laryngeal cancers [13 14].

Human papillomavirus (HPV) has an important role in the pathogenesis and prognosis of oropharyngeal cancers. HPV-associated oropharyngeal squamous cell carcinoma has been shown to be more responsive to therapy and to have a better outcome than HPV-negative tumours. HPV has also been detected to varying degrees in hypopharynx and laryngeal cancers [15]. Nonetheless, no differences in outcome have been seen in patients with HPV-positive nonoropharyngeal primary cancers [16 17].

Over the past decades, the role of the head and neck surgeon in the treatment of advanced pharyngolaryngeal cancer has completely changed. Surgery has lost ground as the first therapy in this setting, and it is increasingly reserved as salvage treatment in cases of recurrent disease after chemoradiation therapy [18], and it may also be indicated for surgical functional rehabilitation or palliation [19]. Many authors have advocated surgical salvage as the primary option for recurrent pharyngolaryngeal tumours. For patients with resectable recurrence and adequate performance status, surgery offers the best chance of achieving locoregional control and prolonged survival [20]. However, salvage surgery is accompanied with significantly more complications, both local and general, compared with primary surgery [21], and significantly affects morbidity, hospitalisation and costs of treatment [22]. The aim of this study was to analyse the results of salvage surgery for recurrence of advanced pharyngolaryngeal squamous cell carcinoma previously treated with radiochemotherapy in our department.

Materials and methods

We performed a restrospective study on 103 patients with advanced pharyngolaryngeal squamous cell carcinoma (hypopharyngeal or laryngeal, Stage III/IV) treated with CCRT at our institution between 1997 and 2010. Patients who suffered from distant metastasis (Stage IVc) or with an unresectable local tumour (T4b) were excluded. 86 patients were treated with CCRT, which consisted of an association of cycles of cisplatin and 5-fluorouracil with a continuous course of external radiotherapy until a final dose of 70 Gy. Induction chemotherapy was used in 9 patients. Eight patients were not eligible for chemotherapy due to low performance status, and were treated with radiotherapy alone. During follow-up, 60 patients (58.3%) suffered a locoregional recurrence. Salvage surgery was offered to 41 of these patients, and was rejected by 3 patients. Moreover, 19 patients were not eligible for surgical treatment. Therefore, 22 patients received palliative care for recurrent disease.

We analysed the results of the 38 patients who underwent salvage surgery, including epidemiology, surgical complications, prognosis and survival.

Results

The study included 38 patients (36 men, 2 women). The median age at diagnosis was 60 years with a mean follow-up of 49.8 months. Recurrences were diagnosed at a mean of 395 days after finaliaing organ preservation treatment. Table I shows the clinical characteristics of patients at initial diagnosis. Table II indicates the characteristics of recurrences and salvage surgery. Patients went under different salvage surgeries, including 22 total laryngectomies, 6 partial laryngectomies (3 transoral laser surgeries and 3 open surgeries), 8 functional neck dissections and 2 tongue base surgeries. Eight patients with local recurrence

Table I. Clinical characteristics of patients at initial diagnosis.

Variables	N	%
Tumour site		
Supraglottis	29	76.31%
Glottis	3	7.89%
Hypopharynx	6	15.78%
Initial T		
T1-2	2	5.26%
T3	24	63.15%
T4	9	23.68%
Unknown	3	7.89%
Initial N		
N0	15	39.47%
N1	5	13.15%
N2	13	34.21%
N3	2	5.26%
Unknown	3	7.89%
Initial stage		
Stage III	14	36.84%
Stage IV	21	55.26%
Unknown	3	7.89%

Table II. Characteristics of recurrences and salvage surgery.

Variables	N	%
Type of recurrence		
Local	22	57.89%
Regional	8	21.05%
Locoregional	8	21.05%
Salvage surgery		
Total laryngectomy	22	57.89%
Partial opened laryngectomy	3	7.89%
Partial transoral laser laryngectomy	3	7.89%
Base of the tongue resection	2	5.26%
Functional neck dissection	8	21.05%

required a functional neck dissection to complete the salvage surgical treatment. All patients had partial defects of the pharynx. We performed 5 reconstructions of pharynx with regional flaps (pectoralis mayor myocutaneal flap) at the time of surgery. The remaining 20 patients going under open surgeries had direct closure of the pharynx. Thirteen patients did not undergo resection of the pharynx. Ten patients required second salvage surgeries for persistence of locoregional disease.

Surgical complications

19 patients had no postoperative complications, with a mean hospital stay of 2 weeks. However, 5 patients died of significant recurrent bleedings. There were 4 salivary fistulas that responded to conservative management, while 7 patients had important pharyngostomas that required reconstruction with pedicled flaps. Three of these patients underwent reconstruction with pectoralis major flap at salvage surgery.

Prognosis and survival

The mean hospital stay was 61.60 days for all patients. Overall, 5 year disease-free period was 31.57%. Total laryngectomy was performed in 65.78% of patients, and 47.36% were treated for regional recurrences. Two of the three partial surgeries required total laryngectomy due to second recurrences, and the third was rescued with partial laser surgery. None of the partial laser surgeries required other surgical treatments. Resection margins were not significantly associated with prognosis (Fig. 1). Five-year overall survival from diagnosis, overall survival after salvage surgery and survival after salvage surgery were 44.20, 37.90 and 45.70%, respectively (Fig. 2).

Discussion

Advanced pharyngolaryngeal cancers are often treated by a combination of radiochemotherapy for an organ preservation approach. It may also be indicated in those patients whose tumour is unresectable or inoperable. However, 30% of patients suffer from locoregional recurrence [8]. First of all, we would like to point out the fact that after failure of CCRT, a high proportion of patients are not considered candidates for salvage treatment. In our series of cases, a third of patients suffering from recurrences were not eligible for salvage surgery. In the paper by Esteller et al., 54% of patients did not have salvage surgery and died as a consequence of disease progression after a median of 3.5 months [18]. Kowalski et al. published a study on 797 patients with recurrent HNSCC who chose supportive care rather than salvage treatment, and reported a median survival of 3.8 months [23]. These results were substantially confirmed by another study in which the estimated 5-year survival rate of patients suitable for salvage surgery was 55.8%, which was much higher than those who were unsuitable for salvage surgery (17.4%, $p < 0.001$) [24]. A short disease-free interval (DFI) has been shown to have significant negative prognostic impact [25]. A review of 68 consecutive patients, primarily treated by irradiation or

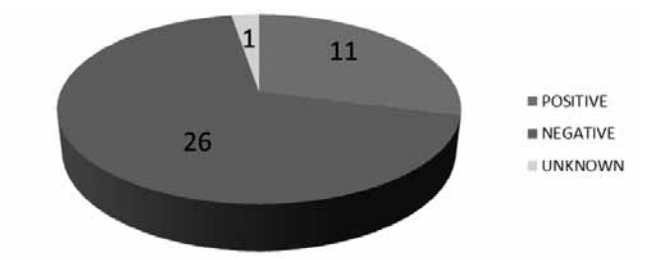

Fig. 1. Resection margins.

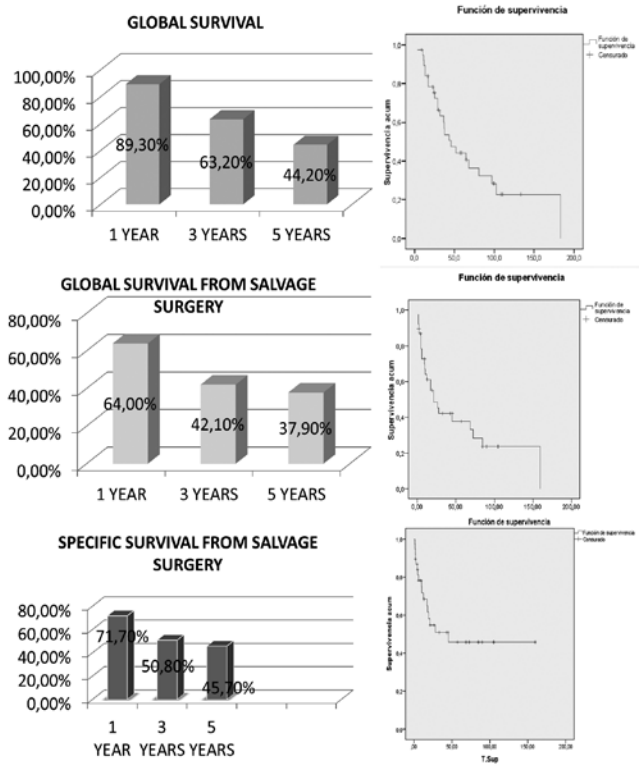

Fig. 2. Overall survival from diagnosis, overall survival after salvage surgery and survival after salvage surgery.

endoscopic surgery, and surgically salvaged by total laryngectomy or supracricoid partial laryngectomy, showed significantly poorer prognosis for recurrences occurring in the first 10 months after primary treatment [26]. In our study, there were 20 patients with recurrences within 10 months following chemoradiotherapy, and 18 of these were rescued after this period. During a 5-year follow-up after salvage treatment, 11 patients in the first group died and 9 patients in the second group died, with no significant difference between groups. This may be explained by the fact that our study included only advanced primary tumours treated with organ preservation therapies, while the study mentioned above took into account both early and advanced tumours, as well as those primarily treated by surgery.

When patients have initially undergone radiation (with or without chemotherapy), then surgery is considered the primary salvage modality when complete resection with negative margins is considered possible. Total laryngectomy remains the gold-standard salvage procedure against which all other surgical techniques are judged [26]. Laryngeal recurrence, in particular, appears to have distinctly favourable survival outcomes relative to other sites [21], and as such, salvage total laryngectomy continues to be an effective means of disease control, with recent studies reporting 5-year overall survival rates of 68 to 70% [27]. Nevertheless, prognosis is poor when a recurrence or new primary head and neck cancer develops in an area previously treated with radiation [28]. 1621 consecutive patients with neoplasms of the larynx were observed at the Sun Yat-sen University Cancer Center. After a median follow-up of 49.5 months (range, 7-176 months), recurrent disease was diagnosed in 253 patients (16.3%). Survival after recurrence was significantly influenced by variables related to both primary and recurrent tumour: age, smoking index, grade, primary site, initial T stage, initial UICC stage and nodal status of the primary tumour, as well as the DFI, extent and location of the recurrence and suitability for surgery were powerful prognostic factors for survival [24 29]. The stage of the recurrent tumour appears to be of substantial importance in predicting prognosis. A prospective study by Goodwin on 109 patients identified a prominent difference in 2-year disease-free survival (DFS) based on recurrent stage (67% for rStage II *vs.* 33% for rStage III and 22% for rStage IV), underscoring the difficulty of successful treatment of advanced disease [7]. In our retrospective study, we did not analyse this aspect due to the lack of information.

In some cases of small recurrent tumours, laryngeal conservation surgery with or without postoperative radiation therapy may be considered. Such partial laryngeal procedures are performed with transoral laser microsurgery or open partial laryngectomy. They may give a second chance for organ preservation in a significant proportion of patients [30]. However, open partial laryngectomy for salvage after failed radiotherapy is more frequently associated with postoperative complications, with reported complication rates of 20 to 28% and with fistula rates of 8 to 14% [31]. In fact, we performed only three partial open surgeries, and all required total laryngectomy due to postoperative complications and second recurrences. Nevertheless, we had good results from transoral laser surgeries (TOL), despite our modest experience with laser for salvage surgeries. Grant et al. evaluated TOL microsurgery in a cohort of patients with recurrent disease (supraglottic and glottis) and reported a locoregional control rate of 88% at 2 years. Furthermore, Steiner et al. reported local control in 74% of patients with glottic recurrences undergoing TOL microsurgery [32 33]. While the complications associated with TOL microsurgery in the primary setting are relatively rare, the risks associated with this procedure in the recurrent setting have yet to be determined. The greatest concern after extensive salvage TOL procedures following prior radiation is the ability of the larynx to heal by secondary intention [26].

Neck recurrences may signal the greater likelihood of distant metastases and consequently poorer prognosis [34]. Wong et al. compared regional recurrence versus local recurrence, showing that patients with regional recurrence had a higher likelihood of successful disease control at the time of surgery (42% *vs.* 29%), but lower 5-year disease free survival (26% *vs.* 42%) [35]. 16 of our patients required

a neck dissection at the moment of salvage surgery; only a third survived after 5 years. Regarding elective neck dissection, most studies have reported that neck dissection does not provide any advantage in patients who develop recurrent laryngeal cancer without clinical evidence of nodal metastases after radiation [36-38].

There is limited information about hospital stay and the costs of salvage surgeries. The median hospital stay in our study was 61.60 days. However, the median hospital stay for patients without complications was much lower (19 days, range 13-30 days) than for those with surgical complications (37 days, range 14-74 days). The study of Esteller et al. [18] found a significant difference in hospital stay in relation to the appearance of surgical complications ($p = 0.001$) in patients who had surgery on the primary tumour. Our most frequent complication of salvage surgery after chemoradiation was pharyngocutaneous fistula, consistent with earlier studies [25 26 39]. According to other investigations, patients undergoing total laryngectomy after radiation therapy have a significantly increased risk of fistualae of approximately 30%; the risk is highest in patients who undergo concurrent chemoradiation [40]. Ganly et al. [42] described that initial treatment with CCRT was the only significant predictor of local complications on multivariate analysis. Moreover, it appears that the severity of fistula increases in patients who underwent preoperative radiotherapy *vs.* those who did not [43]. Another factor is extent of surgery [18 41 44]. Extensive resections and reconstructions were performed after chemoradiation due to a larger extent of the tumour, resulting in more compromised healing and susceptibility to infections. The most likely explanation for this is related to the nutritional and immune status of patients. These patients have poor nutritional and immune status in the initial months and it may take several months to return to normality [18]. Schwartz et al. [22] reported that a history of weight loss 6 months before surgery, preoperative hypoalbuminaemia and anaemia were independent predictors of wound complications after laryngectomy. Some groups refer that the morbidity of CCRT may be limited by the use of prophylactic gastrostomy tubes as reported by Lee et al. and Barbaro et al. [46 47]. We usually use nasogastric tubes in our patients rather than gastrostomies. In all likelihood, we could improve our results if gastrostomies were used more frequently and earlier.

As mentioned above, pharyngocutaneous fistula remains a troublesome complication following salvage laryngectomy. Both length of hospital stay and time until oral diet initiation are markedly prolonged for these patients. The recent study of Patel et al. showed that the use of either a pectoralis myofascial onlay flap or a fasciocutaneous free flap interposed into the pharyngeal defect resulted in a decreased incidence of fistula formation. These patients might also suffer from pharyngocutaneous fistulas, but the healing period is shorter [41]. Simon et al. performed a retrospective study on 21 patients treated previously with chemo/radiotherapy, and concluded that surgical interventions for salvage, palliation, or functional improvement can be safely performed once vascularised grafts are used [48]. However, studies on the incidence of major peri-and postoperative complications after procedures use vascularised tissue transfer still show highly variable rates that range between 10 and 66% (for doubly irradiated patients). There is still debate whether or not flaps help to decrease the incidence of such fistulas [7 19 49]. There is no doubt that pedicled flaps represent the standard choice for salvage surgery after primary chemoradiation protocols due to poor general conditions, advanced stage of disease and low life expectancy [50]. Moreover, microvascular anastomosis is less favourable in an anatomical site previously subjected to surgery or radiation therapy [51]. Deganello et al. reported that the use of alternative non-microvascular techniques in high-risk patients is functionally and oncologically sound, and can even lead to cost savings [52]. This is particularly important in elderly patients and in those affected by severe medical comorbidities in which the extended surgical time and stress of free flap reconstruction are contraindicated [53]. In our series, we performed 5 salvage surgeries with pectoralis major myocutaneal flaps, and 7 of our patients suffering from a pharyngostoma required a pedicled flap for closure. Nowadays, we always associate a pectoralis major flap in all salvage surgeries after any type of previous treatment with radiotherapy in order to prevent fistula complication.

Our study shows a 5-year overall survival from diagnosis and overall survival after salvage surgery of 44.20 and 37.90% respectively, which are similar to other studies [6 54]. It is interesting that the specific survival after salvage surgery (45.70%) is higher than overall survival. This might be explained by the fact that these patients usually suffer from other concomitant diseases which may compromise survival. We found no significant difference regarding resection margins for salvage surgery. A British study of 352 patients with recurrent head and neck squamous cell carcinoma who underwent salvage surgery found no significance difference in 5-year survival between patients with positive margins and those with negative margins [55]. As explained by those authors, a negative resection margin does not guarantee residual tumour is not present within unresected tissue. Although margins are always carefully studied, they form a three-dimensional structure and hence it is possible that tumour cells may be missed by the pathologist as a result of sampling errors during preparation of specimens. Recurrent disease, moreover, differs from primary malignancy in that it is typically infiltrative and multifocal, and spreads broadly in microscopic deposits that may be outside the initial radiated or operative field [56]. These small foci are undetectable on imaging or clinical exam, but can lead to treatment failures or geographic radiotherapy misses. However, there are some studies in which resections margins did have a significant impact on survival [19 30].

The most important limitation of our study is that it is retrospective. The major criticism of retrospective studies is that the data collected were not originally designed for a research application. Therefore, some factors responsible for the treatment outcomes might be omitted in the analysis, thereby contributing to bias [24]. We encourage further prospective studies to validate the available data from this and previous investigations.

Conclusions

Despite the severe complications of salvage surgery, it remains the best option to treat recurrences of advanced head and neck squamous cell carcinoma after organ preservation protocols. Pharyngocutaneous fistula remains the main complication after surgery, but the use of either locoregional or free flaps seems to reduce its frequency and severity. The final decision for treatment of pharyngolaryngeal recurrences depends on the experience acquired by the medical group in charge of each case. Therefore, further studies are required to define standard protocols to provide the best option treatment. New modalities of treatment such as intensity-modulated radiation therapy may be included to improve the results of salvage surgery.

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HEAD AND NECK

Pectoralis major myocutaneous flap for head and neck reconstruction: risk factors for fistula formation

Lembo miocutaneo di muscolo grande pettorale per le ricostruzioni del distretto testa-collo: fattori di rischio per la formazione delle fistole

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SUMMARY

The pectoralis major myocutaneous flap (PMMF) is a safe and versatile flap used widely for head and neck cancer reconstructions, but one of the major and most feared complications is oro- or pharyngocutaneous fistula. Herein, we attempt to establish risk factors for fistula formation in reconstructions of mucosal defects in the head and neck using PMMF through retrospective analysis of PMMF performed during 3 years at a single institution, with a total of 84 procedures. There were 69 men and 15 women, with a mean age of 59.5 years. There were 15 cases of partial flap loss, two total flap losses and 31 fistulas. The independent risk factors for fistula formation were preoperative serum hemoglobin < 13 g/dl, preoperative serum albumin < 3.4 g/dl and hypopharynx reconstruction. The PMMF is still a very useful flap and this is the first multivariate analysis analysing risk factors for fistula formation. These findings are helpful in selecting patients with elevated risk of fistula formation, and therefore preventive measures can be undertaken to avoid potentially serious complications.

KEY WORDS: Head and neck Neoplasms • Reconstructive surgical procedures • Pectoralis muscle • Fistula

RIASSUNTO

Il lembo miocutaneo di muscolo grande pettorale (PMMF) è sicuro e viene ampiamente utilizzato nella chirurgia ricostruttiva dei tumori del distretto testa-collo, nonostante la principale e più temuta complicanza sia la formazione di fistole oro e faringocutanee. Il presente studio ha come obiettivo quello di stabilire i fattori di rischio per la formazione di fistole nella ricostruzione dei difetti della testa e del collo mediante PMMF attraverso un'analisi retrospettiva delle ricostruzioni eseguite in 3 anni in un singolo centro. Sono entrati a far parte dello studio 84 pazienti, 69 uomini e 15 donne, con una età media di 59,5 anni. Complessivamente si sono verificati 15 casi di parziale perdita di sostanza, 2 perdite totali di lembo e 31 fistole. I fattori di rischio indipendenti per la formazione di fistole sono stati: Emoglobinemia preoperatoria < 13 g/dl; albumina sierica preoperatoria < 3.4 g/dl; ricostruzioni dell'ipofaringe. Il PMMF è versatile e molto utile. Questo studio rappresenta la prima analisi multivariata che valuta i fattori di rischio correlati alla formazione di fistole. I risultati derivanti da questo studio potrebbero essere utili per selezionare i pazienti con rischio elevato di formazione di fistole e quindi prendere preventivamente misure atte ad evitare gravi complicanze.

PAROLE CHIAVE: *Neoplasmi della testa e del collo • Procedure di ricostruzione chirurgica • Muscoli pettorali • Fistula*

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Introduction

Since it was first described in 1979 by Stephen Aryan, the pectoralis major myocutaneous flap (PMMF) has been considered the workhorse for head and neck reconstructions. Many qualities, such as its proximity to the head and neck region, the reliability of its pedicle and the short learning curve, have contributed to the widespread use of this technique and its overall good success rates [1-4].

Complication rates vary in the literature, ranging from 13 to 65%. However, there is no consensus on the definition of complications, and there is a great variety of scenarios, ranging from minor to major complications, with very different implications on surgical outcome [4-12].

When the PMMF is used to reconstruct mucosal defects, one of the most feared complications is dehiscence of the suture, which can lead to salivary leakage and the formation of orocutaneous or pharyngocutaneous fistula. It may lead to prolonged hospital stay, infection, wound dehiscence and vascular rupture, with a marked increase in morbidity.

Many authors describe risk factors associated with fistula formation, such as nutrition status, comorbidities, extent of the resection and prior irradiation [4-14]. However, there is no description of risk analysis for fistulas in cases in which the PMMF was used.

The objective of this study is to analyse variables associated with postoperative fistula formation in head and neck resections in which the PMMF was used for reconstruction of a mucosal defect, as well as establish independent risk factors for fistula formation.

Materials and methods

We retrospectively reviewed the records of all head and neck resections in which a PMMF was used for mucosal reconstruction in a single institution (Instituto do Câncer do Estado de São Paulo - ICESP) from January 2010 to December 2012, for a total of 84 surgeries.

The PMMF was harvested with the usual technique described previously [2 8 15]. The dermis and subcutaneous tissue of the flap were sutured to the underlying muscle with interrupted stitches to avoid any displacement of the skin from the muscle during flap harvesting. An additional skin incision from the superior border of the skin paddle to the midclavicular point was made, and fasciocutaneous flaps were elevated to expose the entire pectoralis major muscle. The PMMF was based only on the pectoralis branch of the thoracoacromial artery, which was dissected until its origin, near the midclavicular point. The pedicle was dissected and the pectoralis major muscle was cut as much as needed to obtain the necessary reach of the flap in each case, although the muscle adjacent to the pedicle was always preserved. After this step, the flap was rotated to the head and neck over the clavicle [16]. The PMMF was inserted into the oral cavity or oropharynx underneath the mandible when this was preserved and through the neck in cases of mandibulectomy. The skin portion of the PMMF was sutured to mucosal borders and the underlying pectoralis muscle was used as replacement for the resected musculature. When employed on hypopharynx defects, the PMMF was not folded as a tube; it was fixed at the vertebral fascia forming a reconstruction of 270° of the hypopharynx. No pharyngeal devices, such as the Montgomery salivary tube, were used on circumferential repairs of the hypopharynx and no variants to the fasciocutaneos flaps were performed.

Demographic data (sex and age), primary location of the tumour, staging based on TNM classification, region reconstructed with the PMMF, previous treatments (radiotherapy, surgery or both) were recorded. Additionally, variables associated with nutritional status were analysed in cases in which the data was available, such as body mass index (BMI), percentage of weight loss from the normal weight to weight when admitted for surgery, preoperative serum haemoglobin and preoperative serum albumin.

The presence of orocutaneous or pharyngocutaneous fistula was established when there was evident salivary leakage through the neck or drainage. Also, an active test for fistula was performed with administration of methylene blue dye orally at the fifth to seventh post-operative day, and any leakage through the neck or drainage was recorded as fistula. All the cases in which fistula was diagnosed were recorded and analysed for variables significantly associated with this outcome. We also conducted multivariate analysis to find independent risk factors for fistula formation.

The SPSS program version 17.0 (SPSS Inc; IL, USA) was used for statistical analysis. Distributions were defined as nonparametric by the Kolmogorov-Smirnov test. The values obtained from the study of each continuous variable were organised and described using means and standard deviation, and relative and absolute frequencies were used for categorised variables. In the comparison of frequency of the phenomenon between groups of categorised variables, Fischer's exact test or chi-squared test were used. Comparison between independent continuous variables was performed using Mann-Whitney's test. The variables that presented $p < 0.2$ in the univariate analyses were eligible for multivariate analysis in which the *odds ratio* and confidence interval were calculated using logistic regression. The cutoff values determined for the risk analyses of serum albumin, serum hemoglobin, percentage of weight loss and BMI were obtained using the Receiving Operator Characteristics curve. In all analyses, we considered a chance of 5% or less to commit a type I or α error ($p \leq 0.05$).

Results

The study group included 69 men and 15 women with a mean age of 59.5 ± 9.5 years. The most common primary tumour location was the oral cavity, followed by the oropharynx, while the least common was the hypopharynx. The majority of cases had advanced stage (III or IV). Free surgical margins were acquired in 75 patients (89.3%). Eighteen patients had been previously treated with radiotherapy and nine patients had been previously submitted to surgery. Ninety-one percent of patients were smokers (Table I).

Regarding complications, there were 15 cases of partial flap loss and two total flap losses. The two total flap losses were due to technical fault in one case and secondary to venous thrombosis of the pedicle in the other. Thirty-one patients developed fistula. In these cases, 12 (38.7%) also presented flap ischaemia, 14 (45.2%) partial flap losses, 22 (71.0%) dehiscence, 13 (41.9%) local infection and 15 (48.4%) were submitted to another surgery. Hospital stay varied from 5 to 81 days, with a mean of 14.6 days. Comparing patients that developed fistula with those without fistula, the median hospital stay was 7 days (range 4-29

Table I. Clinicopathological data of patients in the study.

Variable	(n = 84)
Gender*	
Male	69 (82.1)
Female	15 (17.9)
Reconstructed region*	
Oral cavity	60 (71.4)
Oropharynx	14 (16.7)
Hypopharynx	10 (11.9)
Stage*	
I-II	9 (10.7)
III-IV	75 (89.3)
Age**	59.5 ± 9.5
Prior radiotherapy*	18 (21.4)
Prior surgery*	9 (10.7)
Body mass index**	21.6 ± 5 kg/m^2
Serum haemoglobin**	12.95 ± 1.8 g/dl
Serum albumin**	3.66 ± 0.8 g/dl
Weight loss (%)**	10.9 ± 9.5

** Number (percentage); ** Average ± standard deviation.*

Table II. Factors associated with oro- or pharyngocutaneous fistula.

Variable	Number of fistulas/total (%)	p
Gender		0.275
Male	27/69 (34.2)	
Female	4/15 (26.7)	
Age		0.275
> 70 years	4/15 (26.7)	
≤ 70 years	27/69 (39.1)	
Reconstructed region		0.011
Oral cavity	19/60 (31.7)	
Oropharynx	4/14 (28.6)	
Hypopharynx	8/10 (80)	
Stage		0.281
I-II	2/9 (22.2)	
III-IV	29/75 (38.6)	
Prior surgery		0.281
Yes	2/9 (22.2)	
No	29/75 (38.6)	
Prior radiotherapy		0.455
Yes	8/18 (44.4)	
No	23/66 (34.8)	
BMI		0.928
< 20 kg/m^2	13/35 (37.1)	
≥ 20 kg/m^2	17/47 (36.1)	
Weight loss		0.264
> 10%	9/33 (27.3)	
≤ 10%	17/43 (39.5)	
Haemoglobin		0.007
< 13 g/dl	19/36 (52.8)	
≥13 g/dl	11/46 (23.9)	
Albumin		0.006
< 3.4 g/dl	15/26 (57.7)	
≥ 3.4 g/dl	11/44 (25)	

days) and 16 days (range 6-81 days) ($p < 0.0001$, Mann-Whitney's test), respectively.

In univariate analysis of factors associated with fistula formation, we identified preoperative serum haemoglobin < 13 g/dl, preoperative serum albumin < 3.4 g/dl and use of the flap for hypopharynx reconstruction as having a positive association with postoperative fistula ($p = 0.007$; $p = 0.006$ and $p = 0.011$ respectively). Sex, age, stage, prior treatment, weight loss, or BMI did not have a statistically significant association ($p > 0.05$) (Table II).

When multivariate analysis was performed, we confirmed the findings of preoperative serum haemoglobin, preoperative serum albumin and use of the flap for hypopharynx reconstruction as independent risk factors for fistula formation (Table III).

Discussion

Many authors defend that considering the current panorama of head and neck reconstructions, the new workhorse is the free flap. Despite this fact, PMMF remains an important tool for complex reconstruction of head and neck defects [17-19], especially in locations where free flaps are not routinely available, such as Brazil.

At Instituto do Câncer do Estado de São Paulo there is a microvascular reconstruction team, but because of the large volume of oncologic head and neck resections it is not possible to use microvascular flaps in all patients. Therefore, priority is given to the most complex reconstructions (e.g. mandible resections involving the chin or craniofacial resections), and many pedicled flaps are still performed.

As another option, in the last decade there have been reports on the use of the internal mammary artery perforator flap (IMAP) for head and neck reconstructions. IMAP has been shown to be a reliable pedicled flap with a wide rotation arc that can be used for cutaneous, pharyngeal and tracheostomal reconstruction. Therefore, it is becoming another important tool for the head and neck surgeon [20-22].

It is common knowledge that the PMMF is a reliable and versatile flap for head and neck reconstructions. When microvascular reconstruction is not available it is the most important reconstruction tool, and it is also very useful in elderly patients or in those with poor clinical conditions. Deganello et al. [18] showed that using alternative non-microvascular techniques, in high-risk patients, the PMMF is functionally and oncologically sound, and can even produce cost savings.

Even if it is one of the most commonly used flaps by the head and neck surgeons, there is still much controversy about which factors lead to complications and therefore worse outcomes during the use of the PMMF [4-14].

Amongst these complications are orocutaneous and pharyngocutaneous fistulas, which we chose to focus on in this report because of their high impact on morbidity.

The incidence of fistula is also quite variable, with values ranging from 10.7% to 45% [3 4 7 9 12 23]. We report a slightly

Table III. Multivariable analysis of risk factors associated with oro- or pharyngocutaneous fistula.

Variable	OR	95% CI	p (Logistic regression)
Hypopharynx	17.0	1.4-202.3	0.025
Haemoglobin < 13 g/dl	5.2	1.5-17.4	0.008
Albumin < 3.4 g/dl	5.5	1.6-18.9	0.007

higher rate than most papers (36%). This may be attributed to the fact that we analysed only mucosal reconstructions, while other authors included skin reconstructions, and the fact that at our institution we perform an active test for fistula with the ingestion of methylene blue dye. Therefore, even minimal salivary leakage is diagnosed.

Most studies on risk factors for complications of PMMF have not independently analysed risk factors for fistula formation. You et al. analysed 120 PMMFs and found that preoperative albumin levels below 3.8 g/dl were associated with increased fistula formation, similar to our findings, but multivariate analysis was not performed, which limits the value of the finding [12].

In the 31 cases of fistula presented, some were associated with infection, partial flap losses, ischaemia and suture dehiscence. However, these findings must be cautiously considered because many cases had multiple complications and it was not possible to establish which started the process and led to the others.

The present paper also documents the association of fistula with preoperative serum haemoglobin levels below 13.0 g/dl, which to our knowledge there are no previous reports of this finding.

It is widely believed that nutritional, haemoglobin and albumin status may influence the outcome of anastomosis, and there are some reports of this association in colorectal surgery [24 25], although few such reports in head and neck surgery, especially when flaps are used.

There has been some research on risk factors for fistula after total laryngectomies and some reports that associate it with abnormally low albumin and haemoglobin, but these studies are not specifically on PMMFs [26 27].

The most significant risk factor in our analysis was the use of the PMMF for hypopharyngeal reconstruction, with a 17-fold increase in the risk of fistula formation. Some authors showed that tumours primarily from the hypopharynx and large hypopharynx resections had a higher rate of fistula formation even without the use of PMMF, an indication of the difficulty in reconstructions of this region [27-29]. Moreover, Qureshi et al. reported on risk factors associated with fistula after total laryngectomy, and PMMF was significantly associated with fistula formation [30].

To our knowledge this is the first report to perform multivariate analysis for risk factors of fistula on head and neck reconstructions using the PMMF. Our findings of preoperative serum haemoglobin of < 13.0 g/dl, preoperative serum albumin < 3.4 g/dl and hypopharynx reconstruction as independent risk factors for fistula formation are of great value. Even though the cutoff levels for albumin and haemoglobin we found are high, there is great importance in the finding that values below normal are already risk factors for fistula, and not only much lower levels as might be expected. Based on these results, the surgeon can identify patients with an increased risk of fistula prior to surgery and focus on actions that may lower the risk, such as nutritional supplementation, or changing the surgical approach, such as preserving the Bakanjiam flap in hypopharynx reconstructions.

Conclusion

The pectoralis major myocutaneous flap is useful for head and neck reconstructions. Independent risk factors for orocutaneous or pharyngocutaneous fistula formation are serum albumin < 3.4 g/dl, serum haemoglobin < 13.0 g/dl and use of the flap for hypopharynx reconstruction.

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HEAD AND NECK

Versatility of the supraclavicular pedicle flap in head and neck reconstruction

Versatilità del lembo peduncolato sovraclaveare nelle ricostruzioni del distretto testa e collo

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SUMMARY

Head and neck surgery has witnessed an increase in microvascular reconstructive procedures with free flaps over the last 20 years as they offer efficient functional recovery. Nevertheless, under certain circumstances they may be contraindicated or cannot be used. We present the use of supraclavicular pedicled flap in three patients with different recipient sites. All patients had acceptable functional and aesthetic outcomes. Donor-site morbidity was satisfactory. Supraclavicular pedicled flap is not only an alternative to free flap reconstruction, but also a first-choice option in head and neck reconstructive surgery.

KEY WORDS: Supraclavicular • Head and neck surgery • Pedicled flap

RIASSUNTO

Nella chirurgia cervico-facciale si è assistito ad un aumento delle procedure ricostruttive con lembi liberi nel corso degli ultimi venti anni, in quanto offrono un efficiente recupero funzionale. Tuttavia, in alcune circostanze possono essere controindicati o non possono essere utilizzati. Vi presentiamo l'uso del lembo peduncolato sovraclaveare in tre pazienti con differente sito ricevente. Tutti i pazienti hanno avuto risultati funzionali ed estetici soddisfacenti. La morbilità del sito donatore è stata trascurabile. Il lembo sovraclaveare potrebbe non solo essere un'alternativa alla ricostruzione con lembi liberi, ma anche un'opzione di prima scelta nella chirurgia ricostruttiva cervico facciale.

PAROLE CHIAVE: *Sopraclaveare • Chirurgia testa e collo • Lembi peduncolati*

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Introduction

Head and neck surgery has witnessed an increase in microvascular reconstructive procedures with free flaps over the last 20 years as they offer efficient functional recovery and better quality of life. However, not all patients are eligible for microvascular reconstructive surgery, depending on previous treatments and comorbidities. In such cases, locoregional pedicle flaps offer an additional opportunity for reconstruction in patients with a high risk of failure of microvascular procedures. The supraclavicular flap is a fasciocutaneous pedicled flap first described by Lamberty in 1979 [1]; it is easy to harvest and has a wide arch of rotation and a good colour match. In addition, donor site morbidity is low due to the natural redundancy of skin in the supraclavicular region. We present our experience with supraclavicular pedicled flap in three patients with different recipient sites.

Case series

Case 1

A 74-year-old woman was referred to our department for a painful mass in the left parotid region. She had previously undergone total parotidectomy with sacrifice of the temporo-facial branch of the seventh cranial nerve and left selective neck dissection followed by adjuvant radiotherapy for an undifferentiated carcinoma of the right parotid gland. On examination, the patient presented multiple nodules in the right parotid and submandibular areas, which were hard and fixed. The skin above the lesions did not present ulcerations, but was hyperaemic. PET-CT showed intense uptake in the left subretromandibular region. FNAB confirmed the recurrence of the undifferentiated parotid carcinoma. We performed surgical resection of the left parotid region, exposing the

masseter muscle and the mandibular periostium, with sacrifice of the left facial nerve and the overlying skin. In choosing reconstructive options, we rejected the use of free flaps due to the age of the patient and evidence of bilateral carotid stenosis. The choice fell on a cutaneous flap pedicled on the supraclavicular artery due to the anatomical proximity and the ability to adapt it to the recipient site. The skin defect in the parotid region was therefore closed with a left supraclavicular pedicle cutaneous flap. In order to improve aesthetic outcomes, we proceeded to flap revision under local anaesthesia 20 days after surgery. (Fig. 1)

Case 2

A 52-year-old woman with a history of tongue squamous cell carcinoma underwent total body PET-CT evaluation for worsening dysphagia, which demonstrated cervical pathological uptake at the level of C6. She had undergone left hemiglossectomy and left radical neck dissection 20 years before, followed by chemotherapy and radiotherapy for a squamous cell carcinoma of the left side of the tongue. The tongue was reconstructed using a radial forearm free flap. Direct microlaryngoscopic examination under general anaesthesia revealed an ulcerated lesion of the posterior face of the right arytenoid cartilage. Histo-

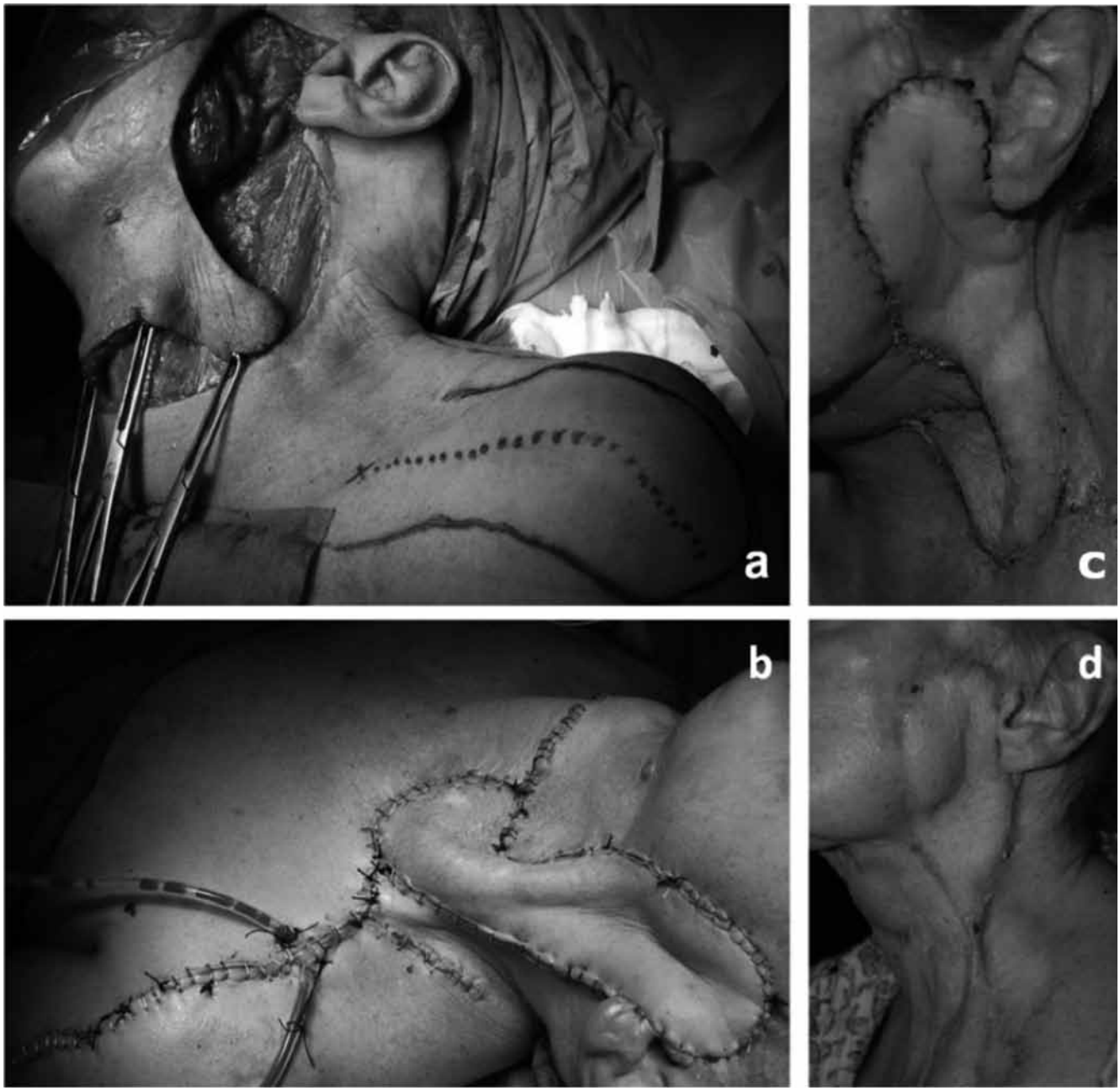

Fig. 1. a) Left revision parotidectomy and Doppler mapping of the SCF artery; b) supraclavicular flap harvesting and suturing to reconstruct the facial skin defect; c) post-operative result at 15 days; d) aesthetic result after 6 months.

logical examination demonstrated G1 squamous cell carcinoma. We performed total pharyngo-laryngectomy with right selective neck dissection with reconstruction of the pharynx. Free flap reconstruction was not recommended because of previous cervical radiotherapy and absence of the left internal jugular vein after past neck dissection. Moreover, reconstruction with a gastric pull-up could not be performed because of unfavourable anatomical conditions. We decided to reconstruct the pharynx with a cutaneous tubulised supraclavicular pedicle flap that was attached to the distal and proximal pharyngeal residuals. A Montgomery salivary stent and a nasogastric tube were also positioned in the neo-pharynx. On post-operative day 15 the patient resumed oral feeding. Definitive histological examination indicated a G1 squamous cell carcinoma pT2pN0.

Case 3

A 82-year-old woman with a painful ulcerated lesion involving the posterior two thirds of the right lingual body. She also suffered from type 2 diabetes, arterial hypertension and ischaemic heart disease. Biopsy revealed a G1 squamous cell carcinoma. MRI with contrast of the oral cavity and neck showed the presence of a lesion on the right side of the lingual body, which did not cross the median raphe, but infiltrated the ipsilateral sublingual gland and genioglossus muscle. No cervical adenopathies were detected. Chest CT with contrast completed the staging without evidence of metastases. The patient underwent conservative trans-mandibular right hemiglossectomy, tracheostomy and right selective neck dissection. Considering the patient's age and comorbidities, we decided to reconstruct the tongue using a cutaneous supraclavicular pedicle flap, which permits reduction of surgery time. A pedicled myocutaneous flap was not used because of its excessive thickness. Histological examination indicated a G1 squamous cell carcinoma pT4apN0. (Fig. 2)

Discussion

Free flaps allow reconstruction of different anatomic structures in the head and neck region with good morphological results and satisfying three-dimensional functional unit restoration. Their success rate is nearly 95% [2], and they represent the gold standard in head and neck reconstruction. In particular, radial forearm free flap (RFFF) [3] and anterolateral thigh (ALT) free flap are widely used for reconstruction of oral cavity, oropharynx, hypopharynx and cervical oesophagus defects, while fibular flap is used when mandibular reconstruction is necessary [4 5]. Free fasciocutaneous flaps require microsurgical expertise, availability of recipient vessels, postoperative intensive care unit monitoring and, most importantly, a patient who can tolerate major surgery [6 7]. Moreover, previous radical neck dissection, history of neck radiotherapy and comorbidities such as ischaemic heart disease can make free flap reconstruction challenging, and in these patients the benefit of a pedicle flap should not be overlooked [8 9]. Among pedicle flaps, we underline the importance of the supraclavicular flap (SCF), a fasciocutaneous flap used extensively by plastic surgeons to resurface the neck and face in patients after severe burn injuries [10]. The history of shoulder flap started in 1842 with Mutter [11], but only in 1979 Lamberty [1] described the axial pattern of the shoulder flap based on the supraclavicular artery. In 1996, Pallua et al. [10 11] identified the vascular pedicle of the SCF, described its angiosomes and demonstrated the versatility of the flap in head and neck reconstruction. Undoubtedly, SCF has several advantages: it is easy and quick to harvest, has excellent skin colour and tissue texture matching the face and the neck, and it has a consistent and wide arc of rotation with a long pedicle, which is well suited for oral, oropharyngeal, and apical facial defects. Use of the SCF eliminates the surgical time required for microvascular anastomosis. This flap requires simple postoperative surveillance and has a very little donor site morbidity.

On the other hand, the main contraindication for SCF harvesting is concomitant radical or functional neck dissection requiring ligation of the vascular pedicle. The surgical technique for SCF is easy to learn and is based on the preservation of the pedicle. The supraclavicular artery is a perforator that arises from the transverse cervical artery in 93% of cases and from the suprascapular artery in 7% of cases [11]. Pallua et al. [10 11] have shown that in any case the origin of the artery is located in a triangle formed by the dorsal edge of the sternocleidomastoid muscle anteriorly, the external jugular vein posteriorly, and the medial part of the clavicle inferiorly. There are two veins draining the flap, one adjacent to the artery drains into the transverse cervical vein, while the second vein drains either into the external jugular vein or the subclavian vein. The flap is raised from a distal to proximal in a plane of dissection deep to the fascia and just superficial to the muscle until the triangular cone, where the supraclavicular artery originates.

Herein, we presented three different sites of reconstruction with SCF: the tongue, hyphopharynx and parotid region, which were well reconstructed without major postoperative complications. All three patients underwent pre-operative Doppler ultrasound to map the course of the supraclavicular artery. This procedure avoids necrosis of the distal portion of the flap as long as the flap elevation does not extend further from the last Doppler ultrasound signal observed for more than 5 cm [7].

Our results are comparable with those of other authors; in particular, Di Benedetto et al. [12] used this flap on the cutaneous and oral lining, considering it as the preferred method for medium to large defects of the cervicofacial area. Chiu et al. [13] also reported several oncologic defect reconstructions with SCF in patients with comorbidities, including obesity, poor nutrition, diabetes and smoking.

This author had one patient (5%) with complete flap necrosis and four with minor recipient site complications that needed only local conservative treatment. Sandu et al. [14] described the use of SCF in 50 patients for complex face, head and neck reconstructions after tumour resection: 44 of the 50 patients had total flap survival with excellent wound healing, four cases, after oral cavity tumour ablation, developed distal tip desquamation and needed only conservative treatment measures and two patients had complete flap necrosis. Granzow et al. [7] compared the outcomes of head and neck reconstructions performed with SCF (18 cases) and free fasciocutaneous flaps (16 cases). Major complications were comparable between the two groups and there were no significant differences. The author concluded that SCF should be considered a first–choice reconstructive option for complex head and neck defects, and the use of free flaps has been replaced with SCF over the past 5 year [7].

Furthermore, SCF does not damage any reconstructive bridge and leaves all other free flap donor sites and recipient vessels intact, allowing for subsequent reconstruction with free flaps transfer if necessary. We started using this flap in high-risk patients with advanced age, advanced tumours, poor nutrition or medical comorbidities, who are not good candidates for potentially prolonged microsurgery. Considering all the advantages of SCF, we think that this flap will continue to play an increasing role in reconstruction of complex defects of the head and neck. We underline the importance of pre-operative Doppler ultrasound of the supraclavicular artery to avoid complications.

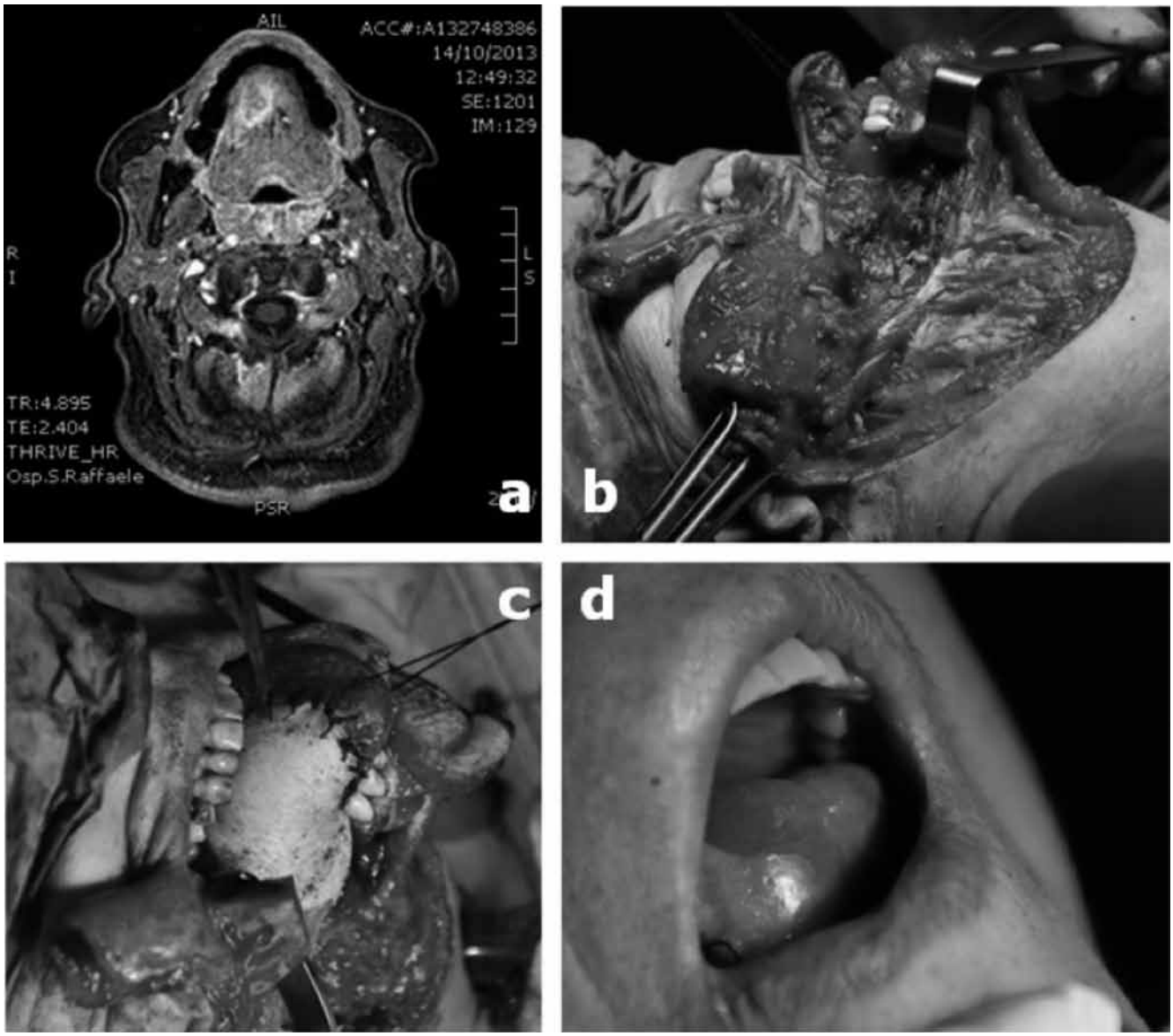

Fig. 2. a) MRI imaging showing the tongue lesion; b) right hemiglossectomy through a trans-mandibular approach; c) reconstruction of the tongue with the supraclavicular flap; d) final outcome.

Conclusions

SCF is not only an alternative to forearm free flaps in high-risk patients who are not good surgical candidates for potentially prolonged microsurgery or had previous radiotherapy, but can also be considered as a first-choice reconstructive option for head and neck defects. Oncological reconstructive teams need to have various options for flap reconstruction in their armamentarium to solve all difficult situations taking into account the overall status of patients. SCF will likely play an increasing role in reconstruction of complex defects of the head and neck.

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Thyroid

Calcitonin measurement in fine-needle aspirate washouts *vs*. cytologic examination for diagnosis of primary or metastatic medullary thyroid carcinoma

Dosaggio della calcitonina nel liquido di lavaggio dell'agoaspirato vs. esame citologico nella diagnosi del carcinoma midollare della tiroide primitivo o metastatico

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SUMMARY

Ultrasound-guided fine-needle aspiration biopsy cytology (FNAB-C) is able to detect approximately 63% of medullary thyroid carcinoma (MTC). The measurement of calcitonin in the needle washout (FNAB-CT) could improve its accuracy. Sixty-two FNAB-C were performed in 38 patients. Serum calcitonin (sCT) was measured before performing FNAB-C. After obtaining a FNAB-C specimen, the needle was washed with 0.5 ml of saline solution to obtain the CT washouts. Receiver operating characteristic (ROC) analysis identified the cut-offs of FNAB-CT and FNAB-CT/sCT. Eighteen MTC were found at final histology. ROC analysis indicated FNAB-CT > 10.4 pg/ml and FNAB-CT/sCT > 1.39 as more accurate cut-off values. Overall accuracy, positive (PPV) and negative predictive values (NPV) were 85%, 100 and 83%, respectively, for FNAB-C, 97%, 100%, 96% for FNAB-CT and 90%, 83% and 93% for FNAB-CT/sCT. The integration of FNAB-C and FNAB-CT resulted in 98% overall accuracy, 100% PPV and 98% NPV; the integration of FNAB-C and FNAB-CT/sCT in 90% overall accuracy, 80% PPV and 95% NPV. One of 2 false negative FNAB-CT and one of 3 false negative FNAB CT/sCT were correctly diagnosed by FNAB-C. Eight of 9 non-diagnostic FNAB-C were correctly classified by FNAB-CT and 7 by FNAB CT/sCT. FNAB-CT should integrate but not replace FNAB-C. FNAB-CT is particularly useful in the presence of non-diagnostic FNAB-C.

KEY WORDS: Medullary thyroid carcinoma • Calcitonin • Lymph node metastases • US-guided fine-needle aspiration biopsy • Cytology

RIASSUNTO

L'esame citologico su agoaspirato ecoguidato con ago sottile (FNAB-C) rappresenta una delle procedure più comuni per la conferma della diagnosi di carcinoma midollare della tiroide (CMT) primitivo e/o metastatico. Tuttavia la sensibilità riportata per questa metodica nella diagnosi del CMT è di circa il 63%. Il dosaggio della calcitonina nel liquido di lavaggio dell'agoaspirato (FNAB-CT) è una metodica recentemente introdotta, proposta al fine di migliorare l'accuratezza diagnostica della citologia convenzionale. Sono stati considerati tutti i pazienti con sospetto CMT primitivo e/o metastatico sottoposti a FNAB-C e FNAB-CT tra Marzo 2012 e Settembre 2013, per i quali era disponibile la conferma istologica. La calcitonina sierica (sCT) è stata dosata prima dell'esecuzione del FNAB-C. Dopo aver prelevato e preparato il campione per l'esame citologico, l'ago è stato lavato con 0,5 ml di soluzione salina per ottenere il dosaggio della CT nel liquido di lavaggio. È stata eseguita un'analisi ROC al fine di identificare i cut-off con più elevata sensibilità ed accuratezza rispettivamente per il FNAB-CT e il rapporto tra FNAB-CT e sCT (FNAB-CT/sCT ratio). L'accuratezza diagnostica dei cut-off stabiliti è stata confrontata con quella del FNAB-C. Sono stati eseguiti 62 FNAB-C in 38 pazienti. L'esame istologico definitivo ha confermato la diagnosi di CMT in 18 lesioni (29,9%). L'analisi ROC ha individuato un valore > 10,4 pg/ml e > 1,39 come cut-off più accurati rispettivamente per FNAB-CT e FNAB-CT/sCT ratio. L'accuratezza, il valore predittivo positivo (VPP) ed il valore predittivo negativo (VPN) sono risultati, rispettivamente, 85%, 100% e 83% per il FNAB-C, 97%, 100% e 96% per il FNAB-CT e 90%, 83% e 93% per FNAB-CT/sCT ratio. L'integrazione di FNAB-C e FNAB-CT ha mostrato una accuratezza pari al 98%, un VPP pari al 100% ed un VPN pari al 98%; l'integrazione di FNAB-C e FNAB-CT/sCT ratio ha mostrato un'accuratezza del 90%, un VPP dell'80% ed un VPN del 95%. Il FNAB-C ha identificato correttamente 1 dei 2 casi risultati falsi negativi al FNAB-CT e 1 dei 3 casi falsi negativi al FNAB-CT/sCT ratio. La procedura del FNAB-CT ha diagnosticato correttamente 8 dei 9 casi non diagnostici al FNAB-C, mentre il FNAB-CT/sCT ratio ne ha individuati correttamente 7. Nella nostra esperienza il FNAB-CT è risultato più accurato del FNAB-CT/sCT ratio. Nella diagnosi del CMT primitivo o metastatico il FNAB-CT può integrare ma non sostituire il FNAB-C ed è particolarmente utile nei casi non diagnostici alla citologia convenzionale.

PAROLE CHIAVE: *Carcinoma midollare della tiroide • Calcitonina • Metastasi linfonodali • Agoaspirato ecoguidato • Esame citologico*

Introduction

Serum calcitonin (sCT) is a key marker in diagnosing medullary thyroid carcinoma (MTC) [1-5] and has been demonstrated to be highly sensitive for differential diagnosis, prognostic assessment, follow-up, and evaluation of treatment response in MTC [3 5 6]. Routine measurement of sCT has been investigated as a screening method for diagnosis of MTC in patients with thyroid nodules [6 7] with the reported advantages of early diagnosis [6 8 9] and improved 10 year outcome of MTC patients diagnosed with sCT screening [8 9]. However, false-positive rates for basal sCT testing remain high and positive predictive value (PPV) low, even with the most recent ultrasensitive assays [6]. As a consequence, the routine sCT measurement in patients with thyroid nodules is still debated and the American Thyroid Association (ATA) has declined to make any recommendation for or against sCT screening [2].

Recently, several European consensus groups recommended sCt measurement routinely [5] or suggested its use in specific conditions (e.g. subjects with family history of MTC, cytology suggestive of MTC or undergoing surgery for goitre) [4].

Since sCT is not helpful in localising primary tumours in the thyroid gland and/or its neck recurrences/metastases in thyroidectomised patients, the localisation of disease should start with careful neck ultrasound examination [2 3 10].

Although MTC can be diagnosed by ultrasound-guided fine-needle aspiration biopsy cytology (FNAB-C) based on typical pathological features [7], the sensitivity of FNAB-C has been demonstrated to be 45-63%, indicating that misdiagnosis often occurs with this approach [11]. Recently, several published studies have demonstrated that high CT concentrations were present in the wash-out of the needle used for FNAB-C both in suspicious lymph nodes and in thyroid nodules histologically confirmed to be metastases or primary MTCs, respectively [2 7 12-15].

Further studies [16-18] showed that the measurement of CT in the needle washout (FNAB-CT) had high sensitivity and specificity in diagnosis of MTC. A major concern in this approach is the cut-off to be used to define the positive value of CT in the washout fluid. This problem is of course strictly dependent on the sCT level that can contaminate the needle and lead to misinterpretation of results. Moreover, there is still no univocal interpretation of the role of FNAB-CT and its correlation with sCT or with FNAB-C. We aimed to prospectively evaluate the accuracy of FNAB-CT or FNAB-CT/sCT ratio, alone or integrated with the results of FNAB-C, in diagnosis of primary or metastatic medullary thyroid carcinoma.

Materials and methods

All patients with suspicious primary and/or recurrent/metastatic MTC who underwent FNAB-C and FNAB-CT before initial surgery or during post-surgery follow-up between March 2012 and September 2013 were considered. Only patients in whom histological evaluation was obtained were included in this study.

All patients underwent to sCT measurement before FNAB-C. After obtaining the cytological specimen by ultrasound (US) guided FNAB, the CT washout was performed.

Demographic, laboratory, clinical, operative, pathologic and follow-up data were prospectively registered for all patients.

Study endpoints

The primary endpoint of the study was to evaluate the accuracy of FNAB-CT and FNAB-CT/sCT ratio in diagnosis of MTC. The secondary endpoint of the study was to evaluate the validity of the integration of FNAB-C with FNAB-CT and FNAB-CT/sCT ratio.

US and US-FNAB

Ultrasonography was performed using a Toshiba Aplio 400 ultrasound instrument (©Toshiba Medical Systems Corporation, Tochigi-ken, JAPAN). A complete neck ultrasonographic mapping, including the thyroid, central and lateral neck node compartments and level of the thyroidectomy scar in thyroidectomised patients, with a high-frequency (10-12 MHz) probe was performed in all patients. According to the available guidelines [1-5], the ultrasound thyroid/neck mass features considered suspicious were: solid aspect, hypoechogenicity, microcalcifications, irregular margins or absent halo sign, intranodular vascularisation and shape (taller than wide) [1-5 19]. The ultrasound lymph nodes features considered suspicious were: loss of echogenic hilum, hyperechogenicity, cystic changes, calcification, abnormal vascularity, heterogeneous echogenicity and a round shape (longitudinal/transverse diameter ratio < 1.5) [1-5 20].

All FNAB were performed under US guidance, using a 21-23 gauge needle. Each lesion was aspirated at least twice. Immediately after the first aspiration, after obtaining a FNAB-C specimen, the needle was washed with 0.5 ml of saline solution and the washout was submitted for CT measurement. All US examinations and US-FNAB were performed by an experienced endocrine surgeon or by a resident under supervision.

Receiver operating characteristic (ROC) analysis was performed to determine the absolute cut-off levels of CT in the washing fluid and the cut-off ratio between FNAB-CT and sCT with the highest sensitivity and accuracy. Diagnostic accuracies of the established cut-offs were compared with that of FNAB-C.

Cytological analysis

The cytologic specimen was prepared using a liquid-

based cytology technique based on a two-step procedure: I) fixation of the material in a methanol-based solution and II) automated processing of the material to obtain a thin layer of cells with a computer-assisted device. The aspirated material is fixed with the haemolytic and preservative methanol-based solution Cytolyt™ (Cytyc Co.) after rinsing the needle in this solution. The cells were spun and the sediment was transferred in the Preservcyt™ (Cytyc Co.) solution to be processed with the ThinPrep 2000™ automated processor. The resulting slide was fixed in 95% ethanol and stained with Papanicolaou, while the remaining material was stored in the Preservcyt™ solution to be used for eventual additional investigations [21]. For each case a thin-layer cytology slide and a series of conventional smears were made either with two different needle passes or with the split-sample technique. All conventional smears are fixed in 95% ethanol and stained with Papanicolaou [22].

The interpretation of FNAB-C was performed by dedicated cytopathologists in thyroid cytology. For the purpose of the study, the results of cytology were classified in two diagnostic categories: negative in case of inadequate/non-diagnostic samples and benign cytology; positive in case of samples with typical features for MTC or MTC metastases.

CT testing

CT was measured with a chemiluminescence immunoassay (CLIA) using a Liaison XL instrument (DiaSorin) with a functional sensitivity of 3 pg/ml. Functional sensitivity is the concentration measurable with a coefficient of variation, CV < 20% interpoled on the imprecision profile built from different sera, at different levels of CT concentration, assayed periodically in a defined period of time. The use of highly sensitive assay has enabled the low cut-off selection.

Definitions

True positive (TP) was defined as the correct prediction of primary and/or recurrent/metastatic MTC; true negative (TN), the correct prediction of no disease; false positive (FP), the incorrect prediction of disease with histological examination negative for MTC; and false negative (FN), the incorrect prediction of no disease with postoperative histological evidence of MTC.

Statistical analysis

Statistical analysis was performed using a commercially available statistic software package (SPSS 15.0 for Windows® - SPSS Inc., Chicago, IL, USA). The chi-squared test was used for categorical variables, while a Student's t-test was used for continuous variables. A p value < 0.05 was considered significant.

The diagnostic performance, including sensitivity, specificity, accuracy, PPV, and negative predictive value (NPV), was evaluated. Sensitivity [TP/(TP+FN)], specificity [TN/(TN+FP)], positive predictive value (PPV) [TP/(TP+FP)], negative predictive value (NPV) [TN/(TN+FN)], and overall accuracy [(TP+TN)/(TP+TN+FP+FN)] of FNAB-C, FNAB-CT, FNAB-CT/sCT ratio and of the integration of FNAB-C respectively with FNAB-CT and FNAB-CT/sCT ratio were calculated. Receiver operating characteristic (ROC) analysis was performed to determine the absolute cut-off levels of CT in the washing fluid and the cut-off ratio between FNAB-CT and sCT with the highest sensitivity and accuracy. Diagnostic accuracies of the established cut-offs were compared with that of FNAB-C.

Results

A series of 38 patients with suspicious primary and/or recurrent/metastatic MTC were included. There were 22 females and 16 males, with a mean age of 54.78 ± 15.01 years (range 17-90). FNAB-C, FNAB-CT and FNAB-CT/sCT ratio was performed on 62 thyroid/neck masses or neck lymph nodes. Overall, 20 patients (32%) were evaluated during post-surgical follow-up after primary surgery for MTC.

The mean value of sCT in all patients was 217.48 ± 599.11 pg/ml (range: 3.00-3110.00). The mean lesion size was 13.98 ± 8.22 mm (range: 3.9-30.9) and 14.05 ± 7.99 mm (range: 6-42.3), respectively, for thyroid/neck masses and neck lymph nodes.

Final histological examination confirmed a diagnosis of MTC in 18 lesions in 15 patients. FNAB-C was positive in 9 cases (14.5%) and negative in the remaining 53 cases (85.5%) (Table I).

ROC curve analysis for FNAB-CT showed an area under the curve (AUC) = 99% (p < 0.0001); on the basis of this curve, the more accurate FNAB-CT cut-off was 10.4 pg/ml leading to a sensitivity of 89% and a specificity of 100% (Fig. 1). ROC curve analysis for FNAB-CT/sCT ratio showed an AUC = 90% (p < 0.0001); on the basis of this curve, the more accurate FNAB-CT cut-off was 1.39 leading to a sensitivity of 83% and a specificity of 93% (Fig. 2).

According to this cut-off, FNAB-CT results were considered positive in 16 cases (25.8%) and negative in 46 cases (74.2%). Similarly, the FNAB-CT/sCT ratio results were considered positive in 15 cases (24.1%) and negative in 41 cases (66.1%) (Table I).

The mean value of FNAB-CT in cases with histological-proven MTC was 1085.19 ± 903.96 pg/ml (range 6.98-2000), which was significantly higher than in non-MTC cases (3.96 ± 1.76 pg/ml, range: 1.64-10.40) (p < 0.0001). FNAB-C correctly identified 9 cases with MTC (TP results) and 44 cases without (TN results). FN results were observed in 9 cases, but no FP results were observed. FNAB-C had a sensitivity of 50%, a specificity of 100%,

Table I. Results of FNAB-C*, FNAB-CT†, FNAB-CT†/sCT‡ ratio, and integration of FNAB-C* with FNAB-CT† and FNAB-CT†/sCT‡ ratio compared with histology.

	Positive for MTC¶ (N)	Negative for MTC¶ (N)
FNAB-C*	9	53
FNAB-CT†	16	46
FNAB-CT†/sCT‡ ratio	15	41
FNAB-C* + FNAB-CT†	17	44
FNAB-C* + FNAB-CT†/sCT‡ ratio	16	40
HISTOLOGY	**18**	**44**

** FNAB-C: ultrasound-guided fine-needle aspiration biopsy cytology; † FNAB-CT: calcitonin in the needle wash-out; ‡ sCT: serum calcitonin; ¶ MTC: medullary thyroid carcinoma.*

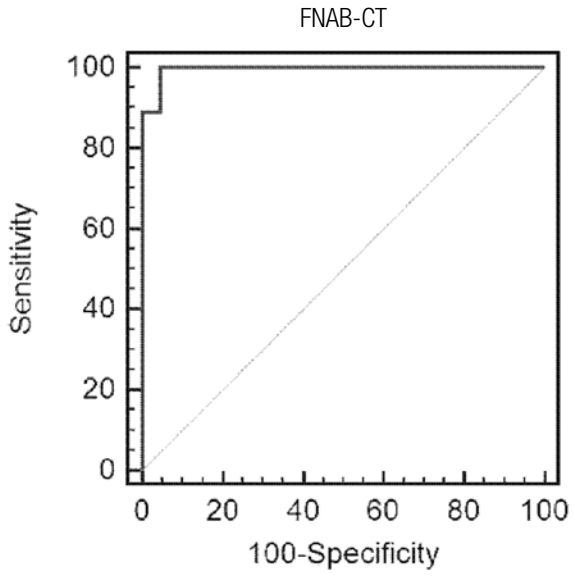
an overall accuracy of 85%, a PPV of 100% and a NPV of 83% (Table II).

FNAB-CT correctly identified 16 cases with MTC (TP results) and 44 cases without (TN results). FN results were observed in 2 cases, but no FP results were reported. For FNAB-CT sensitivity was 89%, specificity 100%, accuracy 97%, PPV 100% and NPV 96% (Table II).

FNAB-CT/sCT ratio correctly identified 15 cases with MTC disease (TP results) and 41 cases without (TN results). FN results were observed in 3 cases; FP results in 3 cases. For the FNAB-CT/sCT ratio sensibility was 83%, specificity 93%, accuracy 90%, PPV 83% and NPV 93% (Table II).

One of 2 patients with a false negative FNAB-CT result and one of 3 patients with a false negative FNAB CT/sCT ratio were correctly diagnosed by FNAB-C. Eight of 9 non-diagnostic FNAB-C were correctly classified by FNAB-CT and 7 by FNAB CT/sCT ratio.

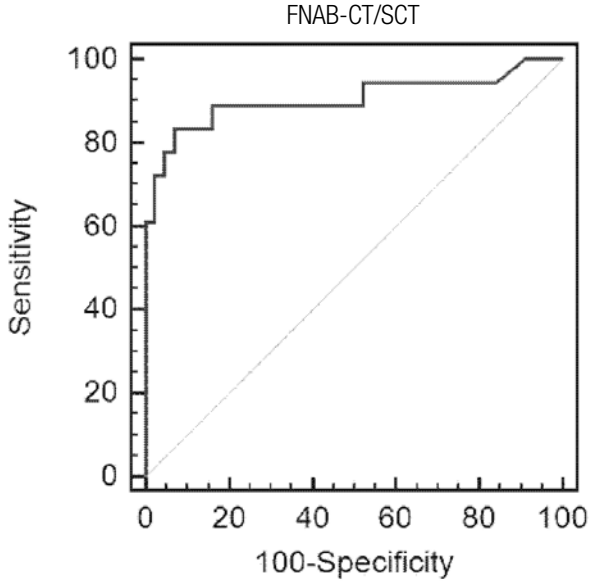
The integration of FNAB-C and FNAB-CT correctly identified 17 cases with MTC (TP results) and 44 cases without (TN results). The FN result was observed in 1 case, but no FP results were reported. The integration of both methods had a sensibility of 94%, a specificity of 100%, an overall accuracy of 98%, a PPV of 100% and a NPV of 98%. The integration of FNAB-C and FNAB-CT/sCT ratio correctly identified 16 cases with MTC disease (TP results) and 40 cases without (TN results). FN results were observed in 2 cases; FP results were observed in 4 cases. The integration of both methods had a sensitivity of 89%, a specificity of 91%, an overall accuracy of 90%, a PPV of 80% and a NPV of 95% (Table II).



*Cut-off = 10.4 pg/ml; sensitivity 89%; specificity 100%; PPV‡ 100%; NPV¶ 96%; accuracy 97%; AUC** = 0.99 (CI†† = 95%, 0.93 - 1.00).*

** ROC: Receiver Operating Characteristic; † FNAB-CT: calcitonin in the needle wash-out; ‡ PPV: positive predictive value; ¶ NPV: negative predictive value; ** AUC: area under curve; †† CI: confidence interval*

Fig. 1. ROC* curve of FNAB-CT†.



Cut-off ratio = 1.39; sensitivity 83%; specificity 93%; PPV¶ 83%; NPV 93%; accuracy 90%; AUC†† = 0.90 (CI‡‡ = 95%, 0.80 - 0.96).*

** ROC: Receiver Operating Characteristic; † FNAB-CT: calcitonin in the needle wash-out; ‡ sCT: serum calcitonin; ¶ PPV: positive predictive value; ** NPV: negative predictive value; †† AUC: area under curve; ‡‡ CI: confidence interval.*

Fig. 2. ROC* curve of the FNAB-CT†/sCT‡ ratio.

Table II. Accuracy, positive predictive value and negative predictive value of FNAB-C*, FNAB-CT†, FNAB-CT†/sCT¶ ratio, and integration of FNAB-C* with FNAB-CT† and FNAB-CT†/sCT¶.

	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
FNAB-C*	50%	100%	85%	100%	83%
FNAB-CT†	89%	100%	97%	100%	96%
FNAB-CT†/sCT¶ ratio	83%	93%	90%	83%	93%
FNAB-C* + FNAB-CT†	94%	100%	98%	100%	98%
FNAB-C* + FNAB-CT†/sCT¶	89%	91%	90%	80%	95%

** FNAB-C: ultrasound-guided fine-needle aspiration biopsy cytology; † FNAB-CT: calcitonin in the needle wash-out; ¶ sCT: serum calcitonin.*

Discussion

The early clinical detection and preoperative confirmation of MTC may represent a diagnostic challenge in clinical practice [23]. Indeed, sCT is a sensitive diagnostic tool for diagnosis of MTC [1-5], but the actual diagnostic accuracy of this marker and its use as a routine test in clinical practice are still a matter of debate [3 23]. The FNAB-C reveals a diagnostic accuracy for MTC less consistent than for differentiated thyroid carcinoma [11 23], with a reported sensitivity of 45-63%, indicating that misdiagnosis often occurs with this approach [11 23 24].

As a consequence, in several cases diagnosis of MTC is still incidentally made postoperatively with the risk of an incomplete surgical treatment. A tailored approach, including total thyroidectomy plus central neck node dissection [25 26], and lateral neck dissection with therapeutic intent, is advisable for adequate treatment but requires early preoperative diagnosis and correct clinical staging of MTC [23].

Recently, several studies have reported that the measurement of CT in the washout of the FNAB needle identifies MTC with high sensitivity and specificity, indicating that this approach may be a useful adjunct to conventional FNAB-C in patients with increased sCT [12-18].

A similar approach is used to identify neck recurrences/metastases of differentiated papillary or follicular thyroid carcinoma with the measurement of thyroglobulin (Tg) in fine-needle aspiration biopsy washout fluid (FNAB-Tg) [27]. When compared with FNAB-Tg, a smaller number of studies have been performed to evaluate the usefulness of CT assay in FNAB fluid alone or combined with cytology. However, the few papers on this topic have consistently shown that FNAB-CT has high accuracy [23].

Despite the emerging role of FNAB-CT for the diagnosis of primary or metastatic MTC [2], to date, there is no established method for FNAB-CT sampling, or an established cut-off of FNAB-CT for diagnosis of MTC.

Boi et al. [12] proposed an 'arbitrary' FNAB-CT cut-off of 36 pg/ml, corresponding to three times the highest value found in controls. Similarly, Kudo et al. [13] performed the technique in a series of five patients: MTC was detected by FNAB-CT in all cases, while cytology was positive for MTC in one case. Moreover, Abraham et al. [15] reported a series of five MTC patients undergoing FNAB-C on suspicious neck lymph nodes prior to surgery, with an accurate localisation of metastases. Massaro et al. [28] evaluated FNAB-CT in 27 patients, and no MTC was diagnosed. This suggests that more study on larger series are necessary to establish a validated cut-off value for FNAB-CT.

In our series, ROC analysis was performed to determine the absolute cut-off levels of CT in the washing fluid and the cut-off ratio between FNAB-CT and sCT with the highest sensitivity and accuracy: we obtained levels of FNAB-CT > 10.4 pg/ml and FNAB-CT/sCT ratio > 1.39 as the more accurate cut-offs.

FNAB-CT was more accurate than FNAB-C (97% *vs.* 85%), but the integration of both methods had better diagnostic performance (98% of accuracy) than FNAB-CT or FNAB-C alone.

Moreover, a fixed cut-off was not always appropriate, particularly in patients with extremely high sCT, due to peripheral blood contamination of needle wash-out fluid. To better characterise this potential interference, we analysed FNAB-CT related with the sCT by using their ratio [28]. The FNAB-CT/sCT ratio was more accurate than FNAB-C (90% *vs.* 85%), and the integration of both methods had better accuracy than cytology alone (90% *vs.* 85%). Unexpectedly, FNAB-CT had a higher diagnostic performance than FNAB-CT/sCT ratio (97% *vs.* 90%) either alone or integrated with FNAB-C (98% of accuracy for FNAB-CT in combination with FNAB-C *vs.* 90% for the FNAB-CT/sCT ratio in combination with FNAB-C).

On the basis of our findings, it seems clear that FNAB-CT should be integrated, but that it cannot replace or substitute FNAB-C in detection of primary or metastatic MTC. Indeed, FNAB-CT is particularly useful to determine correct diagnosis in the presence of non-diagnostic FNAB-C. Eight of 9 non-diagnostic FNAB-C were correctly classified by FNAB-CT and 7 by FNAB CT/sCT ratio.

On the other hand, it seems obvious that cytological examination cannot be eliminated or replaced, because it is essential for diagnosis, and has very high specificity and sensitivity, particularly when the CT is not conclusive; one of 2 patients with a false negative FNAB-CT result and one of 3 patients with a false negative FNAB CT/sCT

ratio were correctly diagnosed by FNAB-C in our series. As a consequence, FNAB-C should be considered complementary to FNAB-CT, and these complementary methods can be considered as essential in identification of patients with MTC as they can contribute to correct diagnosis and aid in planning appropriate therapy.

Conclusions

FNAB-CT, in addition to cytology, should be considered the standard in pre-surgical diagnostic work-up of MTC and of suspicious neck MTC recurrences/metastases. This may have important implications in the management of MTC. FNAB-CT should integrate but not substitute FNAB-C to detect MTC; it is especially helpful in the case of non-diagnostic FNAB-C.

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Thyroid

Aesthetic comparison between synthetic glue and subcuticular sutures in thyroid and parathyroid surgery: a single-blinded randomised clinical trial

Confronto del risultato estetico tra colla sintetica e suture intradermiche nella chirurgia tiroidea e paratiroidea: una sperimentazione clinica in singolo cieco

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SUMMARY

The aim of our study was to compare, in terms of aesthetic results, the use of synthetic glue to intradermal absorbable sutures in post-thyroidectomy and parathyroidectomy wound closure in a single blinded, randomised, per protocol equivalence study. From September 2008 to May 2010, patients undergoing thyroid or parathyroid surgery (with an external approach) at the Otolaryngology Department of the University Hospital of Modena were assessed for eligibility. In total, 42 patients who had had synthetic glue application on surgical incisions (A) and 47 patients who had subcuticular sutures on their surgical incisions (B) were enrolled. The mean of the endpoint (based on the Wound Registry Scale) of group A at 10 days was 1.4, while that in group B (based on the Stony Brook Scar Evaluation Scale) was 2.9. Statistically significant ($p = 0.002$) and clinically significant (difference of the means = 1.5) differences in the aesthetic results were found between groups A and B at 10 days, with better results in group B. On the other hand, at 3 months, the mean of the endpoint in group A was 3.1 while that in group B was 2.8; no statistically significant ($p = 0.62$) or clinically significant (difference in means = 0.3) differences were found between groups A and B. In conclusion, synthetic glue differs from subcuticular suture in post-thyroidectomy or post-parathyroidectomy incision for early aesthetic results, with better outcomes for subcuticular sutures. At 3 months, there were no differences in aesthetic outcomes between groups. Moreover, sex, incision length, age, cold/hot blade and correspondence of the incision with a wrinkle in the skin did not seem to influence aesthetic outcomes with this type of incision.

KEY WORDS: Thyroid surgery • Parathyroid surgery • Neck surgery • Aesthetic outcomes • Synthetic glue • Intradermal absorbable sutures • Subcuticular sutures

RIASSUNTO

L'obiettivo del nostro lavoro è stato di confrontare, in termini di risultati estetici, l'uso di colla sintetica con l'uso di suture intradermiche riassorbibili nella chiusura delle ferrite post tiroidectomia e post paratiroidectomia mediante uno studio in singolo cieco, randomizzato per protocollo di equivalenza. Da settembre 2008 a maggio 2010, i pazienti sottoposti a tiroidectomia o a paratiroidectomia (con approccio esterno) presso il Dipartimento di Otorinolaringoiatria del Policlinico di Modena sono stati valutati per l'ammissione nello studio. In totale 42 pazienti che avevano ricevuto l'applicazione di colla sintetica sulle loro incisioni chirurgiche (A) e 47 pazienti che avevano avuto suture intradermiche sulle loro incisioni chirurgiche (B) sono stato arruolati nello studio. La media dell'end point (in base alla Wound Registry Scale) del gruppo A a 10 giorni è stata di 1.4, mentre quella del gruppo B (in base alla Stony Brook Scar Evaluation Scale) è stata di 2,9. Una differenza statisticamente significativa (p = 0.002) e clinicamente significativa (differenza delle medie = 1,5) nei risultati estetici è stata riscontrata tra i gruppi A e B a 10 giorni, con migliori risultati per il gruppo B. D'altra parte, a 3 mesi, la media dell'end point nel gruppo A è stata di 3.1 mentre quella nel gruppo B è stata di 2.8; nessuna differenza statisticamente significativa (p = 0,62) o clinicamente significativa (differenza in medie = 0.3) è stata trovata tra i gruppi A e B. In conclusione la colla sintetica differisce dalla sutura intradermica nell'incisione post tiroidectomia o post paratiroidectomia per quanto riguarda i primi risultati estetici che risultano essere migliori con le suture intradermiche. A 3 mesi, non c'erano più differenze in termini di risultati estetici tra i due gruppi. Inoltre il sesso, la lunghezza dell'incisione, l'età, il tipo di lama (fredda o calda), e la corrispondenza dell'incisione con una piega cutanea non sembrano influenzare i risultati estetici con questo tipo di incisione.

PAROLE CHIAVE: *Chirurgia tiroidea • Chirurgia paratiroidea • Chirurgia cervicale • Risultati estetici • Colla sintetica • Suture intradermiche riassorbibili • Suture sottocutanee*

Introduction

The head-neck region is anatomically complex regarding the presence of different organs and tissues. Surgery in this region also raises significant aesthetic problems because the neck and face are among the areas most exposed to the vision of others, and thus are aesthetically important.

Several different materials and suturing techniques are used in head and neck surgery, depending on the region in which the suture is performed, although in head and neck surgery, the use of subcuticular absorbable sutures is very popular. This kind of suture has many benefits, for example, little tissue reaction, rapid reduction and absence of mark points [1], and for all these reasons, our standard for all incision closures in regions particularly exposed is the subcuticular absorbable synthetic monofilament suture. On the other hand, in recent years, the use of tissue glue (e.g. octylcyanoacrylate) has gained favour in surgical practice for quicker and painless closure of lacerations, and the use of tissue adhesive is increasingly becoming an alternative to sutures.

In the literature, there are many comparative studies on different types of suture, but in general, have focused on the closure of excisional wounds or on suturing techniques not limited to one single region, but also including higher tension areas such as the extremities [2]. However, as is well known to every surgeon, each region in the human body has a different behaviour with regard to scar formation, both in rapidity of healing and in aesthetic results.

Thyroidectomy and parathyroidectomy classically require anterior neck incisions that are at risk of undesirable aesthetic results when scars do not form as expected. This type of incision is particularly important from an aesthetic point of view as its location is particularly exposed. Moreover, thyroid and parathyroid surgery is most often practiced in young women. In fact, the incidence of thyroid and parathyroid disease is three times higher in women than in men, and the incidence peaks in the third and fourth decades of life [3]. For all these reasons, the aesthetic outcomes of this kind of surgery are very important.

For the above-mentioned reasons, we carried out a prospective, randomised, controlled trial to compare, in terms of aesthetic results, the use of synthetic glue to intradermal absorbable suture in post-thyroidectomy and parathyroidectomy wound closure.

The purpose was also to see whether other variables such as age, sex, size and type of incision (hot or cold), and correspondence of the incision with a skin wrinkle influenced the post-operative healing process in terms of aesthetic results.

Methods

The IRB approval was requested and obtained (Comitato Etico Provinciale di Modena, 2454/C.E.). The present study was also registered on www.clinicaltrial.gov (NCT00754182). A CONSORT 2010 statement was used to report the present randomised controlled trial (RCT).

From September 2008 to May 2010, patients undergoing thyroid or parathyroid surgery (with an external approach) at the Otolaryngology Department of the University Hospital of Modena were assessed for eligibility for inclusion. Patients who had prior neck surgery and patients who required concomitant neck dissection were excluded from the study. During pre-operative clinical history collection, consent to participate in the study was obtained from the patient, after adequate information was given by the ENT surgeon. In the case of consent, the patient was included in the study, and consecutively randomised for treatment based on a block randomisation list, obtained by six permuting blocks (1 = AABB, 2 = ABAB, 3 = BBAA, 4 = BABA, 5 = ABBA, 6 = BAAB) randomly distributed to create the list. To the A patient group (study group), a glue suture (Dermabond; Ethicon Inc, Norwood, MA, USA) was assigned to close the skin, while to the B patient group (control group) a subcuticular suture (Caprosyn; Syneture, U.S. Surgical, Div. Tyco Healthcare, Norwalk, CT, USA) was utilised. In both cases, the skin was closed after strap muscle approximation and accurate subcutaneous suture placement. The primary outcome was aesthetic result based on an equivalence comparison of sutures at 10 days and at 3 months, while the secondary ad-hoc outcome was whether correspondence of the incision with a wrinkle of the skin, age < 45 years, incision length (higher versus lower than the mean) and sex could have played a role in the aesthetic results, independently of the type of suture used. Further post-hoc analyses included comparison of the results between the sutures for each variable considered in the scoring system, at 10 days and at 3 months, and whether they were able to identify in which subheading of the endpoint the aesthetics results differed. A 10 days (8-11 days was considered acceptable) and 3 months (10-14 weeks was considered acceptable), follow-up was performed. For controls, a picture of the surgical scar was obtained after suture removal and accurate cleaning of the scar to remove as much residual material from the suture as possible. All images were stored in a database. A plastic surgeon, blinded for the type of treatment, was then asked to review the images, assigning a score to each scar. Two different scoring systems were used as endpoints. To evaluate the 10-day aesthetic results, the 6-point (1, step-off of the borders; 2, contour irregularities; 3, margin separation; 4, edge inversion; 5, excessive distortion; 6, overall appearance) Wound Registry scale [4] was used, while to evaluate the 3-month aesthetic results, the 5-point Stony Brook Scar Evaluation Scale [5] (1, width < 2 mm; 2, height; 3, colour; 4, hatch or suture marks; 5, overall appearance) was used. For every category, one point was assigned (0 = bad; 1 = good), and the points in each category were then summed to obtain for every scar a score ranging from 0 (worst) to 6 (best) for 10-day

results, and a score ranging from 0 (worst) to 5 (best) for 3-month results. The aesthetic results were also collected in a database for further analyses.

Statistical considerations

A per protocol two-sided equivalence comparison was established with a statistical significance level of 95%. Patients who accomplished at least one rating were considered per protocol, and hence included in the final analyses. A power of 80% and a clinical difference of 1 point of the end point scale were considered significant. An ad-interim analyses was planned in November 2009 to determine patient numbers, based on preliminary differences found between the groups. Once an adequate patient number had been obtained in the interim analyses, the study was stopped for final analysis of results. All patients who had at least one rating (either at 10 days or at 3 months) were analysed. The Mann-Whitney-Wilcoxon test was used to compare results (NCSS 2004, Kaysville, UT, USA).

Results

In total, 235 patients were assessed for eligibility (Fig. 1). Of these, 95 were excluded from the study because they did not meet inclusion criteria or declined to participate; 140 patients were randomised for treatment. Two patients were excluded from group A analyses because of postoperative bleeding, and one patient was excluded because

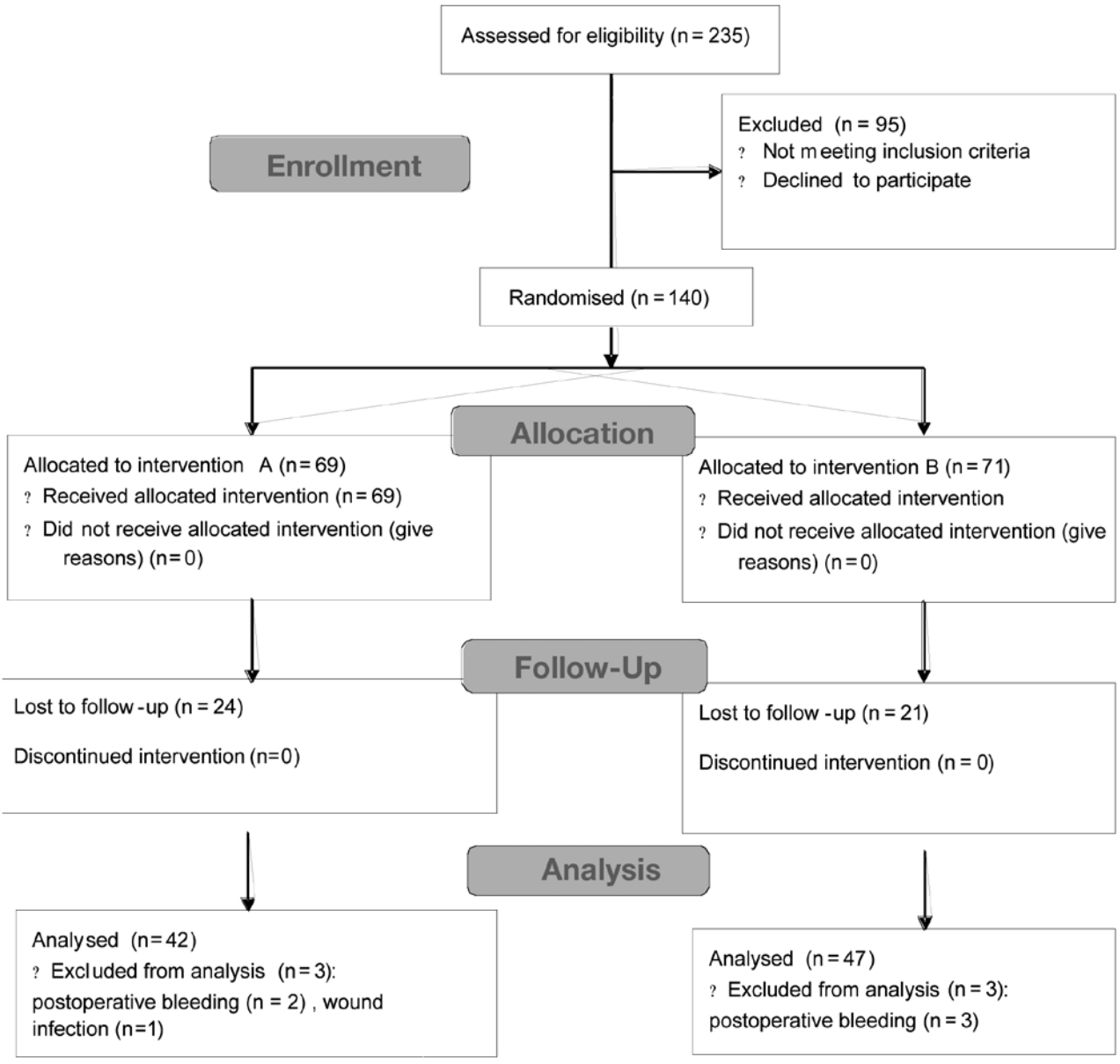

Fig 1. Flow-chart (according to CONSORT 2010).

Table I. Patient summary.

	A				B				Overall			
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD
Patients (total)	42	47.19			47	52.81			89	100		
Sex												
f	32	76.19			37	78.72			69	77.53		
m	10	23.81			10	21.28			20	22.47		
Age	42	100	53.12	13.14	47	100	53.57	15.19	89	100	53.36	14.18

of wound infection. Three patients were excluded from group B analyses because of post-operative bleeding. In total, 42 patients from study group (A) and 47 patients from control group (B), in total 89 patients, were analysed per protocol (Tab. I). Aesthetic results are summarised in Table II.

Main outcome

The mean of the endpoint of group A at 10 days was 1.4, while that of group B was 2.9. A statistically significant (p = 0.002) and clinically significant (difference of the means = 1.5) difference in the aesthetic results was found between groups A and B at 10 days, with better results in group B. On the other hand, at 3 months, the mean of the endpoint in group A was 3.1 while in group B it was 2.8. No statistically significant (p = 0.62) or clinically significant (difference in means = 0.3) difference was found between groups A and B at 3 months.

Secondary outcomes

Concerning other ad-hoc analyses, none showed a statistically significant difference either at 10 days or at 3 months, apart from incision length at 3 months, which appeared to favour better aesthetic results at 3 months in the case of larger incisions (> 7 cm, mean length; p = 0.04). However, it did not show a clinically significant difference (0.7). Mean incision length was 6.9 cm (range 4-11).

Other post-hoc analyses

Statistically significant differences were found for the subheading 'step-off of the margins' (p = 0.007), 'margin separation' (p = 0.01), 'margin eversion' (p = 0.03) and 'overall appearance' (p = 0.03) in the 10-day endpoint scale, with better results for subcuticular sutures. None of the other single parameters analysed showed a statistically significant difference, either at 10 days or at 3 months.

Table II. Aesthetic results.

	Mean aesthetic results (N)		Difference (in absolute value)	p
	A (42)	B (47)		
A vs B				
10 days	1.4	2.9	1.5	0.002
3 months	3.1	2.8	0.3	0.62
	Yes (55)	No (34)		
Wrinkle correspondence				
10 days	2.1	2.1	0	0.86
3 months	2.9	2.9	0	0.77
Age	≤ 45 (26)	> 45 (63)		
10 days	2.1	2.1	0	0.87
3 months	2.9	3	0.1	0.55
Incision length	≤ 7 cm (60)	> 7 cm (29)		
10 days	2.1	2.2	0.1	0.54
3 monhs	2.7	3.4	0.7	0.04
Blade (cold/hot)	Cold (81)	Hot (8)		
10 days	2.1	2.1	0	0.79
3 months	3	3	0	0.76
Sex	Male (20)	Female (69)		
10 days	2.1	2.1	0	0.24
3 months	3	2.9	0.1	0.2

Discussion

In head and neck surgery, there is widespread use of skin-absorbable sutures performed with intradermic continuous suture. This kind of suture has many benefits: for example, little tissue reaction, rapid reduction and absence of mark points. On the other hand, one possible disadvantage is a rapid decrease in tensile strength [6].

The use of tissue glue (e.g. butylcyanoacrylate, octylcyanoacrylate) is currently popular for closure of superficial lacerations, especially in children. The cyanoacrylate group of tissue adhesives has been studied for use in surgical procedures for over 40 years [7]. These adhesives work by polymerising in an exothermic reaction when contacting a fluid or basic medium. For a number of years, the first widely used variety was *N*-butyl-2-cyanoacrylate [8]. This particular adhesive is significantly weaker than conventional monofilament sutures and is not particularly flexible [9]. More recently, a new tissue adhesive designed to address the limitations of the butyl-2-cyanoacrylate

group, 2-octyl cyanoacrylate (Dermabond; Ethicon Inc., Norwood, MA USA), has been approved by the US FDA. This cyanoacrylate has more flexibility and greater breaking strength, and may therefore be indicated for use in a wider variety of wound types [10]. In the literature, several practical advantages of cyanoacrylates have been noted. In particular, they are less time-consuming to apply than sutures, leading to shorter, more efficient patient encounters with less need for nursing, monitoring and sedation [2]. For all these reasons, cyanoacrylates are often used for the closure of excisional wounds in children. Moreover, since cyanoacrylates form an antibacterial barrier over the incision, sterility is maintained even without the application of topical antibiotics [11]. Regarding the aesthetic outcomes, there have been reports suggesting acceptable cosmetic outcome of wounds closed with tissue adhesive in the repair of simple lacerations and surgical incisions under lower tension [12].

In a study carried out in 2002, the cosmetic results of the cyanoacrylate group were equal to or better than suture-closure with absence of suture marks, and possibly a lower degree of scar formation due to minimum handling of the tissue [13]. Another study showed that cyanoacrylate tissue adhesive is associated with a low rate of dehiscence, low infection rate and provides excellent cosmetic results for closure of both traumatic lacerations and surgical incision with results comparable to those obtained with standard wound closure techniques [14]. On the other hand, other studies [2] have shown that cosmetic outcome is significantly better in patients treated with conventional sutures.

In general, several publications have shown good cosmesis and faster times of skin closure using glue for laceration closure [15]. There are, however, only a few studies looking at tissue glue for surgical incisions. Moreover, these include different types of incisions with varying lengths and different locations [16]. Our study focused exclusively on post-thyroidectomy incisions. This type of incision is particularly important from an aesthetic point of view not only because of its exposed and visible location, but also because of the predominance of thyroidectomy in women. Furthermore, the incidence of this disease peaks in the third and fourth decades of life [17].

Based on our results, and considering primary outcome, a difference in aesthetic results between sutures was found at 10 days. Statistically significant ($p = 0.002$) and clinically significant (difference of the means = 1.5) differences in aesthetic results were found between groups A and B at 10 days, with better results in group B. These results were attributed to an increased step-off, eversion or separation of the margins, based on the results of post-hoc subheadings analyses. Thus it seems that the poorer results with glue may to be attributed to a poorer juxtaposition of the margin, both in excessive, insufficient or irregular juxtaposition. On the other hand, at 3 months, no statistically significant ($p = 0.62$) or clinically significant (difference in means = 0.3) differences were found between groups A and B.

Regarding other ad-hoc analyses, none showed a statistically significant difference either at 10 days or at 3 months, apart from incision length at 3 months, which showed better aesthetic results at 3 months in the case of larger incisions (> 7 cm, mean length; $p = 0.04$), but this did not reach a clinically significant difference (0.7 of the end point scale), and the imbalanced number of patients (60 ≤ 7 cm vs 29 > 7 cm) between groups could have biased the results.

The results of our primary outcome are in accordance with some literature studies, where it has been found that the kind of suture employed did not have an important influence on aesthetic results at 3 months [13].

In present study, two different scales were used at 10 days and three months [4 5]. As reported in the methods section, only one plastic surgeon rated the results, and multiple raters weren't used since the scales had already been validated by former studies, and thus did not require further investigations concerning interobserver or intraobserver variability and reliability. We would like also to emphasize that as the per protocol analyses was chosen in advance, since a considerable drop-out was expected due to the large proportion of patients coming to our institution from outside the region. Most of these patients completed their follow-up by referring to ENT specialists, endocrinologists or family doctors that sent them to us only for the operation. Nevertheless, a per protocol analysis was considered acceptable, since the drop-out was not considered to be related to a particular kind of suture, and moreover, the drop-out rate is balanced between groups (35% group A vs 30% group B). The exclusion of 5 (3.5%) patients out of 140 randomised, was motivated by post-operative bleeding: in these cases, the sutures were completely removed, without any significant difference in management of airway obstruction between group A and B, and then placed again after haemostasis.

The authors emphasise that aesthetic results are not the only important factors that must be considered when analysing suture materials and other factors may play a role in the final choice of material. First of all costs, but also operating times, which were not systematically measured in our study, although we can empirically confirm what had already been reported in the literature, i.e. the glue is faster to apply compared to traditional sutures [14]. We also recommend that adequate information be given to medical and nursing personnel when introducing new materials such as glue into clinical practice, since there may be some aspects that could significantly alter performance, and thus the results of the study. In particular, for glue it is very important to avoid contact of the wound with water or other dressing materials, and in general to avoid the adhesive part of the dressings coming into contact with the wound. Therefore, the medical and nursing staff

need proper information about the use of this new material, which should be provided before starting the study, in order to avoid systematic biases related to incorrect management of patients who received study treatment.
The results of this study should be confirmed by similar experiences with other individual head and neck regions (such as the parotid region of the face).

Conclusions

Synthetic glue differs from subcuticular sutures in post-thyroidectomy or post-parathyroidectomy incision, with better aesthetic results for subcuticular sutures in the early stages. However, at 3 months, there are no differences in aesthetic outcomes between synthetic glue and subcuticular sutures. Moreover sex, incision length, age, cold/hot blade and correspondence of the incision with a wrinkle of the skin did not seem to influence aesthetic outcomes in this type of incision.

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Voice

Voice disorders in primary school teachers

Disturbi vocali nelle educatrici delle scuole d'infanzia

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SUMMARY

Previous reports focusing on the high prevalence of voice disorders in teachers have suggested that vocal loading might be the main causal factor. The aim of our study was to assess the prevalence of voice disorders in a sample of primary school teachers and evaluate possible cofactors. Our sample was composed of 157 teachers (155 females, mean age 46 years). Participants were asked to complete two self-administrated questionnaires: one with clinical data, and the second an Italian validated translation of VHI (voice handicap index). On the same day they also underwent a laryngostroboscopic exam and logopedic evaluation. The results were compared with those of a control group composed of accompanying individuals. Teachers presented a higher rate of abnormalities at laryngostroboscopic examination than the control group (51.6% vs. 16%, respectively). Among these, 7.1% presented nodules. In our sample, vocal fold disorders were not correlated with years of teaching, smoking, coffee consumption, or levels of anxiety. Our findings are in agreement with previous reports on the prevalence of pathologic disorders among teachers; nonetheless, the prevalence of nodules was lower than in previous investigations, and voice loading was not correlated with laryngostroboscopic findings. Current Italian law does not include any guidance regarding voice education and screening in subjects with high vocal loading. Our work stresses the need for such legislation.

KEY WORDS: Voice disorders • Vocal folds nodules • Laryngostroboscopy • Teachers

RIASSUNTO

Lavori precedenti hanno focalizzato l'attenzione su una elevata prevalenza dei disturbi vocali negli insegnanti ed il sovraccarico vocale potrebbe esserne il principale responsabile; scopo dello studio è stato quello di valutare tale prevalenza in un campione di insegnanti delle scuole dell'infanzia e determinare eventuali concause. Il campione studiato era costituito da 157 insegnanti (155 donne, con età media di 46 anni). È stato loro chiesto di completare due questionari: il primo riguardante la storia clinica, il secondo costituito dalla versione italiana del VHI (Voice Handicap Index). Nella stessa giornata sono stati sottoposti a laringostroboscopia ed a valutazione logopedica. I risultati sono stati comparati con quelli di un gruppo di controllo costituito dalle persone che accompagnavano gli insegnanti. Gli insegnanti presentavano un tasso più elevato di anomalie all'esame laringostroboscopico rispetto ai controlli (51.6% vs. 16%). Tra gli insegnanti il 7.1% presentava noduli delle corde vocali. Nel nostro campione non è emersa alcuna correlazione tra i disordini vocali e l'età di insegnamento, il fumo, il consumo di caffè ed il livello di ansia. I nostri risultati concordano con la letteratura riguardo la prevalenza di alterazioni tra gli insegnanti; tuttavia la prevalenza di noduli è risultata minore rispetto a quello registrata in lavori precedenti ed il carico vocale non ha presentato correlazioni con i rilievi laringostroboscopici. La legge italiana non prevede protocolli di educazione vocale e di screening nei soggetti con elevato carico vocale. Il nostro lavoro ne sottolinea la necessità.

PAROLE CHIAVE: *Disordini vocali • Noduli delle corde vocali • Laringostroboscopia • Insegnanti*

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Introduction

Subjects using their voice as a professional instrument more frequently develop voice disorders; among these, teachers present a high prevalence of voice changes compared with other professional categories [1-3]; voice changes may arise from interaction of occupational (vocal loading), behavioural and lifestyle factors.

Vocal loading is defined as a combination of the duration of voice use and environmental features; teachers are often obliged to use load voice without any amplification for several hours a day [4].

Different papers report a correlation between voice disorders and the length of time working as a teacher. Moreover, among environmental factors, teachers working in noisy rooms present a higher rate of voice disorders and a higher score in voice handicap index (VHI) questionnaire [3 5 6].

During their professional education, a small number of teachers receive information about the correct use of

voice [7]. Some also undergo medical evaluation [8], since logopaedic therapy may be useful in the treatment of dysfunctional dysphonia [9].
Voice disorders provoked by professional use are more often chronic and can lead to an increase in working days missed [4 8 10]. Nodules in teachers have been reported to be present in 13-14% of individuals [11 12].
Other factors have been correlated with voice disorders and nodules in teachers, including sex (women are more frequently affected), age between 40 and 59 years and family history of voice disorder [3 13].
Job stress may play a bidirectional role; highly stressed teachers more frequently present voice disorders [14] and subjects with high strain are at risk for developing physical and mental stress [15 16].
Lifestyle related factors (smoking, alcohol and coffee consummation, infections of the upper respiratory tract) have been described as cofactors for voice disorders, although one report has suggested that they are correlated with voice disorders mostly in other professional categories rather than in teachers [17].
Several investigations have assessed voice quality with questionnaires [3 15 18 19], while those based on stroboscopic evaluation have reported a high prevalence of vocal fold alterations [12 20]. Laryngostroboscopy is an endoscopic procedure that allows evaluation of vocal fold vibratory function during phonation [21].
The aim of our study was to assess the prevalence of vocal fold disorders and quality of voice in a sample of primary school teachers through self-completed questionnaires, laryngostroboscopic examination and logopaedic evaluation.

Materials and methods

Our sample was composed of 157 teachers (155 females, 2 males) aged between 28 and 60 years (mean 46 ± 8), from 23 primary schools randomly selected in the city of Milan. The average duration of teaching was 22 years.
The results were compared with those of a control group consisting of 75 subjects (72 females, 3 males) aged between 22 and 75 years (mean 43 ± 11). This sample was randomly selected among individuals accompanying the teachers and who did not perform work with high vocal loading. Since most teachers were females, the vast majority of the controls were also females.
All subjects were examined at the outpatient clinic of San Raffaele Resnati in Milan. Data were collected between March 2011 and July 2012.

Questionnaires

Before clinical evaluation, subjects were asked to complete two self-administered questionnaires. The first, composed of 21 questions and mainly based on clinical experience, is designed to gather general information on the patient's health and more specific elements regarding voice disorders [22]. Subjects were asked to provide the following information: personal data (gender, age, name of school), behavioural habits (smoking, alcohol, caffeine), health conditions related to voice disorders (diseases, interventions, drugs, endocrine disorders), occupation (years of teaching, methods of use of voice), voice symptoms and physical discomfort (frequency of any disorder, symptoms of hoarseness, throat disorders, previous specialist consultations), effect of voice problems (changes in teaching method, influence on work, ability to communicate, ability to socialise, and emotional interference).
The second questionnaire is the Italian validated translation [23] of the VHI [24], a voice-related quality of life tool. It is divided into physical (P), emotional (E) and functional subscales (F). The questionnaire consists of 30 questions and answers are rated on a five-point scale "0 = never", "1 = almost never," "2 = sometimes," "3 = almost always", "4 = always" . Each of the three parts has a maximum score of 40 points that corresponds to serious pathological situation. Only teachers were asked to complete the questionnaires.

Clinical examination

Both groups underwent laryngostroboscopic evaluation. In the sample of teachers, two refused to undergo laryngoscopic examination.
Laryngeal examination was performed with a XION flexible endoscope in combination with multifunctional videolighting Nomad C (Portable ENT Endoscopy and Documentation System – XION - Germany), which includes both a continuous and strobe source of light. The results were archived using a video-recording program (Divas software). After examination of laryngeal morphology in a normal white light source, vocal function was assessed with strobe light during pronunciation of the vowel /i/. Fundamental frequency was assessed. During the continuous light examination, morphological evaluation of vocal folds was performed.
During the stroboscopic exam, parameters modified by Ricci Maccarini [25] and based on the criteria encoded by Hirano were saved [26]: motility, profile, morphology, vibration amplitude, frequency, symmetry, glottic closure, mucosal wave, place of the phonatory vibration and attitude of supraglottic structures. In order to facilitate the collection of information, a summary form was used.
Logopaedic evaluation was made with MDVP (multidimensional voice program, KayPentax, Japan) software, while subjects were asked to pronounce a prolonged (at least 10 sec) vowel /a/; parameters were obtained from the 3 central seconds previously sampled at 50,000 Hz.
During acoustic analysis, we considered, in addition to the fundamental frequency, the 11 parameters recommended by De Colle [27]: 1) Jitt% = Jitter Percent (Fundamental Period), 2) vF0% = Fundamental Frequency

Variation, 3) Shim% = Shimmer percent (Width of Peak), 4) vAm% = Peak-Amplitude Variation, 5) NHR = Noise to Harmonic Ratio, 6) VTI = Voice Turbulence Index, 7) SPI = Soft Phonation Index, 8) FTRI% = Frequency Tremor Index, 9) ATRI% = Amplitude Tremor Index, 10) DVB% = Degree of Voice Breaks, 11) DSH% = Degree of Sub-harmonics.

Statistical analysis

Data were coded and recorded in an Excel database; statistical analysis was performed with SPSS software (SPSS 21.0). For all data, we carried out frequency analysis and descriptive statistics; different statistical methods were applied depending on the variable analysed. In all statistical analyses, a $p < 0.05$ was considered significant. To compare categorical variables between groups, a Chi-square (χ^2) or Fisher's exact test was used, as appropriate. Data are presented as n (number of cases) and % (percentage within group). To compare continuous variables a Student's t test was used for independent samples or a Mann-Whitney test for variables not showing a normal distribution. The Kruskal-Wallis test was used to compare three or more groups. Data are presented as means ± SD (standards deviation). To compare the rate of laryngostroboscopic alterations in relation with teaching experience, the median age of teaching was used. Since males present a lower fundamental frequency, values of the 2 males in teachers group and the 3 males in the control group were not considered in statistical analysis.

Results

There was no significant difference between teachers and controls considering age. Teachers presented a higher rate of abnormalities at laryngostroboscopic examination than controls (51.6% vs. 16%, respectively, $\chi^2 = 26.71$; $p < 0.001$). Results are shown in Figure 1.

The presence of any anomalies in stroboscopic parameters or laryngoscopic evidence of vocal cord pathology were considered as abnormal in laryngostroboscopic examination. The observed laryngoscopic vocal cord pathologies in both groups are summarised in Table I.

Among teachers, 7.1% presented nodules. Table II details the stroboscopic anomalies in both groups. Teachers with anomalies of glottic closure more frequently presented incomplete closure (38 of 46 cases), while the mucosal wave was of small amplitude in 36 of 39 teachers with abnormalities.

The median age of teaching was 22 years. Comparing the presence of vocal fold pathology with years of teaching, a higher frequencies of abnormalities in individuals with fewer years of teaching was observed, although the difference was not statistically significant. The results are shown in Table III ($\chi^2 = 1.64$; $p = 0.2$).

Teachers demonstrated a lower fundamental frequency than controls (174.9 ± 27.4 vs. 235.9 ± 29.6; Mann Whitney test, $p < 0.001$). Subjects with abnormalities at laryngostroboscopic examination showed a lower fundamental frequency (181.9 ± 35.1 vs. 202.0 ± 43.8; Mann Whitney test, $p < 0.001$). Parameters of multiparametric voice analysis obtained with the MDVP system are listed in Table IV.

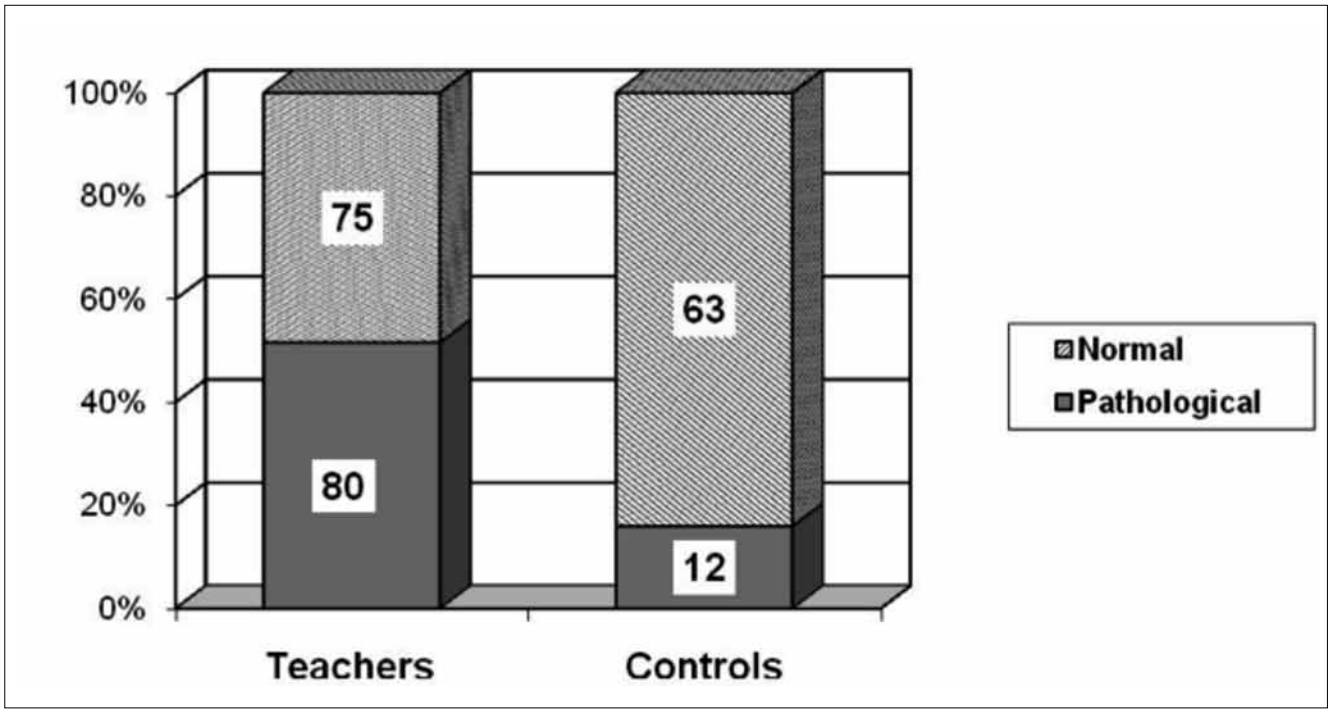

Fig. 1. Histogram of laryngostroboscopic abnormalities in teachers and controls.

Table I. Observed vocal cord pathologies. * χ^2 test or Fisher's exact test.

	Teachers		Controls		P*
	(n/N)	%	(n/N)	%	
Cordal thickening	7/155	4.5	0/75	0.0	0.09
Capillary ectasia	6/155	3.9	0/75	0.0	0.18
Nodules	11/155	7.1	0/75	0.0	0.02
Sulcus	5/155	3.2	1/75	1.3	0.67
Reinke's oedema	2/155	1.3	1/75	1.3	0.99
Pre-contact	4/155	2.6	0/75	0.0	0.31
Cysts	1/155	0.6	2/75	2.7	0.25

Table II. Anomalies in stroboscopic parameters. * χ^2 test or Fisher's exact test

	Teachers N = 155 n (%)		Controls N = 75 n (%)		P*
Motility vocal folds	0	(0.0)	0	(0.0)	
Profile vocal folds	11	(7.1)	4	(5.3)	0.78
Morphology vocal folds	21	(13.5)	2	(2.7)	0.01
Morphology false vocal folds	2	(1.3)	0	(0.0)	0.99
Vibration amplitude vocal folds	6	(3.9)	0	(0.0)	0.18
Frequency vibratory cycle	9	(5.8)	2	(2.7)	0.51
Symmetry cordal vibration	21	(13.5)	4	(5.3)	0.06
Glottic closure	46	(29.7)	3	(4.0)	<0.01
Morphology incomplete glottic closure	45	(29.0)	3	(4.0)	<0.01
Mucosal wave	39	(25.2)	2	(2.7)	<0.01
Place of the phonatory vibration	1	(0.6)	0	(0.0)	0.99
Attitude of supraglottic structures	1	(0.6)	0	(0.0)	0.99

The following was reported in the first questionnaire: smoking (22.4%), alcohol (8.3%), coffee consumption (84%), respiratory tract infections (70.5%), nasal allergy (34.6%), deviation of the nasal septum (17.9%), hormonal problems (21.2%), gastro oesophageal reflux disease (32.1%), stress (59.4%), anxiety (50%), surgery (9.6%), chronic treatment (29%) and hormonal disorder (26.5%). None of the parameters collected with the first questionnaire was associated with laryngostroboscopic anomalies (Table II).

During teaching activities, 17.3% of teachers declared to use a low tone, 62.8% a moderate tone and 19.9% a high tone. No correlation was found with abnormalities at laryngostroboscopy ($\chi^2 = 1.4$; $p = 0.5$). However, the reported frequency of voice disorders (0.9% never, 62.8% sometimes, 23.1% often and 3.2% always) was associated with the presence of disorders at laryngostroboscopic examination ($\chi^2 = 17.5$; $p = 0.001$).

Among teachers, 77.6% presented hoarseness, 27.6% shortness of breath, 28.8% tired voice, 35.3% weak voice, 21.8% fatigable voice, 13.5% difficulty to use bass tones, 37.2% difficulty to use high tones, 18.6% need to use low tone voice, 26.3% need to use high tone voice, 55.8% referred dry throat, 46.8% sore throat and 40.4% dysphagia. Previously reported laryngostroboscopic alterations were significantly correlated with tired voice (35.56% without anomalies vs. 64.44% with; $p = 0.04$), weak voice (31.48% vs. 68.52%; $p = 0.002$), difficulty to use bass tones (19.05% vs. 80.95%; $p = 0.004$) and difficulty to use high tones (34.48% vs. 65.52%; $p = 0.007$).

Only 31 of 155 teachers reported previous ENT consults for voice disorders; 26.3% of teachers with abnormalities at laryngostroboscopic examination had never undergone medical consultation for the problem.

Finally, the first questionnaire investigated the effect of

Table III. Contingency table between years of teaching experience (median 22 years) and vocal folds abnormalities.

	Teaching experience		
Laryngostroboscopy	More than 22 years (N)	Less than 22 years (N)	Total
Normal	42	33	75
Pathologic	36	44	80
Total	78	77	155

Table IV. Parameters of voice analysis in teachers and controls. *Student's t-test or Mann-Whitney test.

	Teachers		Controls		P*
	Mean	SD	Mean	SD	
F0 (Hz)	192.34	33.45	205.49	33.70	<0.01
Jitt%	1.85	1.37	0.83	0.77	<0.01
Vf0%	4.95	7.59	2.13	4.32	<0.01
Shim%	7.31	3.19	4.34	2.02	<0.01
vAm%	17.63	6.52	19.19	8.38	0.26
NHR	0.18	0.06	0.14	0.04	<0.01
VTI	0.05	0.02	0.05	0.02	<0.01
SPI	9.72	5.43	5.61	2.92	<0.01
FTRI%	0.55	0.66	0.41	0.39	0.01
ATRI%	5.50	3.68	6.74	3.63	0.02
DVB%	0.74	2.67	0.69	5.94	<0.01
DSH%	3.32	4.27	1.26	3.38	<0.01

voice disorders on social and professional activities of teachers: 31.4% reported having modified/adapted their teaching method, 37.2% changed judgment on the profession of educator, 42.3% changed their way of communicating, 5.8% reported a change in their social skills and 20.5% reported interference with their emotional state. Comparison of the effects of voice disorders with the presence of laryngostroboscopic anomalies shows a significant correlation with interference on emotional state (5.8% with anomalies vs. 14.8% without; $\chi^2 = 6.629$; $p = 0.01$).

The scores in the second questionnaire (VHI test) showed a distribution in the range between 0 and 64 (median 12). The VHI score was higher in subjects with laryngostroboscopic disorders than in the other subgroup (18.35 ± 13.8 vs. 13.45 ± 11.46; Mann-Whitney test, $p = 0.026$).

Discussion

The aim of the present investigation was to assess the prevalence of voice disorders in teachers using both anamnestic and clinical evaluation. Several previous reports have focused on the same problem using self-administered questionnaires, with a prevalence of voice disorders of 32.1% to 68.7% of teachers and a 3.5-fold increased risk of developing voice disorders during their occupational life [18 28-30]. A previous study reported a prevalence of 20.2% of organic lesions, 29% of functional disorders and 8% of chronic laryngitis in a teaching staff in Spain; subjects were studied with questionnaires, functional vocal examination, acoustic analysis and videolaryngostroboscopy [12]. In our sample, the prevalence of pathologic subjects was 51.6% vs. 16% of controls, in accordance with previous publications [11].

The most frequent laryngostroboscopic findings included reduced amplitude of the vocal wave associated with phase asymmetries (29% of teachers) and vocal fold hypotrophy with incomplete glottic closure (11% of teachers). These anomalies may arise from persistent vocal adaptation to increased vocal loading, and may be anatomically correlated with weakened vocal muscle [31].

On the other hand, we found vocal fold nodules in only 7.1% of teachers; in previous reports, the prevalence has ranged from 6% to 14% [11 30 32 33].

Notably, 35.5% of teachers presented clinical symptoms of gastro-oesophageal reflux, compared with only 2.7% of controls; since gastro-oesophageal reflux may be potentiated by psychological stress [34], it is likely that emotional factors may play a role in this finding.

Although previous papers have identified several cofactors for increased risk of voice disorders [14 29 32], smoking, coffee and stress, in our sample none of these factors correlated with laryngostroboscopic abnormalities. In contrast, we found that job-related stress correlated with the duration of teaching, and it should be noted that a high proportion of teachers referred that voice disorders interfered with their emotional state and social activities.

In our sample, vocal fold disorders were not correlated with years of teaching, and teachers with fewer years of teaching presented a higher rate of abnormalities than subjects with a longer job activity. One possible explanation for this finding is that younger teachers have less experience in job related voice practice, and some subjects may present an "intrinsic predisposition" to develop vocal fold abnormalities.

Finally, it must be underlined that 85.9% of the total sample declared voice disorders at some time during teaching; nonetheless, only 20% of these, and 26.3% of subjects with focal fold abnormalities, underwent medical consultation for the problem. The finding has already been reported in other reports [3 8]. It has been hypothesised that teachers consider voice problems an "expectable problem" and that they are unaware that there are therapeutic possibilities that can reduce or prevent them.

Conclusions

Our study highlights the high prevalence of laryngostroboscopic anomalies in teachers, although only a relatively small proportion presented nodules. Vocal loading may play a role in these findings, although vocal fold disorders did not correlate with years of teaching. In our opinion, the present study stresses the need for a preventive voice program for all teachers, possibly at the beginning of their work activity [35].

Abbreviations

VHI = Voice Handicap Index
ICAWS = Interpersonal Conflict at Work Scale
OCS = Organizational Constraints Scale
QWI = Quantitative Workload Inventory
PSI = Physical Symptoms Inventory
MDVP = Multi-Dimensional Voice Program
F0 = Average Fundamental Frequency (Hz)
Jitt% = Jitter Percent (Fundamental Period)
vF0% = Fundamental Frequency Variation
Shim% = Shimmer percent (Width of Peak)
vAm% = Peak-Amplitude Variation
NHR = Noise to Harmonic Ratio
VTI = Voice Turbulence Index
SPI = Soft Phonation Index
FTRI% = Frequency Tremor Index
ATRI% = Amplitude Tremor Index
DVB% = Degree of Voice Breaks
DSH% = Degree of Sub-harmonics
GERD = Gastro-Oesophageal Reflux

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Vestibology

STANDING, a four-step bedside algorithm for differential diagnosis of acute vertigo in the Emergency Department

Lo STANDING, un algoritmo bedside a quattro step per la diagnosi differenziale delle vertigini acute nel Dipartimento di Emergenza

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SUMMARY

Vertigo is generally due to a benign disorder, but it is the most common symptom associated with misdiagnosis of stroke. In this pilot study, we preliminarily assessed the diagnostic performance of a structured bedside algorithm to differentiate central from non-central acute vertigo (AV). Adult patients presenting to a single Emergency Department with vertigo were evaluated with STANDING (SponTAneous Nystagmus, Direction, head Impulse test, standiNG) by one of five trained emergency physicians or evaluated ordinarily by the rest of the medical staff (control group). The gold standard was a complete audiologic evaluation by a clinicians who are experts in assessing dizzy patients and neuroimaging. Reliability, sensibility and specificity of STANDING were calculated. Moreover, to evaluate the potential clinical impact of STANDING, neuroimaging and hospitalisation rates were compared with control group. A total of 292 patients were included, and 48 (16.4%) had a diagnosis of central AV. Ninety-eight (33.4%) patients were evaluated with STANDING. The test had good inter-observer agreement (k = 0.76), with very high sensitivity (100%, 95%CI 72.3-100%) and specificity (94.3%, 95%CI 90.7-94.3%). Furthermore, hospitalisation and neuroimaging test rates were lower in the STANDING than in the control group (27.6% *vs.* 50.5% and 31.6% *vs.* 71.1%, respectively). In conclusion, STANDING seems to be a promising simple structured bedside algorithm that in this preliminary study identified central AV with a very high sensitivity, and was associated with significant reduction of neuroimaging and hospitalisation rates.

KEY WORDS: STANDING • Benign paroxysmal positional vertigo • Vestibular neuronitis • Bedside algorithm

RIASSUNTO

La vertigine è generalmente dovuta ad una patologia benigna, ma rappresenta il sintomo più comunemente associato ad una mancata diagnosi di stroke. In questo studio pilota, abbiamo valutato in modo preliminare la validità diagnostica di un algoritmo bedside strutturato per differenziare le vertigini acute (VA) di origine centrale da quelle di origine non centrale. I pazienti adulti che si presentavano presso il nostro Dipartimento di Emergenza con vertigini venivano valutati con lo STANDING (SponTAneous Nystagmus Direction, head Impulse test, standiNG) da uno dei cinque medici del Pronto Soccorso adeguatamente istruiti, o in maniera tradizionale dal resto dello staff medico (gruppo di controllo). Il gold standard era rappresentato da una valutazione audiologica completa effettuata da un audiologo esperto e associata agli esami per immagini. Sono state calcolate la ripetibilità, la sensibilità e la specificità dello STANDING. Inoltre, per valutare in modo preliminare il potenziale impatto clinico dello STANDING, sono state confrontate le percentuali di richiesta di esami per immagini e di ospedalizzazioni con quelle del gruppo di controllo. Sono stati reclutati 292 pazienti, per 48 dei quali (16,4%) era stata diagnosticata una vertigine di origine centrale. Novantotto pazienti (33,4%) sono stati valutati con lo STANDING. L'intero algoritmo ha mostrato una buona concordanza tra gli esaminatori (K = 0,76), con una sensibilità (100%, 95%IC 72,3-100%) e una specificità (94,3%, 95%IC 90,7-94,3%) molto alte. Inoltre, le percentuali di ospedalizzazione e di richiesta di esami per immagini sono state più basse nel gruppo valutato con lo STANDING rispetto al gruppo di controllo (rispettivamente 27,6% vs. 50,5% e 31,6% vs. 71,1%). In conclusione, lo STANDING sembra un algoritmo semplice e promettente, identificando nella nostra popolazione non selezionata le VA di origine centrale con un'alta sensibilità e con una riduzione significativa del numero di esami per immagini e ospedalizzazioni.

PAROLE CHIAVE: *STANDING • Vertigine parossistica posizionale benigna • Neuronite vestibolare • Algoritmo bedside*

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Introduction

Vertigo is the illusion of the true rotational movement of self or surroundings and is a frequent complaint of patients presenting in the emergency department (ED) [1]. It is often associated with the presence of nystagmus and is most likely due to vestibular system dysfunction. Imbalance or disequilibrium refers to a sense of unsteadiness often indistinguishable by patients, and often by physicians, from true vertigo [2 3]. Many other symptoms of altered orientation in space are referred to as dizziness; the latter often represents several overlapping sensations and can be caused by many pathophysiological mechanisms and a variety of disorders, not necessarily vestibular in nature, such as presyncope (hyperventilation, orthostatic hypotension, vasovagal attacks, decreased cardiac output), anxiety disorders (panic syndrome, agoraphobia), hypoglycaemia and drug intoxication (alcohol, barbiturates, benzodiazepines): these conditions are defined as "pseudo-vertigo".

Vertigo is caused in 24-43% of cases by a benign peripheral disorder [4] such as benign paroxysmal positional vertigo (BPPV) or vestibular neuronitis (VN). However, although the most common causes of dizziness and vertigo are benign, differential diagnosis must include potentially life-threatening central disease [5]; indeed, vertigo can be the manifestation of central neurological disease such as cerebellar or brainstem stroke [6]. BPPV is characterised by recurrent short lasting vertigo triggered by head movements and can be revealed by diagnostic manoeuvres such as the Dix-Hallpike and Pagnini-McClure positionings [7-9]. The clinical features of VN are the subacute onset of vertigo associated with spontaneous nystagmus lasting days to weeks. Vestibular neuronitis is generally self-limiting and commonly attributed to viral aetiology. Similar clinical symptoms commonly occur in cerebellar infarction, sometimes without any accompanying neurological symptoms or signs except for acute vertigo (AV) and gait ataxia [3 10 11]. Several clinical tests to differentiate central from non-central AV have been investigated, but none reaches adequate sensitivity and specificity to be used as stand-alone test [11]. For this reason, clinical evaluation of patients with vertigo is often difficult and rarely conclusive, usually leading to an overuse of consultants and neuroimaging tests. Moreover, computed tomography (CT) brain scan, the test most commonly performed in the ED on a patient with dizziness [12], can easily miss central disease because of its low sensitivity, particularly in the posterior fossa [13 14]. Although magnetic resonance imaging (MRI) of the brain is more sensitive, it is not always readily available and is not a practical screening test in the emergency setting. All these pitfalls and technical obstacles contribute to the fact that in practice dizziness (a term used to encompass vertigo, pseudovertigo, imbalance or disequilibrium) is the symptom most commonly associated with a missed diagnosis of stroke [14 15]. We believe that the development of simple, reliable and accurate predictors is a crucial step to optimise the use of neuroimaging studies, improve diagnostic accuracy, enhance patient flow through the ED and reduce unnecessary hospitalisation.

The aim of this pilot study was to preliminarily assess the reliability and diagnostic accuracy of a simple structured clinical algorithm (STANDING: SponTAneous Nystagmus, Direction, head Impulse test, standiNG) that we developed to differentiate central from non-central AV in the emergency setting, and to evaluate in an explorative fashion if its use might be associated with a reduction of the neuroimaging burden and hospitalisation.

Materials and methods

Clinical setting and selection of participants

Consecutive adult patients presenting to the ED with AV with no associated focal neurological deficit (isolated vertigo) were prospectively evaluated in a single level III ED (mean attendance 60,000 people/year), between May 2011 and January 2012. All patients underwent clinical anamnesis and complete neurological examination. Exclusion criteria were the presence of pseudo-vertigo, severe cognitive impairment, or severe symptoms of dizziness that prevented the patient's cooperation, as well as refusal to participate the study.

Management strategies

Patients with isolated vertigo underwent ordinary clinical examination (control group) or clinical examination together with simple structured clinical algorithm (STANDING) by one of 5 emergency physicians, who had already completed a workshop managed by an expert clinician in assessing dizzy patients, consisting of 5 hours didactic and practical sessions, comprehensive of 15 STANDING proctored examinations.

After initial clinical assessment, with or without STANDING, the referring ED physician determined if the vertigo was of central or non-central origin and as necessary ordered further tests (in suspicious of a central AV, usually a head CT scan). Afterwards, within 24 hours, all patients underwent complete examination by a clinician expert in assessing dizzy patients. If central origin was suspected or uncertain (disagreement between expert physician and the attending emergency physician), the diagnosis was corroborated by brain MRI (see below) and in-hospital observation. Central vestibulopathy was diagnosed by the presence of a lesion in the posterior fossa in brain imaging or by the presence of a possible transient insult in the same region that required active treatment (vertebro-basilar transient ischaemic attack, TIA) [16]. When central vestibulopathy was diagnosed,

patients were admitted and treated accordingly. Otherwise, when both the attending emergency physician and the expert physician agreed on the non-central origin of vertigo, neuroimaging tests and in-hospital observation were not mandatory. The hospital's Institutional Review Board approved the study.

The STANDING test

The STANDING test is a structured diagnostic algorithm based on previously described diagnostic signs and bedside manoeuvres that we logically assembled in four sequential steps (Fig. 1).

1) First, the presence of nystagmus was assessed with Frenzel's glasses in supine position after at least 5 minutes of rest. When no spontaneous nystagmus was present in the main gaze positions, the presence of a positional nystagmus was assessed by the Pagnini-McClure manoeuvres first and then by the Dix-Hallpike positionings [7]. The presence of a positional nystagmus of the paroxysmal type was considered typical of BPPV.

2) Instead, when spontaneous nystagmus was already present in supine position and was persistent, the direction was examined: multidirectional nystagmus, such as bidirectional gaze-evoked nystagmus (i.e. right beating nystagmus present with gaze toward the right and left beating nystagmus present with gaze toward the left side), and a pure vertical (up or down beating) or torsional nystagmus were considered signs of central vertigo.

3) When the nystagmus was unidirectional (i.e. nystagmus beating on the same side independent of gaze direction and head position), we performed the head impulse test (HIT) [17]. When an acute lesion occurs in one labyrinth, the input from the opposite side is unopposed and as a result, when the head is rapidly moved toward the affected side, the eyes will be initially pushed toward that side and, immediately after, a corrective eye movement (corrective "saccade") back to the point of reference is seen. When the corrective "saccade" is present the HIT is considered positive and indicates non-central AV, whereas a negative HIT indicates central vertigo [18].

4) Patients showing neither spontaneous nor positional nystagmus were invited to stand and gait was evaluated. When there was an inability to maintain an upright stance without assistance, they were suspected to have central disease (Fig. 1).

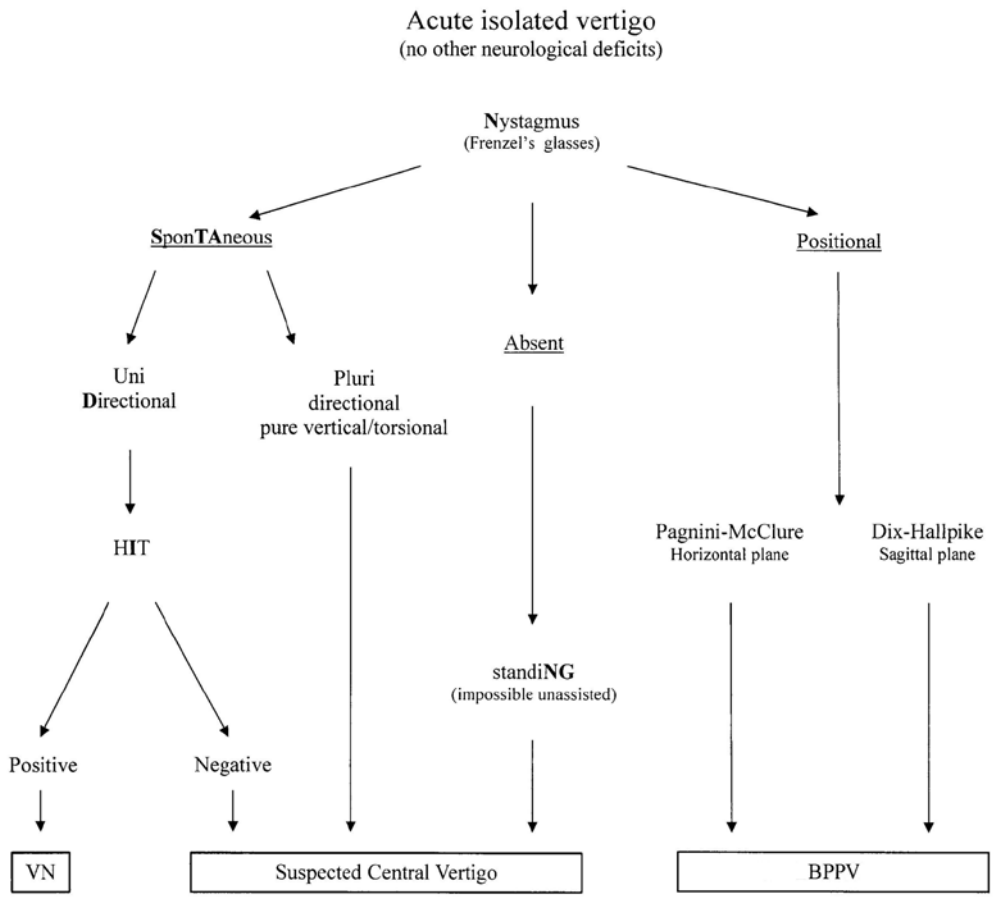

Fig. 1. Diagram of the STANDING approach. VN = Vestibular neuronitis; HIT = head impluse test; BPPV = benign paroxysmal positional vertigo.

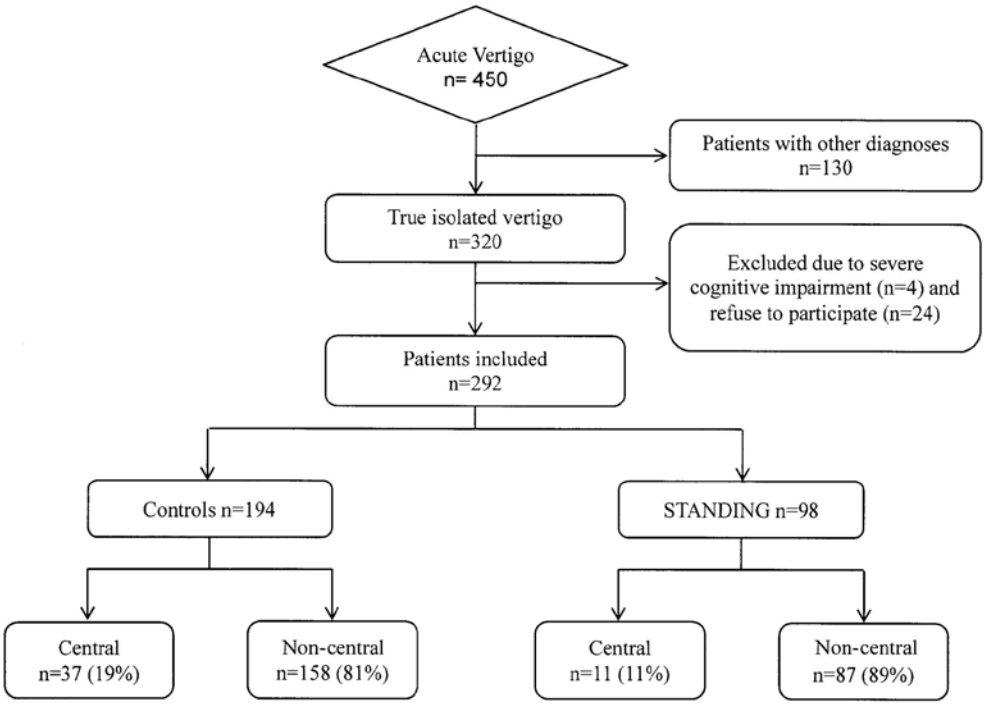

Fig. 2. Study flow diagram.

Neuroimaging

We performed a CT brain scan using a Somatom Definition AS128 instrument (Siemens, Erlangen, Germany) on every patient suspected to harbour central vertigo. When the CT was negative but central vertigo was still suspected, patients underwent MRI within 24-72 hours after initial evaluation. Patients underwent brain MRI stroke-protocol with a 1.5 Tesla Magnetom Vision/Plus (Siemens, Enlargen, Germany) instrument including; 1) multi-planar T1; 2) axial T2 or fluid attenuated inversion recovery (FLAIR); and 3) axial DWI sequences.

Statistical analysis

We express continuous variables as means ± standard deviation (SD), and dichotomous variables as percentages. The inter-observer reliability of two emergency physician was calculated by Cohen's k for each step of STANDING in a subgroup of patients (n = 30). We also tested the inter-observer agreement between the STANDING test and audiological evaluation. We assessed the diagnostic accuracy for central vestibulopathy of the STANDING test, calculating sensitivity, specificity, positive and negative predictive values with 95% confidence intervals (CI). To assess the potential clinical impact of the STANDING test, we compared the baseline characteristics and the neuroimaging test and hospitalisation rates of patients examined with the STANDING test with those of a control group, using a student's t-test for continuous variables and Fisher's exact test for dichotomous variables.

Calculations were performed using the SPSS statistical package (version 17.0, SPSS, Chicago, Illinois, USA).

Results

Patient characteristics

A total of 450 patients complaining of vertigo (Fig. 2) were evaluated in our ED during 8 months (0.8% of the overall presentations): among these, 130 (28.8%) were actually pseudo-vertigo, 4 (0.8%) patients presented a severe cognitive impairment and 24 (5.3%) refused to participate in the study and a definite diagnosis could not be made. The remaining 292 patients were included. The study population had a mean age of 58.2 years and 61% were females (Table I); at least one cardiovascular risk factor was present in 44.8% of patients.

Forty-eight patients (16.4%) of 292 had a final diagnosis of central disease: among these, 21 (43.8%) had a vertebro-basilar TIA and 14 had a stroke (29.2%), (Table II). A total of 244 patients (83.6%) had non-central AV, most often BPPV or VN (Table II).

CT brain scan was performed on 169 (57.9%) patients and revealed central disease in 26 (15.4%); 19 patients (6.5%) underwent head MRI that showed central disease

Table I. Baseline characteristics, neuroimaging tests and hospitalisation rates of ED patients presenting with acute vertigo.

	All patients n = 292	STANDING n = 98	Controls n = 194	Difference* % (95% CI)
Females (%)	178 (61%)	56 (57.1%)	121 (62.4%)	-5.2 (-17.9, +7.2)
Age (Mean ± Ds)	58.2 ± 16.3	60 ± 16.3	57.3 ± 11.3	+2.7 ± 22.1
CV risk factors (%)	131 (44.8%)	45 (45.9%)	86 (44.3%)	+1.6 (-11.1, +14.4)
Central Vertigo (%)	48 (16.4.%)	11 (11.2%)	37 (19.1%)	-8 (-15.3, +1.9)
CT brain scan (%)	169 (57.9%)	31 (31.6%)	138 (71.1)	-39.5 (-50.7, -27)
Brain MRI (%)	19 (6.5%)	10 (10.2%)	9 (4.6%)	5.6 (-1, +11.9)
Hospitalisation (%)	125 (42.8%)	27 (27.6%)	98 (50.5%)	-23 (-34.1, -10.4)

*CT: computed tomography; MRI: magnetic resonance imaging; CV risk factor: at least one of the following cardiovascular risk factors: diabetes, blood hypertension, smoke, dyslipidaemia; hospitalisation included both admission to general or neurological wards and in the observation unit; * absolute differences between STANDING and control groups.*

Table II. Specific diagnosis in patients evaluated with STANDING or routine tests (controls).

	STANDING n = 98 (%)	Controls n = 194 (%)
Central vertigo	11(11.2)	37 (19)
Ischaemic stroke	3 (3.1)	8 (4.1)
Haemorragic stroke	1 (1.0)	2 (1.0)
Cerebral tumour	2 (2.0)	3 (1.5)
Vertebrobasilar TIA	4 (4.1)	17 (8.7)
Other central diseases	1 (1.0)	6 (3.1)
Non-central vertigo	87 (88.7)	157 (80.9)
BPPV	60 (61.2)	104 (53.6)
VN	18 (18.3)	25 (12.9)
Other causes	9 (9.1)	28 (14.4)

TIA: transient ischaemic attack; other central disease: hydrocephalus, multiple sclerosis, epilepsy; BPPV: benign paroxysmal positional vertigo; VN: vestibular neuronitis; other causes: Menière's disease, migraineous vertigo.

in 7 (36.8%). A total of 125 patients (42.8%) were hospitalised: 91 (31.1%) of these patients were observed in-hospital for at least 24 hours; the other 34 (11.6%) were admitted to an internal medicine or neurology ward.

STANDING reliability and accuracy

Ninety-eight (33.6%) of the 292 patients were initially evaluated by ED physicians using the STANDING test. Of these, 60 patients (61.2%) had paroxysmal positional nystagmus, while 24 (24.5%) had spontaneous nystagmus that was pluridirectional in 2 (8.3%) and unidirectional in 22 (91.7%) cases. Among these, the prevalence of right and left beating nystagmus was similar (52.4% left and 47.6% right). HIT was performed in 23 patients and was negative in 4 (17.4%) and positive in 19 (82.6%) patients. In one (4.1%) of 24 cases, HIT was not applicable due to patient intolerance.

Fourteen patients (14.3%) did not show nystagmus; 10 of these patients, when invited to stand, revealed an inability to maintain an upright stance, and were diagnosed with potential central disease.

The reliability of the STANDING test between two ED physicians was tested in 30 patients. The Cohen's kappa of the first (spontaneous *vs.* positional nystagmus), second (unidirectional *vs.* pluridirectional or pure vertical/torsional nystagmus), third (HIT) and fourth (standing) step was 0.86, 0.93, 0.73 and 0.78, respectively. The Cohen's kappa of the final result of the test (central *vs.* non-central AV) was 0.76.

After performing the STANDING test, central vertigo was suspected by ED physicians in 16 (16.3%) of 98 patients and was confirmed by a clinician who was expert in assessing dizzy patients in 13 patients (13.2%). The STANDING test showed high agreement (95.9%) with audiological examination corresponding to a Cohen's kappa of 0.86.

Eleven (68.7%) of the 16 patients with suspected central vertigo, according to STANDING, had a final diagnosis of central vestibulopathy, whereas no patient with negative STANDING had a final diagnosis of central disease. Test characteristics are reported in Table III.

STANDING test vs. ordinary evaluation

When we compared the STANDING group to the control group, there were no statistically significant differences in gender, age, or prevalence of cardiovascular risk factors

Table III. STANDING test characteristics.

	Central vertigo Final diagnosis	Non-central vertigo Final diagnosis	Total
Central vertigo STANDING	11	5	16
Non-central vertigo STANDING	0	82	82
Total	11	87	98

Sensitivity: 100% (95% CI: 72.3-100%); specificity: 94.3% (95% CI: 90.7-94.3%); positive predictive value: 68.8% (95% CI: 49.7-68.8%); negative predictive value: 100% (95% CI: 96.3-100%).

(Table I). Central vertigo was slightly more common in the control group than in the STANDING group, but the difference was not significant.

In the STANDING group, 31 patients (31.6%) underwent CT brain scans that were positive in 3 patients (9.6%); 10 patients (10.2%) also underwent a brain MRI that was positive in 5 (50%). Hospitalisation was requested in 27 patients (27.6%), in most cases 24-48 hours observation (18 patients, 66.7%). CT and hospitalisation rates were significantly lower in the STANDING group than in the control group (Table I).

Discussion

In this study, a structured bedside algorithm (STANDING) performed by emergency physicians showed good reliability and high accuracy for detecting central vestibulopathy in an unselected population presenting with acute vertigo. The application of STANDING was associated with lower neuroimaging and hospitalisation rates than in controls.

Vertigo is a relatively common complaint that is often diagnosed and treated in the ED. In our study, conducted in an unselected population presenting to a level III ED, we found that about 1% of overall attendances presented with vertigo and that about 70% of these patients had true vertigo. In previous studies, similar results were found [1 18], but the prevalence was higher (1-10%) when all forms of dizziness were included [19].

Although vertigo is usually ascribable to benign aetiologies such as peripheral vertigo, in previous studies up to 25% of patients had central nervous system disease [1 20] and up to 5% of acute vertigo may be due to cerebrovascular disease [1]. In our cohort, a significant fraction (16.4%) had a central disease. Because of this concern, ED evaluations for vertigo are often lengthy, involve substantial use of diagnostic resources, and require many consultants. Although the use of neuroimaging and admission in patients with vertigo are disproportionately high, this does not correspond with improvements in the overall diagnostic yield for stroke [1 12]. Accordingly, in our cohort, CT brain scan was performed in more than half of the population with a low diagnostic yield (15.4%). In order to optimise both patient care and use of healthcare resources, some bedside techniques have recently been developed to assess stroke in patients with acute vertigo. Early studies investigated the association between individual symptoms, signs, or risk factors with the presence of central nervous system disease. Among these, multiple prodromal episodes of dizziness, neurologic symptoms including diplopia [21] and age over 50 years [13] were strongly associated with stroke. However, these studies provided a low level of evidence [11] due to their retrospective nature. More recently [22], in a series of 120 patients with vertigo/dizziness, Ozono et al. reported that the risk factors for cerebrovascular disease such as hypertension, heart disease and diabetes were also risk factors for central vertigo/dizziness; moreover, to predict a central origin for vertigo/dizziness, only gaze nystagmus was a significant factor. Cnyrim et al. considered the usefulness of finding skew deviation, gaze-evoked nystagmus, negative HIT, impaired vertical smooth pursuit and deviation of subjective visual vertical in a population of 83 patients with rotatory vertigo, postural imbalance and horizontal-rotational nystagmus, without additional inner ear, brainstem or cerebellar symptoms; the authors found that when all 5 signs were combined, the sensitivity and specificity in diagnosing central vertigo increased to 92% [23]. Similarly, based on the presence of negative HIT, central-type nystagmus, skew deviation and abnormal vertical smooth pursuit, classification of acute vestibular syndromes (distinguishing between vestibular neuritis and cerebellar or brainstem infarction) appeared to be reliable even in a stroke unit, as pointed out by Chen et al. [24]: despite the relative inexperience in neuro-otology of the stroke team, the sensitivity and specificity of bedside ocular motor testing were comparable to those reported by expert neuro-otologist. In another study, a structured bedside clinical examination was proposed [10]. Kattah et al. described a 3-step bedside oculomotor examination called HINTS (Head Impulse-Nystagmus-Test of Skew) for differentiating stroke from

acute peripheral vestibulopathy. The results of their study confirmed that a normal HIT is the single best bedside predictor of stroke, and showed that the HINTS appears to be more sensitive for stroke than early MRI. Furthermore, a fourth step (HINTS "plus") has been recently added to the HINTS protocol that includes assessing the presence of new hearing loss, generally unilateral and on the side of the abnormal head impulse test [25]: recent evidence suggests that the presence of such hearing loss more often indicates a vascular rather than viral cause of the acute vestibular syndrome presentation. Thus, in cases of inner ear strokes, in which HINTS eye movements are indistinguishable from vestibular neuritis, comorbid sudden hearing loss may be the only clue to stroke.

There are at least three important differences between our study and that of Kattah et al. First, we included all patients with acute vertigo without overt neurological signs, thus an unselected population which included not only patients with acute vestibular syndrome but also patients with other vestibulopathies and even those who did not have vestibular disease. We believe that in practice, to rule out a life-threatening disorder such as posterior cerebrovascular disease, the most effective way is to "rule in" one of the non-central specific disorders. Therefore, the STANDING algorithm provides the essential tools to recognise the most frequent peripheral vestibular diseases (BPPV and VN) and can help emergency physicians to identify the population of patients with central disease. However, by including all kind of vertigo we failed to submit all patients to a strong gold standard (brain MRI) as Kattah et al. have done.

Second, we propose a diagnostic algorithm, which includes nystagmus examination performed by emergency physicians, while in the HINTS study oculomotor examination was performed by expert neuro-opthalmologists. Nystagmus assessment is a key diagnostic feature in patients presenting with dizziness because the presence of specific types of nystagmus may be the only indicator of a potentially serious pathology, even if CT or MRI imaging are negative [26]. One prior study showed that ED physicians report in charts the presence or absence of nystagmus in most patients presenting with acute dizziness, but that they do not utilize this sign for diagnostic purposes [27]. In our study, STANDING showed good reliability and high accuracy in emergency physician hands. Finally, we point out that patients with presumed vertigo at the end of clinical examination not infrequently (14.3%) showed any signs of nystagmus. Our results indicate that these patients, due to the high prevalence of central disease (36%), should be carefully assessed.

In a recent study, Navi et al. [28] reported that the ABCD2 score is a useful tool to differentiate cerebrovascular from non-cerebrovascular causes of dizziness. However, the authors noted several limitations to their approach. In particular, the retrospective nature of the study may have overestimated the performance of the score. Moreover, the ABCD2 score does not include nystagmus examination, precluding comparison with the STANDING and the HINTS that remain the two diagnostic algorithms specifically developed for vertigo examination.

In an era in which efficiency and cost containments are warranted, STANDING may be a quick and inexpensive method that reduces healthcare costs. Indeed, STANDING was associated with a significant reduction of neuroimaging and hospitalisation rates. To our knowledge, this is the first study showing the potential clinical impact of using a structured bedside diagnostic algorithm in vertiginous patients presenting to the ED.

Limitations

Our data should be interpreted in the context of several limitations. First, it was limited to a single tertiary care referral centre with daily audiologist consultations and thus it is uncertain that STANDING will yield similar results in other settings. Second, our study lacks a strong gold standard (e.g. MR in all patients), and thus the derived sensitivity, specificity and accuracy of the test may have been overestimated. Third, the study was not randomised. Thus, the different CT and hospitalisation rates may be not accurate. Fourth, among central causes of vertigo we identified 40% of patients diagnosed with central diseases with vertebro-basilar TIA. Although *National Institute of Neurological Disorders and Stroke* criteria state that isolated vertigo should not be defined as TIAs, a recent study reports that in patients with definite vertebrobasilar stroke, isolated vertigo is the most common symptom preceding vertebrobasilar stroke [29]. Moreover, since patients with vertebrobasilar TIA were reported to have the same risk of subsequent stroke as those with carotid TIA [17], it may be useful to have a practical clinical prediction algorithm to identify subgroups of patients at high-risk of vertebrobasilar stroke.

Conclusions

Although our results should be interpreted with caution, in our unselected cohort the STANDING test appears to show high sensitivity and specificity to detect central vestibulopathy, with good reliability in the emergency setting. STANDING seems to be associated with a reduction of neuroimaging burden and hospital admission rates, and may thus be promising tool for evaluation of acute vertigo. This data, largely exploratory, should be confirmed in a properly designed clinical trial.

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Otology

Combined endoscopic-microscopic approach for vestibular schwannoma removal: outcomes in a cohort of 81 patients

Approccio combinato endoscopico-microscopico per l'asportazione del neurinoma vestibolare: risultati ottenuti su un gruppo di 81 pazienti

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SUMMARY

Patients affected by vestibular schwannomas typically report a number of symptoms and minor disabilities after surgery. Therefore, surgeons dealing with this pathology should also try to achieve a good QoL for patients who have undergone tumour removal. The aim of this study was to analyse QoL in subjects undergoing surgery for vestibular schwannomas and to try to establish a relationship with both the tumour size and post-surgical alterations (e.g. facial motor dysfunctions, difficulties in balance, persistence of headache and tinnitus). A retrospective analysis was performed on a consecutive series of 81 patients affected by vestibular schwannomas and treated by a combined microscopic-endoscopic approach. Three groups of patients were identified on the basis of tumour size. Group 1 (lesions < 25 mm) with 31 patients (38%); Group 2 (lesions > 26 mm and < 40 mm) with 39 patients (48%); Group 3 (lesions > 41 mm) with 11 patients (14%). Data obtained with the Short Form Questionnaire showed a statistically significant difference in QoL in those undergoing intervention compared with a control group of healthy subjects. The Glasgow Benefit Inventory Questionnaire showed that 25 (31%) patients felt better, 11 (14%) felt similarly, and 45 (55%) felt poorer health conditions in comparison to the pre-surgical period. Concerning the relationship between preservation of facial nerve function and QoL, using the Glasgow Health Status Inventory, it appeared that only 34% of subjects with good facial nerve function (RGS grade I-II) complained of worsening of QoL, while 45% of those with serious facial nerve injury (RGS grade IV-V) referred poorer QoL. Moreover, the possibility of recovery of facial nerve function during the months following surgery was clearly highlighted by our analysis. Our study confirmed the close relation between tumour size and post-surgical QoL, which is worse for patients affected by larger lesions.

KEY WORDS: QoL • Facial nerve • Vestibular schwannoma • Headache • Vertigo • Endoscopic surgery

RIASSUNTO

I pazienti affetti da un neurinoma vestibolare tipicamente lamentano un certo numero di sintomi e di piccole disabilità in seguito all'intervento chirurgico di asportazione del tumore. Per questo motivo, i chirurghi che si confrontano con tale patologia dovrebbero anche cercare di ottenere una buona QoL per i pazienti che si vengono sottoposti alla rimozione dei tale lesione. L'obiettivo di questo studio è stato di analizzare la QoL nei soggetti operati per tale patologia e cercare di stabilire una connessione tra le dimensioni del tumore e le alterazioni post-chirurgiche (es. disfunzioni motorie del nervo facciale, difficoltà nell'equilibrio, persistenza di cefalea e acufene). Un'analisi retrospettiva è stata eseguita su una serie consecutiva di 81 pazienti affetti da neurinoma vestibolare e trattati con un approccio combinato micro-endoscopico. Tre diversi gruppi di pazienti sono stati identificati sulla base delle dimensioni tumorali. Gruppo 1 (lesioni < 25 mm) con 31 pazienti (38%); Gruppo 2 (lesioni > 26 mm e < 40 mm) comprendente 39 pazienti (48%); Gruppo 3 (lesioni > 41 mm) con 11 pazienti (14%). I dati ottenuti mediante lo Short Form Questionnaire hanno mostrato una differenza statisticamente significativa nella QoL dei soggetti operati rispetto al gruppo controllo dei soggetti sani. Il Glasgow Benefit Inventory Questionnaire ha mostrato che 25 (31%) pazienti si sentivano meglio, 11 (14%) si sentivano allo stesso modo, e che 45 (55%) si sentivano peggio rispetto al periodo pre-chirurgico. Per quanto concerne la relazione tra preservazione della funzionalità del nervo facciale e la QoL, attraverso il Glasgow Health Status Inventory, è invece emerso che solo il 34% dei soggetti con una buona funzionalità del nervo facciale (RGS grado I-II) lamentava un peggioramento della QoL, contro il 45% di quelli con una seria compromissione del nervo facciale (RGS grado IV-V). La nostra analisi ha inoltre evidenziato la reale possibilità di recupero della funzionalità del nervo facciale durante i mesi successivi all'intervento chirurgico. In conclusione il nostro studio ha confermato la stretta connessione esistente tra la dimensione tumorale e la QoL del periodo post-operatorio che risulta peggiore nei pazienti affetti da lesioni più voluminose.

PAROLE CHIAVE: *QoL • Nervo facciale • Neurinoma vestibolare • Cefalea • Vertigine • Chirurgia endoscopica*

Introduction

Vestibular schwannomas (VS) account for 8-9% of intracranial tumours and 80% of tumours found within the cerebellopontine angle [1]. Unilateral progressive hearing loss, tinnitus, vertigo, and disequilibrium are the most common symptoms at diagnosis [1]. The management of VS has traditionally involved surgical removal of the tumour via skull base surgery. Technical success is measured by surgical outcomes such as preservation of facial nerve function and hearing. However, more recently, examination of patient-oriented outcomes, such as postoperative health-related quality of life (HRQoL) following VS surgery from the patient's perspective, has become an important measure of treatment outcome [2-11].

Many symptoms and minor disabilities may persist after surgery including hearing loss, facial nerve dysfunction, vestibular dysfunction, visual problems, tinnitus and headaches [5-7 9-11]. Several research teams have addressed this issue by attempting to evaluate the effect on QoL following various treatment options [12-14]. The assessment of QoL has mostly been made using generic widely known assessment tools such as the Short Form Questionnaire (SF-36) [15 16] and the Glasgow Benefit Inventory (GBI) [17].

The aims of the present study were first to evaluate the QoL in patients treated for VS using a combined endoscopic and microscopic approach. Second, we investigated the influence of the anatomical features of the tumour and other post-operative outcomes on post-operative QoL.

Materials and methods

In September 2013, a retrospective review was performed on the medical charts of 127 patients treated for VS in our department between January 2006 and March 2013.

Inclusion criteria were:

- patients older than 18 years of age;
- patients treated through a retrosigmoid approach with a combined microscopic and endoscopic technique.

Exclusion criteria were:

- patients with bilateral VS affected by NF2;
- patients treated through a trans-labyrinthine or middle cranial fossa approach;
- patients with recurrent pathology.

Facial nerve function was evaluated at hospital discharge using the Rough Grading System (RGS) facial grading system [18]. At least 6 months after surgery, clinical follow-up was performed on all patients and facial nerve outcome was re-evaluated. To investigate the QoL at follow-up, patients were invited to complete a questionnaire including four sections:

1) *GBI* to investigate the social, psychological and physical spheres.
2) *Glasgow Health Status Inventory (GHSI)* to investigate the correlation between facial nerve dysfunction and QoL.
3) *Short Form Questionnaire (SF-36)* to evaluate QoL and compare the results with a control group of healthy subjects.
4) *Persistence of headache* (A: no headache; B: mild pain; C: moderate pain not affecting normal activities; D: intense pain limiting normal activities).

Statistical analysis

Data obtained were analysed with SPSS 19.0 statistical software. To compare the clinical outcome and QoL of the three groups (on the basis of tumour dimensions and involvement of the internal auditory canal), Chi-square, Student's test, Anova test and Kruskal-Wallis test were used; a $p < 0.05$ considered statistically significant.

Standard surgical steps

All of the operations were performed under the control of Nerve Integrity Monitoring (NIM). A craniotomy (median diameter 3-4 cm) was performed behind the intersection between the Frankfurt line and the posterior mastoid edge. The dura was incised and the two flaps were set with silk thread. After studying the cisterna magna under microscopic vision, it was opened until complete deliquoration was obtained. The cerebellar lobe was retracted posteriorly to obtain adequate access to the tumour. At this point, endoscopic reconnaissance (performed with a 0° endoscope) could be made to evaluate all structures and, in particular, the course of the facial nerve. Next, the two arachnoid sheets covering the tumour were separated. The intracisternal portion of the tumour was approached and debulking of the lesion could be started with an ultrasonic aspirator in a centrifugal direction. After separation of the tumour from the cerebellum, the entry zone was identified by the surgeon with minimal drilling of the posterior bony part of the internal acoustic pore (the extent of which varied between different patients) to better visualise the acoustic and facial nerves. At this point, an endoscope was introduced (typically we use 30, 45 or 70° endoscopes with 4 mm diameter and 14 or 18 cm length; Storz, Culvery City, CA, USA). During this phase, in most cases the endoscope allowed complete visualisation of the lateral extent of the tumour and its connections with nervous structures. The dissection proceeded in a medio-lateral direction (from the meatus as far as the level of the internal auditory canal) using homemade tools of different sizes. After that, accurate inspection was performed to identify any possible residual tumour and to verify the anatomical integrity of the facial and cochlear nerves. Moreover, in those cases in which major cellularity of the internal acoustic pore was present, damage caused by the opening of petrosal cells could be detected and promptly repaired with muscle fragment and fibrin sealant. The facial nerve was finally stimulated to confirm its functional integrity. An accurate suture of the dura inci-

Table I. Summary of post-surgical outcomes in the different patient groups.

	N of patients	Drilling of IAC			Occurrence of post-surgical complications	Facial nerve function at discharge (RGS)			Facial nerve function at clinical follow-up (RGS)			QoL (GBI)		
		None	Slight	Important		I-II	III-IV	V-VI	I-II	III-IV	V-VI	Better	Equal	Worse
Group 1 (diameter < 25 mm)	31 (38.2%)	32%	46%	22%	9%	50%	39%	11%	92%	8%	0%	84%	13%	3%
Group 2 (diameter > 26 and < 40 mm)	39 (48.1%)	33%	54%	13%	17%	18%	51%	31%	55%	35%	10%	5%	41%	54%
Group 3 (diameter > 41 mm)	11 (13.5%)	30%	50%	20%	50%	20%	30%	50%	25%	62%	13%	0%	9%	91%

IAC: internal auditory canal; RGS: rough grading system; QoL: quality of life; GBI: Glasgow benefit inventory.

sion was made and the bony operculum repositioned. At the end of surgery, all patients were monitored within an intensive care unit (ICU) until the following day.

Results

A total of 81 patients were included in the present study. Mean age at surgery was 52.8 years (SD ± 1.42) (range 19-84); 51% were male and 49% female. The pathology involved the left side in 55% of patients, and the right side in 45%.

Mean duration of symptoms (since the first symptom until radiological diagnosis) was 31 months (median, 24 months). Hearing loss was the most common symptom of VS in the majority of patients (65%). Tinnitus was the most common symptom in 18% and vertigo in 12% of patients. Concerning hearing capacity before surgery, the majority of our patients (68%) had an inadequate hearing level according to the guidelines of the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) [19]. A retrosigmoid approach was performed considering the surgical experience of senior surgeons (LP, AP, GP), although hearing level was not serviceable in most patients. The most frequent presurgical comorbidity was arterial hypertension (28%) followed by diabetes (19%).

Accurate analysis of radiological features of lesions was performed by analysing the final preoperative MRI scan taken using gadolinium contrast agent. The mean diameter of the tumours was 27.65 mm (range 7-50 mm), also taking into account intracanalicular extension. Three different groups of patients were identified on the basis of tumour dimension:

- group 1 comprising small lesions < 25 mm: 31 patients (38%);
- group 2 comprising medium-sized lesions > 26 mm and < 40 mm: 39 patients (48%);
- group 3 comprising large lesions > 41 mm: 11 patients (14%).

A summary of post-surgical outcomes considering the different groups of patients is presented in Table I. Relative to internal auditory canal (IAC) involvement, 51 (63%) patients had a tumour occupying all of the IAC, 10 (12%) had a tumour occupying half of the IAC and 18 (22%) a tumour limited to the medial third of the IAC, while 2 (3%) of patients showed no involvement of the IAC. Drilling of the posterior portion of the IAC was necessary in 20% of cases.

Anatomical integrity of the facial nerve was present in 95% of all patients, while total resection of the nerve was necessary in 5%.

On the other hand, resection of the cochlear nerve was performed in the majority of patients. Anatomical integrity of the cochlear nerve was preserved in 32% of Group 1 patients and 9% of Group 2 patients. Of the 81 patients, according to the AAO-HNS classification, 78 patients had post-operative grade D with anacusis, 1 had grade B, 1 grade C, and 1 grade D with only residual hearing.

Tumour removal was macroscopically complete in all 81 patients considering both the intracisternal and intracanalicular areas.

Overall, 81% of patients had no complications after surgery. The main postsurgical complication was liquorrhoea, reported in 8% of patients. Other complications were bleeding in the posterior cranial fossa (3/81, of which only 2 required a revision surgery), dizziness (5%), trigeminal deficit (4%), cranial nerve deficits (other than VII and VIII) (3%) and meningitis (2%).

Facial nerve outcome was evaluated in all patients at discharge. A mild level of deficit (I-II by the RGS) was observed in 30% of patients, a moderate deficit (III-IV) in 44% of patients and a major deficit (V-VI) was observed in 26%.

At clinical follow-up, 92% of patients in Group 1 showed good facial nerve function (I-II), while in the immediate postoperative period, only 50% in this group obtained this performance. Among patients in Group 2, 55% showed a

Tabel II. Correlation between facial nerve dysfunction and QoL (sec. Glasgow Health Status Inventory).

Facial nerve grade (sec. RCS)	Better QoL	Same QoL	Worse QoL	Total
Grade I-II	24 (49%)	13 (23%)	19 (34%)	56 (69%)
Grade III-IV	4 (20%	7 (35%)	9 (45%)	20 (25%)
Grade V-VI	0%	1 (20%)	4 (80%)	5 (6%)

RGS: Rough Grading System; QoL: quality of life.

good facial nerve function (I-II) in comparison to 18% observed at discharge. For patients in Group 3, 25% showed good facial nerve function (I-II) at clinical follow-up, while at discharge only 20% of this group had obtained this performance. Moreover, in this latter group, it must be underlined that there was an important reduction in patients with severe facial nerve deficit (V-VI), which decreased from 50% at discharge to 13% at clinical follow-up, the majority (62%) showing a moderate facial nerve deficit (III-IV).

Overall, at follow-up evaluation, patients in our study showed a positive trend for facial nerve function recovery. In fact, subjects with good facial nerve function (I-II) increased from 30% at discharge to 69% at clinical follow-up. Subjects with moderate facial nerve deficit (III-IV) decreased from 44 to 25% and patients with severe facial nerve deficit (V-VI) decreased from 26 to 6%. Concerning additional motor disturbances related to facial nerve function, taste alteration and lacrimation deficit were both examined. Lacrimation deficit was predominant in comparison to taste alteration in all three groups of patients. No correlations were found between lesion dimensions and post-surgical headache.

Data obtained using the Glasgow Benefit Inventory (GBI) questionnaire showed that, for our patients, 25 (31%) felt better, 11 (14%) felt similarly, and 45 (55%) felt worse in comparison to the pre-surgical period. Concerning these data, no statistically significant differences were found between different age groups or social categories.

A significant correlation ($p < 0.001$) was observed between QoL after discharge and tumour dimensions: 91% of patients in Group 3 complained of a worsening compared with the presurgical condition *vs.* only 3% of patients in Group 1.

Regarding correlations between facial nerve dysfunction and QoL, the Glasgow Health Status Inventory (Table II) showed that a worsening of QoL occurred in only 34% of subjects when a good function of the nerve was maintained (grade I-II). On the other hand, patients with severe facial nerve injury (grade IV-V) showed a higher frequency of QoL worsening with a rate of 45%.

The absence of vertiginous symptoms before treatment was significantly related to the worsening of QoL after surgery ($p < 0.05$). On the other hand, the presence of vestibular imbalance before treatment was slightly correlated to this aggravation.

From the SF-36, a statistically significant difference was observed for QoL between our patients and the control group of healthy subjects ($p < 0.05$).

Finally, only one case of tumour recurrence (1/81) was observed in our patients (< 2%).

Discussion

Quality of life

Although there are numerous definitions of QoL, there is general agreement that it involves the patient's subjective assessment of their life situation. The World Health Organization's definition of QoL states that it is an individual's perception of their position in life in the context of their own culture and value systems. The definition further outlines that QoL is a broad complex concept spanning the person's physical health, psychological state, level of independence, social relationships and their relationships with their environment [20].

Larger tumours have traditionally been associated with greater surgical morbidity [4]. Irving et al. [8] demonstrated that overall postoperative QoL was worse for patients with a tumour size greater than 1.5 cm compared with those less than 1.5 cm. However, this has not been consistently demonstrated in many QoL studies [3-5 9].

With the SF-36, a clear dissatisfaction was noted between our patients and the control group. In particular, our patients reported significant limitations in terms of physical function and mental health. However, we found no correlation between VS dimension and QoL after surgery. This finding is similar to those reported by Alfonso et al. [9 21].

Nevertheless, in contrast to the SF-36 questionnaire, the GBI showed an important relationship between tumour dimension and QoL after surgery. In fact, only 3% of patients with a small VS (Group 1) complained of worsening of QoL, while 54% of patients in Group 2 and 91% in Group 3 referred poorer QoL.

With the Italian version of the GBI and GHSI, 55% of our patients reported a poorer QoL. This result is similar to that reported in other studies [4 11].

In our study, no correlation was found between QoL and different age groups, occupation, or the patient's qualifications. This result is in contrast with those of Nikolopoulos et al. [4] who found an improvement in postoperative QoL in older patients compared with younger patients. On the other hand, Tufarelli et al. [22] noted that patients

over 45 years of age perceived a worsening of QoL after VS surgery.
Another interesting finding from our analysis concerns subjects who achieved an improvement in symptoms after surgery. Overall, 31% of our patients felt better after tumour removal and, in particular, 84% of these had small lesions (Group 1).
Many patients undergoing surgical intervention for VS feel significantly affected by facial weakness and consider it one of the most difficult aspects of recovery [23]. It is well-known that tumour size is correlated with postoperative facial nerve outcome for VS [24 25]. In this context, it is surprising that several studies failed to demonstrate a statistically significant correlation between tumour size and patient-perceived QoL measures [26].
Concerning facial nerve function, our results demonstrated a statistically significant difference in QoL obtained by subjects with good facial nerve outcome (grade I-II) in comparison to those with severe nerve damage (grade V-VI). Our data also confirmed that wider tumours with involvement of the IAC are much more commonly associated with post-surgical facial motor dysfunction. This concept should be considered when planning treatment for individual patients, especially when deciding to switch from a 'wait and scan' policy to one of surgical removal.
Similar results were reported by Falcioni et al. [27] Those authors observed that the results for lesions larger than 3 cm were not satisfactory in a high percentage of cases; in fact, in this group of patients, there were still 12.1% of cases in which the facial nerve was interrupted plus an additional 20.6% of RGS Grades IV-VI 1 year after surgery in cases with anatomical preservation of the nerve.

Facial nerve function outcomes

With advances in facial nerve monitoring and surgical techniques for small- and medium-sized tumours, long-term facial nerve preservation rates are reported to be greater than 90%, but which is substantially lower for large tumours [28]. Rates of anatomic preservation are now routinely greater than 90%, although even with anatomic preservation of the nerve functional deficits may still occur [23].
Despite the fact that total integrity of the facial nerve was obtained in 95% of our patients with a normal electric response at nerve integrity monitoring, only 30% had attained good facial nerve function (grade I-II) at discharge. Nevertheless, our study confirmed the real possibility of recovery during the months following surgery. In fact, at first evaluation 6 months after the operation, the proportion of subjects with grade I-II RGS function increased to 48%. This was more evident in patients in Group I (92% from a previous rate of 50%) compared with subjects in Groups 2 and 3.
Interestingly, we did not observe any correlation between the presence of extra motor symptoms and grade of facial nerve dysfunction. In a publication from 2003, Yen et al. noted the same finding [29].

Vertigo and dizziness

A few studies have attempted to correlate validated QoL measures with balance dysfunction. Nicoucar et al. [25] reported that patients with balance problems had lower scores in all 7 categories of the SF-36 questionnaire with values for social functioning and vitality being statistically significant.
A study conducted by Rigby et al. [30] on patients' perception of the impact of postoperative symptoms on activities of daily life revealed that balance dysfunction was the most significant symptom for 14.3% of patients, ranking second to hearing loss. Its impact was rated as even more significant than that of facial weakness.
In our study, the presence of vestibular imbalance was also an important aspect closely related to QoL during the post-surgical period. From our data, it can be noted that a higher percentage of patients who did not complain of vertigo before surgery reported a worsening of QoL (57%) in comparison to subjects who had already experienced vertiginous attacks (26%).

Headache

Concerning headache, we verified that, in our patients, it did not have an important impact on ability to work and perform normal activities after discharge. In particular, the overall percentage of subjects complaining of disabling headache was 6%. This result appears to contradict previous studies [21 24] that reported higher rates of headache during the follow-up period. We hypothesise that this finding could be related to the lower number of subjects who underwent drilling of the posterior wall of the internal auditory canal.

Hearing function

Hearing preservation represents a difficult outcome of this surgery [31 32]. The hearing loss that occurred in 95% of our patients after surgery did not appear to be related to better or worse QoL. The high rate of hearing loss, which is lower in some reports, reflects our policy of surgical radicality (100% of subjects had total removal of the tumour). Hearing preservation in patients with medium or large sized acoustic neuromas in the authors' experience is not very likely. Actually, although in selected patients with small tumours and good preoperative hearing good tonal audiometry can be achieved post-operatively, in most of these patients poor post-operative vocal audiometry performances prevent satisfactory results.

Considerations on the role of endoscopy

Special mention must be made about the rate of liquorrhoea in our patients after surgery. In fact, this complication was present in 8% of patients, which is lower in comparison to data reported in other studies [33 34]. In our opinion, this outcome is closely connected to better visu-

alisation of the air cells guaranteed by the endoscope in the case of a highly pneumatised posterior wall of the internal auditory canal. We must also consider that drilling the posterior portion of the IAC was necessary in only 20% of patients, thanks to the use of endoscopic visualisation, and partially due to the erosion of the IAC by the enlarging neoplasm, which facilitated endosocpic procedures to the intracanalicular portion of the mass.

In this particular condition, endoscopic view allows us to note damage occurring to this area and permit its prompt sealing. Moreover, by using 45 and 30° endoscopes during the intrameatal phase, we could clearly visualise the extent of the tumour within the internal auditory canal, allowing its complete removal in all cases.

The possible disadvantages related to an endoscopic approach to VS are still debated. Application of the endoscope seems to be associated with risks of iatrogenic neural or vascular injury [35], and King and Wackym [36] reported the possibility of thermal injury caused by heat generated by the light of the endoscope. Nevertheless, thermographic evaluation by Hori et al. [37] did not reveal a significant increase in local temperature using an endoscope. Gerganov et al. [38] concluded that the application of the endoscope does not lead to heat-related or mechanical neural or vascular injuries, because the risk of loss of waves I, II, and V, both transiently or permanently, did not depend on application of the endoscope and was similar in the endoscope-assisted group and the no-endoscope group.

Conclusions

In conclusion, tumour size seems to be the most relevant factor influencing both facial nerve function and QoL outcomes after VS surgery. In fact, a consistent percentage of our patients with large tumours did not obtain good (RGS Grade I or II) facial nerve function postoperatively and showed QoL outcomes that were clearly worse compared with patients treated for smaller lesions. Nevertheless, this study showed the real possibility for many subjects to recover and improve facial nerve function during the months following the operation. Finally, even when good facial nerve function was obtained and important complications were avoided, our report underlines a possible decline in the patient's QoL. For this reason, patients undergoing VS surgery must always be aware of this possibility and their surgical selection should be carefully evaluated.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Barbed anterior pharyngoplasty: an evolution of anterior palatoplasty

Faringoplastica anteriore con fili autobloccanti: una evoluzione della palatoplastica anteriore

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SUMMARY

We present a new surgical technique for the treatment of snoring and mild obstructive sleep apnoea syndrome. This is a modification of anterior palatoplasty, and its main features are the use of self-locking (barbed) threads and the possibility of stabilise the palatal suture by fixing it to anatomical bone and fibrous structures. The technique is described in detail and some preliminary results are presented.

KEY WORDS: Snoring • Pharyngoplasty • Palatoplasty • Snoring surgery

RIASSUNTO

Viene presentata una nuova tecnica per il trattamento chirurgico del russamento delle forme di OSAS lieve. Si tratta di una modifica della classica palatoplastica anteriore, caratterizzata dall'impiego di fili autobloccanti e dalla possibilità di stabilizzare la sutura palatale ancorandola a strutture anatomiche osteo-fibrose vicine. Tale tecnica viene dettagliatamente descritta e vengono forniti alcuni risultati preliminari.

PAROLE CHIAVE: *Russamento • Faringoplastica • Palatoplastica • Roncochirurgia*

Acta Otorhinolaryngol Ital 2014;34:434-438

Introduction

It is well known that the noise of snoring is generated mainly at the level of soft palate and surrounding structures; therefore, surgical treatment of snoring has been based on procedures that aimed to shorten/reduce soft palate or to stiffen the soft palate itself to decrease vibrancy [1-3]. Taking into account surgical proposals of several authors, we developed a new pharyngoplasty technique to reduce snoring and prevent obstruction in mild obstructive sleep apnoea syndrome (OSAS). Its main indication, according to our protocol, is represented by a anteroposterior pattern of palatal vibration/obstruction.

In 2007, Pang and Woodson [4] presented the expansion sphincter pharyngoplasty (ESP), a new method of treating sleep respiratory obstruction due to palatal collapse; this technique requires dissection of the lower edge of palatopharyngeal muscle and its attachment to " the arching fibers of the soft palate anteriorly… through the muscle bulk itself " on both pharyngeal sides. ESP, which can be associated with tonsillectomy when needed, proved to be effective in OSAS treatment and is now widely performed.

In 2009, Pang et al. [5] published the results of anterior palatoplasty [6], a modified CAPSO [7] technique that was used for treatment of 77 patients with mild or moderate OSAS. Their results showed the effectiveness of this procedure considering both obstruction and snoring.

Lately, in 2012 Mantovani et al. [8] designed the "Roman Blinds" technique, a non-resective surgical procedure that shortens and stiffens the soft palate by means of threads anchored to fibro-osseous attachments: the posterior nasal spine and both the pterygoid hamuli. Later, they considered the possibility of utilising self-locking threads to perform this type of uvulo-palatal lifting [9].

Our method allows stabilisation of the palatal suture (after removing the mucosal flap), and anchoring it to fixed points such as pterygoid hamuli, palatal aponeurosis and both pterygo-mandibular raphes (Fig. 1) employing barbed self-locking threads with no need for knots: this can be considered an evolution of anterior palatoplasty that can be referred to as *barbed anterior pharyngoplasty* (BAPh).

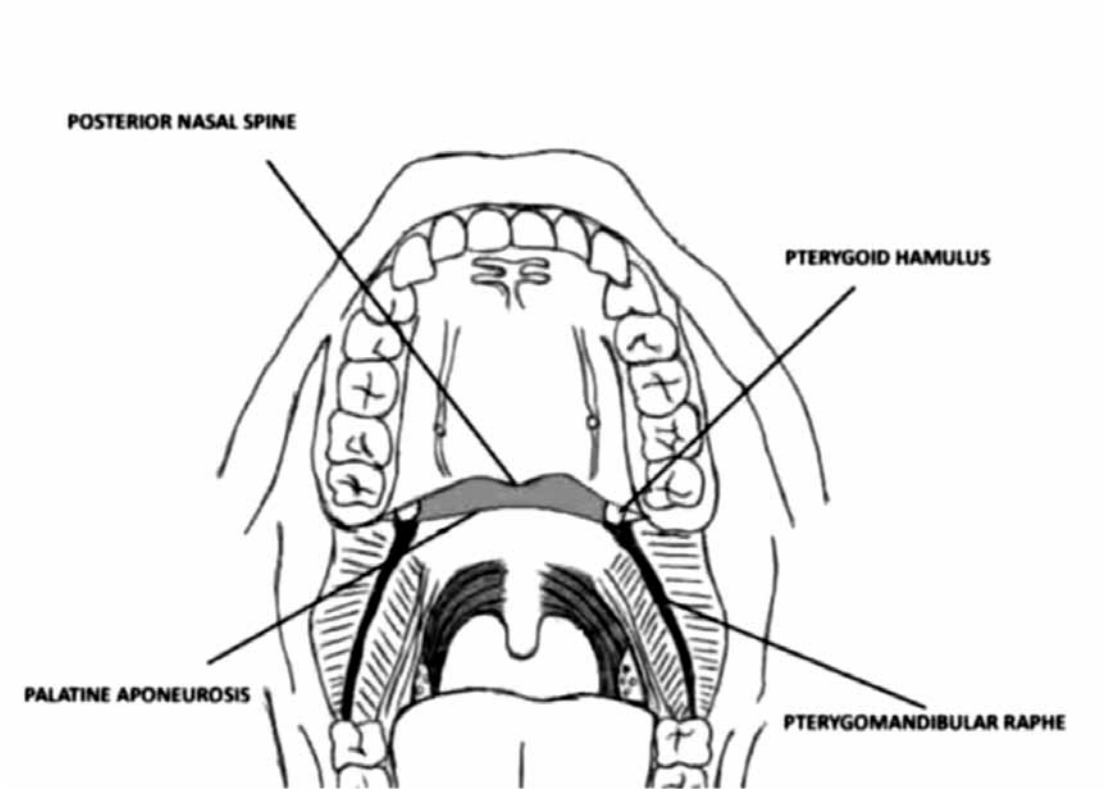

Fig. 1. The landmarks of barbed anterior pharyngoplasty.

Materials and methods

Subjects

We performed our technique on a group of 24 selected subjects presenting heavy snoring or with a mild OSAS syndrome (AHI < 15); mean AHI = 7.2, range from 0.7 to 14. The group was composed of 17 men and 7 women, with mean age of 46 (range from 34 to 55) and an average BMI of 28.6 (from 24.3 to 30.1).

We recruited, in this first stage, only patients with tonsil grade 0 and 1, or who had formerly been subjected to tonsillectomy.

All subjects had requested surgical treatment because the intense noise during the night represented an important discomfort for their bed partners. Each patient underwent sleep endoscopy (preliminarily or in the same session of surgery) to confirm the actual site and pattern of vibration and obstruction [10 11].

Hardware

Surgical instruments used for our procedure are the same used in classical Pang anterior palatoplasty: i.e. McIvor mouth gag, electrocautery, bipolar cautery forceps, needle holder and scissors.

The specific device for this procedure is the barbed thread, which allows to suture the different muscular and mucosal planes and to suspend the suture itself to the support points without tying knots. Barbed threads allow better maintenance of the suture itself since the tension is distributed along the entire length of the wire, and not only in correspondence of knots as in normal sutures. Among the available types of barbed threads we chose the QUILL® knotless tissue closure device, Angiotech Pharmaceutical Inc., Vancouver, Canada, because it is provided with two needles. We used the 0 polydioxanone absorbable (in six months) thread in the 24 × 24 ½ cm configuration, with two 36.5 mm circle needles (Fig. 2). This is a 48 cm thread, with a barb direction transition point in the middle; the two halves of the thread, with an opposite direction of barbs, can be used to perform the different layer of palatal suture.

Anaesthesia

Surgery was conducted under general anaesthesia with oral-tracheal intubation; the surgeon sits at the head of the patient without magnification of the surgical field.

Surgical technique

The first step in our procedure is to mark reference points with a dermographic pen: the end point of osseous palate on the midline (the posterior nasal spine), the relief of pterygoid hamulus and pterygomandibular raphe of both sides.

Then, as in Pang's anterior palatoplasty, the mucosal palatal flap is dissected and removed: this flap consists of a

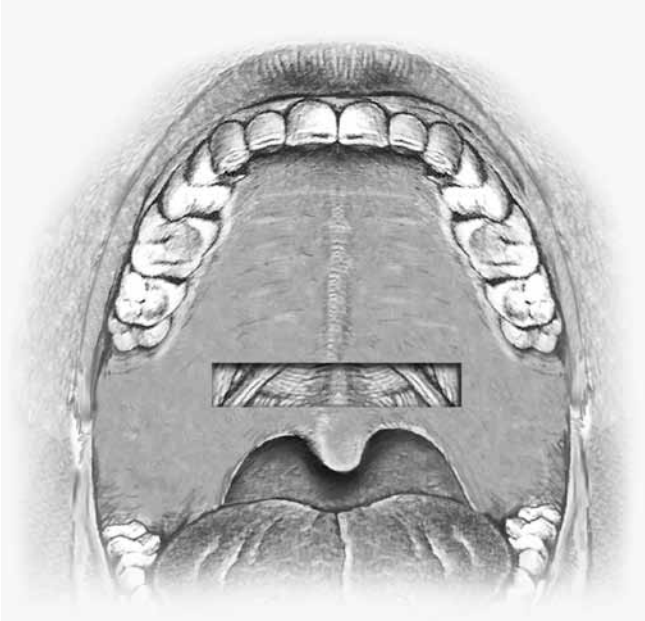

Fig. 2. The area of mucosal removal.

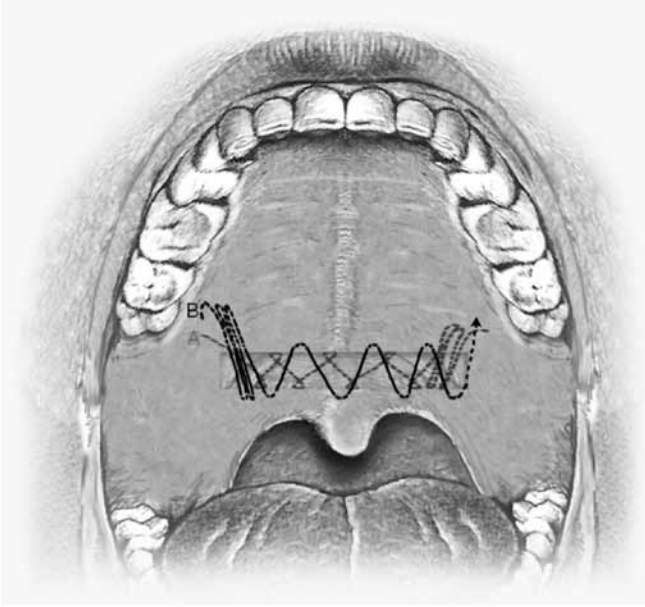

Fig. 3. The intramuscular suture.

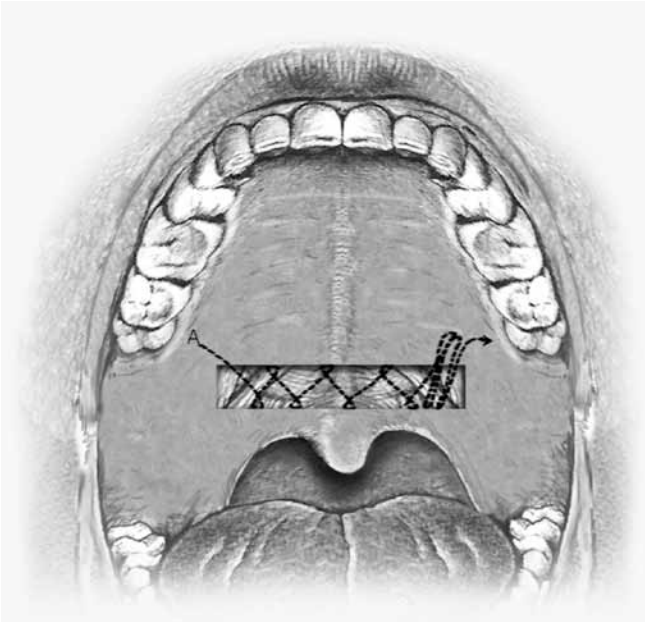

Fig. 4. The submucosal suture.

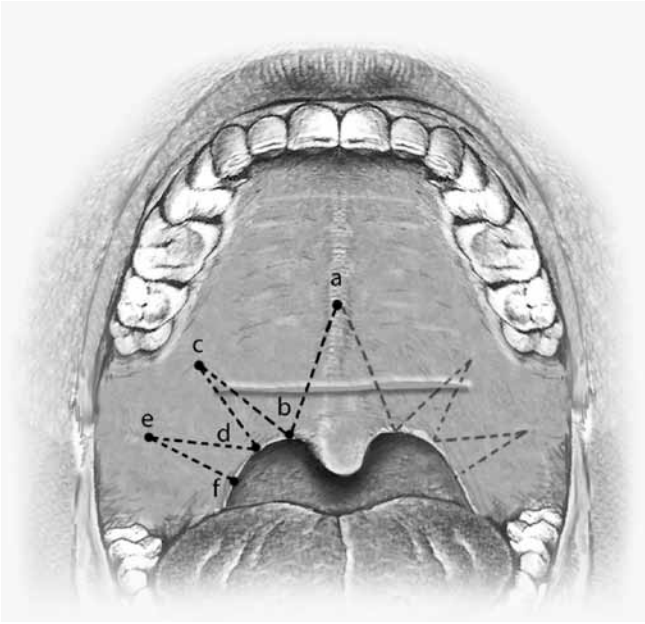

Fig. 5. The final Roman Blind technique suture.

rectangular portion of palatal mucosa whose upper corners are located close to the hamuli, a few mm below their reliefs; the excision area extends for 10-12 mm (depending on soft palate length) in the central part of the soft palate between the edge of osseous palate and the uvula attachment (Fig. 2). When removing the mucosal strip, it is quite important to remove the submucosal layer at the same time, containing many minor salivary glands, in order to expose the naked muscular surface. Haemostasis is performed using bipolar cautery forceps.

1st Layer: muscular suture (Fig. 3): with one of the two needles we enter into the soft palate in correspondence of right pterygoid hamulus and exit at the level of the lower right angle of the area where the mucosal flap was removed (A); the thread must be pulled out completely until the transition point blocks the progression of the thread itself; starting from here, we tighten the underlying muscles (levator palati, palatoglossal and/or palatopharyngeal muscles) with a 8 shaped intra muscular continuous suture. When this step is completed (5 or 6 passes are requested), it is stitched 2 or 3 times, and once more in the muscular plane, connecting the left edge of the wound to the left hamulus, in order to achieve a firm fixing point. The thread is then cut at the mucosal level.

2nd Layer: sub mucosal plane (Fig. 4): The needle of the other segment of the thread that starts from the barbs transition point is used to connect, with 3 or 4 sub mucosal stitches, the right hamulus to the right edge of the wound (B); a submucosal continuous suture is then performed connecting the lower edge of the wound to the palatine aponeurosis and emerging at the level of the left hamulus. The thread is cut again at the exit point. At this time, the distance between horizontal edges of the wound is reduced to about 1.5-2 mm and both the extremities of the suture are well anchored to pterygoid hamuli.

The Roman Blind Technique (Fig. 5): in order to further stabilise the soft palate and to juxtapose the edges of the wound, we lastly perform, using another double barbed wire, the Roman Blind Technique as proposed by Mantovani et al.: i.e. intra muscular stitches connecting on both sides the posterior nasal spine (a), the edge of soft palate (b), the hamulus region (c), the posterior pillar (d), the mandibular raphe (e) and back to the posterior pillar (f).

At the end of the procedure, the soft palate is shortened and pulled forward; the distance between the soft palate and the posterior pharyngeal wall is increased; the wound is closed in the near absence of visible threads.

Results

Preliminary results, based on bed partners' opinions, confirmed that all patients obtained a consistent reduction of snoring and even disappearance of noise in some cases, once the uvular oedema was resolved and palatal fibrosis was established. The mean score in the Snoring Visual Analogic Scale was reduced from 9.2 to 2.9. In mild OSAS patients, which were a minority (7/24), the mean AHI changed from 8.9 to 3.8.

All patients were discharged on the first day after the procedure: antibiotic and analgesic therapy was prescribed; when uvular oedema was present, we prescribed corticosteroid therapy for 5 days. Some dietetic restrictions were applied, as during the course of post-tonsillectomy.

Postoperative pain, in the patients' opinions, was mild to moderate for the first 5-6 days, then slowly decreased; after two weeks pain had usually disappeared.

In many cases (19/24), the extremity of the thread was partially extruded for a short segment, due to the natural retraction of the tissue; in these patients, it was necessary to cut the protruding piece of the wire.

We did not observe any velar insufficiency or dehiscence of the wound. After 4 to 6 weeks, a fibrous scar was observed in correspondence of the palatal wound, with a consequent increase in velar stiffness.

Discussion

The innovations we added to Pang's anterior palatoplasty permit, in our opinion, good stability of the suture, producing a better development of palatal fibrosis that provides an effective final stiffness. This effect is further supported by the needful use of barbed self-blocking threads, thanks to their property of spreading the tension along the entire length of the wire. The practical execution of the surgical procedure is, moreover, made easier because knots are not required: this is a considerable advantage in a small field such as the oral cavity.

In our experience, postoperative discomfort is not significantly different from that observed in anterior palatoplasty, when considering both postoperative pain and recovery time.

Conclusions

We believe that barbed anterior pharyngoplasty is an effective surgical procedure for the treatment of snoring and mild OSAS; the indication is represented by the anteroposterior pattern of palatal vibration/obstruction. It ensures valid palatal stiffness with a good shortening of the velum without significant tissue removal. Furthermore, the technique prevents disjunction of the margins of the palatal wound that we sometimes observed in classical anterior palatoplasty.

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Case series

Late treatment of orbital fractures: a new analysis for surgical planning

Trattamento tardivo delle fratture orbitarie: una nuova analisi per la programmazione chirurgica

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SUMMARY

Surgical treatment of orbital fractures should be performed without delay; in some cases acute management is not possible due to general conditions and might be delayed for weeks or months. In the latter case, the fractured fragments can consolidate improperly, causing secondary deformities of the orbital region with aesthetic and functional alteration. Surgical planning of secondary deformities is critical for adequate pre-operative planning. In the last decade an increasing number of dedicated software applications for surgical planning have been developed. Standard computed tomography (CT) or the relatively new cone beam CT can be used for diagnostic purposes, pre-surgical visual treatment outcome and virtual surgery. In this report, the authors propose their pre-operative planning analysis for surgical correction of secondary deformities of orbital fractures. The treatment of orbital fracture must, in fact, analyse not only the bone structures but the soft tissue and surrounding periorbital region. The position of the orbit in the space should be determined in relation to the surrounding structures compared to the contralateral side, if this is not affected by the trauma or pre-existing malformations.

KEY WORDS: Orbital fracture outcomes • Surgical planning • Two-dimensional analysis • Three-dimensional analysis

RIASSUNTO

Il trattamento chirurgico delle fratture orbitarie dovrebbe essere teoricamente effettuato il più precocemente possibile; in molti casi tuttavia l'intervento deve essere rimandato per qualche settimana o mese a causa delle condizioni generali del paziente. In questo ultimo caso è possibile che i frammenti fratturati si consolidino in posizioni errate causando deformità secondarie alla regione orbitaria con alterazioni funzionali ed estetiche. Un adeguato ed attento programma chirurgico delle deformità secondarie diventa quindi di fondamentale importanza per una perfetta riuscita del trattamento sia da un punto di vista di integrità delle strutture ossee che per quanto riguarda gli aspetti estetici. Nell'ultimo decennio si è sviluppato un numero sempre maggiore di software per la programmazione chirurgica. Sia tramite TC che tramite la nuova tecnologia Cone Beam è possibile ottenere file da poter utilizzare per scopi diagnostici, di previsualizzazione chirurgica o di chirurgia virtuale. In questo lavoro gli Autori propongono la loro metodica di programmazione pre-chirurgica nella correzione delle deformità secondarie alle fratture orbitarie. La valutazione e, di conseguenza, il trattamento di queste fratture deve essere basato non solo sulle strutture ossee ma anche, e soprattutto, sui tessuti molli della regione periorbitaria. È fondamentale quindi analizzare la posizione dell'orbita nello spazio in relazione alle strutture che la circondano ed alla regione controlaterale, se scevra da esiti traumatici o da malformazione pre-esistenti.

PAROLE CHIAVE: *Risultati nelle fratture orbitarie • Programmazione chirurgica • Analisi bidimensionale • Analisi tridimensionale*

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Introduction

Orbital fractures, like all fractures of the maxillo-facial skeleton, require early surgical treatment, at most within a week after the trauma. Sometimes however, surgical treatment needs to be delayed for weeks or even months, either for general reasons or due to the occurrence of life-threatening injuries. In these cases, the fractured fragments can consolidate improperly [1 2]. Orbital fractures can be isolated, part of an extended fracture (such as Le Fort III fracture) or part of comminute fractures of the midface. The success of delayed trauma surgery depends on diverse aspects of the preoperative evaluation of the defect. Computed tomography (CT) and cone-beam CT (CBCT) is widely used to support the surgical planning process. Three-dimensional (3D) visualisation techniques can also be used in order to facilitate surgical planning. Moreover, diverse image-reformatting software packages have been developed for the this purpose (e.g. Analyze; Mayo Clinic, Jacksonville, FL; Mimics; Materialise NV, Leuven, Belgium; 3-D Doctor; Able Software Corporation, Lexington, MA; SliceOmatic; TomoVision, Montre-

al, Quebec, Canada). These tools supply the surgeon with a 3D analysis and measurements, and some also provide a surgical simulation platform. Solid free-form fabrication (SFF) technologies, originally developed for industry, have been receiving a great deal of attention in the medical sector in the past few years. SFF-manufactured anatomical models find applications particularly in oral, maxillofacial and neurological surgery to assist diagnosis, planning treatment and manufacturing implants. The effectiveness of SFF models has been shown in various surgical procedures [3,4]. Currently, the SFF techniques used in medical applications are 3D printing (3D-P), stereolithography (SLA), selective laser sintering (SLS), fused deposition modelling (FDM) and electron-beam melting (EBM). In the present paper, the authors propose their pre-operative analysis for the correction of secondary post-traumatic orbital deformities. Three-dimensional graphic rendering was done using the Dolphin Imaging Plus 11 software (Dolphin Imaging and Management Solutions, Chatsworth, CA).

Clinical examination

The first phase of objective examination includes aesthetic evaluation of the patient, highlighting any change of appearance and facial expressions, bipupillary line alignment, enophthalmos, eye movement alterations, the position and movement of the eyelids and the inclination of the palpebral fissure with its symmetry and direction. Palpebral ptosis can often appear simply due to loss of upper eyelid support from the displaced eyeball (false ptosis). It is important to distinguish this form of ptosis from a true one, which is caused by damage to the elevator palpebrae superioris muscle or damage to the 3rd cranial nerve. In the latter case, there is also a defect of ocular motility of the four recti muscles. With simple inspection, it should be possible to locate the region affected by the trauma, to identify any losses of hard or soft tissue substance and evaluate the integrity or possible involvement of the optic nerve, of the 3rd, 4th, 6th and 7th cranial nerves. In normal conditions, the eyeball protrudes from the orbital frame by between 18 and 20 mm and a regression of 2 mm is considered the limit beyond which surgical correction is advised. Evaluation of diplopia is fundamental for therapeutic strategy. Diplopia is closely connected to enophthalmos and can occur in primary gaze or habitual position. The red glass test should be performed for diplopia and/or the Parks 3-step test and/or Bielschowsky's test in the case of vertical diplopia along with the Hess screen test. The forced duration test is an objective method for examining extrinsic ocular motility; a positive result allows the exclusion of secondary paralysis of the oculomotor muscles due to orbital fractures. In orbital trauma, in addition to basic examination with visual acuity test, ophthalmological evaluation also includes split lamp, ophthalmoscopic examinations including careful evaluation of ocular motility and binocular visual field, and electromyography to assess muscular function and of course CT and MR.

Surgical planning

Computed tomography provides analysis of the orbit on the axial, coronal and sagittal planes. CT images should be of a maximum thickness of 1 mm; the axial scans should be parallel to the Frankfurt plane on the lateral (the plane passing through the porion and lower orbital point). The acquired images should be oriented according to a standardised model referred to as reslicing, which can be performed either by the technician or by the treating physician, thanks to the introduction of software which allows both two-dimensional analysis on axial, coronal and sagittal reconstructions as well as on three-dimensional views (Dolphin Imaging®).

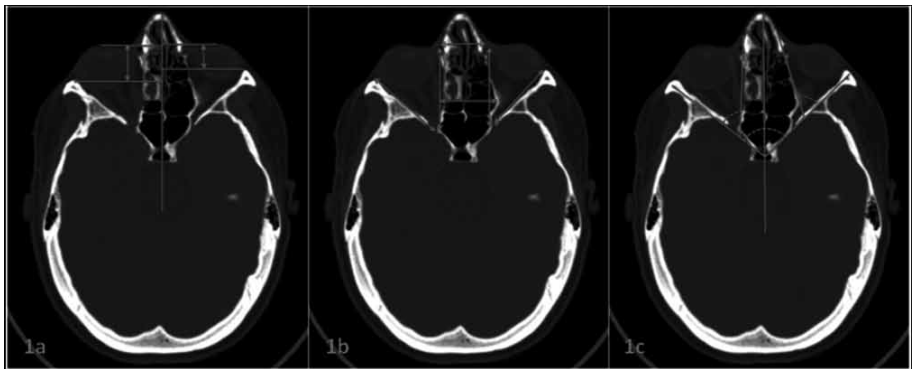

Fig. 1. a. A line from the nasion and passing through the nasal septum and the sphenoidal sinus; a line through the most retruded point of the lateral wall of the orbit; a line tangent to the corneal apex; position of the zygomatic bones and the nasion; analysis of optic nerve curvature. **b**. Inter-dacryl distance; transverse dimension of the ethmoid; length of the medial and lateral walls. **c**. The angle subtended to the extensions of lines passing through the lateral walls of the two orbits; the angle subtended to the extensions of lines passing through the medial and lateral wall of an orbit.

Two-dimensional evaluation axial plane

A line projected from the nasion and passing through the nasal septum and the sphenoidal sinus represents the plane of symmetry. Selection of axial images that best represent the equator of the eyeball is then made. (Fig. 1a).

Linear measurements

• Protrusion or intrusion of the eyeball expressed as exo- or enophthalmos (normal values are 10-14 mm for children and 15-

19 mm for adults). Two lines are drawn perpendicular to the median. The first represents the reference plane and passes through the most retruded point of the lateral wall of the orbit, while the second represents a projection of the eyeball and is at a tangent to the corneal apex (Fig. 1a). The projection of these two lines on a sagittal median plane corresponds to the quantification of the exophthalmos or enophthalmos in relation to the values codified by Hertel for exophthalmometry.
- Position of the zygomatic bones (Fig. 1a).
- Position of the nasion (Fig. 1a).
- Analysis of optic nerve curvature (Fig. 1a).
- Inter-dacrial distance (the distance between the two anterior lacrimal crests, dacryon) (Fig. 1b). The normal range of measurements for this distance is about 18 mm in newborn infants and 25 mm in adults. Hypertelorism is classified as slight (30-34 mm), moderate (35-39 mm) or severe (greater than 39 mm). This value can also be evaluated in coronal reconstructions.
- Transverse dimension of the ethmoid (Fig. 1b).
- Length of the medial and lateral walls (Fig. 1b).

Angular measurements
- The angle identified by the lines passing through the lateral walls of the two orbits (normally 90°). (Fig. 1c).
- The angle identified by the lines passing through the medial and lateral wall of an orbit (approximately 45°) (Fig. 1c).

Two-dimensional evaluation coronal plane

A line projected from the crista galli to the anterior nasal spine and passing through the nasal septum (if not deviated) represents the plane of symmetry (Fig. 2c).

Linear measurements
- Interdacrial distance (select the coronal section in which both anterior lacrimal crests are visible and measure the most cranial portion) (Fig. 2a).
- Transverse dimension of the ethmoid (Fig. 2c).
- Vertical dimension of the orbit (Fig. 2b).
- Position of the superior and inferior orbital margins in relation to the contralateral orbit or reference planes (occlusal plane, maxillary plane, interzygomatic plane and median sagittal plane) (Fig. 2c).
- Position of the orbital floor and roof (Fig. 2c).

A posterior coronal section where the superior orbital margins are both visible at the same time and helps determining the orbital parameters, the angle of the orbital floor in relation to median reference plane; if reference points are unavailable, a linear measurement system can be adopted based on a plane passing through the palatine shelves of the maxillary bones. Projections of the reference points used on the sagittal median plane can be made to evaluate any discrepancy.

Two-dimensional evaluation sagittal plane

Linear measurements

Select sagittal sections parallel to the sagittal median plane. Some reference points should be defined tangent to

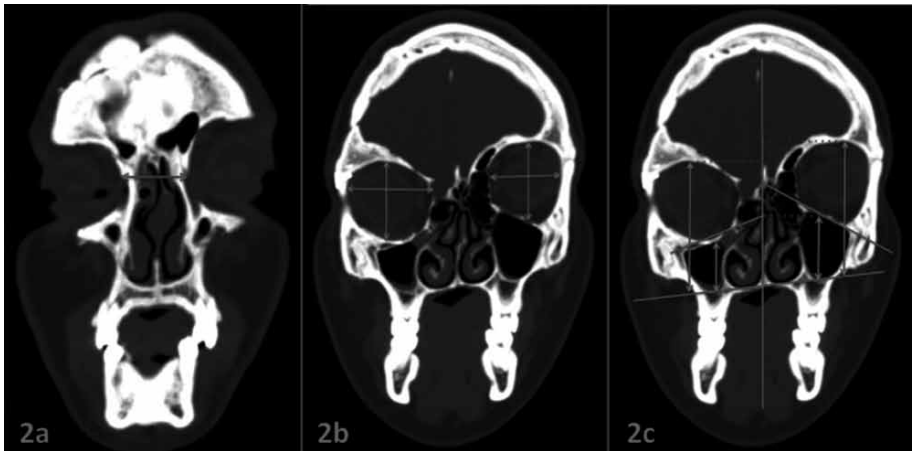

Fig. 2. a. Interdacryl distance. **b.** Vertical dimension of the orbit. **c.** A line from the crista galli to the anterior nasal spine and through the nasal septum; position of the superior and inferior orbital margins in relation to the contralateral orbit or reference planes; transverse dimension of the ethmoid; position of the orbital floor and roof.

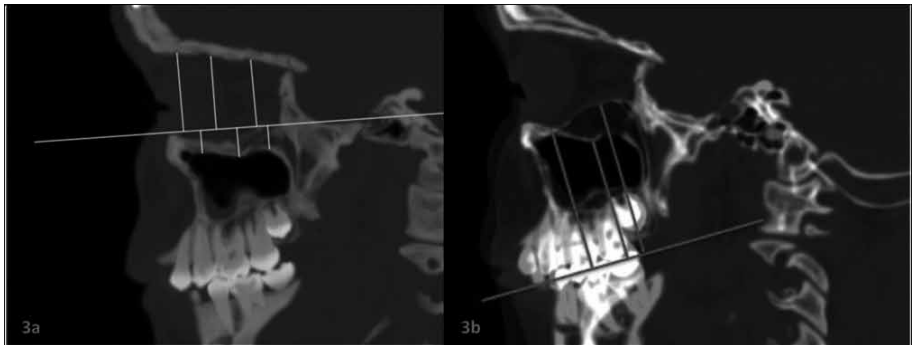

Fig. 3. a. Heights of the orbital cone. **b.** Distances of the floor and roof from a reference plane.

the sections to be measured in order to achieve symmetry between the two sides. It is suggested to use the plane at a tangent to the lacrimal sac at its most lateral point, the plane passing through the exit point of the optic nerve and a plane passing through the medium section of the eye. The measurements can be repeated on multiple slices.

- Heights of the orbital cone (Fig. 3a).
- Distances of the floor and roof from a reference plane (occlusal plane, Frankfurt plane) or in relation to the values of the superimposed healthy orbit (Fig. 3b).

Three-dimensional evaluation

Craniometric routine includes initial evaluation of the individual parts of the orbit on a frontal view of a three-dimensional bone window CT image. Next, the vertical diameter of the eye area is measured, taken between the most concave points of the superior and inferior orbital margins. The transverse diameter is then measured from the frontozygomatic suture to the frontonasal suture and, at a lower level, the maximum transverse diameter from the most concave points of the lateral and medial margins of the orbit. If any reference points is absent, other points, such as the mesiovestibular cusps of the first upper molars, may be used to obtain some absolute linear values (Fig. 4a). The soft tissue window is then superimposed to identify the lateral and medial palpebral canthi and palpebral fissure (Fig. 4b). Linear measurements are then made from certain skeletal points considered as references, such as the frontozygomatic suture for the lateral canthus and the lacrimal bone for the medial canthus. All these measurements should be made in relation to the planes perpendicular to the median axis (Fig. 4b).

The angle of the palpebral fissure and the line passing through the medial and lateral canthus can then be measured in relation to the median axis. Finally, orthogonal projections are made in relation to this latter axis to compare the position on the two- and three-dimensional reference planes with that of the healthy orbit. The values for the linear measurements are compared to highlight any discrepancies. Further analysis can be carried out using mirror-image superimposition of the image of the healthy orbit on the diseased one to graphically highlight asymmetries on both the skeletal and cutaneous planes.

Finally, certain programs can be used to evaluate orbital volumes. The analysis provides values in mm^3. Reference figures from large population samples are not yet available for this type of data, and thus the evaluation should be made in comparison to the healthy orbit (Fig. 5).

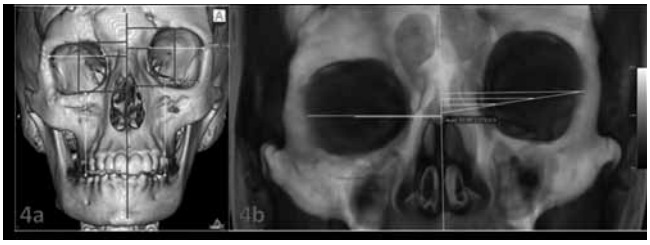

Fig. 4. a. Three-dimensional craniometric evaluation. **b.** Soft tissue craniometric evaluation.

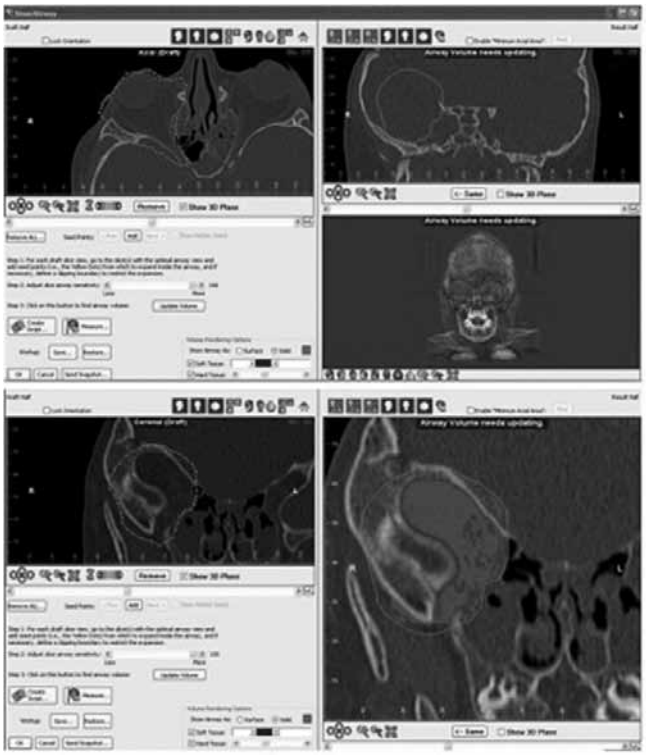

Fig. 5. Software to evaluate the orbital volumes.

Clinical cases

Case 1

A 27-year-old female presented with sequelae of trauma involving the orbit and zygomatic maxillary region with avulsion of left eyeball. She was treated at another location for reduction of facial fracture. Despite this, left enophthalmos was evident (Fig. 6a-b). The patient underwent removal of the plate previously placed on the margin of left orbit through the same subpalpebral approach. Titanium mesh was positioned on the floor reaching the medial wall (Fig. 6d). The patient experienced minimal swelling postoperatively, which resolved in about two weeks. At two weeks follow-up, we observed that the left enophthalmos was no longer evident (Fig. 6c). Three years later, the patient showed very good facial aesthetic improvement.

Case 2

A 26-year-old female presented with right exophthalmos and diplopia following trauma that occurred three weeks before. Evaluation of ocular mobility revealed limited

movement in the upper gaze of the right eye (Fig. 7a). She was diagnosed with fracture of medial wall of the right orbit (Fig. 7b). With a transcaruncolar endoscopic approach, biocompatible collagen membrane was placed between the medial wall and the orbital periosteum (Fig. 7d). The patient experienced minimal swelling postoperatively, which resolved in about one week. At two weeks follow-up, we observed with satisfaction that right exophthalmos and diplopia were no longer visible, and right ocular rotations improved with elimination of anomalous movements (Fig. 7c). Three years later, the patient showed excellent facial aesthetic and functional improvement.

Case 3

A 22-year-old male presented with outcomes of bilateral fracture of the orbital roof. He was treated in an emergency setting at another location for cerebral haematoma evacuation and bilateral exophthalmos with tarsorrhaphy. The patient came to our observation at one month after trauma. The evaluation of visual acuity revealed bilateral amaurosis that remained from the trauma. He underwent three sequential surgeries: orbital decompression, orbital expansion and finally medialisation of orbital walls with cranioplasty (Fig. 8d). Postoperative radiologic and clinical controls showed satisfactory results and the ophthalmologic examination revealed recovery of vision (visual acuity of 2/10 in the left eye and 3/10 in the right eye) and bilateral ocular bulb motility. The patient experienced swelling postoperatively, which resolved in about four weeks. At two months follow-up, bilateral exophthalmos was improved (Fig. 8c). Three years later, the patient showed very good facial aesthetic and functional improvement. Evaluation of visual acuity revealed a marked improvement (left eye: 4/10; right eye: 9/10).

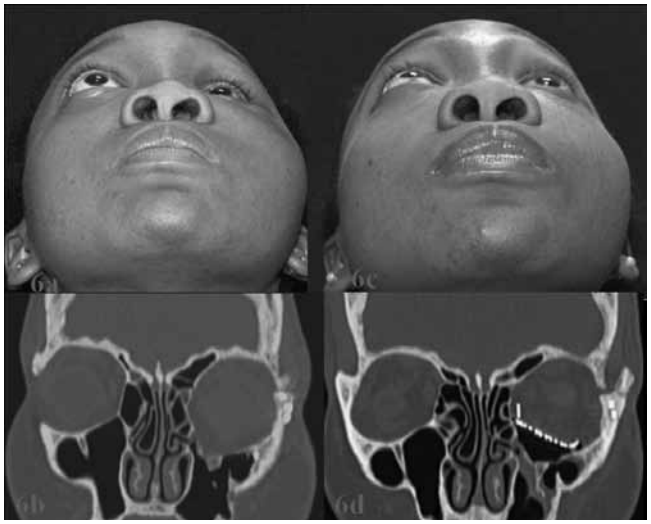

Fig. 6. Preoperative axial view (a) of the patient and pre-operative coronal CT scans (b). Left enophthalmos is evident. Postoperative axial view (c) of the patient and postoperative coronal CT scans (d). A titanium mesh was positioned on the left orbital floor to the medial wall, and left enophthalmos was no longer apparent.

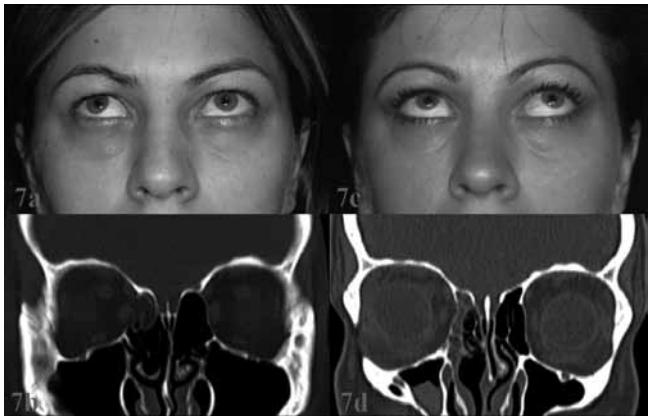

Fig. 7. Preoperative frontal axial view (a) of the patient and pre-operative coronal CT scans (b). Limited movement of the right eye in the upper gaze was evident along with fracture of right orbital medial wall. Postoperative frontal view (c) of the patient and postoperative coronal CT scans (d). A biocompatible collagen membrane was positioned on the right orbital floor to the medial wall;left enophthalmos and diplopia disappeared, and right ocular rotations improved.

Discussion

Sequelae of orbital fracture can be associated with aesthetic and functional defects such as enophthalmos, diplopia, facial asymmetry, hypertelorism and dystopia. Clinically, enophthalmos is defined as a backward and usually downward (hypoglobus) displacement of the globe into the bony orbit [1]. It is due to depression of the bony orbit, fat necrosis or atrophy, scar contracture of the retrobulbar tissue tethering the ocular globe in a posterior position, and/or entrapment or fibrosis of extraocular muscles [1]. It occurs more frequently after fracture of the lamina papyracea with herniation of the orbital content in the ethmoid. A study conducted on corpses by Hammerschlage in 1982 showed that 90% of observed enophthalmos cases were caused by fracture of the medial wall. In these cases, however, the enophthalmos does not always cause significant functional disorders, such as those occurring due to dislocation of the malar bone and entrapment of the inferior rectus muscle and the small oblique muscle. Clinical examination is fundamental to investigate the consequences of trauma. It can assess globe position in relation to orbital rim, eyelid rim, midline facial structures and lateral orbit. The instrumental exams to evaluate the enophthalmos consist of Hertel exophthalmometry, but it is accurate in defining the difference in globe position only if the area of the lateral orbital rim has been identified as being correctly positioned anteriorly and posteriorly, and is symmetric with the contralateral side. It can be useful to evaluate orbital volume, since some authors have found a correlation between enophthalmos and increasing orbital volume, even if these measurements are taken only 3-4 weeks after trauma [1].

In case of obsolete fractures, diplopia is usually second-

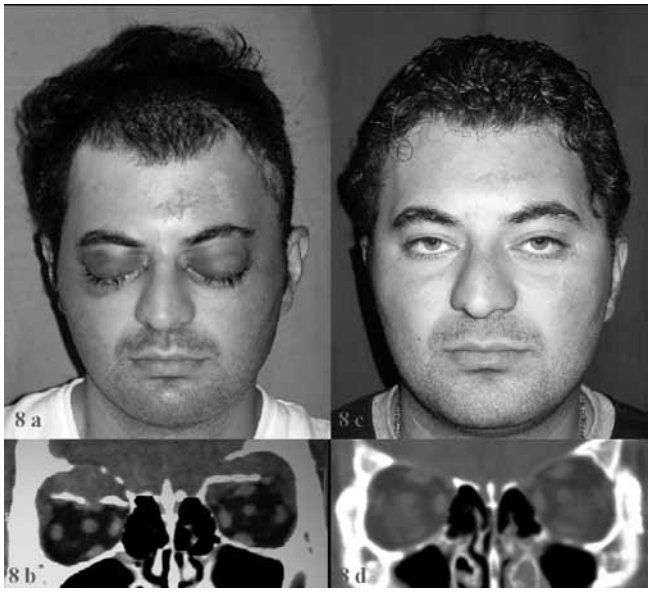

Fig. 8. Preoperative frontal axial view (a) of the patient and pre-operative coronal CT scans (b). Bilateral exophthalmos and bilateral fracture of the orbital roof were evident. Postoperative frontal view (c) of the patient and postoperative coronal CT scans (d). Bilateral exophthalmos was improved. Evaluation of visual acuity revealed a marked improvement.

ary to entrapment of one or more muscles (inferior rectus, medial rectus or inferior oblique) or of the adjacent fat. In this case, a forced duration test will have a positive result. The reconstructive principles for late reconstruction of the complex orbital fractures involve osteotomy, movement, reposition and fixation of all fractured bones, and repositioning of the globe. In order to correctly plan surgery, clinical and instrumental examination and radiological findings are both important. While image diagnosis is essential for defining the details of bone displacements and injuries to soft tissue, instrumental diagnosis is important for evaluating the functional damage caused by the trauma and is indispensable for assessing recovery following the surgical treatment [5].

Traditional radiological examination of the head in the four projections (axial, lateral, occipito-buccal and postero-anterior) is of little use, whereas panorex and x-rays are recommended in two projections (lateral and antero-posterior) when there is a fracture of the upper jaw. A CT scan with axial, coronal, sagittal and 3D reconstructions, however, is essential, not only for confirming orbital bone injuries but also for planning surgical treatment. Cone beam CT, which has recently been introduced, with a very brief exposure allows the reconstruction of the facial skeleton both in 3-D and three standard reconstructions [6]. Each reconstruction allows the study of several parameters to analyse. Due to the 3-D CT scans, however, it is possible to have an overall view of the various traumatic displacements and, together with the information acquired from the measurements of the other CT reconstructions, to define the surgical programme.

Advancements in computer technology have made it possible to accurately simulate the surgery and lead to precise surgical planning. In fact, these programs permit calculating orbital volume, and thus to compare the affected with the non-affected orbit. In particular, this comparison can be made both in absolute terms, in mm^3, and in relative terms by graphically superimposing the orbital margins and bone walls. These data are also relevant from a repositioning perspective and can be used to build three-dimensional digital models to create personalised implants for morphological recovery of the bone structures. Traditionally, medical sculptors employed their anatomical modelling expertise to manufacture implants using clay and wax [7].

Currently, however, shape reconstruction techniques for the skull surface involve both clay and spatulas as well as the use of Computer Aided Design (CAD) tools [8]. Previous studies have explored computer-aided implant design in the maxillofacial area [9 10]; these procedures are highly effective but time-consuming as they require a great deal of manual input, and the design process remains costly in terms of labour, materials and monetary resources.

Some software packages (i.e. MIMICS, Dolphin Imaging) simulate osteotomies and skeletal repositioning for reliable evaluation of surgical outcome. Diverse studies [11] have described the use of CAD/Computer-Aided Manufacture (CAD/CAM) for late reconstruction of orbital fractures, confirming increased surgical accuracy [2]. They have focused attention on orbital volume, and not considering linear and angular measurements as we described. From an aesthetic point of view, it is important to plan surgery in order to re-establish symmetry; the authors advocate the use of 3D CT-scan reconstruction to obtain mirror-image superimposition of the image of the normal orbit on the fractured one in order to graphically highlight asymmetry, both skeletal and cutaneous. Three-dimensional intraoperative navigation of previously acquired CT images represents a technical evolution in surgical planning and is used to verify the precision of the reconstruction during the operation [12]. A further field of application is pre-and post-surgical examination for a precise evaluation of the results of skeletal repositioning. Dimensional accuracy is a major concern for the clinical application of 3D medical models, and has been previously studied [13 14]. Whereas CT scans are useful for the study of bone structures, it is well known that MRI provides much more reliable indications on the parenchymatous structure. In our case, MRI with axial and coronal reconstructions, is useful for highlighting both morphological alterations and changes in the position of the orbital content, particularly the muscles, endo-orbital fat and optic nerve curvature. The three case studies herein highlight the successful results obtained in treating orbital fractures with this type of analysis. Each aspect is analysed in its totality, yielding a result that is suitable not only for the

selected parameters, but also for the selected one in relation with the other. Compared to previous surgical treatment planning, this kind of analysis allows study of the orbit in every aspect, leading to perfect reconstruction of the bony orbit and the periorbital region.

Conclusions

In our experience, we believe that analysis of the orbit is a fundamental process in pre-operational planning and post-operative evaluation of traumas directly or indirectly involving the orbital and periorbital region. Compared to traditional analyses, this new one takes into account different aspects. The first, in fact, analysed linear measurements and bony tissues without evaluating the relationship of these with periorbital soft tissue, especially improving the bone, and not just the "aesthetic" aspects. This new analysis allows a more detailed study of the bony structures, which are analysed in several aspects and in most planes, but also and especially, the soft tissue periorbital region, which is responsible for the aesthetic appearance of the patient. The possibility to superimpose the healthy portion with that of the deficit also allows analysing in detail potential shortcomings and, therefore, how to resolve these. The diagnostic and instrumental accuracy achieved in recent years through the use of three-dimensional reconstructions and elaboration software allows the required surgical procedures to be planned with satisfactory precision and adapting treatment to each individual case. The position of the orbit in the space should be determined in relation to the surrounding structures compared to the contralateral side, if this is not affected by the trauma or pre-existing malformations. In the three cases described herein, we obtained successful results both in bony structures and in soft tissue aspects.

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12th ANNUAL INTERNATIONAL ENT CONFERENCE • ***January 17-24, 2015 • Alba di Canazei – Italy***

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1st WINTER COURSE APPENNINO CENTRO MERIDIONALE • ***January 26-29, 2015 • Roccaraso (AQ) – Italy***

President: Marco de Vincentiis – Tel. +39 340 2211463.

1st INTERNATIONAL LIVE SURGERY COURSE ON TRANSNASAL ENDOSCOPIC SURGERY
January 28-30, 2015 • Brescia – Italy

Course Directors: Piero Nicolai and Marco Fontanella

7th COURSE OF CLINICAL VESTIBOLOGY • ***January 29-30, 2015 • Pisa – Italy***

Director: Augusto Piero Casani

4° CORSO TEORICO PRATICO DI LARINGOLOGIA PEDIATRICA • ***February 2-3, 2015 • Rome – Italy***

Direttori del Corso: Sergio Bottero, Angelo Ghidini – E-mail: marilena.trozzi@opbg.net – Website: www.ospedalebambinogesu.it

TRAINING DI CHIRURGIA IMPLANTOLOGICA DELLE SORDITÀ • ***February 4-5, 2015 • Pavia – Italy***

Director: Marco Benazzo – E-mail: pietro.canzi@unipv.it – Website: www.bquadro-congressi.it

NORTH AMERICAN RHINOLOGY & ALLERGY CONFERENCE – ***February 5-8, 2015 • Boca Raton – Florida***

Email: info@NARAConference.org – Website: naraconference.org

CORSO DI ANATOMIA CHIRURGICA ENDOSCOPICA DEI SENI PARANASALI
March 1-2, 2015 • Arezzo – Italy

Course Directors: Fabio Pagella and Enzo Emanuelli – Tel. +39 0575 1948541 – Fax +39 0575 1948500 – E-mail: info@iclo.eu – Website: www.iclo.eu

2nd ANNUAL OSAS SURGERY INTERNATIONAL COURSE • ***March 1-3, 2015 • Celebration – Florida***

Website: osasconference.com

5th NATIONAL CONGRESS AIOCC (ASSOCIAZIONE ITALIANA ONCOLOGIA CERVICO CEFALICA)
March 2-3, 2015 • Rome – Italy

Directors: Marco De Vincentiis and Gaetano Paludetti – Honorary President: Giorgio Iannetti – E-mail: segreteria@stilema-to.it – Website: www.aiocc.it

10th SURGICAL ANATOMY IN HEAD & NECK CANCER PROCEDURES • ***March 4-6, 2015 • Arezzo – Italy***

Course Directors: Marco Benazzo and Fausto Chiesa – E-mail: info@iclo.eu – Website: www.iclo.eu

CORSO DI ANATOMIA E CHIRURGIA CERVICO-FACCIALE • ***March 4-6, 2015 • Nîmes – France***

E-mail: pierfrancesco.pelliccia@hotmail.it

27th SVO INTERNATIONAL WINTER COURSE • ***March 15-21, 2015 • Sesto - Val Pusteria – Italy***

President: Gregorio Babighian – Website: www.otologytoday.it

8° CORSO INTERNAZIONALE "BIENNALE MILANO MASTERCLASS"
A. CHIRURGIA ENDOSCOPICA RINOSINUSALE, ORBITA E BASE CRANICA
B. RINOPLASTICA: DA MINIMAMENTE INVASIVA A STRUTTURALE
March 20–24, 2015 • Milan – Italy

Direttori: Paolo Castelnuovo e Pietro Palma – Segreteria Organizzativa: MZ Congressi, via C. Farini 81, 20159 Milano – Tel. +39 02 66802323 – Fax +39 02 49542900 – E-mail: mima@mzcongressi.com – Website: www.milanomasterclass.it

HANDS-ON COURSE ON ENDOSCOPIC MIDDLE EAR SURGERY
March 21-22, 2015 • Arezzo – Italy
March 23, 2015 • Modena – Italy

Directors: Livio Presutti and Daniele Marchioni – Tel. +39 0575 1948501 – Fax + 39 0575 1948500 – Email: info@iclo.eu

CENACOLO ITALIANO DI AUDIOVESTIBOLOGIA • ***March 21-May 16, 2015 • Chieti – Italy***

Director: Giampiero Neri – E-mail: info@nsmcongressi.it – Website: www.nsmcongressi.it

3° MASTER DI LARINGOLOGIA OTOLOGICA • ***March 30 - April 2, 2015 • Vittorio Veneto (TV) – Italy***

Director: M. Lucioni – Chairman: G. Rizzotto – E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

INTERNATIONAL CONGRESS OF KOREAN SOCIETY OF OTORHINOLARYNGOLOGY-HEAD & NECK SURGERY
April 24-26, 2015 • Seoul – Korea

President: Sang Hag Lee

5th INTERNATIONAL HANDS-ON COURSE "TRANSNASAL CORRIDORS TO SKULL BASE AND ORBIT"
April 28-30, 2015 • Wien – Austria

Course Directors: P. Castelnuovo, P. Nicolai, M. Tschabitscher – Organizing Secretariat: informazioni@attingo-edu.it – E-mail: www.attingo-edu.it

16th WORLD CONGRESS OF RHINOLOGY • ***April 30-May 2, 2015 • São Paulo – Brazil***

President: Aldo Stamm – E-mail: secretaria@malulosso.com.br – Website: http://www.rhinology2015.com/Scientific-program.htm

VI CONGRESO IBEROAMERICANO DE IMPLANTES COCLEARES Y CIENCIAS AFINES
May 20-23, 2015 • Sao Paulo – Brasil

Tel. 55 11 5081 7028

VERTIGO ACADEMY INTERNATIONAL • ***May 22-23, 2015 • Moscow – Russia***

Chairman: O. Nuri Ozgirgin (Turkey) – Website: www.vainternational.org

102nd NATIONAL CONGRESS SIO, ITALIAN SOCIETY OF OTORHINOLARYNGOLOGY HEAD AND NECK SURGERY • ***May 27-30, 2015 • Rome – Italy***

President: Giuseppe Spriano – Organizing Secretariat: NordEst Congressi – Tel. +39 06 68807925 – Fax +39 06 68212211 – E-mail: nec@nordestcongressi.it – Website: www.sio2015.com

3rd CONGRESS OF EUR OPEAN ORL-HNS • ***June 7-11, 2015 • Prague – Czech Republic***

President: Jan Betka – E mail: orl-hns2015@guarant.cz – Website: http://www.europeanorl-hnsprague2015.com

27° CONGRESSO NAZIONALE SPIGC • ***June 11-13, 2015 • Brescia – Italy***

President: Gian Luca Pariscenti – Website: www.spigc.it

5th HANDS ON DISSECTION ADVANCED COURSE: "FROM REMOVAL TO RECONSTRUCTION IN HEAD & NECK CANCERS" • *June 16-19, 2015 • Paris – France*

Directors: Marco Benazzo, Department of Otolaryngology HN Surgery, University of Pavia; Fausto Giuseppe Chiesa, Department of Otolaryngology HN Surgery, IEO Milan. Organizing Secretariat: Bquadro Congressi srl, via S. Giovanni in Borgo 4, 27100 Pavia. Tel. +39 0382 302859 – Fax +39 0382 27697 – E-mail: bolla@bquadro-congressi.it – Werbsite: www.bquadro-congressi.it

41° CONGRESSO CONVENTUS SOCIETAS ORL LATINA • *July 6-8, 2015 • Torino – Italy*

President: Francesco Pia

22nd INTERNATIONAL CONGRESS ON THE EDUCATION OF THE DEAF • *July 6-9, 2015 • Athens – Greece*

Website: www.iced2015.com

WORLD CONGRESS ON LARYNX CANCER 2015 • *July 26-30, 2015 • Queensland – Australia*

Website: www.wclc2015.org

SYMPOSIUM & 52nd INNER EAR BIOLOGY WORKSHOP • *September 12-15, 2015 • Rome – Italy*

Directors: Gaetano Paludetti and Diana Troiani – Website: www.ieb2015.it

2nd SIR (SOCIETÀ ITALIANA DI RINOLOGIA) NATIONAL CONGRESS • *September 17-19, 2015 • Udine – Italy*

President: Marco Piemonte – E-mail: nec@nordestcongressi.it – Website: www.nordestcongressi.it

INTERNATIONAL WORKSHOP "OPEN PARTIAL HORIZONTAL LARYNGECTOMIES (OPHL) VERSUS TRANSORAL LASER MICROSURGERY (TLM) IN LARYNX CANCER"
October 8-10, 2015 • Castel Brando (TV) – Italy

Chairman: G. Rizzotto – Email: mail@nordestcongressi.it – Websites: www.nordestcongressi.it, www.oncolarynx.it

XXXIX CONVEGNO NAZIONALE AOOI (ASSOCIAZIONE OTORINOLARINGOLOGI OSPEDALIERI ITALIANI)
October 16-17, 2015 • Genova – Italy

President: Felice Scasso – E-mail: nec@nordestcongressi.it – Website: www.nordestcongressi.it

7th INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE AND INNER EAR DISORDERS
October 17-20, 2015 • Rome – Italy

Website: meniere2015.eu

VII INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN RHINOSINUSITIS AND NASAL POLYPOSIS *October 22-25, 2015 • Panama*

Information: congresors2015@gmail.com

3rd VIS (SOCIETÀ ITALIANA DI VESTIBOLOGIA) CONGRESS • *October 30-31, 2015 • Modena – Italy*

SIOP (SOCIETÀ ITALIANA DI OTORINOLARINGOIATRIA PEDIATRICA) NATIONAL CONGRESS
November 5-7, 2015 • Rome – Italy

E-mail: info@formazionedeventisrl.it – Website: www.formazionedeventisrl.it

JANUARY-DECEMBER 2016

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

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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