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Review

Supracricoid laryngectomy for recurrent laryngeal cancer after chemoradiotherapy: a systematic review and meta-analysis

Laringectomia sopracricoidea per il trattamento del cancro laringeo dopo recidiva di radioterapia: revisione sistematica della letteratura e metanalisi

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SUMMARY

Residual or recurrent laryngeal cancer after irradiation is a difficult clinical problem with a rate that ranges from 13% to 36% of cases. Supracricoid laryngectomy (SCL) with cricohyoidopexy (CHP) or cricohyoidoepiglottopexy (CHEP) provide reliable oncological and functional results for selected primary and recurrent patients with glottic and supraglottic carcinomas. We conducted a systematic review and meta-analysis to assess the oncological and functional outcomes of patients treated with open partial horizontal laryngectomy types IIa and IIb (CHEP, CHP) in terms of the recurrence of squamocellular cancer of the larynx after radiotherapy failure. The databases searched included MEDLINE, PubMed and EMBASE (from January 1990 to December 2015, English language). The meta-analysis was performed with a mixed random effects model using the DerSimonian and Laird method. The heterogeneity was measured with the I^2 statistic. Fourteen papers out of 276 were included and comprised a total of 291 patients. The five-year overall survival was 80.2% (CI 0.719-0.885; $I^2 = 62\%$; $p = 0.003$), and the 5-year disease-free survival was 89.5% (CI 0.838-0.952; $I^2 = 52\%$; $p = 0.022$). The indications for SCL after the failure of radiation therapy (RT) were similar to those specified for previously untreated patients. We therefore hypothesised that careful assessment of tumour extension might be responsible for the high 5-year OS and 5-year DFS. The early postoperative recovery outcomes indicated that the mean time until decannulation was 35.6 days (CI 24.3-46.9; $I^2 = 95\%$; $p < 0.001$), and the mean time until nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG) removal was 28.3 days (CI 22.7-33.8; $I^2 = 86\%$; $p <= 0.001$). These data are according to authors who prefer the initial removal of the NGT and the initiation of oral alimentation with a tracheostomy tube to protect and clean the airways and permit the suction of any residual food that might be present.

KEY WORDS: Laryngeal cancer • Recurrence • Radiotherapy • Supracricoid laryngectomy • Meta-analysis

RIASSUNTO

La recidiva e la persistenza del cancro della laringe dopo radioterapia rappresentano eventi insidiosi, i cui tassi di incidenza variano dal 13% al 36%. L'intervento di laringectomia sopracricoidea (LSC), con cricoioidopessia (CIP) o cricoioidoepiglottopessia (CIEP), è in grado di garantire risultati oncologici e funzionali affidabili per i pazienti selezionati affetti da carcinoma glottico o sopraglottico, sia in caso di neoplasia primitiva che di recidiva. La presente metanalisi ha lo scopo di valutare i parametri oncologici e funzionali nei pazienti trattati con LSC per recidiva di carcinoma squamocellulare della laringe dopo fallimento di radioterapia. La ricerca è stata effettuata sui databases MEDLINE, PubMed ed EMBASE (da gennaio 1990 a dicembre 2015, solo in lingua inglese). Per la metanalisi è stato impiegato il metodo DerSimonian e Laird con effetto "midex random"; l'eterogeneicità è stata misurata mediante I^2. Sono stati inclusi nella ricerca 276 articoli, tra i quali ne sono stati selezionati 14 per la metanalisi, per un totale di 291 pazienti. L'analisi statistica ha mostrato una sopravvivenza globale (OS) a 5 anni del 80,2% (IC 0,719-0,885; $I^2 = 62\%$; $p = 0,003$) e una sopravvivenza libera da malattia (DFS) a 5 anni del 89,5% (IC 0,838-0,952; $I^2 = 52\%$; $p = 0,022$). Le indicazioni chirurgiche per una LSC dopo fallimento di radioterapia non cambiano rispetto a quelle adottate per pazienti con tumore primitivo. Pertanto, è stato ipotizzato che l'attenta valutazione dell'estensione del tumore, in caso di recidiva, potrebbe essere responsabile dell'alto tasso di OS e DFS a 5 anni. Per quanto riguarda i parametri di valutazione funzionale precoce postoperatoria, il tempo medio di decannulazione è stato di 35,6 giorni (IC 24,3-46,9; $I^2 = 95\%$; $p < 0,001$), mentre il tempo medio di rimozione del sondino naso-gastrico (SNG) o della gastrostrostomia percutanea endoscopica (PEG) è stato di 28,3 giorni (IC 22,7-33,8; $I^2 = 86\%$; $p <= 0.001$). Questi dati sono in accordo con gli Autori che preferiscono la rimozione precoce del sondino nasogastrico. In tal modo si può riprendere l'alimentazione orale quando è ancora presente il tubo endotracheale a protezione delle vie aree e permettere l'aspirazione degli eventuali residui alimentari.

PAROLE CHIAVE: *Cancro della laringe • Recidiva • Radioterapia • Laringectomia sopracricoidea • Meta analisi*

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Introduction

Residual or recurrent laryngeal cancer after irradiation is a difficult clinical problem with a rate that ranges from 13% to 36% [1-4]. Although several treatment options exist for patients affected with laryngeal cancer at first presentation [5 6], the options for those with recurrent cancer are limited based on the initial treatment received [7]. Cancers that recur after radiation therapy (RT) often exhibit aggressive behaviour, arise in a field in which lymphatic drainage is unpredictable and are associated with poor control rates [8]. Total laryngectomy is a frequently recommended option even for early recurrent cancers after chemoradiotherapy, but this procedure substantially impairs the quality of life primarily due to the permanent tracheostoma and the loss of the voice [9]. Supracricoid laryngectomies (SCLs) were recently classified by the European Laryngological Society [10] as Open Partial Horizontal Laryngectomies Type II, which include reconstructions either by cricohyoidoepiglottopexy (CHEP; renamed OPHL Type IIa) or cricohyoidopexy (CHP; renamed OPHL Type IIb). Both of these procedures provide reliable oncological and functional results for selected primary and recurrent patients with glottic and supraglottic carcinomas [11-14]. Several reports regarding the effectiveness of SCLs in terms of survival and functional results considering residual and recurrent cancer have been published.

The aim of this systematic review and meta-analysis was to evaluate the pooled oncological and short-term postoperative recovery outcomes of supracricoid laryngectomies with CHEP and CHP in the setting of recurrent laryngeal squamocellular cancer (SCC) after chemoradiotherapy.

Materials and methods

Data sources and searches

We aimed to identify all papers that assessed the oncological and functional outcomes of patients treated with supracricoid laryngectomy for recurrence of SCC of the larynx after RT failure. The databases searched included MEDLINE, PubMed and EMBASE (from January 1990 to December 2015). We applied English language and abstract availability restrictions. Our search included the following keywords: laryngeal cancer, supracricoid laryngectomies, subtotal laryngectomy, cricohyoidopexy, cricohyoidoepiglottopexy, and/or retrospective study, prospective and randomised clinical study.

Selection of studies

Publications were included if they included patients affected with recurrent laryngeal SCC after initial treatment with RT that was salvaged with supracricoid laryngectomy and reported the 5-year overall survival (OS), 5-year disease free survival (DFS) and short-term postoperative recovery outcomes.

We included only full published papers and excluded abstracts and reviews. Papers containing inadequately separable oncological or functional data, series that included patients treated with different procedures and those focusing on other topics or other surgical techniques were excluded.

Outcome measures

The primary outcome was 5-year overall survival (OS). The secondary outcomes were 5-year disease-free survival (DFS), short-term postoperative recovery outcomes and 5-year OS and 5-year DFS according to the T stage (early and locally advanced). Short-term postoperative recovery outcomes included the mean time until decannulation and the mean time required for oral feeding restoration, which is expressed as the mean time until nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG) removal. According to T stage, patients were divided into two groups for statistical analysis, i.e., early (rT1-T2) and locally advanced (rT3-T4) groups.

Data extraction

Initial selection was performed via the screening of the titles and abstracts by two pairs of independent reviewers (GR and CAL, PC and DT). For detailed evaluations, full-text copies of all studies except one (Shenoy et al., 2000) that were possibly relevant were obtained. The data from each study were extracted independently by paired and independent reviewers (GR and CAL, PC and DT) using a pre-standardised data abstraction form. The data extracted from the publications were independently checked for accuracy by two additional reviewers (PC and PD). We resolved any possible disagreements by consensus in consultation with a third reviewer (CAL) when needed.

Quantitative analysis

The meta-analysis was performed with a mixed random effect model using the DerSimonian and Laird method. The results were graphically represented using Forest plots. The proportions and 95% CIs for each outcome were separately calculated for each trial with the grouped data using the intention-to-treat principle. The choice to use the proportions was driven by the design of meta-analysis, which was based on the included studies. The tau^2 was used to define the between-studies variance. The P value was set at 0.05. The homogeneity assumption was examined with the Q test with a degree of freedom (df) equal to the number of analysed studies minus 1. The heterogeneity was measured with the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. The I^2 was calculated from the basic results obtained from a typical meta-analysis as $I^2 = 100\%$ Å ~ (Q – df)/Q, where Q is Cochran's heterogeneity statistic, and df is the degrees of freedom. A value of 0% indicates no observed heteroge-

neity, and larger values indicate increasing heterogeneity. We performed an "a priori" sub-analysis of the oncological outcomes according to the early (rT1-T2) and locally advanced (rT3-T4) stages of recurrent laryngeal SCC. Next, we performed an "a priori" comparison of the same oncological outcomes between early (rT1-T2) and locally advanced (rT3-T4) stages of recurrent laryngeal SCC. For comparisons, we performed the meta-analyses with the odds ratios (ORs), and 2-sided p-values < 0.05 were considered significant.

The analyses were conducted with OpenMetaAnalyst (version 6) and SPSS version 20 (IBM SPSS).

To evaluate potential publication bias, we used a weighted linear regression and a modified Macaskill's test, which provides more balanced type I error rates in the tail probability areas relative to other publication bias tests [15]. GR conducted the statistical analyses.

Limitations

This systematic review and meta-analysis has some limitations that need to be addressed. We included only full papers in the English language and excluded abstracts. Moreover, all of the included studies were retrospective. We observed substantial heterogeneity ($I^2 > 50\%$) according to the Cochrane guidelines in 4 of 10 outcomes considered.

Results

Study selection

We identified 276 references. One hundred eight-seven papers were excluded after reading the titles, and 70 were excluded after reading the abstracts. We analysed 19 retrospective studies in full paper format because no prospective or randomised studies were found. Fourteen references including 291 patients fulfilled our search criteria [7 9 13 16-18 20-25 27 28]. Six of these studies involved mixed series [7 9 16 17 22 23] because they included patients who underwent primary SCL and salvage SCL after RT failure. The remaining eight papers focused only on salvage surgeries. Five references were excluded, including 3 mixed series whose authors [12 19 29] reported only the cumulative data for the series, one paper [30] that was not available and one [26] study that included other surgical techniques. Figure 1 illustrates the study selection process.

Characteristics of studies included

The 14 papers included 291 adult patients. The 5-year OS and 5-year DFS were reported in all papers with the exceptions of Farrag et al. [22], Pellini et al. [23] and de Vincentiis [7]. For the papers of Sperry et al. [16], Nakayama et al. [17], Deganello et al. [20], Leon et al. [21] and Marchese-Ragona et al. [27], it was possible to extract these data from the text. All papers with the exceptions of Leone et al. [9] and Nakayama et al. [17] reported the short-term post-operative recovery outcomes, and Sperry et al. [16] and Pellini et al. [23] reported only the cumulative data for their series. The main characteristics of the studies included are reported in Table I.

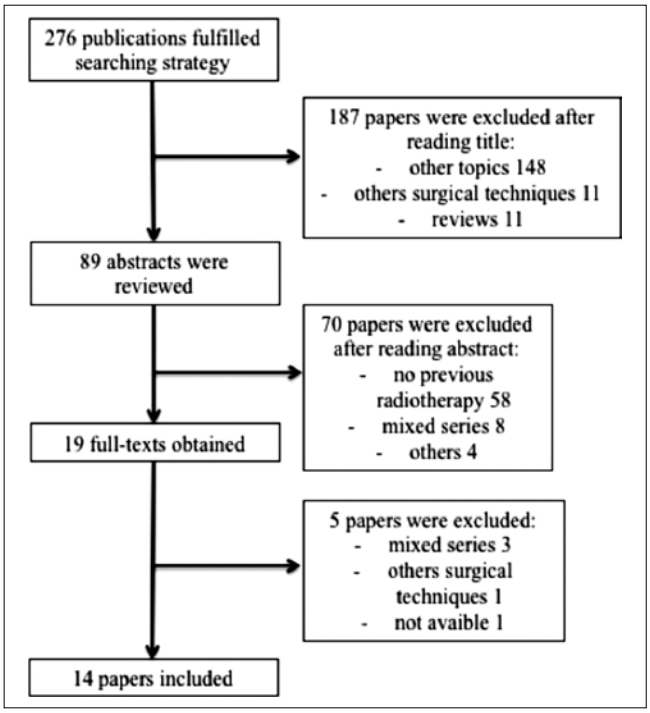

Fig. 1. We identified 276 references. One hundred eight-seven papers were excluded after reading the title, and 70 were excluded after reading the abstracts. We analysed 19 retrospective studies in full paper format. Fourteen references including 291 patients fulfilled our search criteria. Five references were excluded, including 3 mixed series whose authors reported only the cumulative data of the series, one paper that was not available and one that included other surgical techniques.

Definitions of oncological and functional outcomes

The oncological outcomes were calculated from the date of surgery. The endpoint for OS was the date of death regardless of cause, whereas the endpoint for DFS was date of recurrence (local, locoregional or metastatic). For the evaluations of short-term postoperative recovery, the outcomes included the mean time until decannulation and the mean time until NGT or PEG removal.

Primary outcome

The 5-year OS was 80.2% (CI 0.719-0.885; $I^2 = 62\%$; $p = 0.003$), and the corresponding Forest plot is shown in Figure 2.

Figure 3 (upper box) shows the Forest plot for 5-year OS for T1-T2 (early stage according to TNM classification [31]) patients (proportion: 0.798; CI 0.686-0.911; $I^2 = 35\%$; $p = 0.167$). The middle box shows the Forest plot for 5-year OS of T3-T4 patients (locally advanced stage; proportion: 0.923; CI 0.806-1.041; $I^2 = 0\%$; $p = 0.697$). The lower box depicts the Forest plot for 5-year OS for early

Table I. Main characteristics of the included studies (R: retrospective, NA: not available, RT: radiotherapy, CHP: cricohyoidopexy, CHEP: cricohyoidoepiglottopexy, +A: arytenoidectomy, NGT: nasogastric tube, PEG: percutaneous endoscopic gastrostomy).

Author, Year	Study Type	Surrtgery	Patients (n)	Age (mean, range) in years	Sex (male, female)	Clinical Stage after RT	Type of Surgery	Follow-Up Period (mean, range) in months	5-year Overall Survival	5-year Disease Free Survival	Decannulation in days	NGT or PEG removal in days
De Vincentiis, 2015	R	RT and laser failure	20	NA	NA	NA	NA	NA	NA	NA	38, 28-80	25, 20-39
Leone, 2014	R	primary and RT failure	4	60, 57-65	4 male	r T1b (1), rT2 (3)	CHP (3), CHEP (1)	41, 12-60	50%	50%	NA	NA
Sperry, 2013	R	primary and RT failure	42	60, 34-79	37 male, 5 female	rT1a (10), rT1b (13), rT2 (12), rT3 (61), rT4 (1)	CHP or CHEP	73, 0-207	95%	90.5%	NA	NA
Nakayama, 2013	R	primary and RT failure	30	62	29 male, 1 female	rpT1 (5), rpT2 (13), rpT3 (9), rpT4 (3)	CHEP (30)	NA	81%	96.6%	NA	NA
Luna-Ortiz, 2009	R	RT failure	8	67, 43-87	6 male, 2 female	rT1 (4), rT2 (4)	CHEP + A (3), CHEP (5)	44, 20-67	50%	50%	16, 3-56	16, 3-60
Deganello, 2008	R	RT failure	31	60.1, 40-72	29 male, 2 female	rT1a (1), rT1b (5), rT2 (16), rT3 (4), rT3 (5)	CHEP 8, CHP 23	45, 6-180	60%	71%	27, 14-59	30, 12-72
Pellini, 2008	R	RT failure	78	59.6, 33-76	78 male	rT1a (6), rT1b (30), rT2 (33), 8 rT3, 1 rT4a	CHEP + A (33), CHEP (29), CHP + A (8), CHP (8)	70, 10-300	81.8%	95.5%	176.5, 12-365	15, 12-90
Leon, 2007	R	RT failure	9	54.4, 43-67	9 male	rT1a (5), rT1b (2), rT2 (1), rT2 (1)	CHEP (5), CHEP + A (1), CHP (3)	mean NA, 4-120	78%	89%	11, 6-60	27, 16-40
Farrag, 2007	R	primary and RT failure	10	NA	NA	rT1 (1), rT2 (7), rT3 (2)	NA	NA	NA	NA	52, 19-123	90, 30-210
Pellini, 2006	R	primary and RT failure	17	NA	NA	r T1a (4), rT1b (3), rT2 (8), rT2 (1), rT3 (1)	CHP	NA	NA	NA	21.7, 6-65	NA
Sewnaik, 2006	R	RT failure	14	mean NA, 49-79	12 male, 2 female	rTis (1), T1 (6), T2 (7)	CHEP 14	16, 3-41	92.8%	85.7%	176.5, 12-365	45, 10-120
Clark, 2005	R	RT failure	6	mean NA, 51-64	NA	rT1a (2), rT1b (1), rT2 (3)	CHEP (4), CHP (2)	19, range NA	72%	100%	9, 6-13	165, 60-300
Marchese, 2005	R	RT failure	7	64, 55-72	7 male	rT2 (6), rT3 (1)	CHP (7)	122, 72-173	86%	86%	NA	42, 20-130
Spriano, 2002	R	RT failure	*15*	65.2, 58-63	15 male	rT1a (4), rT1b (3), rT2 (6), rT2 (1)	CHEP (7), CHEP + A (4), CHP (3), CHP + A (1)	63.5, 36-104	80%	93.3%	21.7, 6-65	23.2, 12-48
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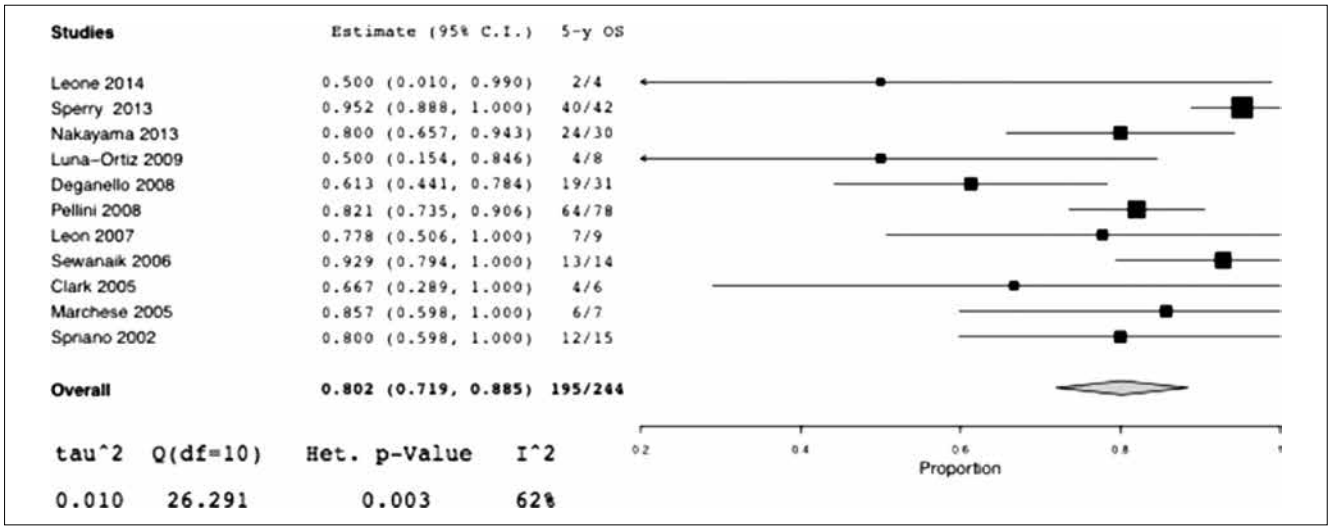

Fig. 2. Forrest plot of 5-year OS for patients treated with supracricoid laryngectomy after radiation therapy failure. Weights: Leone 2014: 2.5%, Sperry 2013 16.9%, Nakayama 2013: 12%, Luna-Ortiz 2009: 4.4%, Deganello 2008: 10.4%, Pellini 2008: 15.7%, Leon 2007: 6.2%, Sewanaik 2006: 12.5%, Clark 2005: 3.8%, Marchese 2005: 6.6%, Spriano 2002: 8.9%.

vs locally advanced SCC patients (OR: 0.670; CI 0.117-3.855; $I^2 = 7\%$; p = 0.340).

Secondary outcomes

The 5-year DFS was 89.5% (CI 0.838-0.952; $I^2 = 52\%$; p = 0.022) as illustrated in Figure 4. Figure 5 (upper box) displays the Forest plot for the 5-year DFS of the T1-T2 patients (early stage; proportion: 0.869; CI 0.792-0.946; $I^2 = 15\%$; p = 0.315). The middle box presents the Forest plot for the 5-year DFS of the T3-T4 patients (locally advanced stage; proportion: 0.911; CI 0.784-1.037; $I^2 = 0\%$; p = 0.812). The lower box shows the Forest plot for the 5-year DFS of early vs. locally advanced stage patients (OR: 0.475; CI 0.093-2.430; $I^2 = 0\%$; p = 0.841).

The mean time until decannulation was 35.6 days (CI 24.3-46.9; $I^2 = 95\%$; $p < 0.001$), and the corresponding Forest plot is presented in Figure 6. The mean time until NGT or PEG removal was 28.3 days (CI 22.7-33.8; $I^2 = 86\%$; $p <= 0.001$; Fig. 7).

Publication bias

No publication bias was detected according to Macaskill's modified test.

Discussion

In most centres in northern Europe and North America, radiotherapy is the primary treatment for patients with early laryngeal SCC [32]. RT is a well-established treatment for selected laryngeal carcinomas that elicits good oncologic and functional results. The reported failure rates range between 9-21% for T1 and 28-37% for T2 glottic carcinomas. In supraglottic laryngeal cancer, the reported failure rates for T1 and T2 lesions are 24-30% and 25%-45%, respectively [33]. Re-irradiation protocols (in combination with radio-sensitising agents) are at significant risk for morbidity [34 35] and remain investigational; they may be considered for patients with unresectable locoregional disease. Therefore, surgery is the preferred modality for curative treatment of recurrent laryngeal cancer after failure of nonsurgical treatments. There are three options for salvage surgery after radiation failure: total laryngectomy, transoral laser microsurgery (TLM) and open partial laryngectomy.

Total laryngectomy is widely considered the classic approach to glottic SCC recurrence after irradiation [36], but considerably impairs the quality of life primarily due to the permanent tracheostoma and the loss of voice [9]. Compared with alternative treatment options for laryngeal cancer, the oncological outcomes of TLM are inferior to those of open partial laryngectomy. TLM has a relatively lower mean larynx preservation rate of 72.3% *versus* 84% for open partial laryngectomy, which reflects a higher locoregional failure rate after TLM [8]. In the radio-recurrent setting, open partial laryngectomies have been less commonly used in the past due to concerns about unpredictable spreading and the postoperative function of the irradiated organ as well as a higher risk of complications [8]. The correct assessment of tumour extension of a recurrent laryngeal carcinoma may be difficult due to the residual inflammatory or functional changes associated with radiation therapy. Many recurrences present with multicentric tumour foci that are localised below intact mucosa and further masked by post-treatment oedema and fibrosis [37]. This pathological phenomenon that results in clinically significant difficulties in correctly restaging the tumour after irradiation justify the classical choice of salvage total laryngectomy in cases of carcinoma recurrence fol-

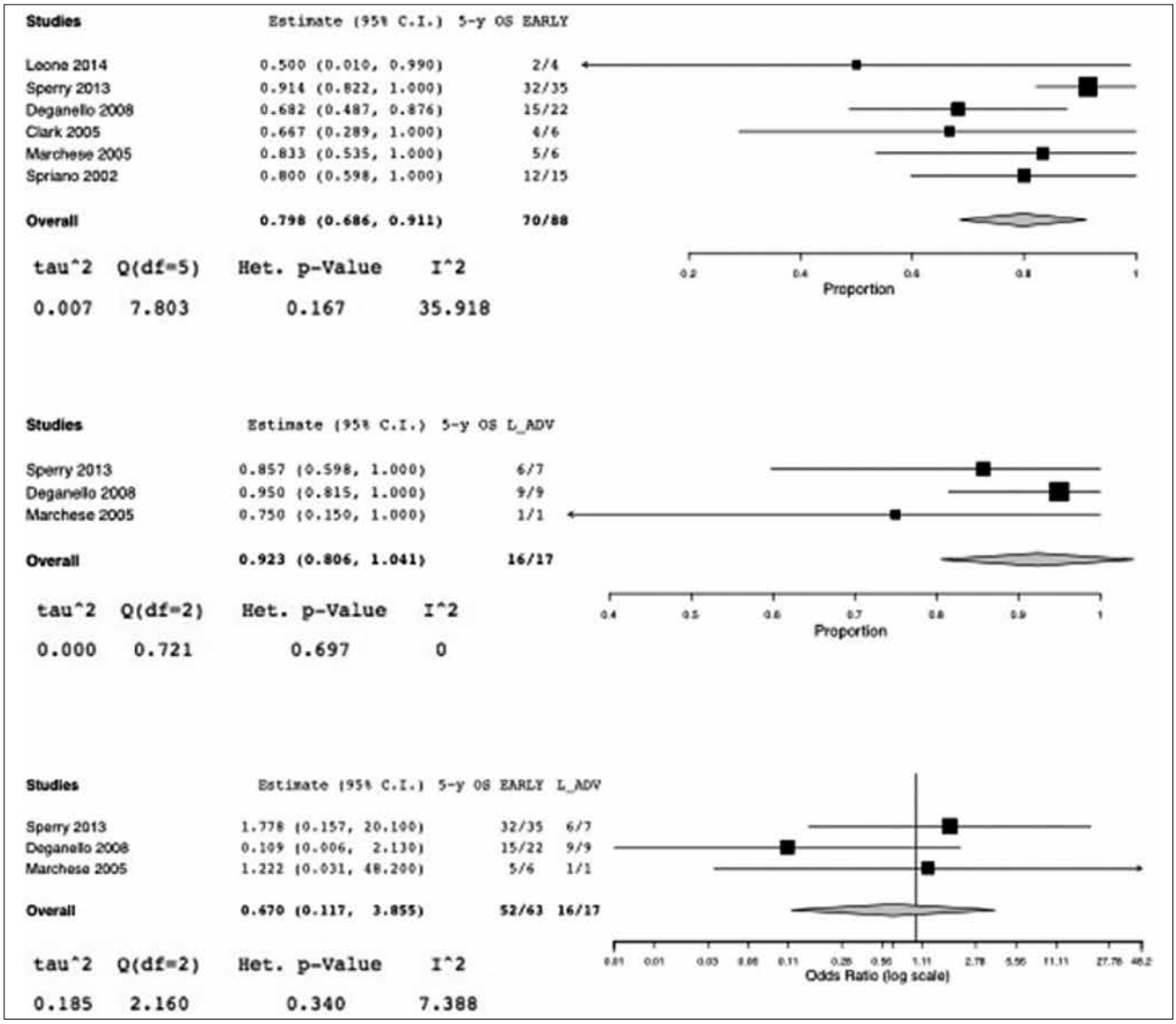

Fig. 3. Upper box: Forest plot of 5-year OS for patients affected with "early" T1-T2 recurrent laryngeal cancer after radiation therapy failure who were treated with supracricoid laryngectomy. Weights: Leone 2014: 4.8%, Sperry 2013 37.3%, Deganello 2008: 20.1%, Clark 2005: 7.6%, Marchese 2005: 11.1%, Spriano 2002: 19.1%.Middle box: Forest plot of the 5-year OS for patients affected with "locally advanced" T3-T4 recurrent laryngeal cancer following radiation therapy RT failure who were treated with SCL. Weights: Sperry 2013 20.6%, Deganello 2008: 75.6%, Marchese 2005: 3.8%. Lower box: Forest plot of the 5-year OS for patients affected with "early" vs. "locally advanced" recurrent laryngeal cancer following radiation therapy failure who were treated with supracricoid laryngectomy. Weights: Sperry 2013 43.4%, Deganello 2008: 32%, Marchese 2005: 21.6%.

lowing radiotherapy failure [29]. There have been several reports about the effectiveness of open partial laryngectomies in terms of survival and functional results in residual or recurrent cancer.

To our knowledge, this is first systematic review and meta-analysis to examine the oncological outcomes according to T stage and short-term postoperative recovery outcomes of SCL for treatment of laryngeal SCC after RT failure.

This systematic review and meta-analysis resulted in the following findings: 1) 5-year OS was 80.2%; 2) 5-year DFS was 89.5%; 3) mean time until decannulation was 35.6 days; and 4) mean time until NGT or PEG removal was 28.3 days. The studies included in this meta-analysis share a common trait, i.e., the strict criteria for patient selection for candidacy for SCL after RT failure [9]. The indications and contraindications after the failure of RT are similar to those that have been specified for patients with previously untreated laryngeal tumours [30]. Therefore, we hypothesise that careful assessment of tumour extension might be responsible for the high 5-year OS and 5-year DFS.

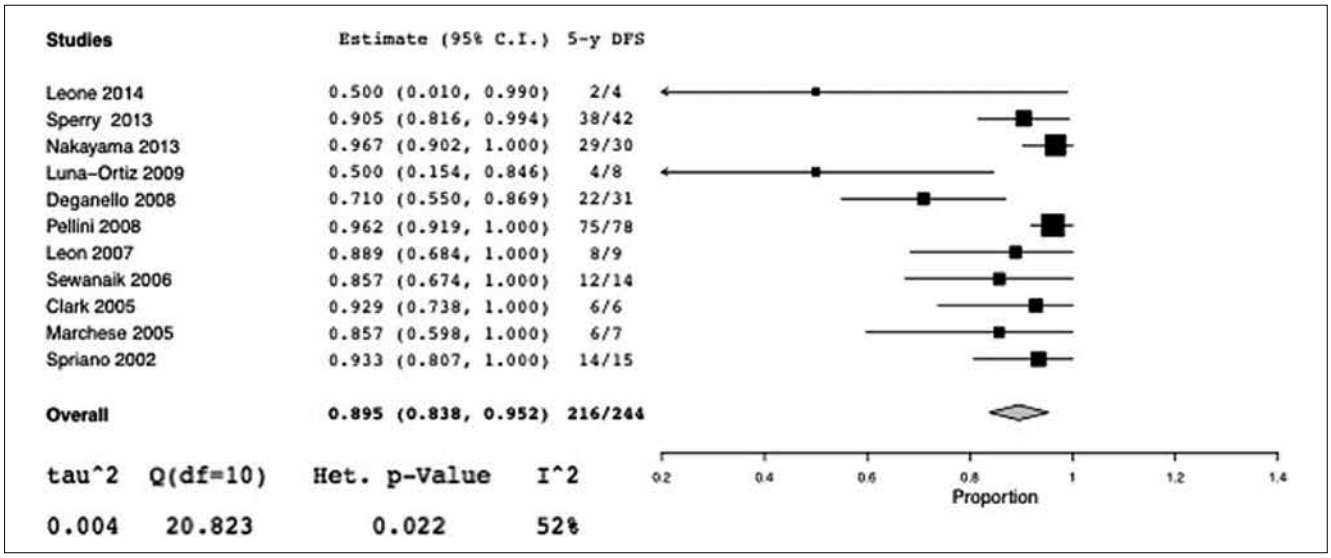

Fig. 4. Forest plot of the 5-year DFS for patients who were treated with supracricoid laryngectomy after radiation therapy failure. Weights: Leone 2014: 1.3%, Sperry 2013 15%, Nakayama 2013: 18.2%, Luna-Ortiz 2009: 2.4%, Deganello 2008: 8.3%, Pellini 2008: 20.8%, Leon 2007: 5.8%, Sewanaik 2006: 6.8%, Clark 2005: 6.5%, Marchese 2005: 4%, Spriano 2002: 10.9%.

In our sub-analysis, we found that 5-year OS for T1-T2 patients (early stage) was 79.8%; interestingly, this rate was 92.3% for T3-T4 patients (locally advanced stage). The 5-year DFS was 86.9% for T1-T2 patients and 91.1% for T3-T4 patients. These data might be attributable to inaccurate staging (i.e., understaging) prior to salvage surgery. In this regard, Zbaren et al. [37] reported that 52% of patients were clinically understaged and that the diagnostic accuracy of clinical evaluation (via fiberoptic laryngoscopy, CT, MRI, or microlaryngoscopic examination findings) was only 38%.

Nevertheless, our statistical analysis demonstrated that the differences between the 5-year OS and DFS of early and locally advanced SCC patients were not significantly different ($p = 0.340$ and $p = 0.841$, respectively). However, these results may have been influenced by the small size of the locally advanced stage group (only 17 patients).

Some of the papers included in this meta-analysis [9 16 23-25 27] reported only clinical TNM. We strongly believe that future studies should also report pathological stage after salvage surgery.

The theoretical advantage of SCL over TL is that at least one functioning crico-arytenoid joint is maintained, and thus a permanent tracheostoma is not required, and the main laryngeal functions (i.e., respiration, phonation and swallowing) are preserved. Nevertheless, swallowing impairment represents the main functional issue due to the modification of the hypopharyngo/laryngeal anatomy. This condition has implications for the quality of life in addition to an association with potentially life threatening complications, such as aspiration pneumonia [38 39].

This meta-analysis demonstrated that the mean time until NGT or PEG removal was 28.3 days, and the mean time until decannulation was 35.6 days. These data accord with the reports of other authors [40 41] who prefer the initial removal of the NGT and initiation of oral alimentation with a tracheostomy tube to protect and clean the airways and permit the suction of any residual food that may be present [13]. However, the proper postoperative management of tracheostomies is still under debate. In contrast, different authors [28 29 42-56] have proposed early removal of the tracheostomy tube to ensure a rapid mobilisation of the residual larynx to avoid any interference with the cough reflex, which limits the incidence of pulmonary infection [13]. These different approaches might be due to personal experience or the preferences of the surgeon.

Some authors [27 36] have suggested that, in consideration of the possibility of long-lasting swallowing disorders, clinicians should consider preoperative PEG in patients undergoing SCL as a salvage surgery for glottic carcinoma after irradiation failure. This suggestion is consistent with the opinion of the majority of the authors of the studies included in the present meta-analysis [13 16 18 22 25 27 28]. SCLs allow for satisfactory functional results, but surgical protocols need to be followed by adequate nursing and rehabilitation protocols. However, there is no evidence regarding when rehabilitation should be initiated, which criteria should be adopted to indicate the initiation and termination of rehabilitation, or which voice and swallowing rehabilitation procedures provide the optimal functional outcomes [57]. Therefore, we recommend that future work should focus on standardising postoperative care and rehabilitation protocols.

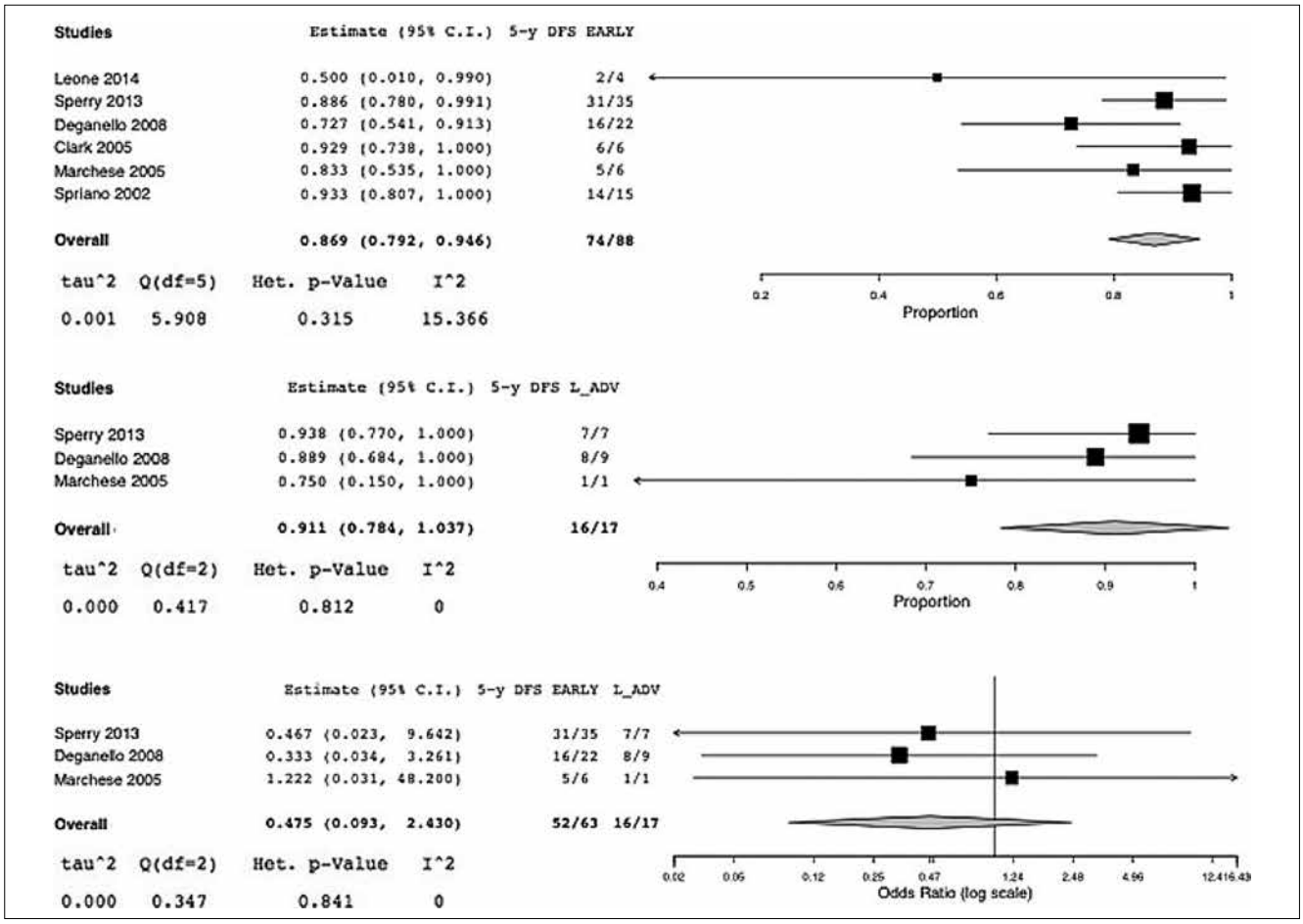

Fig. 5. Upper box: Forest plot of the 5-year DFS for patients affected with "early" T1-T2 recurrent laryngeal cancer after radiation therapy failure who were treated with supracricoid laryngectomy. Weights: Leone 2014: 2.4%, Sperry 2013 35.3%, Deganello 2008: 14.6%, Clark 2005: 14%, Marchese 2005: 6.2%, Spriano 2002: 27.4%. Middle box: Forest plot of the 5-year DFS for patients affected with "locally advanced" T3-T4 recurrent laryngeal cancer after radiation therapy failure who were treated with supracricoid laryngectomy. Weights: Sperry 2013 57.3%, Deganello 2008: 38.2%, Marchese 2005: 4.5%. Lower box: Forest plot of the 5-year DFS for patients affected with "early" vs. "locally advanced" recurrent laryngeal cancer following after radiation therapy failure who were treated with supracricoid laryngectomy. Weights: Sperry 2013 29%, Deganello 2008: 51.3%, Marchese 2005: 19.7%.

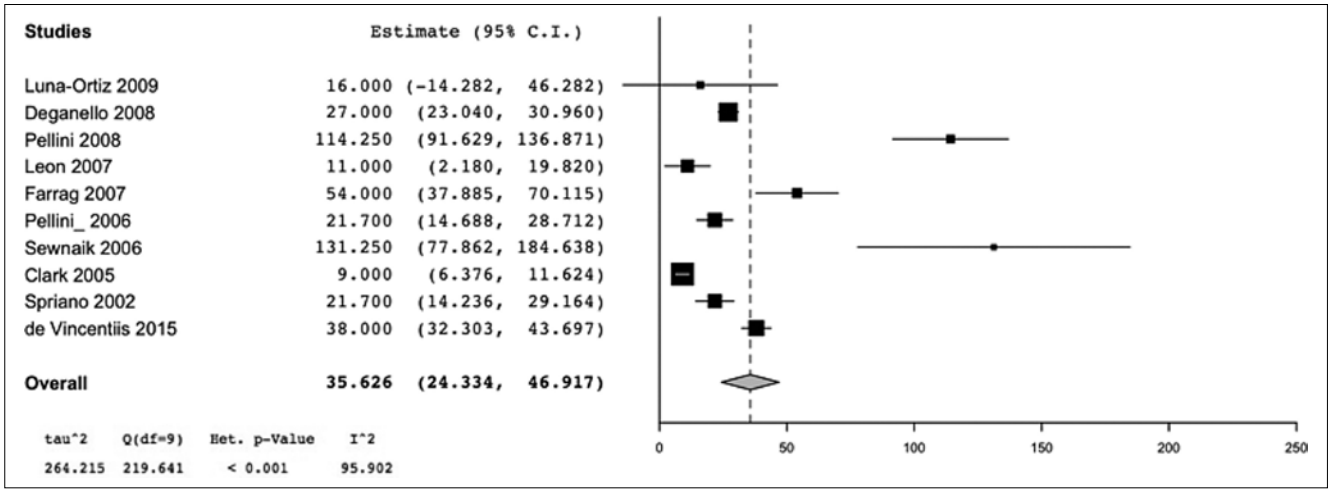

Fig. 6. Forest plot of the mean time until decannulation (days) for patients who were treated with supracricoid laryngectomy after radiation therapy failure. Weights: Luna-Ortiz 2009: 6.5%, Deganello 2008: 12.2%, Pellini 2008: 8.2%, Leon 2007: 11.5%, Farrag 2007: 9.9%, Pellini 2006: 11.8%, Sewanaik 2006: 3.2%, Clark 2005: 12.3%, Spriano 2002: 11.8%, de Vincentiis 2015: 12%.

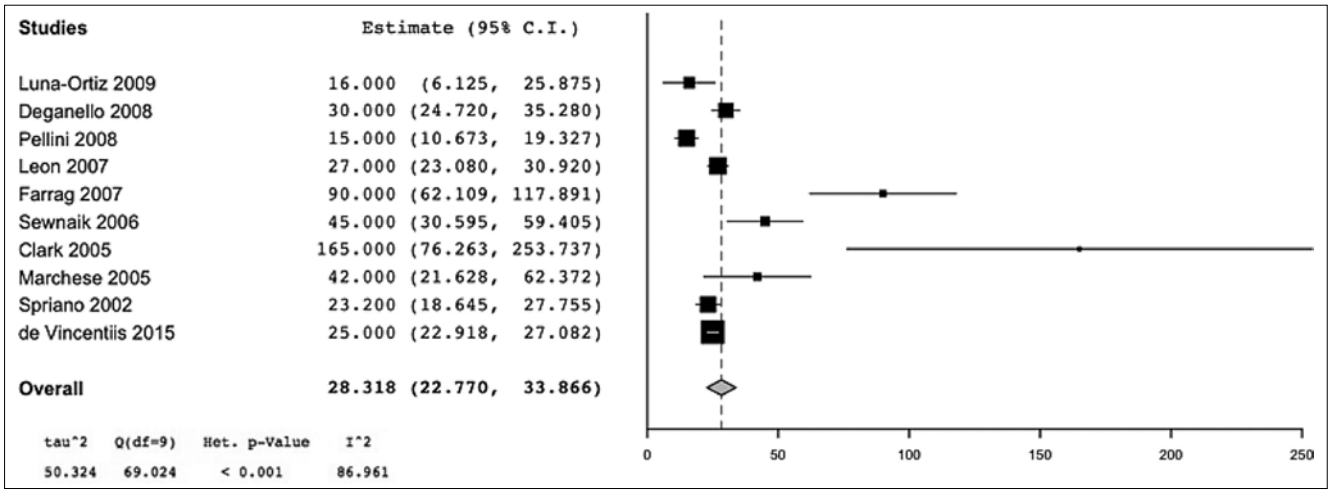

Fig. 7. Forest plot of the mean time until NGT or PEG removal (days) for patients who were treated with supracricoid laryngectomy after radiation therapy failure. Weights: Luna-Ortiz 2009: 10.5%, Deganello 2008: 13.9%, Pellini 2008: 14.5%, Leon 2007: 14.7%, Farrag 2007: 3.1%, Sewanaik 2006: 7.6%, Clark 2005: 0.3%, Marchese 2005: 5%, Spriano 2002: 14.3%, de Vincentiis 2015: 15.5%.

Conclusions

Recurrent laryngeal cancer after irradiation is a difficult clinical problem. Although total laryngectomy has been widely considered for many years to be the treatment of choice, this meta-analysis demonstrated that supracricoid laryngectomy for recurrent laryngeal cancer after chemoradiotherapy provides reliable oncological and short-term postoperative recovery outcomes.

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Head and neck

Functional outcomes of supraglottic squamous cell carcinoma treated by transoral laser microsurgery compared with horizontal supraglottic laryngectomy in patients younger and older than 65 years

Risultati funzionali in pazienti over e under 65 affetti da carcinoma squamocellulare sopraglottico trattati con chirurgia laser trans-orale o tradizionale laringectomia orizzontale sopraglottica

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SUMMARY

The treatment of supraglottic carcinoma remains a controversial issue. Five accepted surgical and non-surgical oncological treatments have been currently established: standard horizontal supraglottic laryngectomy (HSL), supraglottic CO2 laser microsurgery (TLM), transoral robotic surgery, radiotherapy alone and radiotherapy in combination with chemotherapy. Some studies have shown that complications of head and neck surgeries increase significantly in patients over 65 years compared to younger patients. We designed a retrospective analysis to assess the rate of complications and functional outcomes of patients treated by TLM and HSL in cases of T1-T3 supraglottic squamous cell carcinomas (SCC) in a tertiary University Hospital. Results were compared between patients younger and older than 65 years. We found significant differences in the rate of aspiration pneumonia ($p = 0.026$), mean time to decannulation ($p = 0.001$) and mean hospital stay ($p = 0.007$) in patients treated by TLM, which was higher and longer in the group of patients over 65 years of age. Regarding HPL, we only found significant differences in the mean time to decannulation ($p = 0.001$), which was longer in the group of patients younger than 65 years. According to our results, TLM or HPL can both be a safe surgical option for patients older than 65 years, but previous evaluation of lung function before surgery is mandatory because of an increased risk of aspiration pneumonia in patients with lung problems, especially when treated by TLM. Concerning functional outcomes in patients older than 65 years, TLM reduces the postoperative rate of tracheostomy, mean time required for decannulation and mean hospital stay compared with HPL. However, no significant difference in the occurrence of aspiration pneumonia, dysphagia or in the mean length of NGT feeding was found.

KEY WORDS: Squamous cell carcinoma • Supraglottis • Complications • Laser CO2

RIASSUNTO

Il trattamento dei carcinomi sopraglottici rappresenta al momento una problematica controversa. Al momento sono disponibili 5 differenti opzioni di trattamento: la tradizionale laringectomia orizzontale sopraglottica (HSL), la laringectomia sopraglottica con laser CO2 (TLM), l'approccio mediante chirurgia robotica, la radioterapia e la radioterapia in combinazione con la radiochemioterapia. Alcuni studi hanno evidenziato come il rate di complicanze della chirurgia del distretto testa collo aumenti significativamente nei soggetti al di sopra dei 65 anni. Abbiamo pertanto voluto effettuare uno studio retrospettivo che confrontasse i risultati funzionali e il rate di complicanze nei pazienti al di sotto e al di sopra dei 65 anni, affetti da carcinomi squamocellulari sopraglottici T1-T3, sottoposti a laringectomia orizzontale sopraglottica tradizionale (HSL) o a TLM presso un Polo ospedaliero Universitario di terzo livello. Il gruppo di pazienti al di sopra dei 65 anni sottoposto a TLM ha mostrato differenze statisticamente significative per quanto riguarda il rate di polmonite ab ingestis ($p = 0.026$), tempo medio necessario al decannulamento ($p = 0.001$) e tempo medio di ricovero ospedaliero ($p = 0.007$) tutti risultati più lunghi rispetto a quelli osservati nei pazienti al di sotto dei 65 anni. Per quanto riguarda la chirurgia open, abbiamo rilevato una differenza statisticamente significativa solo per il tempo medio necessario per il decannulamento ($p = 0.001$) risultato essere più lungo nel gruppo di pazienti più giovani di 65 anni. In accordo coi nostri risultati sia la TLM che l'approccio open rappresentano opzioni sicure nei pazienti al di sopra dei 65 anni, ma in cosiderazione dell'aumentato rischio di polmonite ab ingestis è mandatoria un adeguata valutazione della funzionalità polmonare preoperatoria, in particolare nei pazienti trattati con TLM. Nei pazienti al di sopra dei 65 anni inoltre la TLM rispetto all'approccio open riduce il rate di tracheostomie postoperatorie, il tempo medio necessario al decannulamento e il tempo medio di ricovero. Tuttavia non è stata rilevata alcuna differenza significativa in termini di rate di polmonite ab ingestis, disfagia o tempo medio di utilizzo del sondino naso gastrico.

PAROLE CHIAVE: *Carcinoma a cellule squamose • Sovraglottide • Complicanze • Laser CO2*

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Introduction

Laryngeal tumours represent approximately 2% of all tumours and are the second most common tumour in the head and neck region [1]. Approximately one-third affect the supraglottic region and 90% are histopathologically squamous cell carcinomas [2].

The treatment of supraglottic carcinoma is still a controversial issue. Many accepted surgical and non-surgical oncological treatments have been currently established. In locally advanced laryngeal carcinomas, total laryngectomy has been the mainstay of treatment for decades [3], but horizontal supraglottic laryngectomy [4] (HSL) and more recently supracricoid laryngectomy, supratracheal laryngectomy, supraglottic CO2 laser microsurgery (TLM) [5-9], transoral robotic surgery (TORS), radiotherapy alone or radiotherapy in combination with chemotherapy are accepted options. These options can be used together or separately. For example, in the case of early or well selected advanced supraglottic carcinoma, this can be treated successfully with HSL, TLM or radiotherapy [10], but robotic surgery is also an option. The addition to radiotherapy and chemotherapy is also generating interest. Key principles must be taken into account to determine patient eligibility for an organ preservation or surgical approach, because even though local control is the main goal of the treatment, the preservation of laryngeal function must be effective to achieve consistent functional outcomes in terms of speech and swallowing. Furthermore, the eligibility of the patients is based on the extent of tumour and not only on the T classification [11-13].

In reality, the proportion of deaths due to cancer has been increasing among elderly people, and this is frequent in developing countries. Patients over 65 years with laryngeal carcinoma have their own particular characteristics. Age is considered a major risk factor for development of laryngeal tumours, although symptoms of cancer are less evident in elderly patients, due to sensory hypofunction and frequent confusion of cancer symptoms with the symptoms of various pre-existing diseases. These factors may result in misdiagnosis or delayed diagnosis [14]. The risk of the surgery also increases in elderly patients due to frequent age-related chronic systemic diseases [15].

Some studies have shown that complications of head and neck surgeries are increased significantly in elderly patients [16 17]. Due to the high rate of complications related to the treatment of these tumours in patients over 65 years of age, surgical treatment is not widely accepted. However, only few studies have compared the rate of complications related to the treatment of supraglottic squamous cell carcinoma between TLM or HSL in elderly patients.

For this reason, the aim of this study was to retrospectively evaluate the rate of complications and oncological and functional outcomes obtained in a series of elderly patients treated by TLM and HPL for cT1-cT3 supraglottic squamous cell carcinomas (SCC) in a tertiary University Hospital and compared with a control group of younger patients.

Materials and methods

A retrospective analysis was performed on previously untreated patients diagnosed with squamous cell carcinoma (SCC) of the supraglottis (cT1-cT3), N -/+, M -/+ according to criteria of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Patients were divided in two groups according to age (younger and older than 65 years). All patients treated with curative intent by TLM or HSL between January 2010 and January 2012 were included, and patients who had received prior treatment with another surgical technique or those who had received prior RT were excluded. Identification of cases was achieved by computerised research on the medical records of our database, using the International Classification of Diseases (ICD-9). This study was approved by the ethics committee of our centre. The demographic data (age, sex), past medical history, comorbidities, stage, imaging, complications, outcomes after surgery, type of surgery, etc., were obtained by review of medical history.

Preoperative examination

Prior to surgery, all cases were discussed in an interdisciplinary committee of head and neck tumours. Preoperative examination of the lesion was carried out by indirect laryngoscopy, videolaryngoscopy and CT or MRI of the neck to evaluate cartilage, preepiglottic and paraglottic space and lymph node involvement. Fine needle biopsies of the neck nodes were normally performed under ultrasonographic control. Patients with lesions suspicious for malignancy were scheduled for laryngeal microsurgery and pan-endoscopy with biopsies, followed by TLM or HSL in cases that were positive for malignancy if they had adequate pulmonary function (pulmonary function tests, such as vital capacity and forced expiratory volume in 1 second, were done in patients with history of chronic obstructive pulmonary disease). After surgery, pTNM classification was presented in the multidisciplinary committee and the need for reoperation or additional radiotherapy (RT) or chemoradiotherapy (QT/RT) was assessed.

Operative technique

The type of surgery, whether TLM or HSL, was selected according to the clinical tumour stage and difficulty of exposure. TLM was performed on tumours not involving the vocal cords or the laryngeal framework or involving not more than 1 arytenoid. When indicated, supraglottic resection was extended to the valleculae, the base of the tongue and the medial wall of the pyriform fossae. The indication for transoral laser CO2 surgery was made if

the tumour was completely exposable during the previous laryngeal microsurgery. If, however, the vocal cords were fixated, the laryngeal framework affected or the base of tongue or hypopharynx was not completely exposable during direct laryngoscopy, an open procedure was indicated.

All patients underwent a general anaesthesia with orotracheal intubation, and resection was performed using a Lumenis CO2 laser device (Yokneam, Israel), with a power setting of 10-12 W, used in superpulsed mode and continuous setting, varying size and shape of the spot according to the moment of the surgery by using the micro-manipulator Acuspot-Acublade (Lumenis). In the case of small tumours, whenever possible, en bloc resection was attempted and the excised piece was pinned and orientated on a corkboard. In larger lesions, a piecemeal resection was often the only option. In all cases surgeons tried to achieve a margin of healthy tissue of 2-3 mm, trying to preserve functions without affecting the oncological radicality of the procedure. During surgery no intraoperative biopsies were performed if the resection was satisfactory. However, when the depth of cancer infiltration was difficult to estimate a frozen section was sent for examination. Subsequently, vaporisation of the surgical site was performed to prevent tumour recurrence when the frozen section was positive [18]. Resection margins were classified as free, uncertain, or affected according to Blanch et al. [18]. In cases of affected margins, re-intervention was performed. Those patients with uncertain margins were followed up and only in the case of finding persistence or recurrence was another surgery was performed.

HSL was indicated in patients regardless of age and stage (cT1-cT3), when resection was not possible by TLM due to the difficulty of exposure of the lesion or the tumour size and when no involvement of the vocal cords or laryngeal framework was seen. Extension to the base of the tongue or the hypopharynx was not considered a contraindication. Preepiglottic o paraglottic space involvement was considering a contraindication to this technique in our centre. However, according with other reports, in selected tumours classified as T3 due to limited paraglottic spread without fixation of the arytenoid cartilage, this surgery can be an option [19]. All the supraglottic laryngectomies included in the study were performed using a modification of the Alonso's technique described by Herranz et al. [20], (In all external neck approaches we always perform a tracheotomy). The type of surgery (endoscopic supraglottic CO_2 laser partial laryngectomy or open partial horizontal laryngectomies) was classified according to the European Laryngological Society (ELS) proposal [21 22]. In all cases, the XII cranial nerve and superior laryngeal nerve were intended to be preserved. Advanced chronic respiratory disease was considered a major contraindication.

Treatment of the neck

In patients treated by HSL who presented positive neck lymph nodes (N1, N2), a selective neck dissection including levels II, III, IV and V was performed in the same surgical procedure. In those patients treated by TLM, the selective neck dissection was performed in a second procedure 3 weeks after the initial tumour resection, accompanied by second look microlaryngoscopy exploration. Patients classified as N0 were followed up and only if metastatic disease became evident was a functional neck dissection with microlaryngoscopy exploration performed.

Oral intake

For patients treated by TLM, oral intake was commenced 6 hours after the procedure if the resection was small. In more advanced tumours, we used a nasogastric feeding tube (NGT) and waited 24-48 hours to start oral intake. In patients treated by HPL, a NGT was inserted and no oral intake was allowed for the first week.

Follow-up

In our department, patients diagnosed and treated for head and neck malignant tumours are followed up for at least 5 years by the Head and Neck Oncology Team. However, for this study we considered a group of patients that has been followed up by a minimum of 36 months (3 years).

Complementary treatment

Additional postoperative radiotherapy was administered to some patients in both groups in advanced neck disease (N2a/b/c) when the histopathological examination revealed extracapsular spread or in those patients with lymphatic micrometastases. Patients with histologically close surgical margins, mainly at the base of the tongue, also received post-surgical radiotherapy for 4 weeks postoperatively followed by weekly doses to reach a total dose of 60 Gy.

Statistical analysis

Statistical analysis was run by the SPSS program for Windows, Version 20.0 (SPSS, Inc. Illinois, USA). Quantitative variables in the study are expressed as mean ± typical deviation. The different variables were correlated by Pearson's chi-square test and for the comparison of continuous variables (mean hospital stay, mean time to decannulation, aspiration pneumonia, NGT mean duration, tracheostomy duration, need of percutaneous gastrostomy) between both groups of elderly patients the Mann-Whitney U test was used. P values of < 0.05 were considered to be statistically significant in all tests**.** We calculated overall survival and disease-specific survival using Kaplan-Meier survival analysis. As reference for overall survival, we used the survival time from the surgery until the last revision or date of death regardless of cause. For disease-spe-

Table I. Type of endoscopic supraglottic CO_2 laser partial laryngectomy according to ELS classification.

Type of cordectomy	Number	%
Type IIa	3	9.7
Type IIb	2	6.5
Type IIIa	6	19.4
Type IIIb	4	12.9
Type IVa	5	16.1
Type IVb	11	35.5
Total	31	100.0

cific survival, we considered the time between the surgery until death by tumour or until total laryngectomy was performed. We calculated the influence of various factors on survival using the log-rank method.

Results

47 patients met the inclusion criteria, 44 (93.6%) patients were male and 3 (6.4%) were females. 31 (65.9%) of them were treated with TLM and 16 (34.1%) were treated with HSL. All data are presented in Tables I, II and III for TLM and in Tables IV and V for HSL.

Other factors are shown in Tables II to VI such as: classification according to the type of endoscopic CO_2 laser supraglottic laryngectomy in the group of patients treated by TLM, results of both groups according to TNM classification, mean hospital stay, mean time to decannulation, post-surgical complications including postoperative bleeding, urgent tracheotomy, number of patients who required NGT or percutaneous gastrostomy tube (PEG), postoperative dysphagia and complications associated with the surgical technique such as aspiration pneumonia and chondritis of the thyroid cartilage.

In the group of patients treated by TLM, we found statistically significant differences between both groups of patients with regards to the presence of comorbidities, specifically in the group of patients over 65 years where diabetes ($p = 0.017$) was found to be more frequent. In terms of post-surgical complications, we found a significant difference in the incidence of aspiration pneumonia which was also higher in the group of patients over 65 years ($p = 0.026$). We also found a difference in the mean time to decannulation ($p = 0.001$) and average hospital stay ($p = 0.007$), which were both longer in the group of patients over 65 years (Tables II, III).

No correlation was found between the need for tracheostomy in patients treated by TLM and T stage ($p = 0.862$). In all patients treated by TLM, we analysed the possible effect of radiotherapy ($< 65 = 10/14$; $> 65 = 7/17$: $p = 0.160$) or cervical neck dissection ($p = 0.316$) on the rate of aspiration pneumonia and there was no statistical correlation. Furthermore, we examined the possible effect of arytenoid resection on the rate of dysphagia ($p = 0.507$) and there was no relation.

In the group of patients treated with HSL, we did not find significant differences between the two groups of patients with regards to the presence of comorbidities or post-surgical complications. We found significant differences in the mean

Table II. Demographic and oncologic data of patients treated with TLM divided according to age.

Variable	TLM elderly	%	TLM younger	%	p
Age	71.24±5.7 (Min: 65;Max:83)		52.3±4.59 (Min 45;Max: 59)		
Sex					
Men	17	100	12	85.7	
Women	0	0	2	14.3	
Diabetes	6	35.3	0	0	0.017
Hypertension	6	35.3	1	7.1	0.073
Tobacco	17	100	14	100	
Alcohol	15	88.2	9	64.3	0.124
T1	1	5.9	1	7.1	0.835
T2	8	47.1	7	50	0.741
T3	8	47.1	6	42.9	0.640
N0	15	88.2	9	64.3	0.262
N1	1	5.9	3	21.4	0.169
N2a	1	5.9	1	7.1	0.239
N2b	0	0	1	7.1	0.245
M0	17	100	14	100	
Primary neck dissection	3	17.6	1	7.1	0.378
Secondary neck dissection	3	17.6	4	28.6	
Neck dissection due to regional recurrence	2	11.7	4	28.6	
Arytenoid resection	5	29.4	8	57.1	
RT	14	51.9	10	71.4	

Table III. Complications and clinical outcomes of both groups of patients treated with TLM divided according to age.

Variable	TLM elderly	%	TLM younger	%	p
Post-Surgical bleeding (Primary procedure)	3	17.6	1	7.1	0.378
Tracheostomy	4	23.5	1	7.1	0.233
Cervical abscess (Neck dissection)	1	5.9	1	7.1	0.708
Chondritis	1	5.9	0	0	0.548
Aspiration pneumonia	7	41.2	0	0	0.026
Laryngeal stenosis	0	0	2	14.3	0.406
NGT	15	88.2	10	71.4	0.235
NGT mean duration	7.53 ± 6.79 (Min:2/Max:27)		3.64 ± 2.84 (Min:1/Max:9)		0.080
PEG	4	23.5	0	0	0.076
Dysphagia	5	29.4	5	35.7	0.590
Failed decannulation	2	11.8	0		0.406
Mean time to decanulation	45.8 ± 132 Days (Min:30/Max:540)		14Days (Only 1 patient needs a traqueostomy)		0.001
Mean hospital stay	17.41 ± 34.3 (Min:2/Max:149)		8.21±3.55 (Min:4/Max:15)		0.007

Table IV. Demographic and oncologic data of patients treated with HSL divided according to age.

Variable	HSL elderly	%	HSL younger	%	p
Age	66.6 ± 2.41 (Min: 65/Max: 71)		49.50 ± 3.1 (Min: 44/Max: 53)		
Sex					
Men	10	100	5	83.3	
Women	0	0	1	16.7	
Diabetes	1	10	0	0	0.563
Hypertension	4	40	1	16.7	0.231
Tobacco	10	100	6	100	
Alcohol	10	100	5	83.3	0.468
T1	0	0	1	16.7	0.460
T2	6	60	3	50	0.382
T3	4	40	2	33.3	0.320
N0	5	50	1	16.7	0.102
N1	3	30	2	33.3	0.382
N2a	0	0	2	33.3	0.320
N2b	1	10	1	16.7	0.372
N2c	1	10	0	0	0.563
M0	10	100	6	100	0
Primary neck dissection	10	100	6	100	0.617
Secondary neck dissection	0	0	0	0	
Arytenoid resection	4	40	2	33.3	
RT	4	40	4	66.6	

time to decannulation (p = 0.001), which was longer in the group of patients younger than 65 years (Tables IV, V).

In all patients treated by HSL, we also analysed the influence of post-operative radiotherapy (< 65 = 4/6: p = 0.368/> 65 = 4/10: p = 0.667) or cervical neck dissection (p = 0.337) in patients on the rate of aspiration pneumonia and possible effect of arytenoid resection on the rate of dysphagia (p = 0.451) and again no statistical correlation was found.

When comparing the two groups of patients over 65 years treated by either TLM or HSL, we found significant differences in the need for tracheostomy (p = 0.001), mean time required for decannulation (p = 0.001) and mean hospital stay (p = 0.003), all in favour of TLM. However, no significant difference was found in the incidence of aspiration pneumonia (p = 0.343), dysphagia (p = 0.117) or in the average length of NFT (p = 0.700) (Table VIII). Finally, in the group of patients treated by TLM a total of

Table V. Complications and clinical outcomes of both groups of patients treated with HSL divided according to age.

Variable	HSL elderly	%	HSL younger	%	p
Post-Surgical bleeding (Primary procedure)	0	0	1	16.7	0.438
Tracheostomy	10	100	6	100	
Cervical abscess (Neck dissection)	0	0	1	16.7	0.438
Chondritis	0	0	0	0	0
Aspiration pneumonia	2	20	1	16.7	0.400
Laryngeal stenosis	0	0	0	0	0
Cervical fistula	1	10	1	16.7	0.230
NGT	10	100	6	100	
NGT mean duration	11.80 ± 9.5 (Min: 6/Max: 38)		8.50 ± 4.5 (Min: 4/Max: 15).		0.248
PEG	2	20	1	16.7	0.600
Dysphagia	3	30	4	66.7	0.329
Failed decannulation	5	50	3	50	
Mean time to decanulation	160.4 ± 126.5 (Min: 31/Max: 407)		233.67 ± 169.66 (Min: 32/Max: 501)		0.001
Mean hospital stay	20.50 ± 7.69 (Min: 14/Max: 39)		21.67 ±10.1 (Min: 12/Max: 40)		0.451

Table VI. Comparision of continuous variables between both groups in elderly patients.

Variable	HSL elderly	%	TLM elderly	%	p
Mean hospital stay	20.50 ± 7.69 (Min: 14/Max: 39)		17.41 ± 34.3 (Min:2/Max:149)		0.003
Need for tracheostomy	10	100	4	23.5	0.001
Mean time to decanulation	160.4 ± 126.5 (Min: 31/Max: 407)		45.8 ± 132 Days (Min:30/Max:540)		0.001
Aspiration pneumonia	2	20	7	41.2	0.343
Dysphagia	3	30	5	29.4	0.117
NGT mean duration	11.80 ± 9.5 (Min: 6/Max: 38)		7.53 ± 6.79 (Min:2/Max:27)		0.700

9 patients (29%) needed total laryngectomy, 7 of whom (22.5%) due to functional reasons, 4 were from the group of patients over 65 years and 3 from the group of patients younger than 65 years (p = 0.637). On the other hand, in the group of patients treated by HSL, none needed total laryngectomy.

In the group of patients treated by TLM, three year overall survival was 67.7%, while the three year disease-specific survival was 83.8%. In the group of patients treated by HSL, the three year overall survival was 62.5%, and the three year disease-specific survival was 75%. There were no significant differences between both techniques according to overall (p = 0.626) or specific survival rates (p = 0.723) (Figs. 1, 2).

Recurrence in the neck was observed in 6 patients treated with TLM, all whom were previously classified as cN0. Those patients were treated with cervical neck dissection. Three patients died from regional recurrence, another due to pneumonia, while 2 patients were alive and disease-free at the last follow-up.

Discussion

In general, functional results of TLM are considered by many authors superior to those obtained by HSL. TLM usually shows less time required to restore the patient's swallowing capacity, shorter hospital stay, less need of tracheotomy, lower incidence of aspiration pneumonia and lower incidence of pharyngocutaneous fistulas [23-28]. In contrast, other authors such as Cabanilla et al. [29] did not consider these differences as significant. In particular, they compared the rate of functional problems after conventional HSL and reported no significant differences, concluding that the lower rate of patients needing temporary tracheotomy is frequently the major advantage of TLM over HSL. In terms of restoring swallowing capacity, they found faster improvement in tumours endoscopically resected by TLM, but long-term results seemed to be similar in both approaches [30]. Usually these functional advantages can be attributed to the more conservative nature of an endoscopic procedure, because healthy tissue is not

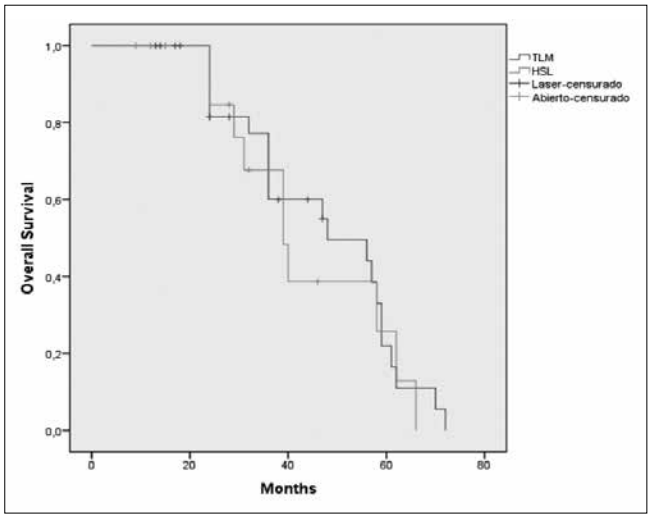

Fig. 1. Kaplan-Meier three-year overall survival according to surgical approach TLM vs. HSL.

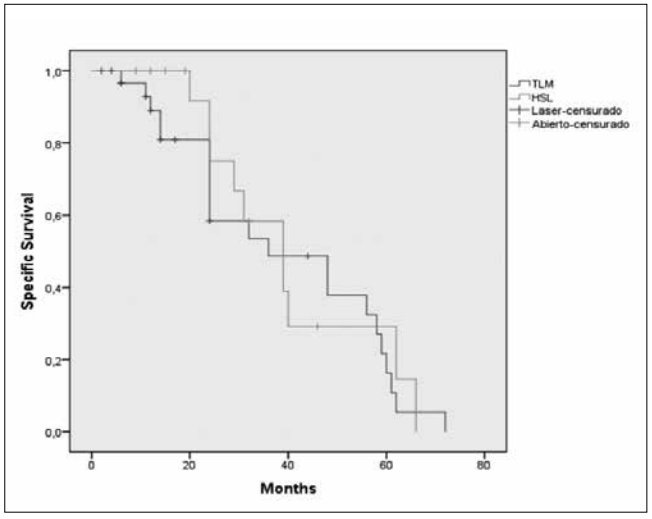

Fig. 2. Kaplan-Meier three-year specific survival according to surgical approach TLM vs. HSL.

involved during the approach. During open procedures, the skin as well as the thyroid cartilage and the soft tissues are involved. The incision and posterior suturing of these structures will almost always result in airway swelling and the need for tracheotomy. This can be avoided in many endoscopic resections [29].

Regarding the incidence of aspiration pneumonia, different results have been reported in the literature. Köllisch *et al.* found an incidence of aspiration pneumonia of 11.5% (3 of 26) in the TLM group compared to 40% (8 of 20) in the HSL group [30]. On the other hand, Cabanillas et al., found no significant differences in the incidence of aspiration pneumonia (11.5%) between groups (TLM vs HSL), but did find a correlation between the mean age of patients that was significantly higher in those who suffered aspiration pneumonia [29]. In our study, we only found a significant difference in the incidence of aspiration pneumonia when comparing both age groups within the group of patient treated with TLM which was higher in the group over 65 years ($p = 0.026$), but when comparing both techniques in the groups of patients over 65 years there were no significant difference.

With regards to mean hospital stay, Cabanilla *et al.* found no differences in the number of days of postsurgical stay between the two surgical approaches. They hypothesised that the shorter hospital stay after transoral resection is compensated by the stay after neck dissection. In another study, Peretti et al. found a better cost-effectiveness ratio for TLM, since it reduced hospital stay by more than 50% compared with open neck supraglottic laryngectomies. In our study, we found a significant difference in mean hospital stay ($p = 0.007$) when comparing age groups in patients treated by TLM, resulting in a longer stay in patients over 65 years. According to the type of technique (TLM vs. HSL) in patients over 65 years old, we also found a statistical difference in mean hospital stay ($p = 0.003$), which was longer in patients treated by HSL.

Regarding the need for tracheostomy, we found no differences between younger and elderly patients in either groups when we compared within the same surgical technique, but we found a significant difference in the need for tracheostomy and mean time to decannulation when we compared the same parameters in patients over 65 years treated with different techniques. Patients over 65 years treated by TLM were found to require fewer tracheostomies and had a shorter time to decannulation (Tab. VII). Others authors [32-35] who compared the results of TLM and HSL such as Cabanilla *et al.* found that the avoidance of tracheostomy was the main functional advantage of TLM, but with no difference in the need for a permanent tracheostomy [29]. Peretti *et al.*performed tracheotomy in only 14% of patients treated by TLM [31].

Regarding the presence of swallowing alterations, we found no differences between either of the techniques or age groups. Most authors have suggested that there is better recovery of swallowing after TLM. These outcomes could be due to the less invasive nature of laser surgery, where the muscular structures involved in swallowing are usually respected, whereas open surgery involves damage to the strap muscles and modification of anatomical structures, and therefore alteration of swallowing mechanics. Other parameters like T classification or psychological motivation have also been correlated to outcomes on swallowing after surgery [29]. This is why the role of postoperative swallowing rehabilitation is so important after these surgeries [31]. Another important issue is the presence of radiotherapy toxicity after HSL treatment. Some authors concluded that radiotherapy influences the swallowing function without affecting the phonatory results [36]. Moreover, Ruberto et al. recently analysed the rate of pexy line rupture in a group of patients treated by par-

tial laryngectomy, and concluded that it is an infrequent complication that may occur in patients with normal postoperative course after partial laryngectomies, further reporting the appearance of symptoms from the beginning of swallowing exercises. Therefore, is very important to follow the patient closely during the postoperative period, because early diagnosis of a rupture in the pexy can prevent respiratory or infectious complications and massive bleedings [18].

We found no statistical correlation between adjuvant therapy or cervical neck dissection and the rate of aspiration pneumonia in either type of surgical procedure. Some authors consider the need for adjuvant radiotherapy, which usually results from histopathological findings on surgical specimens, the strongest support for an endoscopic versus an open approach [37]. However, we are not able to give a strong recommendation based on our results about this topic, and probably the small number of patients in this arm does not provide sufficient statistical power. Despite this, we always try to avoid the use of radiotherapy in patients treated by HSL.

Nowadays, transoral robotic surgery (TORS) appears to be an interesting option for resection of head and neck cancer. This technique was introduced in 2006 and the first supraglottic partial laryngectomy with TORS was described in 2007 by Solares et al. who performed an experimental resection of the supraglottis in a cadaver, a dog model and later in a woman with a supraglottic carcinoma [38]. After that, Weistein et al. treated the first three human patients with supraglottic carcinoma by TORS [39]. Later, other authors have attempted to demonstrate the advantages of this new technique by overcoming the limitations of TLM, namely improved visualisation of the surgical field due to the high definition and three dimensional imaging and improved dexterity, due to more degrees of freedom of movement of the robotic arms, filtration of physiological tremor and greater comfort for the surgeon [38]. Other authors suggest that the robotic technique is considerably more comfortable, less fatiguing for the surgeon than the endoscopic technique and less operative time is required, perhaps due to the previous experience of surgeons with endoscopic techniques [40]. However, this technology is not yet available in all centres.

Our study has a number of limitations. Primarily its retrospective nature and the small sample size can limit the validity of our results, as well as the lack of validated questionnaires done on patients. Another limitation is the subjective assessment of the swallowing improvement and the absence of a voice test after surgery. Prospective studies analysing the functional outcomes of these two different approaches to treat supraglottic squamous cell carcinoma will most likely help to decide which surgical path will be more beneficial for the patient, especially in the case of elderly patients.

Conclusions

In conclusion, TLM or HSL can both be a safe surgical option for patients older than 65 years, but previous evaluation of lung function before surgery is mandatory because of an increased risk of aspiration pneumonia in patients with lung problems, especially when treated by TLM. Concerning functional outcomes in patients older than 65 years, TLM reduces the postoperative rate of tracheostomy, the mean time required for decannulation and the mean hospital stay compared with HSL. However, no significant difference in the occurrence of aspiration pneumonia, dysphagia, or in the mean length of NGT feeding was found.

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HEAD AND NECK

Head and neck reconstruction with pedicled flaps in the free flap era

Ricostruzioni del distretto testa collo con lembi peduncolati nell'era dei lembi liberi

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SUMMARY

Nowadays, the transposition of microvascular free flaps is the most popular method for management of head and neck defects. However, not all patients are suitable candidates for free flap reconstruction. In addition, not every defect requires a free flap transfer to achieve good functional results. The aim of this study was to assess whether pedicled flap reconstruction of head and neck defects is inferior to microvascular free flap reconstruction in terms of complications, functionality and prognosis. The records of consecutive patients who underwent free flap or pedicled flap reconstruction after head and neck cancer ablation from 2006 to 2015, from a single surgeon, in the AOUC Hospital, Florence Italy were analysed. A total of 93 patients, the majority with oral cancer (n = 59), were included, of which 64 were pedicled flap reconstructions (69%). The results showed no significant differences in terms of functional outcome, flap necrosis and complications in each type of reconstruction. Multivariate regression analysis of flap necrosis and functional impairments showed no associated factors. Multivariate regression analysis of complicated flap healing showed that only comorbidities remained an explaining factor (p = 0.019). Survival analysis and proportional hazard regression analysis regarding cancer relapse or distant metastasis, showed no significant differences in prognosis of patients concerning both types of reconstruction. In this retrospective, non-randomised study cohort, pedicled flaps were not significantly inferior to free flaps for reconstruction of head and neck defects, considering functionality, complications and prognosis.

KEY WORDS: Head and neck reconstruction • Oral cavity reconstruction • Pedicled flap • Free flap • Head and neck cancer

RIASSUNTO

La trasposizione di lembi liberi microvascolari rappresenta oggi la procedura maggiormente diffusa nelle ricostruzioni del distretto testa-collo. Tuttavia, non tutti i pazienti sono candidati ideali per ricostruzioni microvascolari, né tutti i difetti richiedono necessariamente lembi microvascolari per ottenere buoni risultati funzionali. Lo scopo di questo studio è quello di valutare se la ricostruzione di difetti del distretto testa-collo mediante lembi peduncolati sia inferiore alle ricostruzioni microvascolari in termini di complicanze, outcome funzionale e prognosi. In una coorte di pazienti consecutivi che sono stati sottoposti a resezione maggiore per carcinomi del distretto testa collo, abbiamo confrontato i dati delle ricostruzioni mediante lembi peduncolati con quelli delle ricostruzioni microvascolari. Tutti gli interventi sono stati eseguiti da un unico chirurgo dal 2006 al 2015. Sono stati inclusi un totale di 93 pazienti, la maggior parte dei quali affetti da carcinoma del cavo orale (n = 59), di cui 64 hanno subito ricostruzione tramite lembo peduncolato (69%). Nei due gruppi non si sono registrate differenze significative in termini di necrosi del lembo, complicanze ed outcome funzionale. L'analisi multivariata ha mostrato che le comorbidità preoperatorie rappresentano l'unico fattore significativo per il rischio di complicanze nella guarigione del lembo (p = 0,019). Nei due gruppi l'analisi di sopravvivenza e l'analisi di regressione proporzionale al rischio di recidiva di malattia o metastasi a distanza non hanno mostrato differenze significative. In questo studio retrospettivo di coorte, non randomizzato, i lembi peduncolati non sono risultati significativamente inferiori rispetto ai lembi liberi in termini complicanze, outcome e prognosi.

PAROLE CHIAVE: *Chirurgia ricostruttiva della testa e del collo • Chirurgia ricostruttiva del cavo orale • Lembo peduncolato • Limbo libero • Neoplasie della testa e del collo*

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Introduction

The head and neck area is a particularly complex region providing very important functions: respiration, voice production, articulation and swallowing. Head and neck cancer resection results in loss of functioning tissue, which can lead to a broad range of functional impairments and in some cases to disfigurement. Only small defects in this region are amenable for primary closure and in general medium sized and large or complex defects require reconstruction [1]. Currently, tumour resection and reconstruction are conducted as a single stage procedure; optimal reconstructive outcomes aim at enhancing residual functions and allowing good mobility

of the preserved structures around the resected area [2]. The inevitable substitution of dynamic structures by static ones has obvious limitations and thus a thoughtful analysis of the anticipated defect and impairment is mandatory.

Nowadays, the most popular method for the management of defects in the head and neck area is represented by the transposition of microvascular free flaps. The introduction of free flaps in reconstructive surgery has provided the head and neck surgeon with a broad variety of available tissues, such as skin, muscle and bone, for optimal restoration of form and function [3-5]. This reconstructive method represents a major evolution in the management of head and neck cancer, with a success rate, as defined by flap survival, of approximately 94% [4 5], resulting in a reduced utilisation of pedicled flaps. Overall, there are no validated contraindications for microvascular reconstruction in head and neck surgery, and in high volume institutions around the world the indications for free flaps are extended to even fragile patients or patients presenting with disadvantageous anatomical conditions (e.g. previous vessel depleted neck or previous chemo-radiation). However, not every defect requires a microvascular free flap reconstruction in order to achieve good functional results [6]. Moreover, surgeons frequently deal with both elderly patients suffering from severe medical comorbidities [7] and pretreated patients presenting recurrent disease or second primary malignancies [8 9], which may preclude or overburden a microvascular procedure [10].

The surgeon must be cautious with the application of advanced reconstructive techniques and should always carefully evaluate the general status and regional anatomy of each patient, in order to select and propose the most appropriate reconstructive solution [11 12]; this calls for the evaluation of valid alternatives.

Several reports have indicated the reliability and good functional results of alternative pedicled flaps [6 7 11-15], which may still have an important role even in the free flap era.

The primary goal of this study was to investigate whether pedicled flap reconstruction in head and neck cancer treatment is inferior to microvascular free flap reconstruction in terms of healing results (flap necrosis and complicated healing of the flap) and functional outcome (deglutition and speech). Additionally, survival and follow-up status of patients were documented in an effort to assess whether the type of flap employed for their reconstruction was associated with a different prognosis.

Materials and methods

This study is retrospective in nature and is therefore discharged from the local institutional review board; nonetheless, the study abided the guidelines of the Declaration of Helsinki.

The clinical and pathological data of patients who underwent microvascular free flap reconstruction or pedicled flap reconstruction following cancer ablation, treated by the senior author (AD), between July 2006 until December 2015 at the Department of Surgery and Translational Medicine, University of Florence, Italy, were reviewed. In all cases the reconstruction restored a separation between different compartments, created by the surgical approach for tumour resection [1] (upper aerodigestive tract and neck contents, oral cavity and nasal/sinonasal cavities, orbital and cranial contents). This aspect represented the first inclusion criteria.

Patients were excluded from this study in case of simultaneous free flap and pedicled flap reconstruction; in case of overlay pectoralis myofascial flap transposition for pharyngeal suture enforcement during salvage total laryngectomy after chemo-radiation failure; in case of flap transposition during the postoperative course of a non-flap surgery for healing problems (e.g. fistula formation [16]); in case of reconstruction by local flaps or skin grafts. The remaining exclusion criterion was inadequate follow-up data.

Out of 143 reconstructive procedures reviewed, 93 patients met the inclusion criteria. Information about age, gender, date of procedure, tumour status (first primary, recurrence or second primary), anatomical site and subsite of cancer, TNM-stage, previous treatments in the head and neck region, vessel depleted neck status, comorbidities, type of tissue defect resulting from resection, type of flap used for reconstruction, surgical margins status, presence of extracapsular tumour spread in positive lymph nodes, adjuvant therapy, functional assessment, length of hospital stay and flap outcome were obtained. Finally, follow-up time and follow-up status were acquired from the last outpatient consultation; the survival status was recovered from the records or checked through telephonic survey.

Functional assessment of swallowing

In order to assess postoperative swallowing function, dietary status was evaluated at the last follow-up consultation of each patient; with regular diet indicating normal swallowing function; moist or soft diet indicating moderate swallowing impairment; liquid diet indicating severe swallowing impairment and tube-dependent intake indicating inability to swallow. Not being able to assess the swallowing function (e.g. passing away of the patient rapidly after surgery) led to a 'not recordable' status. Any impairment regarding swallowing was noted as a 'swallowing disorder' in the functional impairment assessment.

Functional assessment of speech

In order to assess postoperative speech function, the intelligibility was evaluated at the last follow-up consultation; with always intelligible indicating normal speech function; usually intelligible, but frequent repetition or face-to-face contact required, indicating moderate speech impairment; difficult intelligibility, even with face-to-face contact, indicating severe speech impairment; and never intelligible, written communication required, indicating

the inability to speak. Not being able to assess the speech function (e.g. total laryngectomy) led to a 'not recordable' status. Any impairment regarding speech function was noted as a 'speech disorder' in the functional impairment assessment.

Statistical analysis

All data were analysed with professional statistics software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data were expressed as mean ± SD, unless otherwise indicated, for continuous variables. Number of cases and percentages were represented for categorical variables. Univariate analysis by means of the Students t-test was applied for parametric continues values, while the χ^2-test was applied for categorical variables, for comparing pedicled flap and free flap outcome measures. Also, for comparing functional outcome in pedicled flap and free flap reconstructions per anatomical site the χ^2-test was used, if the number of cases was small ($n \leq 5$) Fisher's exact test was used. Patients with a 'not recordable' status were excluded from this analysis.

Subsequently, binary logistic regression analysis was applied to assess independent correlations of existing functional impairments after reconstruction, complicated healing of the flap and flap necrosis. Target variables were converted into binary variables, in order to appropriately fit into a logistic regression model. The co-variates used in this model were age, type of flap used for reconstruction, tumour status (first primary, recurrence or second primary), anatomical site of cancer, previous treatment for cancer, type of tissue defect resulting from resection, and existing comorbidities.

Furthermore, to compare the survival distribution of patients who received either pedicled flap or free flap reconstruction, a Log-Rank test was applied and a Kaplan-Meier survival curve was computed regarding patients with a follow-up time over three years, but inferior to the 95th-percentile of the follow-up time. In addition, due to their important prognostic role, the presence of extracapsular tumour spread in positive lymph nodes and the status of surgical margins were analysed in both types of reconstruction by the χ^2-test. Patients who did not receive a neck dissection (previous vessel depleted neck) were excluded from the analysis for extracapsular tumour spread.

Finally, with the purpose to assess an estimate of the effect regarding the type of flap used for reconstruction on the development of recurrences, distant metastases or second primaries, after adjustment for explanatory variables, a Cox-regression was applied. Covariates were age, type of flap used for reconstruction, tumour status (first primary, recurrence or second primary), T-stage, N-stage, surgical margin status and the presence of extracapsular tumour spread in positive lymph nodes. A p value of < 0.05 was regarded as statistically significant.

Results

The rate of total flap necrosis in this series was 1 of 93 (1%), while 7 patients (8%) required further surgery for flap healing complications. Analysis of the pathological reports regarding tumour resection showed that there was no significant difference in surgical margin status between both types of reconstruction, nor concerning extracapsular tumour spread in positive lymph nodes. Table I and Table II display the characteristics of the population comparing pedicled flap with free flap reconstructions.

Patients who underwent a pedicled flap reconstruction were older than patients who underwent a free flap re-

Table I. Cohort characteristics.

N = 93	Pedicled Flap reconstruction (n = 64)	Free Flap reconstruction (n = 29)	P-value
Age:	64.5 (SD ± 9.7)	58.2 (SD ± 10.4)	**0.005***
Gender:			0.874†
Male (n = 62)	43 (67%)	19 (65%)	
Female (n = 31)	21 (33%)	10 (35%)	
Anatomical site:			0.073†
Oral Cavity (n = 59)	39 (61%)	20 (69%)	
Oropharynx (n = 17)	9 (14%)	8 (28%)	
Larynx (n = 6)	6 (9%)	0 (0%)	
Hypopharynx (n = 4)	4 (6%)	0 (0%)	
Oesophagus (n = 3)	3 (5%)	0 (0%)	
Other (n = 4)	4 (6%)	1 (3%)	
Previous treatment:			**0.006†**
None (n = 52)	29 (45%)	23 (79%)	
Previous RT (n = 3)	1 (2%)	2 (7%)	
Previous surgery (n = 15)	11 (17%)	4 (14%)	
Previous surgery + RT (n = 15)	15 (23%)	0 (0%)	
Previous CT+RT (n = 3)	3 (5%)	0 (0%)	
Previous surgery and CT+RT (n = 5)	5 (8%)	0 (0%)	
Vessel Depleted Neck:			**0.004†**
None (n = 69)	41 (64%)	28 (97%)	
Unilateral (n = 12)	11 (17%)	1 (3%)	
Bilateral (n = 12)	12 (19%)	0 (0%)	
Comorbidity:			**< 0.001†**
None (n = 55)	28 (44%)	27 (94%)	
Diabetes (n = 2)	2 (3%)	0 (0%)	
Neurological disease (n = 1)	0 (0%)	1 (3%)	
Severe cardiovascular disease (n = 19)	18 (28%)	1 (3%)	
Multiple (n = 16)	16 (25%)	0 (0%)	

**Student's t-test †χ^2-test. Bold script indicates significant values.*

Table II. Tumour-defect characteristics.

N = 93	Pedicled Flap reconstruction (n = 64)	Free Flap reconstruction (n = 29)	P-value
Tumour Status:			**0.005†**
First primary (n = 54)	30 (47%)	24 (83%)	
Recurrence (n = 27)	23 (36%)	4 (14%)	
Second primary (n = 13)	11 (17%)	1 (3%)	
Tissue Defect:			**0.045†**
Soft Tissue (n = 56)	39 (61%)	17 (59%)	
Bony + Soft Tissue (n = 17)	8 (12%)	9 (31%)	
Soft Tissue + marginal (n = 20)	17 (27%)	3 (10%)	
pT-stage (grouping):			0.262†
T1-T2 (n = 21)	15 (23%)	6 (21%)	
T3 (n = 19)	10 (16%)	9 (31%)	
T4 (n = 26)	16 (25%)	10 (35%)	
rT1-rT2 (n = 8)	7 (11%)	1 (3%)	
rT3 (n = 5)	4 (6%)	1 (3%)	
rT4 (n = 14)	12 (19%)	2 (7%)	
pN-stage (grouping):			0.075†
N0 (n = 28)	20 (31%)	8 (28%)	
N+ (n = 38)	21 (33%)	17 (58%)	
rN0 (n = 17)	15 (23%)	2 (7%)	
rN+ (n = 10)	8 (13%)	2 (7%)	
Adjuvant therapy:			0.070†
None (n = 35)	29 (45%)	6 (21%)	
RT (n = 32)	20 (31%)	12 (41%)	
CT+RT (n = 26)	15 (24%)	11 (38%)	
Present (n = 31)	19 (37%)	12 (41%)	

**Student's t-test †χ2-test. Bold script indicates significant values.*

construction (mean 64.5 *vs* 58.2, p = 0.005), and more often presented a recurrence or a second primary (36% and 17% *vs* 14% and 3%, p = 0.005). Furthermore, patients who underwent a pedicled flap reconstruction were more often identified with a unilateral or bilateral vessel depleted neck (17% and 19% *vs* 3% and 0%, p = 0.004) and suffered more often from comorbidities (56% *vs* 6%, p < 0.001) than patients who underwent free flap reconstruction. Finally, the resulting defect more frequently involved soft tissue or soft tissue and marginal mandibular resection in patients who underwent pedicled flap reconstruction (88% *vs* 69%); while reconstruction for segmental bony tissue defects (which also include soft tissue defects) was more frequently achieved by means of a free flap reconstruction (12% *vs* 31%, p = 0.045). Table III shows that, when corrected for the anatomical site of cancer resection, the degrees of impairment for swallowing function and speech between pedicled flap and free flap reconstructions were not statistically significant.

Table IV shows that the differences in healing results and flap related complications were not statistically significant between the two groups, although patients who underwent a free flap reconstruction were admitted for a longer period of time than those who underwent a pedicled flap reconstruction (mean 21.1 days *vs* 17.6 days, p = 0.028). In multivariate regression analysis regarding the development of functional impairments, no associated factors were found; also, no associated factors were found in multivariate regression analysis regarding necrosis of the flap after reconstruction. However, a considerable trend towards significance concerning comorbidities was found regarding the probability of facing a flap necrosis (p = 0.057); and the multivariate regression analysis showed that only the presence of comorbidities remained an explaining factor for complicated flap healing (p = 0.019, OR = 2.018), Table V. Of note, a pedicled flap reconstruction provided uneventful healing process in 81% of fragile patients who suffered from severe comorbidities.

Figure 1 displays the overall survival of patients with a follow-up time over 36 months, receiving pedicled flap and free flap reconstructions; the differences were not statistically significant (Log Rank: p = 0.857). Figure 2 displays the development of recurrences, distant metastasis or second primary cancers, overtime, after pedicled flap and free flap reconstructions. Although the odds (hazard ratio = 0.665) for developing a recurrence, distant metastasis or second primary cancer were higher for patients who underwent pedicled flap reconstruction, as compared to patients who underwent a free flap reconstruction, this difference was not statistically significant corrected for age, tumour status (first primary, recurrence or second primary), T-stage, N-stage, surgical margin status and the presence of extracapsular tumour spread in positive lymph nodes.

Discussion

In our study, comparison of outcomes in patients who underwent a pedicled flap or a free flap reconstruction showed no statistically significant differences in terms of functional outcomes, flap necrosis, or complications. Furthermore, multivariate regression analysis showed that only the existence of comorbidities remained an explaining factor for complicated flap healing. In addition, there was no significant differences in terms of overall survival between patients who underwent a pedicled flap reconstruction and those who underwent a free flap reconstruction. Finally, proportional hazard regression analysis, regarding the development of recurrences, distant metastases or second primary cancers, showed no significant differences between patients who underwent a pedicled flap reconstruction and patients who underwent a free flap reconstruction. In our cohort, pedicled flap reconstruction did not seem be inferior to free flap reconstruction in terms of complications, functional outcome, survival,

Table III. Functional assessment outcome in different types of reconstruction per anatomical site.

Functional Impairment (n = 76)	None (%) (n = 39)	Swallowing Disorder (%) (n = 20)	Speech Disorder (%) (n = 3)	Both (%) (n = 14)	P value
Oral Cavity (n = 57)					0.614*
Pedicled Flap (n = 38)	18 (48%)	11 (29%)	2 (5%)	7 (18%)	
Free Flap (n = 19)	11 (58%)	6 (31%)	0 (0%)	2 (11%)	
Oropharynx (n = 14)					0.626*
Pedicled Flap (n = 6)	2 (33%)	1 (17%)	1 (17%)	2 (33%)	
Free Flap (n = 8)	4 (50%)	2 (25%)	0 (0%)	2 (25%)	
Other (n = 5)					0.800†
Pedicled Flap (n = 4)	3 (75%)	0 (0%)	0 (0%)	1 (25%)	
Free Flap (n = 1)	1 (100%)	0 (0%)	0 (0%	0 (0%)	

Diet (n = 91)	Regular diet without restriction (%) (n = 48)	Moist or soft diet (%) (n = 37)	Liquid diet (%) (n = 6)	P value
Oral Cavity (n = 57)				0.747*
Pedicled Flap (n = 38)	20 (52%)	17 (45%)	1 (3%)	
Free Flap (n = 19)	11 (58%)	8 (42%)	0 (0%)	
Oropharynx (n = 17)				0.549*
Pedicled Flap (n = 9)	3 (33%)	5 (56%)	1 (11%)	
Free Flap (n = 8)	4 (50%)	4 (50%)	0 (0%)	
Other (n = 17)				0.689*
Pedicled Flap (n = 16)	9 (56%)	3 (19%)	4 (25%)	
Free Flap (n = 1)	1 (100%)	0 (0%)	0 (0%)	

Speech (n = 76)	Always intelligible (%) (n = 59)	Usually intelligible (%) (n = 12)	Difficult intelligibility or never intelligible (%) (n = 5)	P value
Oral Cavity (n = 57)				0.371*
Pedicled Flap (n = 38)	30 (79%)	7 (18%)	1 (3%)	
Free Flap (n = 19)	17 (90%)	1 (5%)	1 (5%)	
Oropharynx (n = 14)				0.150*
Pedicled Flap (n = 6)	2 (33%)	2 (33%)	2 (33%)	
Free Flap (n = 8)	6 (75%)	2 (25%)	0 (0%)	
Other (n = 5)				0.800†
Pedicled Flap (n = 4)	3 (75%)	0 (0%)	1 (25%)	
Free Flap (n = 1)	1 (100%)	0 (0%)	0 (0%)	

χ^2-test †Fisher's exact test.

Table IV. Healing outcomes.

Flap Healing (n = 93)	Healing uneventful (%) (n = 81)	Minor complications (%) (n = 5)	Further surgery required (%) (n = 7)	P value
Pedicled Flap	56 (87%)	3 (5%)	5 (8%)	0.902*
Free Flap	25 (86%)	2 (7%)	2 (7%)	
Flap Necrosis (n = 93)	None (%) (n = 85)	Partial Necrosis (%) (n = 7)	Total Necrosis (%) (n = 1)	
Pedicled Flap	59 (92%)	4 (6%)	1 (2%)	0.634*
Free Flap	26 (90%)	3 (10%)	0 (0%)	
Admission length (n=93)	Mean	Standard deviation	Standard error mean	
Pedicled Flap (n = 64)	17.6	± 6.8	0.9	**0.028†**
Free Flap (n = 29)	21.1	± 7.8	1.5	

χ^2-test, †Students t-test. Bold script indicates significant values

Table V. Estimation of probability of complicated flap healing.

Variable	Coefficient	Standard error	P value	OR*	95% CI†	
Age	0.00	0.37	0.998	1.000	0.930	1.076
Type Flap	-1.440	1.132	0.203	0.237	0.026	2.179
Tumour status	-2.018	1.765	0.253	0.133	0.004	4.230
Anatomical Site	0.602	0.482	0.211	1.826	0.710	4.692
Previous treatment	0.275	0.522	0.598	1.317	0.473	3.663
Tissue Defect	-0.130	0.497	0.793	0.878	0.331	2.326
Comorbidity	0.702	0.300	**0.019**	2.018	1.121	3.634

**OR odds ratio. †CI confidence interval. Bold script indicates significant values.*

development of cancer relapse, or distant metastases.

The type of flap used for reconstruction depends on the needs of the recipient site; in some situations free flaps are required (e.g. in segmental bony reconstructions), whereas pedicled flaps cannot always offer the amount or type of desired tissue [17]. Furthermore, the anatomical site of the defect can sometimes be out of reach for a pedicled flap, since the length of the vascular pedicle limits the required distance of transfer. However, premorbid patient factors and regional anatomy (e.g. comorbidity or previous head and neck cancer treatment) are also important in deciding which flap is employed for reconstruction [18].

Randomised controlled trials are not feasible; consequently, the nature of studies comparing the outcome of reconstruction in head and neck surgery is restricted to descriptive reports, stratifying, wherever possible, for patient and tumour factors. Thus, the outcome of free flap and pedicled flap reconstructions cannot easily be compared and bias is inevitable.

The small cohort and heterogeneity of the reconstructed defects represent the major limitation of our study. Nevertheless, this series replicates a comparable scenario of many low volume centres where a careful selection of patients undergoing microvascular reconstructive surgery is performed. All reconstructive surgical procedures and follow-up consultations were conducted by a single surgeon (AD), diminishing inter-patient variability to minimise bias concerning treatment and evaluation. Furthermore, all reconstructions with local flaps or grafts were excluded a priori, focusing only on major resections with flap transposition.

Several authors have reported that free flaps have advantages over pedicled flaps in head and neck reconstruction. Firstly, tissue dimensions and thickness can be tailored to the size of the defect and vascularised bone can be used to reconstruct complex defects, which leads to superior aesthetic results [19]. Secondly, some reports state that free flaps provide superior speech outcome over pedicled flaps [18 20]. Thirdly, it is reported that swallowing function, following free flap reconstruction in comparison to pedicled flap reconstruction, is improved [20], while other authors were unable to substantiate this finding [18 21]. Considering the results of our study, we cannot support these findings, either for superior swallowing function or for superior speech function.

A videofluorographic swallowing study is certainly the golden standard for the assessment of swallowing disorders. However, at our institution, this is not routinely prescribed to all patients, but only in case of aspiration problems. Therefore, we used a rough assessment concerning the quality of swallowing and speech, which was already used in previous reports from both our group [7 15] and from others [22-24], for this assessment was relatively simple to apply during follow-up consultation visits.

Frequently pedicled flaps even seem to be preferable over free flaps [25-27]. Many reports regarding the elderly in relation to microvascular free flap reconstruction agree that age is a risk factor for poor surgical outcome [10 28-30]. McCrory et al. described that operative time, resection-reconstruction, was statistically much longer for free flap than for pedicled flap procedures (9 hours 35 min *vs* 4 hours 58 min) [28]. Long surgical times was a significant factor for the development of postoperative complications in a series of 104 free flaps in patients aged 65 and older [10]. Furthermore, older patients are less capable of coping with large fluid shifts and significant blood loss [10], whereas free flap reconstructions are more often associated with the need for blood transfusion [29]. In addition, cardiovascular disease proves to be an important factor in free flap reconstructive failure [10], a condition which proves to affect the majority of adults past the age of 60 years [31], and furthermore with increasing age there is a greater likelihood of postoperative complications after free flap reconstruction [27], even with successful microvascular reconstructions [32].

Besides age, diabetes also appears to interfere with free flap survival [33]. However, the impact of diabetes on free flap survival is still much debated. While some authors support that diabetes interferes with free flap survival [7 34], Cooley et al. reported that patients with diabetes are not at increased risk either for flap failure or for abnormal healing of the anastomoses as long as normal glycaemia is maintained [35].

Our study shows that more than 80% of patients suffering from comorbidities who underwent a pedicled flap recon-

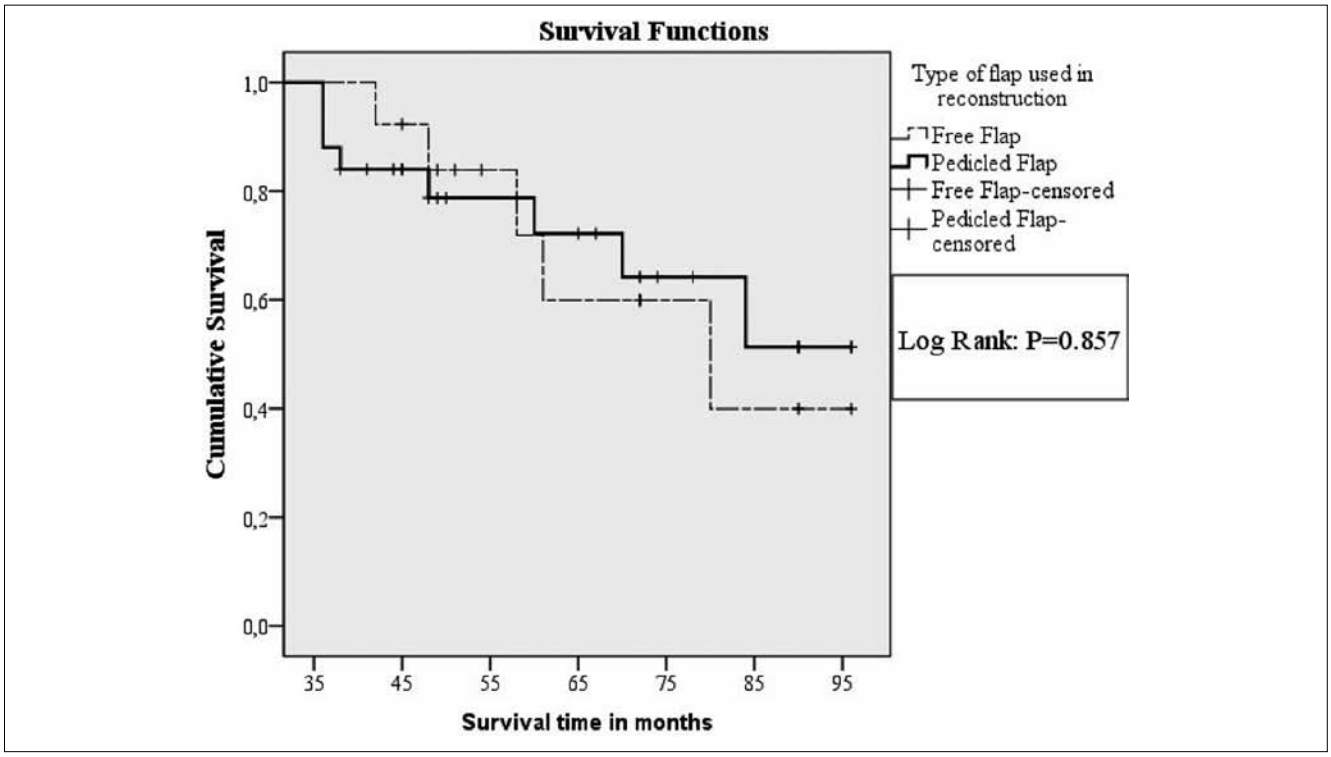

Fig. 1. Kaplan Meier curves of overall survival in patients with a follow-up time over 36 months, but less than 97 months, who underwent either a pedicled flap (n = 25, bold line) or a free flap (n = 13, dotted line).

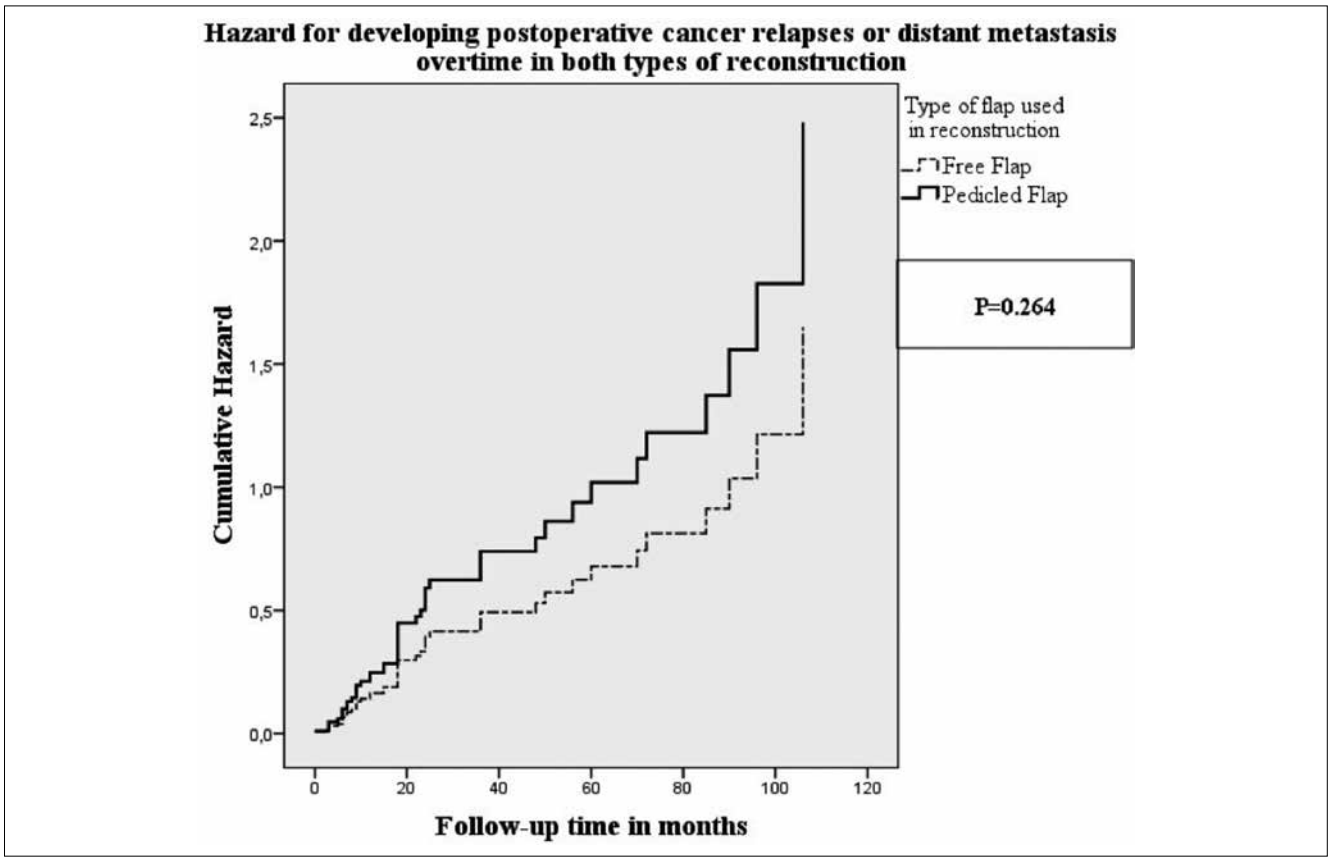

Fig. 2. Cumulative hazard curves regarding the development of recurrences, distant metastasis or second primary cancers in patients who underwent either pedicled flap (n= 64, bold line) or free flap (n = 29, dotted line) reconstruction.

struction had uneventful healing of the flap. Only 2 patients suffering from comorbidities underwent a free flap reconstruction, 1 of these patients had complicated flap healing. This suggests that a reconstruction by means of a pedicled flap is a safe procedure in patients who are suffering from comorbidities. Further research with a larger population should be conducted in order to assess whether pedicled flap reconstructions in patients suffering from comorbidities are less prone to complicated postoperative healing than free flap reconstructions.

The use of free flaps for reconstruction in previously irradiated patients or patients who underwent prior chemoradiation is also much debated in literature. In a review, Wong et. al. points out that prior chemotherapy and/or radiotherapy can cause significant scarring and vessel damage to the utilised vessels for microvascular free flap reconstruction with obvious negative consequences [36]. Furthermore, Schultze-Mosgau et al. reported a reduced clinical success rate (84%) of free vascular grafts in head and neck patients with previous radiotherapy of 60-70 Gy [37]. Moreover, in a study of 429 patients who underwent free flap reconstruction in the head and neck, preoperative radiotherapy (irrespective of irradiation doses) was significantly associated with fistulae formation and wound infection, while previous neck irradiation at doses of more than 60 Gy proved to be a significant risk factor for free flap failure, overall local complications, haematoma, longer duration of enteral nutrition and hospital stay [38]. In a multicentre survival analysis after free flap reconstructive surgery of head and neck squamous cell carcinoma by Salvatori et al. [39], pre-treated patients had significantly worse survival than those with first primary tumours (43.1% and 54.1% respectively). Accordingly, also in our series, patients presenting with recurrence or second primaries showed worse survival than those with first primary tumours. However, this was irrespective to the type of employed flap (pedicled flap or free flap). Based on our policy, the greatest majority of pre-treated patients received a pedicled flap reconstruction; among them 21 of 34 patients (62%) who underwent pedicled flap reconstruction were confirmed alive at the end of our study.

Since intake of alcohol ≥ 30 g/day is related to the development of head and neck cancer [40], many head and neck cancer patients suffer from alcohol-related problems. Both acute alcohol withdrawal as well as other alcohol-induced disorders negatively influence the outcome of microvascular free flap tissue transfers [41-43].

Consequently, those patients presenting the above mentioned factors, which are associated with a higher rate of free flap failure or postoperative complications, are less eligible for microvascular free flap reconstructive surgery, whereas locoregional pedicled flaps may offer a reliable alternative for reconstruction [44-49].

Furthermore, a pedicled flap reconstruction brings some additional benefits for both patient and surgeon. Most sites of pedicled flaps have a low donor-site morbidity with donor sites that can be closed primarily. Also, many pedicled flaps can be harvested and transferred rapidly, which leads to decreased operating time and a corresponding decrease in the morbidities of prolonged general anaesthesia.

Our results showed that the admission length of patients who underwent a pedicled flap reconstruction were shorter than in those who underwent a free flap reconstruction. Other papers pointed out that pedicled flap reconstructions were associated with shorter intensive care stay than free flap reconstructions [7 28]. Consequently, free flap reconstructions are usually more expensive procedures than pedicled flap reconstructions [15 25 28].

Conclusions

In our patient cohort, pedicled flaps were performed in two-thirds of cases and were not significantly inferior to free flaps in terms of functionality, complications, or prognosis. This study highlights how, in a low volume setting, careful selection of patients receiving free flap reconstruction is advisable in order to maintain high success rates; in this scenario, pedicled flaps are a viable option in patients considered suboptimal for a microvascular reconstruction. A well thought and careful analysis of every patient is needed to offer the best solution in the light of individualised treatment [1].

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Head and neck

Fibular osteofasciocutaneous flap in computer-assisted mandibular reconstruction: technical aspects in oral malignancies

Ricostruzione mandibolare con lembo osteocutaneo di fibula e programmazione computer assistita: aspetti tecnici nei tumori maligni del cavo orale

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SUMMARY

Virtual surgical planning technology in head and neck surgery is witnessing strong growth. In the literature, the validity of the method from the point of view of accuracy and clinical utility has been widely documented, especially for bone modelling. To date, however, with its increased use in head and neck oncology, and consequently the increased need for bone and soft tissue reconstruction, is important to carry out the virtual programme considering not only bone reconstruction but also all aspects related to the reconstruction of soft tissue using composite flaps. We describe our approach to virtual planning in the case of composite flaps. The study reports six consecutive patients with malignant disease requiring mandibular bone and soft tissue reconstruction using fibular osteocutaneous flaps. In all six patients, the resection and reconstruction were planned virtually focusing on the position of cutaneous perforator vessels in order to schedule fibula cutting guides. There were no complications in all six cases. The technique described allowed us to schedule composite fibula flaps in mandibular reconstruction virtually with good accuracy of the position of the bone segment in relation to the cutaneous paddle, important for soft tissue reconstruction. Despite the limited number of cases, the preliminary results of the study suggest that this protocol is useful in virtual programmes using composite flaps in mandibular reconstruction. Further investigations are needed.

KEY WORDS: Fibular osteofasciocutaneous flap • Mandibular reconstruction • Virtual surgical planning • Computer-assisted mandibular reconstruction • Fibula harvestin

RIASSUNTO

L'utilizzo della pianificazione virtuale in chirurgia testa e collo è in forte crescita. In letteratura, la validità del metodo dal punto di vista dell'acuratezza e l'utilità clinica sono stati ampiamente documentati, in modo particolare per il rimodellamento osseo del lembo. Al giorno d'oggi, l'aumentato utilizzo della programmazione virtuale in chirurgia oncologica testa-collo e, conseguentemente, la maggiore necessità di ricostruzioni sia ossee che dei tessuti molli, rendono importante realizzare il programma virtuale considerando non solo la ricostruzione ossea, ma anche tutti gli aspetti relativi alla ricostruzione dei tessuti molli con lembi compositi. Descriviamo nel seguente articolo il nostro approccio alla pianificazione virtuale nel caso di lembi compositi. Lo studio riporta sei pazienti consecutivi con malattia maligna programmati mediante ricostruzione mandibolare computer assistita e lembi osteo-fascio-cutanei di perone. In tutti i sei pazienti, la resezione e la ricostruzione sono state progettate concentrandosi sulla posizione dei vasi perforanti cutanei, al fine di programmare la posizione più corretta delle guide di taglio a livello del perone in funzione della posizione dei vasi perforanti stessi. La tecnica descritta ci ha permesso di programmare lembi osteo-fascio-cutanei di perone nella ricostruzione mandibolare computer assistita, con buona precisione della posizione del segmento osseo rispetto alla padella cutanea, importante per la ricostruzione dei tessuti molli. Nonostante il numero limitato di casi, i risultati preliminari dello studio suggeriscono che questo protocollo è utile nella programmazione virtuale. Sono necessarie ulteriori indagini.

PAROLE CHIAVE: *Lembo osteofaciocutaneo di perone • Ricostruzione mandibolare • Programmazione chirurgica virtuale • Ricostruzione mandibolare computer assistita*

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Introduction

Tumours involving the mandible bone require complex reconstructive planning. In the late 1980s, the use of the fibula free flap (FFF) to reconstruct mandibular defects was described [1] and over the following years, many authors have contributed to optimize the technique [2-6]. Today, this option is the gold standard for mandibular reconstruction in many centres. In particular, in extended bone and soft tissue resections, this flap can be modelled with multiple osteotomies and can provide bone, muscle and skin for composite reconstruction [7]. The surgical procedure is safe, even in elderly head and neck cancer patients [8].

One of the most delicate aspects of mandibular reconstruction is the technique of bone modelling because of the non-linear nature of the mandibular bone. The risk of prolonging the period of ischaemia and not restoring correct bone-to-bone contact, and maxillo-mandibular and occlusal relationships, can ultimately lead to a higher rate of complications and poor aesthetic and functional results. In the past, stereolithographic models have helped immensely in surgical planning [9-12] but recently, the introduction of computer-assisted mandibular reconstruction (CAMR) with its pivotal role in virtual surgical planning has further increased the accuracy of preoperative planning resulting in greater precision of the surgical procedure and reducing surgical time. CAMR requires careful planning in order to obtain the best oncological, functional and aesthetic outcome.

Virtual surgical planning technology in Head and Neck surgery is witnessing strong growth [13]. It is increasingly being adopted in many centres since a precise and functional reconstruction can be achieved with a vascularised fibula flap [14-19] after tumour ablation as demonstrated in many studies [20-22]. Other benefits are improved facial appearance and function after dental rehabilitation, which must be considered an integral part of the reconstructive programme [23-26] in order to improve the residual quality of life of cancer patients [27]. Moreover, this technology can significantly reduce operating time, especially in complex reconstructions.

One important aspect that we believe could be of interest to the scientific community is the scheduling of fibula cutting guides, their design, and intraoperative osteo-fascio-cutaneous flap management. In this paper, we discuss our experience with computer-assisted mandibular reconstruction (CAMR) using fibular osteo-fascio-cutaneous flaps in six patients. Our attention was focused on the correct positioning of the cutting guides, in order to reduce all possible mismatches with skin perforator vessels during composite flap harvesting.

Materials and methods

Six consecutive patients (three women and three men, mean age 61 years) were included in the study. They all suffered from malignant disease in the oral cavity requiring reconstruction with a fibular osteo-cutaneous flap previously planned with CAMR. The preoperative demographic data are summarised in Table I.

Informed consent was obtained from all patients. The work described has been carried out in accordance with the Declaration of Helsinki and approved by the authors' local institutional review board.

Virtual surgical planning

After the acquisition of a 64-slice high-resolution computed tomographic (CT) scan of the patient's craniofacial skeleton and angiographic CT scan of the lower legs (the donor site for bone and vessels), the Dicom data were sent to the modelling company. 3D rendering was performed using CMF software 6.1 (Materialise, Leuven, Belgium), which produces a three-dimensional model of both the mandible and the fibula. Before the web meeting with the biomedical engineers, the perforator vessels in the lower leg, in addition to the results of the previous assessment with angio CT, were identified using a hand-held Doppler and marked on the skin. The distance between the lateral malleolus and the perforator skin vessel was registered (Fig. 1a). Furthermore, preliminary measurements for the resective and reconstructive programme were made on the CT scan

Table I. Preoperative demographic data, planned fibular segments, skin island maximum diameter, distance between malleolus and skin perforating vessel, and ischaemia time.

Sex	Age, years	Pathol	U.C.	Res, cm	# seg	SP diam, cm	Distance M P, cm	Ischaemia time, min
M	59	SCC	BS	8.859	2	7.0	14.5	60*
F	69	SCC	BS	7.759	2	8	10.7	65*
F	44	SCC	B	7.685	1	8	12.3	73
F	71	SCC	BS	7.064	2	6	11.2	73
M	57	SCC	BSB	11.669	3	10	13.6	80
M	69	SCC	BS	7.728	2	10	16.9	75

Pathol: pathology affecting the mandibular bone; SCC: squamous cell carcinoma; U.C.: Urken classification of mandibular defects: C, condyle; R, ramus; B, body; SH, symphysis (half); S, symphysis; Res: length of planned resection (cm); # seg: number of fibular segments planned for mandibular reconstruction; SP diam: skin paddle maximum diameter (cm); Distance M P: distance between malleolus and skin perforator vessel (cm); Ischaemia time: time calculated from pedicle detachment to flap revascularisation (min).

**Fibula modelling and mounting on the plate performed before detaching the vascular pedicle.*

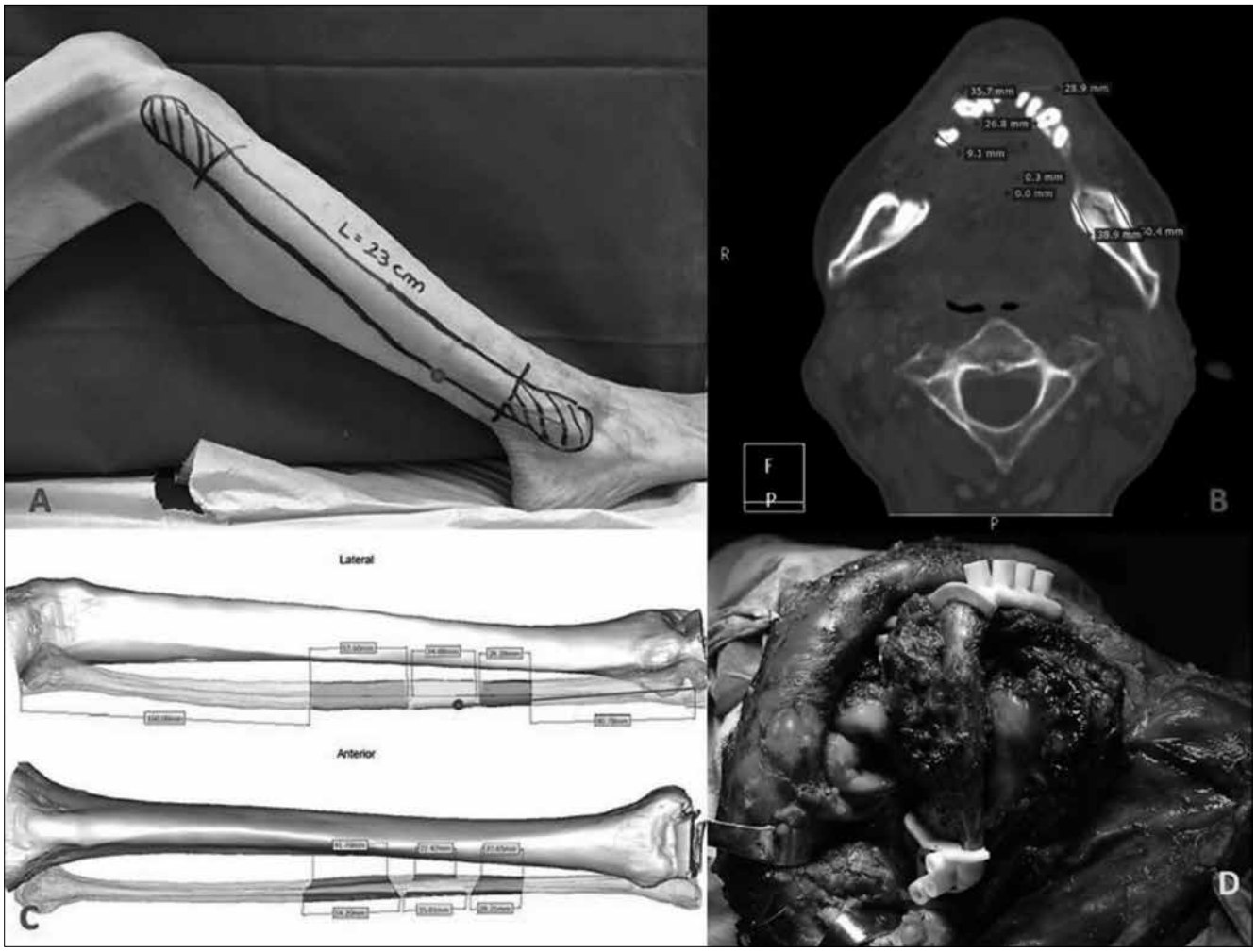

Fig. 1. a) Preoperative measurements of the distance between the malleolus and the perforator vessel; b) Preliminary measurements of the resective and reconstructive programme from CT scan; c) Reproduction of the distance between the malleolus and the perforator vessel on the virtual programme for fibula harvesting; d) Mandibular cutting guides.

(Fig. 1b). In all cases, the presence of the patient was scheduled during the course of the web meeting, in order to avoid any doubt if by chance any form of conflict had occurred between the planned resection and the position of the perforating vessels. Moreover, the presence of the patient is very important during the web meeting because this technology improves patient education and communication [28].

During the web meeting between surgeons and biomedical engineers, the following were sequentially determined:

1. the amount of bone resection required (resulting from the clinical and radiological data, i.e. CT scan and MRI) allowing at least a 3 cm margin over the osteotomy to fix the patient-specific plate (PSP);
2. the side of the FFF (as a function of reconstructive requirement);
3. the type of reconstruction concerning the number of bone segments (segment length not less than 2.0 cm);
4. fibula and customised plate insetting and final position in relation to the remaining mandible and craniofacial skeleton;
5. the degree of obliquity of the osteotomies both on the mandible and fibula;
6. the number, position and inclination of screw holes both on the mandible (minimum of two on each mandibular stump) and fibula segments;
7. the shape and position of the cutting guides.

With an osteofasciocutaneous flap, the choice of the segment to be taken depends upon the measurements previously made in such a way as to have the skin perforator vessel in the most suitable position for soft tissue reconstructive purposes and which does not interfere with the osteotomy lines (Fig. 1c). A distance of 8 cm from the lower osteotomy to the ankle must be maintained for stability of the malleolar joint; proximally, a 7 cm bone segment is maintained to protect the peroneal nerve. Fibula cutting guides were all flange guides in order to be as compact as possible. The resection/reconstruction data were used to prepare autoclavable cutting guides to be used during mandibular resection and fibula harvesting as well as to model the final reconstructed mandible and the patient specific plate (PSP) (DePuy Synthes TRUMATCH®).

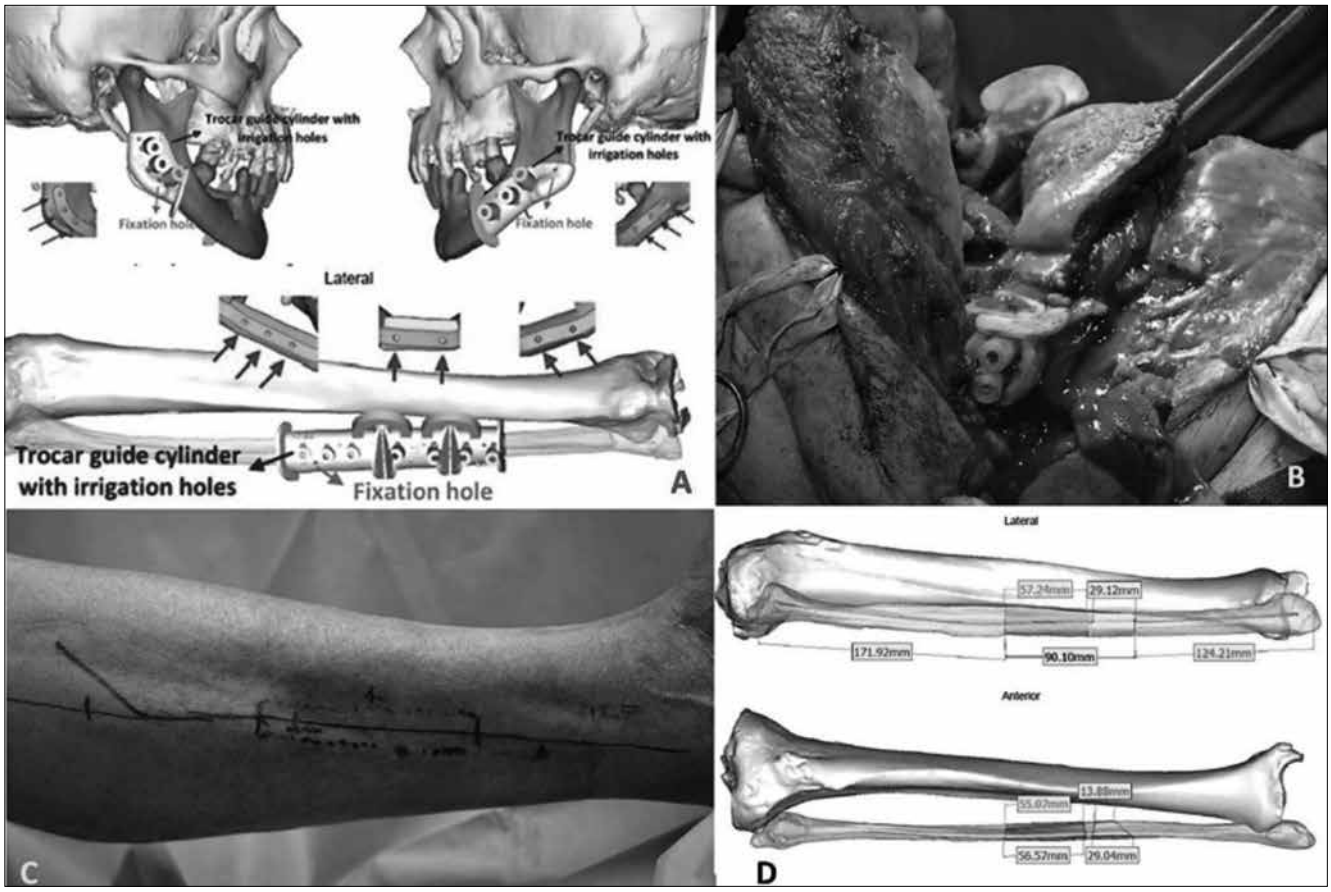

Fig. 2. a) Mandibular and fibular cutting guides were provided with fixation holes for temporary fixation and trocar guides for PSP fixation screws; b) Mandibular osteotomies completed with soft tissue resection; c) Preoperative measurements of virtual surgical planning and of the distance between the malleolus and the perforator vessel are drawn on the leg skin; d) Virtual surgical planning measurements.

Surgery

Access to the resection was via a visor flap. After neck dissection, access to the mandible was made and the cutting guides were secured in the planned position (Fig. 1d). Mandible and fibula cutting guides were provided with fixation holes for temporary fixation and trocar guides for PSP fixation screws (Fig. 2a); this planning allowed any type of pre-plating to be avoided. The osteotomies were completed with a sagittal or reciprocating saw following the cutting guides and the tumour was carefully removed. Normally, 45 degree osteotomies were planned and performed on both the mandible and fibula to obtain maximum bone-to-bone contact [29]. Finally, the operation was completed with soft tissue resection (Fig. 2b). Frozen sections were then taken on the mandibular periosteum, bone marrow, and soft tissues to check the radicality.

At the same time, a second surgical team proceeded to harvest the fibula. With the help of a hand-held Doppler and using the preoperative measurements of the distance between the malleolus and the perforator vessel, the position of the vessel itself was marked on the skin (Fig. 2c). In addition, the virtual surgical planning measurements were annotated on the leg skin (Figs. 2c, d). An incision was made in the skin along the peroneus longus muscle, maintaining a distance of 2 cm from the posterior intermuscular septum, which could easily be palpated posteriorly to the muscle. According to the location of the perforator vessel found by preoperative mapping, the incision was curved slightly anteriorly in the region of the skin paddle. Despite the fact that mapping of the perforator vessels and thus positioning of the skin island is possible preoperatively using Doppler sonography, the skin paddle should not be designed until the cutaneous branches are clearly seen intraoperatively [30 31]. In the standard situation, the skin paddle is centred vertically along the septum with its centre at the junction between the middle and lower third of the fibula. If only one perforator is enclosed, the flap size should not exceed 6 x 10 cm [31].

After identification of the perforator vessels and dissection, the fibular guides were secured to the bone to replicate the cuts for both the end and closing wedges in previously planned osteotomies (Fig. 3a). After po-

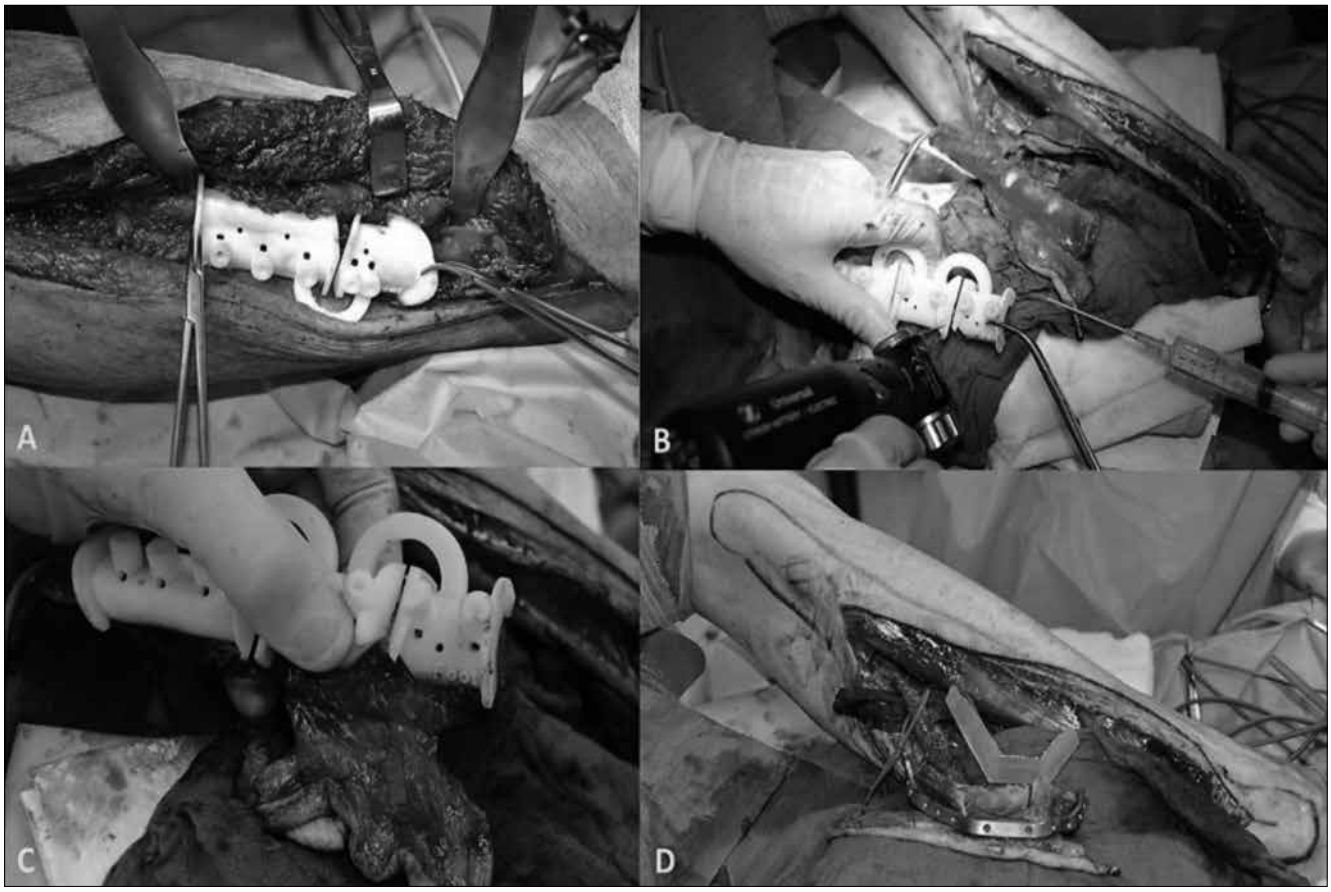

Fig. 3. a) Check of fibula cutting guides; b) Modification of the fibula cutting guides; c) Modified guide not interfering with perforator vessels; d) Fibula modelled before detaching the vascular pedicle.

sitioning and fixation of the cutting guides, the fibular distal and proximal osteotomies were performed with a margin of about 2 cm, proceeding then to the final shaping upon receipt of the results of the frozen sections. This still retained the excess periosteum/fascia at the level of these margins to 'wrap' the jawbone creating a 'guide' for the ossification [32]. In two cases, there was interference between the cutting guide and the perforator vessel during the picking phase, and before fixing the template, we modified (minor correction of the flanges) the template itself so that it did not interfere with the vessel and did not create compression on the vessel itself (Figs. 3b, c). In two cases, the fibula was modelled and mounted on the patient specific plate (PSP) before detaching the vascular pedicle (Fig. 3d). The shaped fibula was then secured to the PSP in the planned position (Fig. 4a). The screw holes from the fibula cutting guides were designed to fit specific holes for the positioning and adaptation of the fibula with the PSP. The fibula and plate were then fixed to the native mandible with extremely precise bone-to-bone contact and positioning (Figs. 4b,c). The fibular pedicle was then positioned and microvascular anastomosis was performed.

Results

In all patients, surgical margins (soft tissues and bones) were tumour-free. No flap failures occurred in any case, either for bone or cutaneous components. An unexpected sub-periosteal extension of the tumour occurred near the cutting line of the guide in only one case. In this case, considering that the periosteal extension occurred at the level of the alveolar process, a 2 cm stepwise enlargement of the mandible resection was carried out without changing the inferior amount of resection, where the positioning of the fibula was planned. In all other cases, no interference with the tumour was noted. Apart from two cases, there was a good correlation between the position of the perforating vessels and the bone segment to be taken. In the majority of cases, the skin paddle containing the vessels appeared positioned approximately at the level of the junction between the middle third and the lower third of the leg. High precision of cutting guides and a good fit of the PSP were found on both the mandible and fibula.

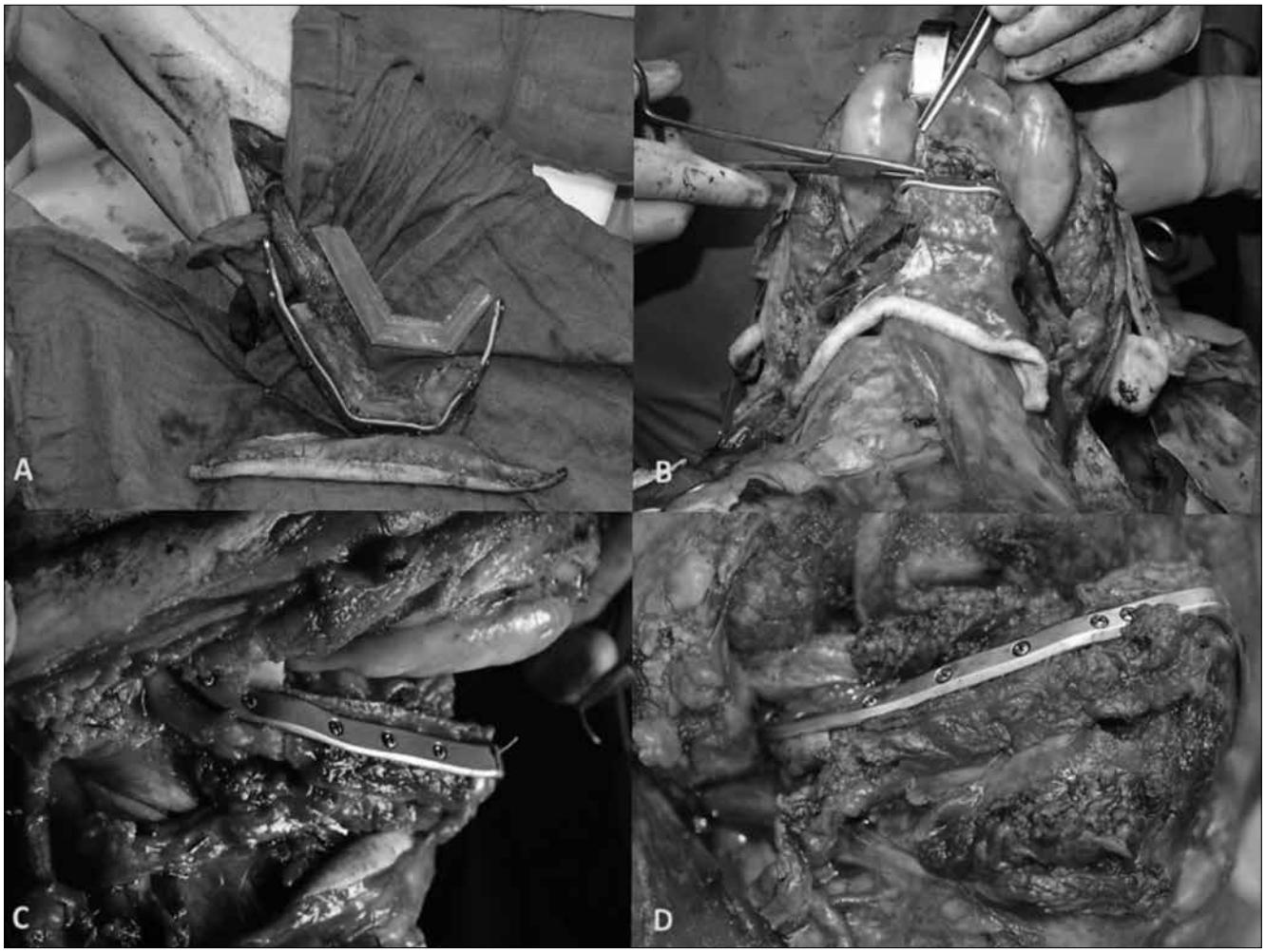

Fig. 4. a) Shaped fibula secured to the PSP in the planned position; b) Fibula and plate fixed to the native mandible; c) Extremely precise bone-to-bone contact and positioning; d) Extremely precise bone-to-bone contact.

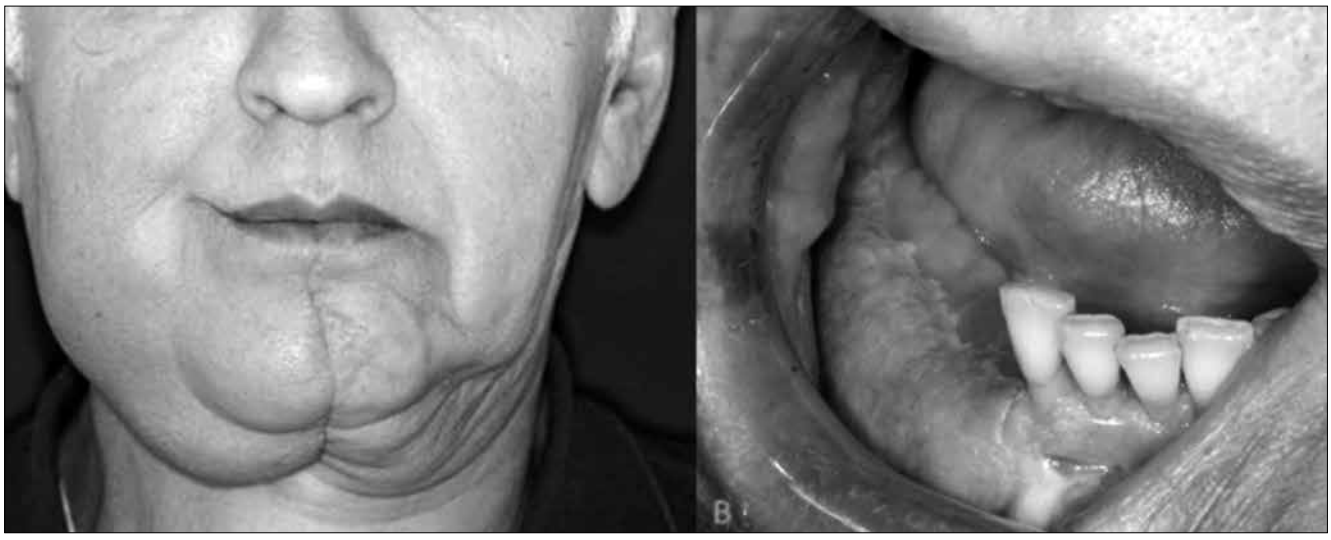

Fig. 5. a) Pleasant aesthetic final result; b) Good intraoral anatomy and morphology.

Ischaemia time was recorded in all six cases, with an average of 71 ± 7 min. Excellent precision was also noted in bone-to-bone contact and position between the mandible and fibula grafts (Fig. 4c, d). In all six patients, a pleasant aesthetic final result was noted with good oral function (Figs. 5a, b).

Discussion

Virtual surgical planning technology in Head and Neck surgery is witnessing strong growth. In the literature, the validity of the method has been widely documented from the point of view of accuracy and clinical utility, especially for bone modelling. Moreover, as widely reported in the literature, this technology is especially useful in minimizing operating time, especially when multiple osteotomies are required. Computer-assisted mandibular reconstruction (CAMR) requires the resection to be scheduled with great precision, in advance of the time of surgery. To obtain maximum accuracy, it is first necessary to identify the extent of the tumour in the soft tissues, in particular the submucosal extent. Accurate knowledge of such extent, especially by annotating on radiologic pictures, allows surgeons to plan the most precise soft tissue resective programme during the virtual surgical planning process. Planning of bone resection is easier, because bone involvement by the tumour is easier to identify.

These decisions must be derived from a careful study of the clinical case, including palpation, as well as excellent quality, complete imaging. In practice, the 'real' time of the decision-making procedure is not at the operating table but during the simulation in the video conference, at which time, the whole team must have all the information needed to minimize a possible staging error. For this reason, we believe it is useful, at least in the early stages of the learning curve, to request the simultaneous presence of the patient during the web meeting. In at least a couple of cases, we have in fact taken steps to revisit the patient to dispel doubts about the true extent of the tumour and further control the position of the perforator vessels.

In order to increase the safety of the procedure, our policy foresees performing final osteotomies on the proximal and distal fibular segments when frozen sections of the mandibular periosteum, bone marrow and soft tissue have demonstrated the complete radicality of resection. To date, however, with the increased use of virtual surgical planning technology in Head and Neck oncology and, consequently, the increased need for bone and soft tissue reconstruction, it is important to carry out the virtual programme considering not only the bone reconstruction but also all aspects related to the reconstruction of soft tissue using composite flaps, and considering that functional outcome is more related to soft tissue reconstruction than to bone reconstruction. In fact, with this strategy, complex orofacial defects can also be reconstructed by adopting a single flap without involving more than one donor site [33]. On the other hand, more dissections are required and the placement of cutting guides on the fibula increases the possibility of a mismatch with perforating vessels during dissection. Therefore, an accurate preoperative knowledge of the perforators is required. In addition to the anatomical knowledge of the higher density of perforating vessels, represented by the skin overlying the lower one-third of the fibula [34 35], several imaging methods can help surgeons to detect perforator vessels including hand-held Doppler, colour Doppler ultrasound, computed tomography, and magnetic resonance angiography. In our experience, the use of the hand-held Doppler associated with CT angiography [36] for the identification of the perforator vessels and manual measurement of the distance between the external malleolus and the vessel itself has proven to be a good method in CAMR with an osteocutaneous flap. It must be said, however, that the surgeon is ready to modify, even if minimally, the morphology of the guides if these interfere with the only perforating vessel [37].

From these cases, we can conclude that there are essentially four critical points in the planning of computer-assisted mandibular reconstruction with a composite free fibula flap in oral malignancies:

1) The potential discrepancy between the position of the perforator vessels for the skin paddle and the positioning of the cutting guides for bone shaping. It is clear that the Doppler study of the perforator vessels can undoubtedly be helpful even though often an imprecise concordance has been noticed. A second factor is the clear usefulness represented by the knowledge of the localised vascular anatomy of the lower limb, demonstrating how the majority of perforator vessels are located at the level of the lower to middle third of the fibula. Such positioning matches well with the need to obtain a vascular pedicle of the fibula of sufficient length to allow correct placement of the same after vascular anastomoses. Should there be a discrepancy between the positioning of the cutting guides and the position of the perforator vessel, the cutting guides can be moved, although not by much (a few centimetres), without compromising the reconstructive surgical planning. Should there be a mismatch between the cutting guide and the perforator flap, the guide could easily be modified to avoid such a phenomenon, without compromising it as the guiding template for the surgeon. *2) The difficulty in positioning the cutting guides on the fibula due to improper skeletonization of the bone on which the guide is placed.* In this case, this would be a technical defect due to lack of knowledge of surgical timing of harvesting and the anatomy of the lower limb. The cutting guides per se, tend to be minimally invasive and are positioned on the external surface of the fibula where they do not impact either the pedicle or the perforator vessels. *3) The potential dis-*

crepancy between the effective extent of the tumour and the planned resection from which the preparation of the cutting guides for the mandible depends. Undoubtedly, the benefit derived from complete planning of the surgical procedure for both the extractive portion as well as the reconstructive one, could be nullified by an understaging that determines the need for a substantial increase in the resection area. On the other hand, the concern of finding oneself in this situation during surgery could paradoxically lead to planning of the bone resection as a systematic over-treatment. In our experience, direct assessment of the clinical and radiological data just prior to the web meeting, and in two cases, during the web meeting, would minimize such a risk. In the event that a planning defect is found, the resection can be increased providing that the comparative and orientation ratios with the cutting guides on the fibula are maintained (i.e. enlargement by 2 cm on the mandibular distal stud implies an enlargement of 2 cm on the fibular distal stud). For this reason, the fibula must be resected with at least 3-4 extra centimetres on both extremities and should not be modelled until the outcome of the frozen section is known. Particularly with the introduction of the PSP, which presents very precise design and characteristics, changes in the surgical programme are often not able to be revised, and for this reason, we always order the stereolithographic model of the mandible reconstruction from the modelling company in order to have the possibility of modelling a standard plate intraoperatively in the case of changes in the resective programme. *4) The extended planned timing of the surgery.* This is undoubtedly a critical aspect that should be quantified and guaranteed. It is in advanced local tumours where a possible therapeutic delay of over a month could weigh heavily on the general treatment outcome, determining among other aspects, a discrepancy between the planned resection and the dimensions of the tumour at the time of surgery and also often an excessive weight loss because patients do not eat well and have pain. The timing objective between the moment of choice of treatment and the effective supply of the same should never exceed 4 weeks and this must be a fixed target.

Conclusions

The possibility of being able to always programme in the most accurate fashion the position of the bone segment in relation to the cutaneous island is nowadays a very important factor in order to obtain maximum accuracy in bone reconstruction, especially with the use of PSP. The application of CAMR in complex defects, where an osteofasciocutaneous flap is used for defect reconstruction, allows excessive handling of the flap itself to be avoided during the modelling phase. Moreover, thanks to virtual surgical planning, all the phases of fibula modelling and mounting on the reconstruction plate can be performed before detaching the vascular pedicle and this is a further advantage, especially in composite flap harvesting. The technique described in this article may be considered a valuable aid in the programming of composite flaps using virtual surgery, however, we agree with Deek and Wei [38] that computer-aided surgery is an important but limited tool because of the many variables inherent in complex reconstruction that are not yet programmed into the computer algorithm.

When planning for soft-tissue reconstruction and coverage, osteoseptocutaneous fibula flap components, including the septocutaneous vessels and the intercomponent relationship, bone cross-section and nutrition, pedicle length, and surgical plan flexibility are important niches to be considered in virtual programmes [38]; however, this clashes with the accuracy of planning of the PSP plaques which, when intraoperative changes are required, these changes are difficult to instigate because the PSP present very precise design characteristics, and intraoperative changes in the surgical programme are often not able to be revised.

These considerations are reflected in the need for surgical teams to make a very precise diagnosis and accurate preoperative assessments so that the virtual surgical planning is highly predictable for both radical and reconstructive phases; moreover, the surgical team must be ready to change the reconstructive programme at every step with the help of traditional methods. Advances in radiological imaging for oral malignancies [39 40] and perforator flaps [41] will help surgeons to develop high-precision programmes for both radical and reconstructive phases. The future study and development of software able to fuse together CT and magnetic resonance angiography [42] data are essential. Future research in the field of virtual surgical planning for soft tissue and tissue engineering will allow interventions to be planned that are increasingly predictable, both aesthetically and functionally. Further investigation is needed in this field.

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Salivary gland

Outcomes of interventional sialendoscopy for obstructive salivary gland disorders: an Italian multicentre study

Risultati della scialoendoscopia interventistica nelle patologie ostruttive delle ghiandole salivari: uno studio multicentrico italiano

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SUMMARY

Interventional sialendoscopy has become the predominant therapeutic procedure for the management of obstructive salivary disorders, but only a few multicentre studies of large series of patients with a long-term follow-up have been published. This Italian multicentre study involved 1152 patients (553 females; mean age 50 years) who, after at least a clinical and ultrasonographic evaluation, underwent a total of 1342 diagnostic and interventional sialendoscopies, 44.6% of which involved the parotid gland. 12% (n = 138) of patients underwent multiple treatments. The procedure was successful in 1309 cases. In 33 cases (2.4%) the procedure could not be concluded mainly because of complete duct stenosis (21 cases). Salivary stones were the main cause of obstruction (55%), followed by ductal stenosis and anomalies (16%), mucous plugs (14.5%) and sialodochitis (4.7%). Complete therapeutic success was obtained in 92.5% of patients after one or more procedures, and was ineffective in < 8%. Untoward effects (peri and postoperative complications) were observed in 5.4% of cases. Sialendoscopy proved to be an effective, valid and safe procedure in the diagnostic and therapeutic management of non-neoplastic obstructive salivary gland diseases.

KEY WORDS: Sialendoscopy • Salivary glands • Endoscopic surgery • Sialoadenitis • Sialolithiasis • Salivary ducts • Multicentre study

RIASSUNTO

Sebbene le tecniche scialoendoscopiche abbiano assunto un ruolo fondamentale nel trattamento delle patologie ostruttive dei dotti salivari, in letteratura sono riportati pochi studi multicentrici sull'argomento. Questo studio basato sull'esperienza di 9 centri italiani è stato condotto su 1152 pazienti (553 donne, età media di 50 anni) per un totale di 1342 procedure scialoendoscopiche, il 44,6% delle quali a carico della ghiandola parotide. Il 12% dei pazienti è stato sottoposto a più interventi. I calcoli salivari sono risultati essere la principale causa di ostruzione (55%), seguiti dalle stenosi e altre malformazioni duttali (16%), dai tappi mucosi (14,5%) e dalla scialodochite (4,7%). La procedura endoscopica è stata portata a termine in 1309 casi mentre in 33 casi è stata interrotta, principalmente a causa della presenza di stenosi duttali complete (21 casi). Dopo una o più procedure il successo terapeutico è stato ottenuto nel 92,5% dei pazienti. Complicanze peri-operatorie e post-operatorie sono state riscontrate nel 5,4% dei casi trattati. La scialoendoscopia rappresenta quindi una procedura efficace e sicura nella diagnosi e nel trattamento delle principali patologie ostruttive dei dotti salivari.

PAROLE CHIAVE: *Scialoendoscopia • Ghiandole salivari • Chirurgia endoscopica • Scialoadenite • Scialolitiasi • Dotti salivari • Studio multicentrico*

Introduction

Obstructive sialadenitis is the most frequent cause of major salivary gland dysfunction, and is more frequent than neoplastic disorders. Although very few prevalence studies are available, epidemiological considerations indicate that about 16,000 patients a year are admitted to hospital because of obstructive salivary gland symptoms in Western Europe [1-3].

Over the last 20 years, the rapid transition from invasive surgery to conservative and minimally invasive treatment has favoured a significant reduction in the number of patients undergoing traditional sialadenectomy [4 5]. Sialendoscopy is a relatively new procedure that allows the endoscopic exploration of salivary gland ducts for diagnostic purposes. The opportunity of using miniaturised instruments (e.g. forceps, baskets, balloons, graspers, laser fibres and microdrills) and injecting steroids and antibiotics also makes salivary gland endoscopy a valid interventional procedure for the functional management of many benign salivary gland disorders. The effectiveness and safety of sialendoscopy in adults is widely known [6-9], as its usefulness in paediatric disorders [10-13], but there are still relatively few descriptions of multicentre experiences with large cohorts of patients and a long follow-up period [3 14-16]. Some reports of single-centre experiences in Italy have recently been published, but no Italian multicentre study has yet been carried out.

The aim of this retrospective study was to collect data from various Italian groups and evaluate the outcomes of interventional sialendoscopy for the management of obstructive salivary gland disorders.

Materials and methods

The study involved 1152 patients (553 females; mean age 50 years, range 2-99) with salivary obstructive disorders who underwent diagnostic and interventional sialendoscopy between February 2001 and February 2014 at nine ENT units (Milan, Pavia, Bologna, Rome 1, Rome 2, Rome 3, Latina, Cagliari and Palermo). The main inclusion criteria were at least one episode of sialadenitis not responding to a medical therapeutic protocol (i.e. antibiotic and/or anti-inflammatory drugs), and an indication for interventional sialendoscopy alone (i.e. without sialendoscopy-assisted transoral or transfacial surgery, or extracorporeal shockwave lithotripsy). The other exclusion criteria were stones larger than 7 mm, multiple intraparenchymal stones, complete distal duct stenosis, acute infectious sialadenitis and patient lost to follow-up. Demographics and clinical data of the patients are summarised in Table I.

All patients underwent complete ENT evaluation and high-resolution ultrasonography using a 7.5 MHz probe; further investigations such as computed tomography (CT), contrast sialography, magnetic resonance (MR) sialography, or cone beam computed tomography (CBCT) were made depending on the individual case and Institution.

Table I. Demographic and clinical data of patients.

Patients	
Sex, N (%)	
Male	599 (52)
Female	553 (48)
Total	1152
Mean age, y (min-max)	50 (2-99)
Preoperative diagnosis	
Salivary stones (%)	695 (53.1)
Stenosis (%)	123 (9.4)
Idiopathic recurrent sialadenitis (%)	356 (27.2)
Autoimmune disorders (%)	45 (3.4)
Radioiodine therapy (%)	21 (1.6)
Radiotherapy (%)	6 (0.5)
JRP (%)	54 (4.1)
Other (%)	9 (0.7)
Total	1152 (100)
Sialendoscopy	
Performed (%)	1342 (100)
Successfully performed (%)	1309 (97.5)
Parotid gland (%)	584 (44.6)
Submandibular gland (%)	725 (55.4)
Unsuccessfully performed (%)	33 (2.5)

Sialendoscopy was performed after a clinical and radiological diagnosis of suspected obstructive sialadenitis had been made. The ductal system of the affected gland was endoscopically explored using semi-rigid salivary sialendoscopes with outer diameters ranging from 0.8 to 1.6 mm (Karl Storz®, Tuttlingen, Germany), which were inserted through the salivary duct after its appropriate dilation by means of standard salivary probes and conical dilators (0000-6 Bowman probes, Karl Storz®, Tuttlingen, Germany), when needed with minimal papillotomy or limited minimal sialodochotomy [16]. A record was made of all diagnostic findings, which were mainly stones, different types of strictures, variable signs of sialodochitis, the presence of mucous plugs, other duct anomalies and other such as foreign bodies (Table II).

The interventional sialendoscopies were mainly carried out to remove stones with the aid of a basket (Karl Storz®, Tuttlingen, Germany; NCircle, Cook Medical Inc®, Bloomington, IN, USA; Boston Scientific®, Marlborough, MA, USA), forceps (Karl Storz®, Tuttlingen, Germany), balloon (Karl Storz®, Tuttlingen, Germany), intraductal holmium:YAG laser lithotripter (Lumenis®,

Table II. Main sialendoscopic findings.

Salivary glands (parotid and submandibular)	
Salivary stones (%)	719 (55)
Localised duct stenosis (%)	152 (11.6)
Diffuse duct stenosis (%)	57 (4.4)
Mucous plugs (%)	189 (14.5)
Sialodochitis (%)	62 (4.7)
Other duct anomalies (%)	61 (4.6)
JRP (%)	62 (4.7)
Other (%)	7 (0.5)
Total	**1309 (100)**
Parotid gland	
Salivary stones (%)	215 (36.8)
Localised duct stenosis (%)	76 (13)
Diffuse duct stenosis (%)	28 (4.8)
Mucous plugs (%)	132 (22.6)
Sialodochitis (%)	31 (5.3)
Other duct anomalies (%)	38 (6.5)
JRP (%)	62 (10.6)
Other (%)	2 (0.4)
Total	**584 (100)**
Submandibular Gland	
Salivary stones (%)	504 (69.5)
Localised duct stenosis (%)	76 (10.5)
Diffuse duct stenosis (%)	29 (4)
Mucous plugs (%)	57 (7.8)
Sialodochitis (%)	31 (4.3)
Other duct anomalies (%)	23 (3.2)
Other (%)	5 (0.7)
Total	**725 (100)**

Israel) carried by a semi-flexible fibre with a diameter of 200 or 365 μm and used at a power of 2.5-3.5 W, a rate of 5 Hz/s, and energy of 0.5-0.7 J., or a manual drill (Karl Storz®, Tuttlingen, Germany). Duct stenoses were dilated by means of simple irrigation, balloon dilation, endoscopic stent positioning (venous catheters, Venflon, Artsana, Grandate, Italy; arterial catheters, Seldinger, Seldicath® PU Cathéter Artériel, Promed, Le Plessis-Bouchard, France; salivary polymeric stent, Optimed®, Ettlingen, Germany; Schaitkin salivary duct cannula, Hood®, USA) (Table III). Therapeutic success was defined as complete when the cause of obstruction was completely removed or the patient was symptom free (Table IV); partial when the cause of obstruction was not completely removed or when the number of episodes of sialoadenitis was reduced; and unsuccessful when the cause of obstruction was not re-

Table III. Interventional sialendoscopy - main procedures used.

Parotid gland	
Endoscopic stone removal (%)	172 (29.5)
Intraductal lithotripsy (%)	37 (6.3)
Manually drills (%)	3 (0.5)
Laser (%)	33 (5.6)
Other (%)	1 (0.2)
Stenosis dilatation	117 (20.0)
Endoscope (%)	89 (15.2)
Balloon (%)	28 (4.8)
Exclusive ductal irrigation (%)	258 (44.2)
Total	584 (100)
Additional procedures during parotid gland sialendoscopy	
Papillotomy or limited sialodochotomy (% of all parotid stones)	34 (15.8)
Ductal irrigation combined to previous procedures (% all procedures)	314 (53.8)
Salivary stent (% all procedures)	88 (15.1)
Submandibular Gland	
Endoscopic stone removal (%)	456 (62.9)
Intraductal lithotripsy (%)	48 (6.6)
Manually drills (%)	2 (0.3)
Laser (%)	41 (5.7)
Other (%)	5 (0.7)
Stenosis dilatation	105 (14.5)
Endoscope (%)	86 (11.9)
Balloon (%)	19 (2.6)
Exclusive ductal irrigation (%)	112 (15.4)
Other (%)	4 (0.6)
Total	725 (100)
Additional procedures during submandibular gland sialendoscopy	
Papillotomy or limited sialodochotomy (% of all submandibular stones)	103 (20.5)
Ductal irrigation combined to other procedures (% of all procedures)	264 (36.4)
Salivary stent (% all procedures)	223 (30.8)

Table IV. Therapeutic success.

Complete therapeutic success, N (%)	**882 (76.6)**
After a single procedure (%)	752 (65.3)
After multiple procedures (%)	130 (11.3)
Partial therapeutic success (%)	184 (15.9)
Unsuccessful treatment (%)	86 (7.5)
Total	1152 (100)

Table V. Miscellaneous.

Side effects*	
Ductal wall perforation (%)	19 (1.4)
Ranula (%)	6 (0.5)
Intraductal wire basket blockage,balloon-laser-forceps rupture (%)	9 (0.7)
Nerve damage (%)	10 (0.8)
Temporary (%)	9 (0.7)
Persistent (%)	1 (0.1)
Other (%)	27 (2.0)
Total	71 (5.4)
Anaesthesia	
Local (%)	921 (70.4)
General (%)	388 (29.6)
Total	1309 (100)
Hospital Admission Modality	
Outpatient (%)	53 (4.1)
DH** (%)	591 (45.1)
One-day surgery (%)	566 (43.2)
Ordinary (%)	99 (7.6)
Total	1309 (100)

** Event/total number of sialendoscopies*

*** Day Hospital*

moved or there was no change in the patient's symptom-related condition. The other parameters analysed were the occurrence of any complications (untoward effects), type of anaesthesia (local or general), and type of hospital admission (outpatient *vs.* day surgery *vs.* one-day surgery *vs.* ordinary hospital admission) (Table V).

The data from all of the referral centres were collected, recorded and comprehensively discussed.

Results

Pre-operative diagnostic evaluation (mainly based on a clinical and ultrasonographic evaluation) identified stones as the main cause of obstruction (695 patients, 53.1%) (Table I); a duct stenosis was found in 123 patients (9.4%), and other causes of salivary obstruction and inflammation in 81 (10.3%). Interestingly, no clear cause of obstruction or inflammation was identified in 356 patients (27.2%). Juvenile recurrent parotitis (JRP) was suspected in 54 paediatric patients.

A total of 1309 sialendoscopies were successful, 584 (44.6%) of which involved the parotid gland (Table I); the sialendoscopic procedure could not be concluded in 33 cases (2.4%), mainly because of complete duct stenosis (21 patients); 157 patients (12% of 1152) underwent multiple treatments.

The main sialendoscopic findings are described in Table II. Salivary stones were the main cause of obstruction of both glands (719 of 1309 procedures, 55%, mean diameter 3.4 mm) followed by ductal stenosis and anomalies (209, 16%), mucous plugs (189, 14.5%) and sialodochitis (62, 4.7%) (Table II). Salivary stones were more frequently encountered in the submandibular duct system (504 of 725, 69.5%), whereas duct stenosis and anomalies (142 of 584, 24.3%,), mucous plugs (132 of 584, 22.6%), and signs of sialodochitis (31 of 584, 5.3%) were more frequent in the parotid duct system.

A basket was the main endoscopic device used to remove stones from both the parotid (172 of 584 procedures, 29.5%) and submandibular gland (456 of 725 procedures, 62.9%). Intraductal laser lithotripsy was used in 74 procedures (33 for Stensen duct stones and 41 for Wharton duct stones), 11.4 % of all cases of salivary stones. A manual drill was used to fragment the stone in five patients. A papillotomy or limited minimal sialodochotomy was necessary to retrieve stones in 103 submandibular procedures (20.5%) and 34 parotid procedures (15.8%).

Duct dilation of the stenosis by means of forced irrigation of saline through the irrigation channel of the flexible semi-rigid endoscope (175 procedures) or a balloon (47 procedures) was used in 16.5% of the sialendoscopies (222 procedures; 117 parotid and 105 submandibular). Ductal irrigation alone was used in 370 procedures (258 parotid and 112 submandibular), and in combination with other sialendoscopic procedures in 314 parotid and 264 submandibular procedures; in most cases, the irrigation was performed using steroids (65.3%), followed by antibiotics (3.4%) and other substances (15.7%).

A salivary stent was positioned during 23.8% of all procedures (311 cases, 223 involving the submandibular gland).

Complete therapeutic success was obtained in 92.5% of patients after one or more sialendoscopic procedures; interventional sialendoscopy was therefore ineffective in fewer than 8% (Table IV).

Complications were observed in 71 interventional procedures (5.4%) (Table V), with duct wall perforation occurring in 19 cases (1.4% of all procedures). Intraductal breakage of a miniaturised instrument (wire basket, balloon, forceps or laser) occurred in nine cases (0.7%). Temporary lingual or facial nerve damage was observed in nine patients, and was persistent in only one case.

Sialendoscopy was performed under local anaesthesia in 921 patients (70.4%) (Table V). The hospital admission modalities were mainly day surgery (hospitalisation of 12 hours) and one-day surgery (hospitalisation of 24 hours) (88.3% of all patients).

Discussion

Healthcare in each field of medicine and at different stages of the clinical pathway is evolving in line with the "precision medicine philosophy", an innovative and pio-

neering approach based on personalised medicine and targeted treatments. In the case of salivary gland disorders, technological improvements such as the miniaturisation of video endoscopic systems, advances in interventional radiology and the development of novel pharmacological strategies now allow tailored management of obstructive recurrent sialadenitis, and increasing knowledge of obstructive mechanisms and how to treat them has overcome the failings of traditional therapeutic algorithms and favoured conservative approaches that leave a functional gland in place in about 97% of patients [3]. Salivary gland surgical resection, together with accompanying risks of nerve injuries, aesthetic problems and longer hospital stays, have been greatly reduced by the growing use of minimally invasive techniques [18 19]. The key role of sialendoscopy in the gland-preserving management of obstructive sialadenitis has been highlighted in the international literature, but only a few published reports describe large patient cohorts [3 14-16]. This Italian multicentre study collected data relating to 1309 sialendoscopic procedures and 1152 patients.

In line with other published reports [6 7], complete or partial success was achieved in 92.5% of the patients after one or more sialendoscopic procedures, making interventional sialendoscopy ineffective in fewer than 8%.

The most frequent endoscopic findings were salivary stones (55%) followed by ductal stenosis (16%) and mucous plugs (14.5%). The relatively small number of treated stones in comparison with previous reports [20-22] is probably due to the selection criteria, which ensured that only patients who underwent sialendoscopy alone (i.e. with stones of < 7 mm) were enrolled. Endoscopically assisted stone removal was carried out using a basket or microforceps in most cases, with the basket being the most effective: holmium:YAG laser lithotripsy allowed the pulverisation of stones > 4 mm in diameter, but was used for only 10.3% of stones.

Laser lithotripsy is a promising technique for the management of salivary stones, but the very few and initial studies published so far [23 24] do not allow any definitive conclusion to be drawn because of the absence of long-term follow-up and possible occurrence of untoward effects such as postoperative duct stenosis. All of our patients undergoing laser-assisted surgery required the positioning of a stent to reduce the rate of duct stenosis. A minimal papillotomy or limited minimal sialodochotomy [25 26] was used in 24.9% of patients with obstructive sialadenitis in order to favour the release of a stone or to gain access to ducts with a very narrow distal ostium. Multiple sialendoscopic procedures increased the rate of success in 11.3% of patients.

Idiopathic recurrent sialadenitis was observed in 27.2% of cases after preoperative diagnostic work-up mainly based on clinical and ultrasonographic evaluations. This is a relatively high number of undetected causes of obstruction given that the combination of multiple imaging modalities has reduced the incidence of idiopathic obstructions to only 5-10% [21], but may be partially explained by the fact that few of our centres used dynamic ultrasonography (i.e. stimulation with citric acid), which helps clinicians to detect even mild duct dilations due to localised stenoses or microliths and the initial signs of salivary gland inflammation. Diagnostic sialendoscopy allowed the identification of microliths, localised duct stenoses, mucous plugs, duct anomalies such as invagination, and signs of sialodochitis that the preoperative work-up was unable to discover.

There were no major complications and the overall rate of untoward effects was 5.4%, which is in line with previously published data [26]. However, there were two interesting events. The first was the guide wire of a basket broken with a 3 mm stone stuck in a secondary branch of the parotid duct system. This required a subsequent combined sialendoscopy-assisted transfacial surgery to remove the stone and foreign body under general anaesthesia, which was done with no major complications [27]. The second was that the blade of the forceps broke inside the duct and had to be removed using biopsy forceps. Although major untoward effects are very rare, patient should be informed that a purely sialendoscopic procedure may be converted to a concomitant or subsequent sialendoscopy-assisted transfacial [28-31] or transoral surgical procedure [32 33].

Most of the sialendoscopies were performed in day surgery or one-day surgery modality under local anaesthesia. Performing sialendoscopy improves with time and experience, depending on the learning curve of the surgeon [34]. It has recently been suggested that 30 sialendoscopic procedures are required before reaching satisfactory operation times and performance ratings [35], and probably completion of the learning curve favours the transition from sialendoscopic procedures performed under general anaesthesia towards one-day surgery to local anaesthesia and outpatient regimens.

Conclusions

The results of this Italian multicentre study of the outcomes of interventional sialendoscopy in a very large sample of patients show that sialendoscopy is an effective and safe means of diagnosing and treating non-neoplastic obstructive salivary gland disease, but need to be validated on the basis of a long-term follow-up, especially in the case of recurrent inflammatory sialadenitis. The findings may be affected by a bias because the heterogeneity of the data did not allow the successful results of sialendoscopy to be stratified on the basis of the preoperative and sialendoscopic findings (i.e. the location of the stone, or the type and extent of stenosis) [36]. In this regard, preoperative diagnostic assessment is essential in order to minimise the risk of failure during interventional sialendoscopy. As long as interventional sialendoscopy is the predominant

procedure in the therapeutic work-up of obstructive salivary disorders, particular attention should be paid to new endoscopy-assisted devices and techniques such as Kolenda's device and pneumatic lithotripsy [37] to reduce the number of patients undergoing more aggressive procedures.

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Sleep apnoea

The role of masseter muscle EMG during DISE to predict the effectiveness of MAD: preliminary results

Il ruolo dell'EMG del muscolo massetere durante la sleep endoscopy nel predire l'efficacia del MAD: nostri risultati preliminari

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SUMMARY

The use of a mandibular advancement device (MAD) increases the activity of the temporo-mandibular (TM) complex and masseter (MM) muscles with the risk of reducing treatment compliance. Predictors of treatment outcome are of importance in selecting patients who might benefit from MAD without side effects. The role of mandibular advancement (MA) during drug-induced sleep endoscopy (DISE) is controversial. In three cases (BMI < 30) affected by non-severe OSAS (AHI < 30 e/h), we recorded the surface EMG signal of MM activity during DISE. At follow-up all cases improved the AHI, two cases that showed transient increase of MM activity did not suffer from changes of overjet and did not complain of discomfort with the use of MAD. The case that showed a continuing increase of MM activity reported TM discomfort without changes of dental occlusion. EMG of MM during DISE may contribute to ameliorate the selection of cases amenable to treatment with MAD.

KEY WORDS: OSAS • Mandibular advancement • Masseter muscle • EMG

RIASSUNTO

È noto che l'applicazione dell'apparecchio per l'avanzamento mandibolare (MAD) aumenta l'attività del complesso muscolare temporo-mandibolare (TM) e del muscolo massetere (MM) con il rischio di ridurre l'aderenza al trattamento. Alcuni parametri clinici riconosciuti predittivi dell'efficacia del MAD sono già utilizzati per la selezione dei casi e tra questi l'avanzamento mandibolare (MA) simulato durante la "sleep endoscopy" è quello principale. Presentiamo qui i risultati della registrazione EMG del muscolo massetere in tre casi di pazienti normopeso affetti da OSAS non-severa (AHI < 30) sottoposti alla MA durante la "sleep endoscopy" e poi trattati con MAD. La poligrafia dinamica di controllo a distanza, documentava una significativa riduzione dell'AHI. I due casi che avevano mostrato un incremento transitorio dell'attività del MM durante la MA non riferivano effetti collaterali, l'altro, che aveva dimostrato un incremento persistente del segnale, riferiva al follow-up un "discomfort" in regione TM senza alterazioni dell'occlusione. L'EMG del massetere potrebbe contribuire a migliorare la selezione dei casi suscettibili di trattamento con MAD.

PAROLE CHIAVE: *OSAS • Avanzamento mandibolare • Muscolo massetere • EMG*

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common sleep disorder characterised by partial to complete collapse of the upper airway despite continued respiratory effort often leading to hypoxia. OSAS affects over 25% of the adult population and is closely related to the obesity epidemic [1]. If untreated, it is recognised as a risk factor for hypertension, ischaemic heart disease and stroke [2 3]. To date, continuous positive airway pressure (C-PAP) therapy is considered the gold standard, but it is estimated that approximately 50% of patients will reject it or discontinue its use even after good initial compliance [4 5]. Surgical treatment has the advantage of 100% adherence, but is not recommended as first-line therapy due to its low success rate in unselected patients [6]. Hence, the choice of treatment, particularly in young individuals, mild or moderate OSAS or severe OSAS who are unwilling or unable to tolerate C-PAP, still remain the biggest challenge. The mandibular advancement device (MAD) is a conservative aid that overtime, thanks to intense research on its effectiveness, has emerged as a viable therapeutic alternative because it is not cumbersome, easily transportable and does not require electricity. The disadvantages are its relatively high costs, side effects (*i.e.* discomfort, excessive salivation and changes in occlusion and/or in the neuromuscular pattern of the face) and, to date, a lower mean success

rate than C-PAP. Therefore, predictors of treatment outcome are of importance in selecting patients who might benefit from MAD without side effects [7 8]. Apart from anthropometric and polysomnographic predictors including cephalometry, low AHI or BMI or age, female gender and supine-dependent-OSA [9 10], the simulation of mandibular advancement (MA) during drug-induced sleep endoscopy (DISE) is recently recommended by the European position paper on DISE [11].

It is well known that the use of MAD during sleep increases significantly the activity of the temporo-mandibular (TM) complex and masseter (MM) muscles [12]. The relationship between recorded forces and MA is almost linear. The pain-related TM disorders could be the result of the strain in the muscles. Moreover, a dose-dependent effect of MAD on occlusal changes has been suggested [13]. Herein, we first introduce the recording of electrical activity of MM during DISE in order to study its behaviour during the MA manoeuvre.

Clinical technique and technology

From May to September 2015, three cases of moderate OSAS (mean AHI: 22 e/h) were enrolled. They were males who refused C-PAP therapy with a mean age of 42 years, mean BMI of 25.5, normal overjet and without comorbidities, especially stomatognathic system disorders, previous treatments for OSAS or occlusion. All patients were submitted to DISE according to the technique described in our recent publication [14]. During DISE, in continuous mode, polysomnography (PSG) monitoring with the addition of the surface electromyography (EMGS) recording of the right and left masseter muscle activities (EMGS-MM) was performed. During the examination, the ENT physician performed the manual MA: for the time necessary to observe the effect by mean of endoscopic view, the mandible is gently advanced (up to 5 mm) by placing the fingers along the ascending ramus and angle [15]. The PSG technician marked on the trace the start and the end of MA (Fig. 1). The effects of MA on the airway and snoring and the electrical activity of the MM were recorded. In all cases, the sites of obstruction were retropalatal and oropharyngeal with a grade and pattern of obstruction > 50% and concentric respectively. During MA the respiratory space, in the sites of closure, is amplified consensually to the increase of blood oxygen level. In two cases, at the beginning of MA, the amplitude of EMG signal increased transiently, about 1-2 seconds. In the other case, the increased amplitude of MM activity lasted for the duration of MA. Basing on DISE findings, we recommended a MAD to all patients. After three months of treatment with a MAD "Bibloc" type (in compliance with the maximum protrusion of 5 mm), all cases were submitted to a PSG using MAD and to a dental visit to evaluate the amount of overjet. Moreover, each patient was questioned about TM discomfort. No significant difference was observed in the mean BMI when comparing the initial findings with that at the repeat investigation (mean BMI: 25). Post-treatment PSG with MAD showed a reduction of AHI ≥ 50% from baseline in all cases. The two cases that revealed a transient increase of electrical activity in MM did not have a change in overjet and did not complain of discomfort. On the other hand, the patient who showed a continuing increased signal of MM activity reported TM discomfort without a change of overjet.

Discussion

Nowadays the importance of treatment to prevent neurobehavioural and cardiovascular sequelae of OSAS is widely accepted. Non-surgical approaches include po-

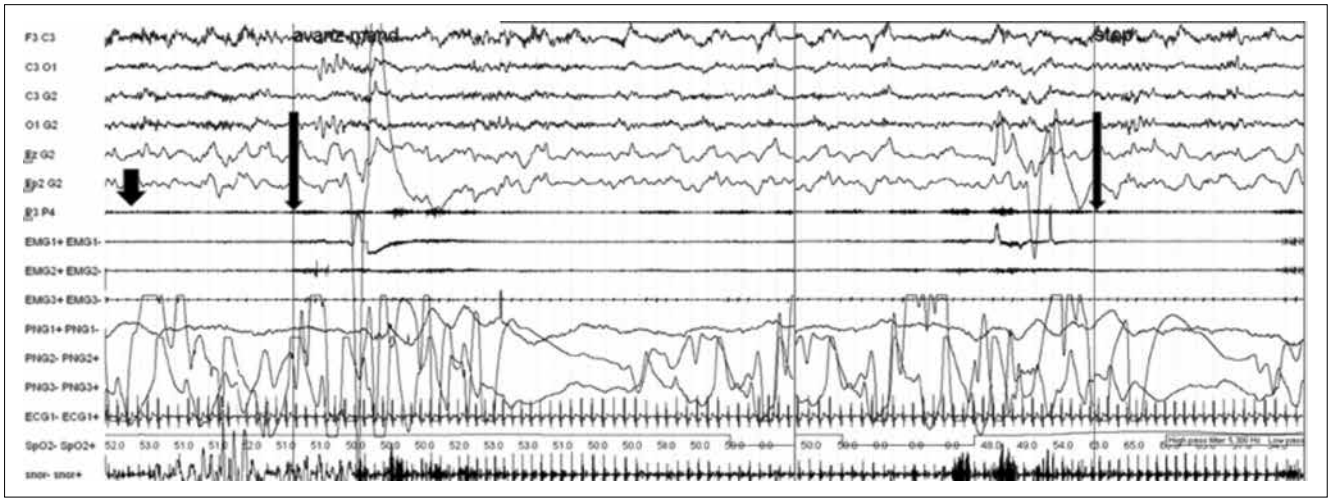

Fig. 1. Electrical activity of the masseter muscle (MM) during advancement of mandible. The short arrow marks the trace of MM-EMG and the longer ones mark, respectively, its beginning and end.

sitional therapy, C-PAP and MAD. In 1995, the *American Academy of Sleep Disorders* defined the following indications for the use of MAD: primary snoring, mild or moderate OSAS, or cases of severe OSAS for individuals who do not tolerate C-PAP [16]. These devices are easy to use, non-invasive and removable. On the other hand, they are expensive and associated with poor compliance [15].

Experimental and clinical studies have demonstrated that the efficacy of MADs depends on the degree of mandibular advancement, with a dose-dependent effect [17]. Nevertheless, in the literature the correlations between the increased activity of the TM complex and MM, due to the MAD use, and the TM discomfort or occlusal change have also been described [13]. Basing on these observations, it seems that the effectiveness of MAD is the result of a tight balance between the degree of mandibular advancement (the more advanced the mandible, the larger respiratory spaces) and muscular activity that determines the onset of side effects.

With the purpose to optimise the predictor value of intra-DISE MA for MAD success, we added the recording of EMGS of MM in the PSG. Herein the MM electrical activity and its behaviour during DISE are described for the first time. Kurtulmus et al. [12] introduced an interesting debate on the relationship between MAD efficacy and MM activity. They demonstrated that MAD during sleep, by activating the MM in mild and moderate OSAS, prevents the upper airway from collapsing. According to their results, all our cases showed an increase of EMG signal and, independently of EMGS-MM behaviour, a significant improvement of AHI. Nevertheless, we observed that the behaviour of MM activity was not unique: the increased EMGS-MM amplitude was transient or continuous. The patient who showed a non-transient EMG-MM increased amplitude, after three months of MAD use, suffered from TM discomfort.

Our results suggest that exist a close relationship between the benefit and disadvantages of MAD and moreover that the amplitude of its effective "field" of action may vary according to the individual. For this reason, the DISE is irreplaceable because it allows to concurrently appreciate the modifications of respiratory spaces and MM activity for extemporaneous integration of the data.

In the light of all these considerations, it is clear that the effectiveness of MAD will be critically dependent on its efficacy. The MAD must be titrated, and the degree of effective MA should be determined not simply on subjective clinical criteria, but also on objective data. In this way, our technique may help to address the need to establish more precise indications for MAD in order to decrease the failure rate by improving compliance and the outcome of treatment.

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Sleep apnoea

A comparative study on oxidative stress role in nasal breathing impairment and obstructive sleep apnoea syndrome

Studio comparativo sul ruolo dello stress ossidativo nei pazienti con insufficienza respiratoria nasale e sindrome delle apnee ostruttive notturne

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SUMMARY

Obstructive sleep apnoea syndrome (OSAS) is a sleep disorder that leads to metabolic abnormalities and increased cardiovascular risk. This study aimed to define the expression and clinical significance of biomarkers involved in oxidative stress in patients with OSAS. A prospective study was designed to compare outcomes of oxidative stress laboratory tests in three groups of subjects. The study involved the recruitment of three groups of subjects, 10 patients with obstructive sleep apnoea syndrome with AHI > 30; 10 patients suffering from snoring at night with AHI < 15; 10 patients with nasal respiratory impairment with AHI < 5. Patients were subjected to skin prick tests for common aero-allergens, nasal endoscopy, active anterior rhinomanometry, fibrolaryngoscopy and polysomnography; and extra-routine diagnostic tests and procedures; analysis of oxidative and antioxidant (plasma thiol groups) biomarkers in blood and urine samples. No statistical differences in age, sex distribution or body mass index were present between the three groups ($p > 0.05$). There were significant differences in AHI among the three groups of patients ($p < 0.05$). No statistical significance was found in the Analysis of Variance (ANOVA) test ($p > 0.05$) between the levels of biomarkers of oxidative stress in the three populations studied. The results of our study show that the nose can play a role in the pathogenesis of OSAS through the production of biomarkers of oxidative stress.

KEY WORDS: OSAS • Oxidative damage • Biomarkers of oxidative stress • Polysomnography

RIASSUNTO

La sindrome delle apnee ostruttive del sonno (OSAS) è una malattia che può portare ad alterazioni metaboliche e a un'aumentata incidenza di patologie cardiovascolari. Questo studio ha lo scopo di definire l'espressione e il significato clinico di biomarkers coinvolti nello stress ossidativo nei pazienti con diagnosi di OSAS. I risultati degli esami di laboratorio dello stress ossidativo sono stati confrontai prospetticamente in tre gruppi di soggetti: 10 con sindrome delle apnee ostruttiva del sonno con Apnea Hypopnea Index (AHI) > 30; 10 con roncopatia notturna e AHI < 15 e 10 con insufficienza respiratoria nasale e AHI < 5. I pazienti sono stati sottoposti a test cutanei per aero-allergeni comuni, rinoscopia anteriore, rinomanometria anteriore attiva, fibrolaringoscopia e polisonnografia. Per la ricerca dei biomarkers dello stress ossidativo sono stati effettuati test diagnostici in campioni di sangue e urine. I gruppi sono risultati omogenei per età, sesso e distribuzione del Body Mass Index (BMI) ($p > 0.05$). Ci sono state differenze significative nell'AHI tra i tre gruppi di pazienti ($p < 0.05$). Nessuna significatività statistica è stata identificata ($p > 0.05$) tra i livelli di biomarkers di stress ossidativo nelle tre popolazioni studiate. I risultati del nostro studio hanno mostrato che il naso può svolgere un ruolo nella patogenesi dell'OSAS, attraverso la produzione di biomarkers di stress ossidativo.

PAROLE CHIAVE: *OSAS • Danno ossidativo • Biomarkers dello stress ossidativo • Polisonnografia*

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a sleep disorder characterised by repeated episodes of partial or complete obstruction of the upper airways during sleep, resulting in a reduction (hypoapnoea) or abolition (apnoea) of airflow [1]. The prevalence of clinically significant apnoea during sleep, in middle age, is about 4% in men and 2% in women [2]. OSAS is associated with important clinical symptoms such as obstructive respiratory symptoms, insomnia, awakenings and excessive daytime sleepiness. In addition, important clinical sequelae such as neuropsychiatric complications, resulting in sleep fragmentation and daytime sleepiness, which lead to an impairment of pro-

fessional, family and social life, cardiovascular and metabolic complications, resulting in intermittent hypoxia, such as pulmonary and systemic hypertension, arrhythmias, heart attack, heart failure, stroke and diabetes may be present. It is also associated with increased morbidity and mortality from cardiovascular disease [1].

The starting point for the diagnosis of OSAS is clinical history and physical examination, which allow for risk stratification in each patient. More specific examinations for diagnosis are: a) multiple sleep latency test (MSLT) to quantify daytime sleepiness and is considered an objective measure of the tendency to sleep during the day; b) sleep endoscopy, which is an endoscopic evaluation of the site of obstruction; Muller's manoeuver; c) polysomnography, which is considered the gold standard for diagnosis, but is expensive and laborious, which has pushed the search for more practical diagnostic systems such as nocturnal oximetry and portable monitors [3-5].

The therapy is focused on three main points. 1) lifestyle intervention. In obese patients, weight loss is a very effective strategy for the treatment of OSAS. In recent years, bariatric surgery procedures are used more frequently for treatment of severe obesity [6]. 2) CPAP (Continuous Positive Airway Pressure). Ventilation with continuous positive airway pressure is today the most effective treatment available for patients with OSAS since the positive pressure acts as a mechanic stent to the upper airway. The main problem associated with CPAP treatment is poor patient compliance due to its side effects [7 8]. 3) Surgery. Surgical therapies for the treatment of OSAS aim to improve airway patency, acting at the level of the specific site (or sites) of obstruction. Because the obstruction may localise to different levels along the upper airway, different surgical techniques have been developed: nasal, oropharynx, tongue and finally multi-level surgery [9-12].

OSAS has a multifactorial pathogenesis, and the main pathogenic mechanism is represented by collapse of the upper airway during sleep as a result of anatomical alterations (including congenital) or changes in neuromuscular control [13-15].

Materials and methods

The study was designed to compare outcomes of oxidative stress laboratory tests in three groups of subjects: 10 patients with obstructive sleep apnoea syndrome (OSAS) with AHI > 30; 10 patients suffering from snoring at night with AHI < 15; 10 control subjects with nasal respiratory impairment and AHI < 5. The inclusion criteria for the study groups were: a) age 18-60 years; b) no previous treatment for OSAS; c) snoring at night with AHI < 15; d) Apnoea-hypopnoea index (AHI) > 30 assessed with polysomnography; e) willingness to provide free and informed consent. The inclusion criteria of the control group were: a) age 18-60 years; b) nasal respiratory impairment (RAA with total nasal resistance > 0.25 Pa/cm^3/s at 150 Pa; c) non-allergic vasomotor rhinitis. The exclusion criteria were the same both for the study and control groups: a) smoking; b) subjects exposed to environmental irritants; c) no comorbidity that increases oxidative stress; d) diabetes; e) obesity; f) asthma-nasal polyposis; g) allergic rhinitis; h) hypertension.

The study protocol considered that both patients (subjects with OSAS and snoring) and controls were subjected to the following routine diagnostic tests: a) prick test for common aero-allergens b) otolaryngology visit with active anterior rhinomanometry, examination that evaluates nasal respiratory function by measuring nasal flow and resistance to the passage of air through the nasal passages; c) nasal endoscopy: examination of the nasal cavity and nasopharynx via an endoscope with flexible optics (2.4 mm diameter); d) polysomnography, which is reference technique for the study of sleep.

The starting point for the diagnosis of nasal respiratory impairment represented by the clinical history and physical examination. Physiologically, the nasal structure generates airflow resistance that can reach -50% of the total respiratory resistance. Therefore, the starting point for the diagnosis of nasal impairment is the Active Anterior Rhinomanometry (AAR) for physiologic estimation of nasal pressure and airflow during normal inspiration and expiration. It is considered the standard technique for a quantitative measure of nasal airflow resistance when performed according to the rules suggested by the Committee on Standardisation. Normal rates for total nasal resistance are < 0.25 Pa/cm^3/s at 150 Pa [16].

Both patients and controls were also subjected to the following extra-routine diagnostic tests: dosage of biomarkers of oxidative stress in the blood and urine; a) Non-Protein-Bound Iron (NPBI); b) Advanced Oxidation Protein Products (AOPP); c) plasmatic and urinary isoprostanes; d) thiol.

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

NPBI it is a low molecular mass iron form with no high-affinity binding to transferrin. Lowering of plasma pH (acidosis), as occurs during ischaemia, involves the activation of a release cascade of the iron and production of free radicals that can cause serious damage to cells [17 18].

Protein carbonyls are formed as a result of a variety of oxidative mechanisms and are sensitive indices of oxidative damage; such mechanisms include the action of Reactive Oxygen Species (ROS) of lipid oxidation products and reducing sugars or their oxidation products.

Isoprostanes are a series of prostaglandin-like compounds formed by direct ROS attack on arachidonic acid (AA) [19].

Thiols are a qualitatively significant component of the antioxidant plasma barrier. In fact, thiol groups (-SH) of the compounds present in plasma (for example, plasma pro-

teins, P-SH) oppose the propagation of radical chain reactions and neutralise the tissue-damaging action of hydroxyl radicals (HO*).

The statistical analysis is based on the comparison between the frequencies of events in a case-control study with independent data, in which the events considered are represented by the positivity to each of the biomarkers examined in the study. Therefore, once the positivity/negativity of each biomarker is defined according to a predetermined reference value (cut-off), cases and controls were compared for the frequencies of subjects positive and negative to the different biomarkers.

For cases we considered both patients with OSAS (AHI > 30) and patients with nocturnal snoring (AHI < 15). Next, statistical analysis was conducted separately for the two diseases, but using the same control subjects, consisting of patients suffering from non-allergic vasomotor rhinitis.

The goal of the study was to determine if the proportions of subjects negative and positive for each biomarker are significantly different between cases and controls.

Because of the difficulty of enrolment, the sample size was rather low, at 10 cases for each of the 2 pathologies and 10 control subjects, for a total of 30 patients.

Statistical analysis used Fisher's exact test or analysis of variance (ANOVA). The objective of the analysis was to determine if the difference between the means (variability between groups) is greater than the internal variability in each group (variability within groups) to verify if the variability provides information on the causes of the phenomena and their relationship. The ANOVA is used to assess the relative importance, in terms of statistical significance, of the different sources of variation (systematic or accidental); the principle underpinning the ANOVA is the relationship between two variances (the systematic and that due to error). This type of analysis is indicated when the populations are more than two (in our case, three). In addition, given the low sample size in our study, this is the only possible analysis that ensures an acceptable level of accuracy.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

	Nasal Stenosis	OSAS	Snoring	P value
Number of subjects	20	20	20	
Age	39	47.3	39,2	> 0.05
Sex (male/female)	13/7	12/8	12/8	> 0.05
BMI	23.54	25.62	25.46	> 0.05
AHI	1.3	36.04	10.18	< 0.0001

Results

The three groups were homogeneous for age and BMI (Table I). There were significant differences between the AHI values of the three groups of patients. No significant difference was found in the analysis with ANOVA test ($p > 0.05$) between the various levels of biomarkers of oxidative stress in the three populations.

Plasma isoprostanes were 60.64 ± 58.79 *vs* 48.44 ± 32.2 *vs* 66.19 ± 54.99 in patients with OSAS, patients with snoring and patients with nasal stenosis, respectively, $p > 0.005$ (Fig. 1). AOPP (Advanced Oxidation Protein Products) were 109.1 ± 33.0 *vs* 103 ± 31.7 *vs* 116.7 ± 29.24 in patients with OSAS, patients with snoring and patients with nasal stenosis, respectively, $p > 0.005$ (Fig. 2).

NPBI were 4.38 ± 5.65 *vs* 3.49 ± 3.38 *vs* 2.66 ± 2.56 in patients with OSAS, patients with snoring and patients with nasal stenosis, respectively, $p > 0.005$ (Fig. 3).

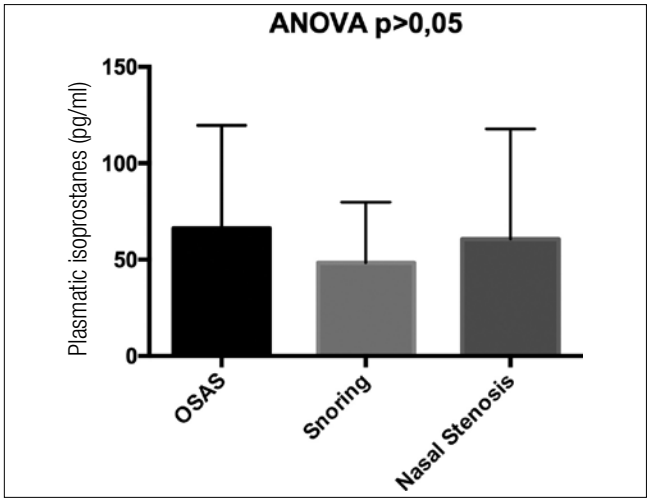

Fig. 1. Differences in the levels of plasma isoprostanes in patients with OSAS, patients with snoring and patients with nasal stenosis.

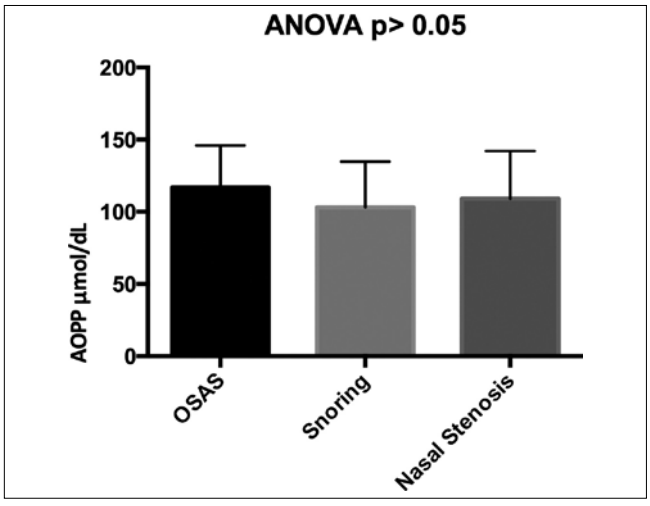

Fig. 2. Differences in levels of Advanced Oxidation Protein Products (AOPP) in patients with OSAS, patients with snoring and patients with nasal stenosis.

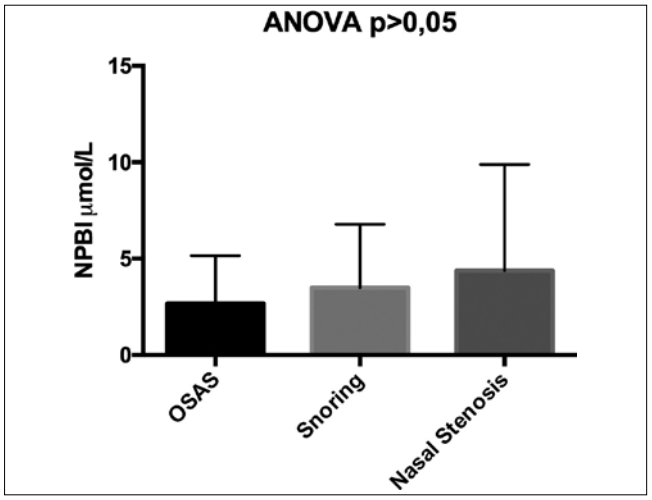

Fig. 3. Differences in the levels of Non-Protein-Bound Iron (NPBI) in patients with OSAS, patients with snoring and patients with nasal stenosis.

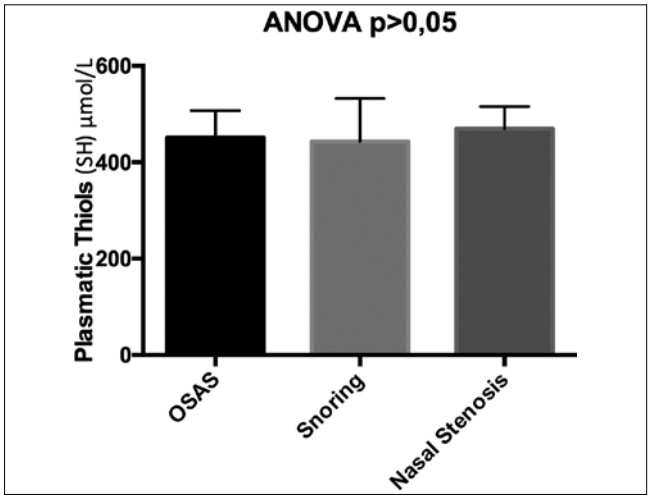

Fig. 4. Differences in the levels of plasma thiol groups in patients with OSAS, patients with snoring and patients with nasal stenosis.

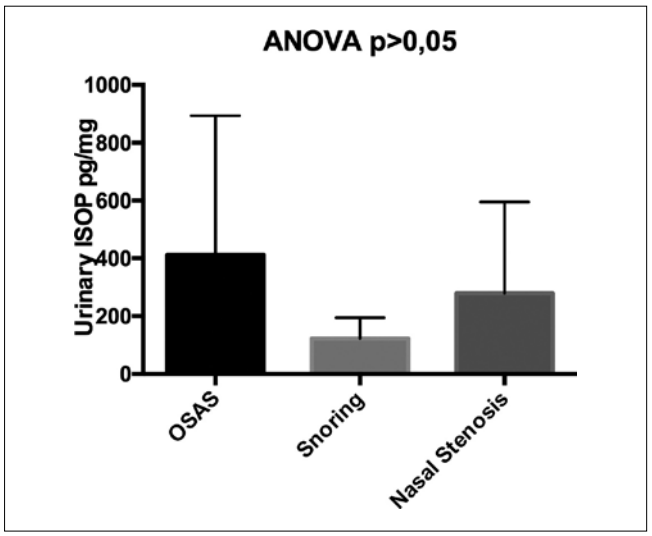

Fig. 5. Differences in levels of urinary isoprostanes in patients OSAS, patients with snoring and patients with nasal stenosis.

Plasma thiol groups were 451 ± 57 *vs* 443 ± 92 *vs* 470 ± 46.96 in patients with OSAS, patients with snoring and patients with nasal stenosis, respectively, $p > 0.005$ (Fig. 4).

Urinary isoprostanes were 412 ± 494 *vs* 137 ± 64 *vs* 311 ± 328.03 in patients with OSAS, patients with snoring and patients with nasal stenosis, respectively, $p > 0.005$ (Fig. 5).

Discussion

Although the primary site of obstruction in patients with OSAS has been identified in the oropharynx-hypopharynx, several studies, based on the induction of nasal obstruction in patients with OSAS, have revealed a positive and significant association between nasal obstruction and OSAS, although the exact nature of this relationship has not been fully clarified [20].

Several epidemiological studies have demonstrated a relationship between the measurement of the air flow at the level of the nose and snoring, but the attempt to find a linear correlation between obstruction, and therefore increase in the resistance, nasal and sleep apnoea has been less successful [21].

The nose is responsible for more than 50% of the total resistance of the upper airway and plays an important role in various physiological functions such as humidification, heating and air filtration. Among the areas of the nose of greater resistance to air flow, there are the vestibule and nasal valve, circumscribed by the alar cartilages, septum and inferior turbinates [22].

The nasal mucosa is a dynamic organ regulated by the autonomic nervous system. The condition of periodic congestion and nasal decongestion was called the "nasal cycle" of Heetderks. This cycle occurs in about 80% of the adult population. In patients with permanent unilateral nasal obstruction, the nasal cycle can contribute to a significant increase in the total resistance of the airways. In healthy individuals, the lateral decubitus increases congestion in the homolateral nasal cavity and reduces the resistance of the air flow in the contralateral nasal cavity. This does not occur due to a hydrostatic effect, but rather as a reflex caused by the asymmetrical pressure on the body. This reflex stops the nasal cycle. However, in the evaluation of both nasal cavities, significant changes were observed in the cross section when comparing supine and lateral decubitus [23].

To fully explain the relationship between the air flow, nasal obstruction and sleep apnoea, some dynamic theories of physics should be explained. Several mechanisms have been proposed to explain the role of the nose in the pathophysiology of OSAS and to clarify the relationship between air flow and nasal breathing during sleep. Such mechanisms include the so-called "Starling resistor model", the instability of the mouth breathing, nasal breathing reflex and the role of nitric oxide (NO) [24].

According to the model of Starling, the function of the upper airway can be represented as a hollow tube with a constriction in the vicinity of the entrance hole, which corresponds to the nostrils, and a posterior segment of folding, which corresponds to the oropharynx. This model predicts that the presence of an additional obstructive factor upstream (nose) generates a suction force and a negative intraluminal pressure downstream (oropharynx), with consequent collapse of the pharynx in predisposed individuals.

The closure of the mouth and correct dental occlusion stabilise the flow in the upper airway. When nasal resistance exceeds a certain level, there is a sort of air by-pass which leads to an oral breathing, responsible for a narrowing of the retrolingual space because of the retraction of the tongue, narrowing of the pharyngeal lumen, and an increase of the oscillations and vibration of the soft palate and the tissues surrounding the pharynx. This passage from nasal to oral breathing is physiologically disadvantageous for the individual, leading to an unstable breathing pattern [25].

A third factor is the nasal respiratory reflex. The experimental application of local anaesthetics in the nasal mucosa of healthy patients leads to a significant increase in obstructive and central apnoea, of the same magnitude as those reported in presence of complete nasal obstruction. Similar results from other experiments have confirmed that activation of the nasal receptor during nasal breathing has a direct positive effect on spontaneous ventilation, leading to greater respiratory rate at rest and minute ventilation. Oral breathing reduces the activation of these nasal receptors, with deactivation of the nasal respiratory reflex and reduction of spontaneous ventilation, which can trigger respiratory events in susceptible individuals with subclinical OSAS or aggravate episodes of apnoea.

Finally, nitric oxide (NO) appears to play a role in maintaining the patency of the upper airways, as a transmitter between the nose, pharyngeal muscles and lungs. NO is produced in significant amounts in the nose and paranasal sinuses and it has been shown (including in clinical practice) that is a potent pulmonary vasodilator, improving oxygenation, ventilation and perfusion. Since the total amount of inspired NO varies according to the nasal flow, it seems logical that a decrease in nasal breathing would result in the reduced transport of NO to the lungs and a reduction in blood oxygenation. NO also plays a role in maintaining muscle tone, in the regulation of neuromuscular pathways of the pharyngeal muscles, spontaneous breathing and in the regulation of sleep. In general, the role of NO in the regulation of nasal function in OSAS, although probably not significant, has not been completely understood [24].

Conclusions

Several studies in the literature have underlined the importance of oxidative stress in the pathogenesis of OSAS; our study, in particular, examined specific biomarkers of oxidative stress in order to define their role and clinical significance in patients with nasal respiratory failure. The levels of these biomarkers were higher in patients compared to the control group, although these differences, as mentioned, were not statistically significant. In light of these results, and considering that the study protocol excluded persons suffering from conditions that can increase oxidative stress or otherwise exposed to factors, such as smoking or particular environmental irritants, which may cause oxidative stress, the increase of those biomarkers in these individuals is probably associated with the underlying condition of nasal respiratory impairment; this shows how the nose, in addition to a mechanical commitment, can be functionally involved in the pathogenesis of these conditions, through the production of biomarkers of oxidative stress that can support an inflammatory state, at first regional and subsequently systemic. The very term nasal respiratory impairment aims to emphasise the wider and systemic importance of the nose in the genesis of oxidative stress damage, a condition that is known to be involved in long-term systemic damage related to OSAS. The common underlying pathological changes between OSAS and subjects with only nasal respiratory impairment may indicate the nose as a key factor in OSAS development or even identify a new category in OSAS syndrome (nasal-OSAS).

Our study may be useful to differentiate patients with mild OSAS from those with moderate or severe disease. It would thus be of value to increase the cohort size with the aim to clarify the role of these biomarkers even in diagnosis with the intent to limit, at least in some patients, the use of polysomnography, which is an expensive and laborious examination, for assessment of disease severity and evaluation of treatment response.

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Rhinology

High-definition video telescopic rhinoplasty

Video rinoplastica ad alta definizione

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SUMMARY

Optical magnification has become an essential tool in rhinologic practice, especially following the popularisation of endoscopic procedures for nasal sinus surgery. We describe the use of VITOM® technology in rhinoplasty, which to our knowledge has not been reported in the international literature to date. This approach to rhinoplasty markedly improves visualisation of the surgical field, thereby improving the understanding of the procedures and enhancing the teaching environment. Since VITOM® technology works by combining the telescope with a standard endoscopic setting, video telescopic rhinoplasty may be easily and inexpensively performed in any ENT department provided with this instrumentation.

KEY WORDS: Rhinoplasty • High definition • Technology

RIASSUNTO

L'ingrandimento ottico è diventato uno strumento essenziale nella pratica rinologica, soprattutto in seguito alla divulgazione delle procedure endoscopiche per la chirurgia dei seni paranasali. Descriviamo l'uso della tecnologia VITOM® nella rinoplastica, un utilizzo non ancora trattato nella letteratura internazionale fino a oggi. Questo approccio alla rinoplastica migliora notevolmente la visualizzazione del campo operatorio, agevolando così la comprensione delle procedure, anche a scopo didattico. Dal momento che la tecnologia VITOM® funziona combinando il telescopio con una telecamera standard, tale approccio alla rinoplastica può essere di facile introduzione senza costi aggiuntivi in qualsiasi reparto ORL dotato di tale strumentazione.

PAROLE CHIAVE: *Rinoplastica • Alta definizione • Tecnologia*

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Introduction

Optical magnification has become an essential tool in rhinologic practice, especially following the popularisation of endoscopic procedures for nasal sinus surgery. In recent years, endoscopic applications have also been reported in the field of rhinoseptoplasty [1]. In these cases, the main drawback is that surgical manoeuvres are limited due to the fact that only one hand is operative, since the other is used to handle the endoscope; hence, a three or four hand approach is usually required. For this reason, we developed, in the ENT department of Imola Hospital, a video telescopic approach to rhinoplasty that allows for high quality definition images, maintaining at the same time the use of two operating hands. This approach is based on a specially designed scope that is attached to a high definition digital camera and displayed on a HD video monitor. VITOM® (Karl Storz Endoscopy, Tuttlingen, Germany) is an emerging technology aimed at providing enhanced visualisation of open procedures requiring magnification to all members of the operating team, useful for documenting uncommon cases, as well as for training and educational purposes. A few applications of this system have already been reported in neurosurgery, paediatric surgery, laryngology and gynaecology [2-5]. In this preliminary study, we describe the use of VITOM® technology in rhinoplasty, which to our knowledge has not been reported in the international literature to date.

Clinical techniques and technologies

VITOM® is a 0° telescope with a diameter of 10 mm and a length of 10 cm, called exoscope, since it is positioned outside the body. The camera head is mounted on the proximal end of the telescope, illumination is provided by a cold light fountain Xenon 300 and images are displayed on a HD monitor. The device is placed in front of and above the patient's head, about 25 cm from the operating field and attached to a ceiling-mounted supporting arm. The limited dimension of the system does not encumber the operating field; it is comfortable for the operator to use who can choose to stay in a sitting or standing position. When the exoscope is positioned, details of lesions are anatomically observed on the monitor as fine vascularisation; cartilage and bone irregularities, as well as scars, are perfectly visible (Fig. 1). In order to follow the flow of the operation,

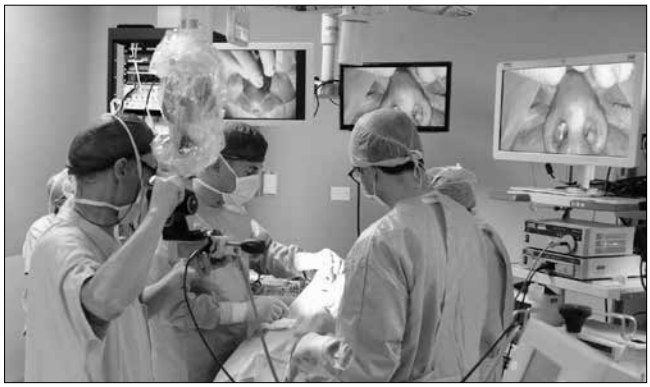

Fig. 1. The supporting arm combined with a 3 CCD camera and VITOM.

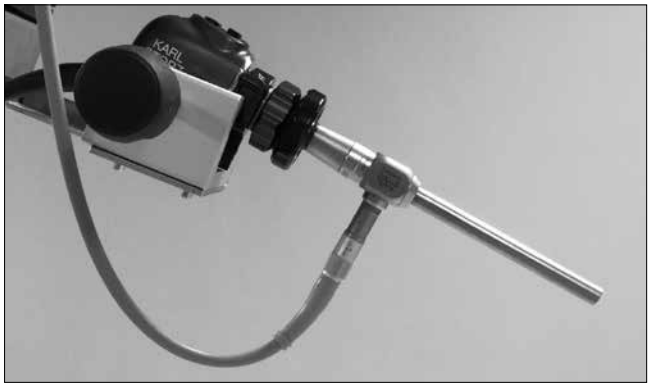

Fig. 2. Typical setting for high-definition video telescopic rhinoplasty.

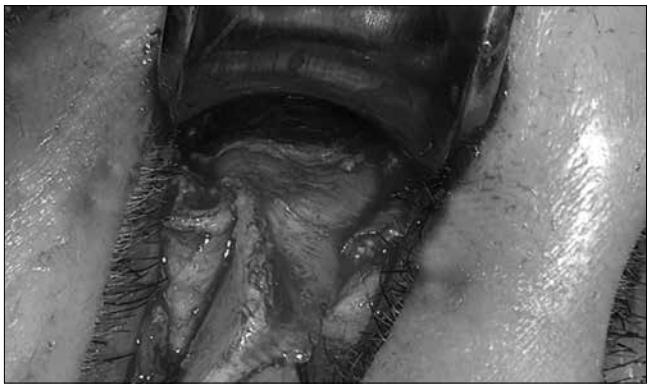

Fig. 3. Exposition of the cartilaginous vault through hemitransfixion incision.

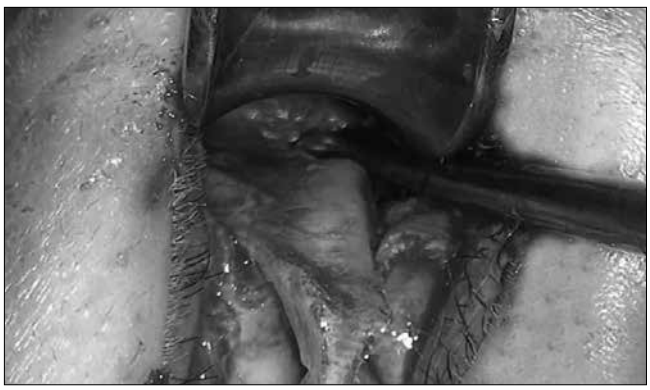

Fig. 4. Subperiosteal elevation of the dorsum.

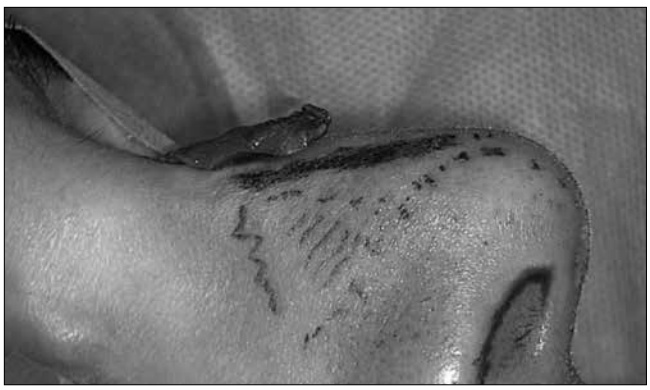

Fig. 5. Resected bony hump.

the supporting device can be rotated in the three planes of space allowing for fine movements of the scope (Figs. 2-4). In this way, the operating field may be always centered on the screen even in case of inevitable movements of anatomical structures during operating manoeuvers such as elevations of the tunnels or osteotomies. This assessment is provided by the nurse or by the second operator.

Discussion

The rapid development in technology, during the last decade, has led to the use of new instruments in the field of rhinoplasty. Technological innovations, even if they cannot substitute traditional surgery, play a role in supporting consolidated techniques and sometimes become real alternatives. This apparent revolution in rhinoplasty is documented by the publication of numerous articles on the use of new instrumentations with a comparison of risks and benefits vs. traditional surgery. VITOM® technology has been used in neurosurgery as an alternative to the operating microscope. VITOM® dramatically has improved surgeon comfort and ease of operating by permitting the surgeon to stand upright and in a comfortable position and avoid the need to extend the arm or assume an awkward position commonly encountered when using the microscope for these approaches. Birck et al. [2] in a recent study of five patients undergoing infratentorial supracerebellar approaches for pineal region lesions, confirmed that surgery with the VITOM® was more comfortable than with the operating microscope. Frykman PK et al. [3] found that VITOM® provides excellent visualisation of paediatric operations with improved surgeon comfort and may serve as a substitute for loupes. Carlucci et al. [4] have recently proposed this technology as an alternative to the operating microscope in endoscopic laryngeal surgery. Vercellino et al. [5] compared the quality of loop excision using a colposcope using the VITOM® system and concluded that VITOM® is a safe and reliable system that can achieve results comparable to those obtained with conventional colposcopy. The potential advantages include patient and

trainee involvement in examination, decision making and documentation.

Conclusions

VITOM® technology markedly improves the visualisation during interventions, thereby improving the understanding of the procedures and enhancing the teaching environment. The system is associated with a computer that is capable of capturing images and video sequences, and storing data. This enable trainees to review the sequence of critical steps of operations to prepare for future cases. The VITOM® permits a natural head and neck position, allowing the surgeon to operate from a comfortable posture without increased operative time or complications. The improved comfort levels may translate into safer and more accurate surgeries. Since VITOM® works by combining the telescope with a standard endoscopic setting, video telescopic rhinoplasty may be easily and inexpensively performed in any ENT department equipped with this instrumentation.

Acknowledgements

This study was approved by the Institutional Review Board at Imola Hospital.

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Otology

3D curved multiplanar cone beam CT reconstruction for intracochlear position assessment of straight electrodes array. A temporal bone and clinical study

Ricostruzione multiplanare 3D di immagini cone beam per l'idenficazione della posizione degli impianti cocleari. Studio su ossi temporali e pazienti impiantati

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SUMMARY

A retrospective review of post-op cone beam CT (CBCT) of 8 adult patients and 14 fresh temporal bones that underwent cochlear implantation with straight flexible electrodes array was performed to determine if the position of a long and flexible electrodes array within the cochlear scalae could be reliably assessed with CBCT. An oto-radiologist and two otologists examined the images and assessed the electrodes position. The temporal bone specimens underwent histological analysis for confirm the exact position. The position of the electrodes was rated as scala tympani, scala vestibule, or intermediate position for the electrodes at 180°, 360° and for the apical electrode. In the patient group, for the electrodes at 180° all observers agreed for scala tympani position except for 1 evaluation, while a discrepancy in 3 patients both for the 360° and for the apical electrode assessment were found. In five temporal bones the evaluations were in discrepancy for the 180° electrode, while at 360° a disagreement between raters on the scalar positioning was seen in six temporal bones. A higher discrepancy between was found in assessment of the scalar position of the apical electrode (average pairwise agreement 45.4%, Fleiss k = 0.13). A good concordance was found between the histological results and the consensus between raters for the electrodes in the basal turn, while low agreement (Cohen's k 0.31, pairwise agreement 50%) was found in the identification of the apical electrode position confirming the difficulty to correct identify the electrode position in the second cochlear turn in temporal bones. In conclusion, CBCT is a reliable radiologic exam to correctly evaluate the position of a lateral wall flexible array in implanted patients using the proposed imaging reconstruction method, while some artefacts impede exact evaluation of the position of the apical electrode in temporal bone and other radiological techniques should be preferred in ex vivo studies.

KEY WORDS: Cone Beam CT • Cochlear implants • Electrode position • Histology • Temporal bone

RIASSUNTO

Questo studio riporta un'analisi retrospettica delle immagini cone beam CT effettuate su 8 pazienti adulti sottoposti ad impianto cochleare MedEl flex 28 e su 14 ossi temporali impiantati con lo stesso tipo di array portaelettrodi. Lo scopo dello studio é di determinare l'affidabilità della metodica cone beam CT nella valutazione della posizione intracocleare degli elettrodi in impianti che si posizionano lungo la parete laterale del lume cocleare, quindi non perimodiolari la cui posizione é più facilmente identificabile. Un otoradiologo e due otologi hanno analizzato le immagini e assegnato la posizione per ciascun elettrodo localizzato nella regione dei 180° e dei 360° del primo giro cocleare e per l'elettrodo apicale scegliendo tra scala timpanica, vestibulare o posizione intermedia L'analisi istologica ha successivamente confermato l'esatta posizione negli ossi temporali. Nel gruppo dei pazienti per l'elettrodo a 180° i tre esperti concordavano sulla posizione in scala timpanica in tutti eccetto un paziente, mentre una discordanza nella valutazione era presente in 3 pazienti per gli elettrodi a 360° e per gli elettrodi apicali. Negli ossi temporali in 5 casi era presente una discordanza per l'elettrodo a 180°, mentre a 360° sei valutazioni erano discordanti tra i valutatori. Una disdcordanza tra le valutazioni più elevata veniva trovata per la la posizione dell'elettrodo apicale (concordanza valutatori 45.4%, Fleiss k = 0,13). Un buon grado di concordanza veniva trovato tra i risultati istologici e le valutazioni tra i valutatori per gli elettrodi localizzati nel giro basale; un grado più basso esisteva per la posizione degli elettrodi apicali (concordanza valutatori 50%, Cohen's k = 0,31) confermando la difficoltà nella corretta valutazione della posizione degli elettrodi nella regione più apicale negli ossi temporali. In conclusione, le immagini cone beam postoperatorie analizzate con la metodica della ricostruzione multiplanare 3D rappresentano una metodica affidabile per lo studio della posizione intracocleare degli elettrodi a posizionamento laterale nei pazienti impiantati. La corretta identificazione del posizionamento dell'elettrodo piu apicale risulta difficile su osso temporale per la presenza di un artefatto più importante o per la minore resistenza delle strutture della parete laterale della coclea (legamento spirale, membrane basilare) nel preparato istologico (osso temporale fresco/congelato) che è responsabile di un maggior numero di traslocazioni dalla rampa timpanica alla rampa vestibolare e di localizzazioni intermedie più difficilmente interpretabili.

PAROLE CHIAVE: *Cone beam CT • Impianti cocleari • Posizione elettrodi • Istologia*

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Introduction

The indications for cochlear implantation during the last decades have extended including not only the severe-profound bilateral deafness, but also sensorineural hearing loss involving only medium-high frequencies or single sided deafness. The so-called soft or minimally invasive surgery and its principles are regularly applied to the standard procedures in cochlear implantation not only in hearing preservation surgeries. In this context, pre- and post-operative imaging have gained importance both for planning of surgery, choice of kind and length of the electrode array to be implanted and correct evaluation of the position of the implanted array [1]. The use of cone beam CT (CBCT) in otology has increased during the last years with a lower dose cross-sectional technique for visualising bony structures in the ear [2] providing a better resolution than multislice helical CT for the bone structure with strong density contrast [3]. Several studies reported the reliability to assess the scalar position of electrodes array using CBCT in isolated temporal bones [4-8] or whole cadaveric heads [9], but the possibility to apply these results in a real clinical situation on cochlear implanted patients has not been studied in detail. The scalar position of the electrodes in implanted patients was analysed in a study including precurved and straight arrays implanted in 61 ears [10] but the reliability of the radiological exam was not reported. Moreover, the results might change in function of the different implanted arrays (i.e. perimodiolar or straight array). Studies in cochlear implanted temporal bones reported excellent reliability in scalar localisation of precurved perimodiolar array [4 7 8], while for slim straight electrodes the position assessment still remains difficult in some cases [6 8]. Diogo et al. [9] reported a lower degree of cochlear implant (CI) metal artefacts in the images of the whole head in comparison with the same isolated temporal bones that present reduced soft-tissue absorption of radiation, but it was still difficult to evaluate the precise location in the more apical regions of the cochlea. Another issue to take in account is the artefact due to the movement of the patient, which is completely absent in studies on cadaveric specimens, considering the duration of the CBCT exam longer than other radiological imaging techniques of the ear. The aim of this study was to validate the 3-dimensional curved multiplanar reconstruction in CBCT images as a method for the assessment of long straight cochlear implant electrodes array scalar position in implanted adult patients and compare the results with a temporal bone radio-histologic study using the same electrode array and surgical technique.

Materials and methods

The scalar position of two electrodes located in the basal turn of the cochlea and a third located in the second turn in temporal bones and in adult implanted patients was assessed by an expert otoradiologist and two otologists by reviewing the CBCT reconstruction images. The scalar position and the ratings of the temporal specimens were successively confirmed by histological analysis. Each step is described in detail below.

Temporal bones

Fourteen fresh temporal bones (seven left and seven right from the same subjects) were prepared with a simple mastoidectomy and posterior tympanotomy. The MedEl flex 28 arrays (Innsbruck, Austria) used for this study were provided by the manufacturer. The temporal bone was fixed to an in-house made temporal bone holder and the electrodes arrays were inserted through an extended round window approach using an in-house made motorised insertion tool [11]. This tool comprised a rotary actuator (RE10CLL, MDP, Miribel, France) connected to a threaded screw that pushed a blunt pin into an insertion tube loading the array. The tool was held steady by a flexible arm. The actuator speed was controlled via laboratory power supply and set at 0.8 mm/sec. The round window was irrigated with saline serum and sodium hyaluronate (Healon, Abbott Medical Optics, Abbott Park, Illinois, USA) was applied before CI insertion. A cone beam CT (CBCT) scan (NewTom 5G, QR s.r.l. Verona, Italy) was performed on the temporal bone specimens after the CI insertion.

Patients

Eight adult patients (nine ears) cochlear implanted with MedEl flex 28 arrays in the cochlear implant program at a tertiary referral centre where prospectively enrolled in a study and accepted to receive a CBCT postoperatively. All patients were operated by the same experienced CI surgeon (EDS) via standard retroauricular approach followed by mastoidectomy and posterior tympanotomy, and extended round window insertion of the array. The patients were discharged at day 1 postsurgery and received a CBCT scan one to three months postimplantation; the activation of the CI was performed between 3 and 4 weeks postoperative. Patients signed a written informed consent, study was approved by the local IRB and performed in accordance with the principles of the 1983 Declaration of Helsinki.

Imaging

The NewTom 5G CBCT scanner (NewTom, Verona, Italy) was used both for patients and temporal bones using the same setting. The system setup used a 200 x 25 mm flat panel detector at 650 mm from the radiation source. One 360° rotation of the x-ray tube took 36 sec. The tube voltage was 110 kV, with a 19-mA charge at the terminals. Total filtrations were 2 mm, with a pitch of 125 µm; this corresponded to a field view of 12 x 7.5 cm diameter. The

images were isometric voxel rendered from the 125 μm sections.

Scalar position assessment

Two otologists and an expert otoradiologist reviewed the CBCT images and assessed the position of the electrode array within the cochlea. The DICOM (Digital Imaging and Communications in Medicine) data were analysed by Osirix program (Osirix v 4.0 64-bit; Pixmeo Sarl, Bernex, Switzerland). This program allowed the realisation of multiplanar reconstructions for the evaluation of the scalar position of the arrays was used for the measurements of the cochlear sizes. The largest cochlear diameter (distance A) going from the centre of the round window membrane to the opposite lateral wall [12] as well as the angular depth of insertion, were calculated on a plane perpendicular to the modiolus axis and coplanar to the basal turn [13]. The round window was considered as the 0° reference angle in accordance with the consensus of cochlear coordinates [14]. The reconstruction plane for the evaluation of the electrodes position was the midmodiolar plane obtained with the curved multiplanar reconstruction (3D curved MPR viewer in Osirix®). This plane was defined as a 3D Bezier path along the electrodes array. Once the path is defined by means of the selection of all the single electrodes the array is straightened and visible in the curved MPR viewer window. In this window the cochlear lumen and the electrodes array can be easily visualised in a dynamic series of midmodiolar section of the cochlea (Fig. 1, for a demonstration video see: *http://www.youtube.com/watch?v=aHDE1SNiooU*). The raters assigned the localisation scala tympani, scala vestibuli or intermediate position for each of the electrodes positioned at 180°, 360° and for the apical electrode both for the temporal bone implanted specimens and for implanted patients.

Histological procedures

Immediately after its insertion in temporal bones the electrode array was fixed with cyanoacrylate glue to the round window region to avoid any displacement during the successive steps. Cochlea was removed from the temporal bone and was fixed in 10% buffered formalin. The specimen was successively dehydrated in graded alcohol and casted in methyl methacrylate resin (10% Polyethylene Glycol 400, 20% Technovit 7200 VLC, Heraeus Kultzer Gmbh, Germany; 70% methylmethacrylate). The specimen was sawed (Leica SP 1660 Saw Microtome, Nussloch GmbH Germany, sawing speed 3) perpendicularly to the basal turn passing through the round window and the images under white light microscope were obtained for the two parts. The half cochlea was successively grinded to visualize the apical electrode if the first cut did not allow its visualisation.

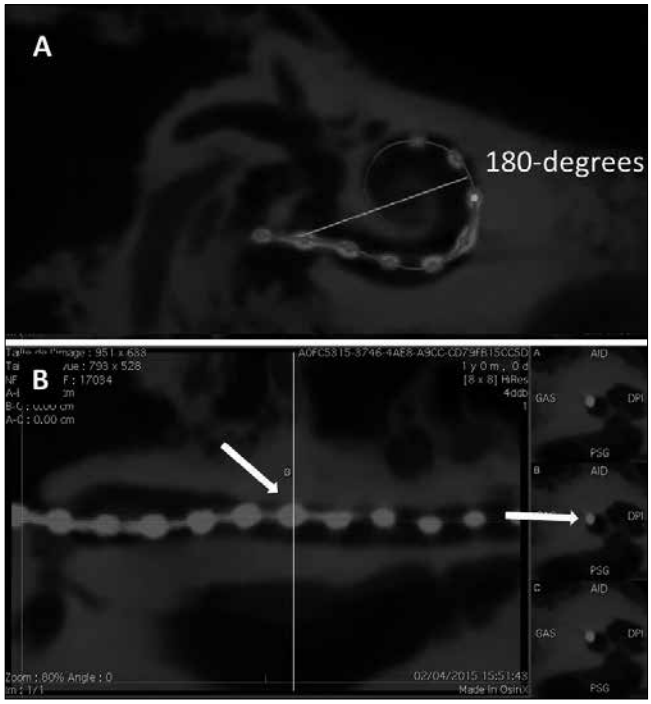

Fig. 1. 3D curved multiplanar reconstruction (MPR) of the electrode array in a temporal bone. A. The electrodes were first selected with the 3D MPR tool defining a 3D Bezier path connecting all the electrodes togheter. B. This function permitted to straighten the electrode array and follow it along its trajectory in the cochlear lumen in a dinamic way accross a continuos series of midmodiolar reconstruction of the cochlea (MPR views on the right down panels). The arrow shows the translocated electrode. The between electrodes part of the array has a very limited metallic artifact thus the assessment of the electrode position is easier in this portion of the array.

Statistical analysis

Results are reported as means ± SD. Inter-rater reliability was calculated using the Fleiss' kappa for three raters and the Cohen's kappa for two raters as appropriate. The averaged pairwise percent agreement among raters for each of the 3 examined electrodes was calculated. "R" statistical software (http://www.r-project.org) was used for statistical analysis.

Results

Table I reports pre- and postoperative cochlear measurement in patients and temporal bones. The mean distances A were 9 ± 0.1 mm and 9 ± 0.07 mm in patients and temporal bones respectively. Among patients, the full insertion of the array was achieved in six ears (angular depth of insertion 498 ± 17 degrees), while in three ears a partial insertion was found. In temporal bones, 8 arrays were fully inserted (angular depth of insertion 464 ± 20 degrees).

Electrode position in implanted patients

There was an overall high agreement within raters for the

Table I. Preoperative and postoperative measurements in temporal bones and patients.

Patient	Distance A (mm)	Angular depth of insertion	Inserted electrodes
1	9.77	480	12
2	9.16	533	12
3	8.93	512	12
4R	8.82	422	12
4L	8.62	507	12
5	9.35	407	10
6	8.91	403	11
7	8.92	461	11
8	9.1	535	12
Temporal bones			
1R	9.07	440	12
1L	9.49	400	12
2R	8.67	270	8
2L	8.85	369	10
3R	9.52	365	11
3L	9.46	387	11
4R	9.22	412	12
4L	8.77	520	12
5R	9.13	472	12
5R	9.02	514	12
6R	8.45	404	11
6L	8.42	529	11
7R	9.48	522	12
7L	9.52	434	12

assessment of the electrodes position within the cochlea (Fig 2). The intracochlear position for the electrode at 180° in the implanted patients showed a great concordance among raters with only 1 evaluation in disagreement, one evaluator rated as inferior an electrode rated as intermediate for the other two evaluators (average pairwise agreement 92.5%, Fleiss k = 0.46). For the electrode at 360°, three evaluations were not in agreement between raters (average pairwise agreement 88.8%, Fleiss k = 0.38). For the position of the apical electrode the raters were more discordant with 4 evaluations in disagreement (average pairwise agreement 70.3%, Fleiss k = 0.35). A consensus on the position of the electrodes from the three raters was obtained after rereading the images and two arrays resulted translocated, both in the second turn (Fig. 2 B-C).

Electrodes position in temporal bones

In temporal bones, the rate of agreement was similar to that found in implanted patients for the electrode at 180° (average pairwise agreement 71.5%, Fleiss k = 0.48) and for the electrode at 360° (average pairwise agreement 61.9%, Fleiss k = 0.35) (Fig. 3). In five temporal bones, the evaluations were in discrepancy for the 180° electrode, while at 360° disagreement on the rating of the scalar positioning was in six temporal bones. A higher discrepancy between rater was found in assessment of the scalar position of the apical electrode (average pairwise agreement 45.4%, Fleiss k = 0.13). In one temporal bone, the raters were in total disagreement with the same apical electrode assessed either as SV, ST or intermediate position (Fig 4). A collective statement on the position of the electrodes from the three raters was obtained after rereading the images; this statement was compared to the histological results.

The histological analysis confirmed the localisation of the electrodes and showed a translocation between scala tympani and scala vestibuli in 6 temporal bones (42%). All the translocation occurred between 150° and 180°. A good concordance was found between the histological results and the consensus between raters for the electrodes at 180° (Cohen's k = 0.54, pairwise agreement 78.7%) and 360° (Cohen's k = 0.71, pairwise agreement 85.7%). The identification of the apical electrode position after the consensus between raters was poor (Cohen's k = 0.31, pairwise agreement 50%), highlighting the difficulty to correctly identify the electrode position in the second cochlear turn in temporal bones.

Discussion

In this study, the CBCT scan was confirmed to be a reliable radiological technique for assessment of intracochle-

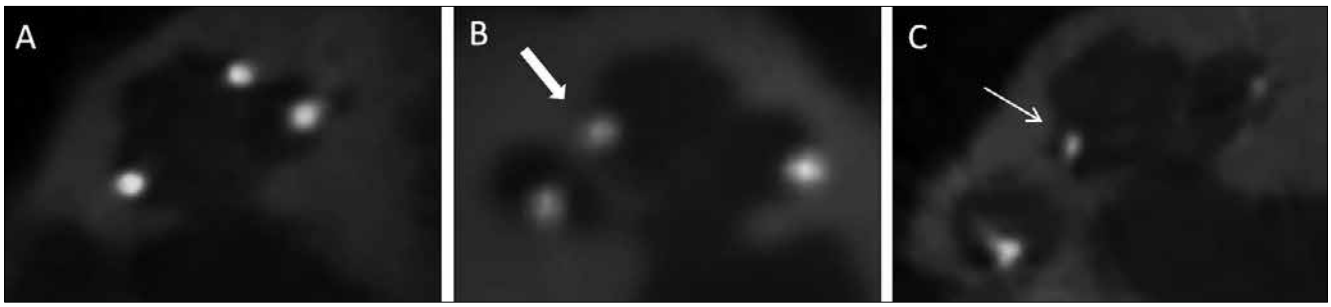

Fig. 2. Cone beam CT in cochlear implanted patients. In A, all raters indicated the three electrodes in scala tympani position. The apical electrode in B (thick arrow) was indicated by all raters as translocated. In C the apical electrode (thin arrow) was considered in intermediate position by two raters and translocated by one, and finally considered as a traumatic insertion after consensus.

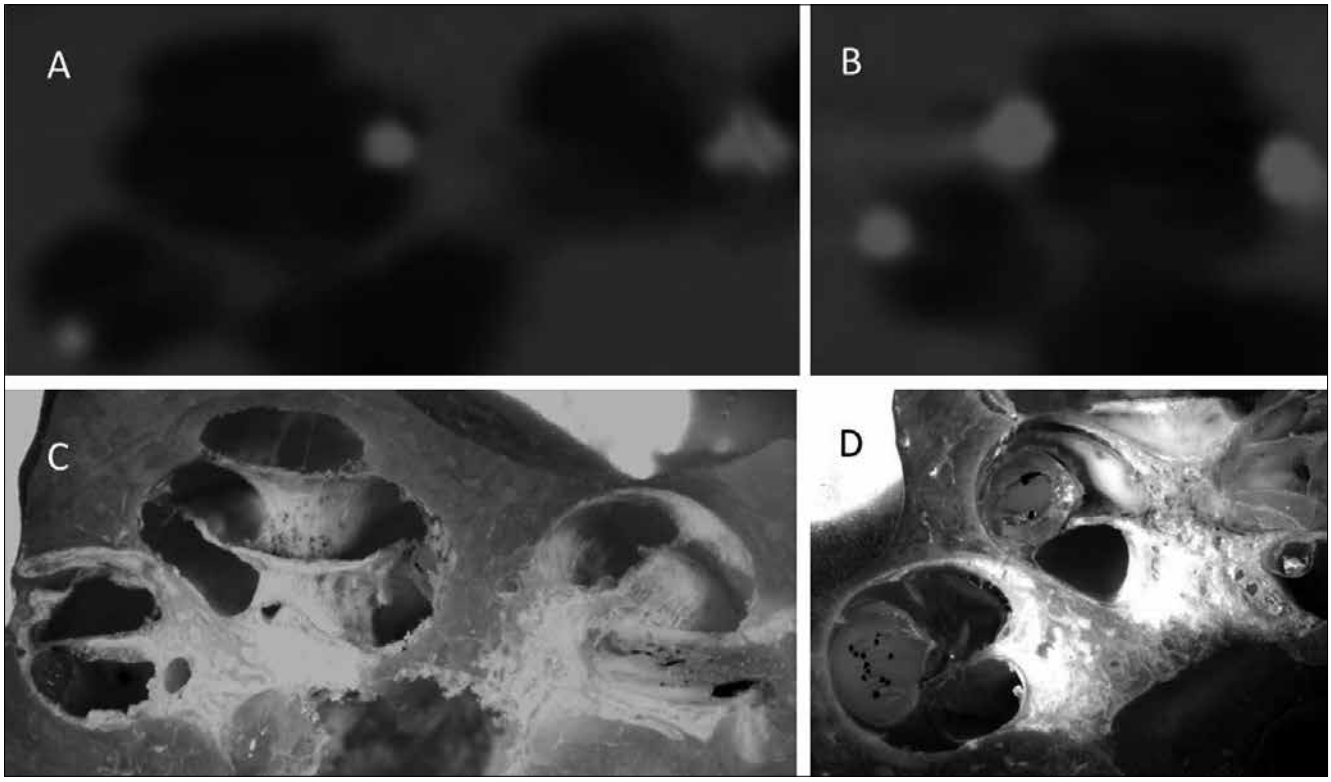

Fig. 3. Electrode array in the scala tympani position (left) and in scala vestibuli (right) in temporal bone specimen. In these examples a full concordance on the electrode localisation on CBCT images (A, B) was obtained among the three raters and after the histological analysis that confirmed the electrode position (C, D).

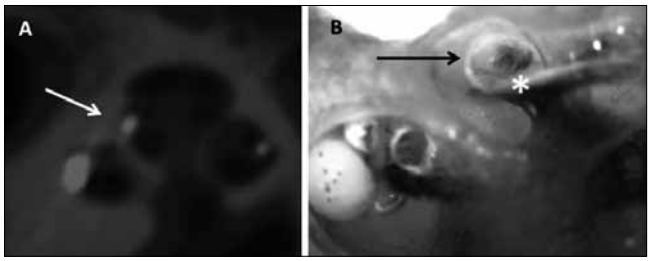

Fig. 4. Difficulty in the assessment of the apical electrode. A. In this specimen the raters assessed the electrode (white arrow) either as scala vestibuli, scala tympani or intermediate position. B. The histology confirmed the translocation (black arrow). * Osseous spiral lamina.

ar location of straight and flexible electrodes array in adult implanted patients. In temporal bones, the assessment of the more apical electrodes was more difficult than in patients. The 3-dimensional curved multiplanar reconstruction as a method to evaluate the electrode position helped to standardise the methodological technique among the raters and was a reliable, rapid and easy tool for intracochlear identification of electrode positions.

Several studies investigated the reliability of the CBCT on the scalar position assessment of cochlear implants. For precurved arrays, Marx et al. [7] reported a high sensitivity (100%) and specificity (90%) in scalar assessment localisation of the array), while in another study the exact position was reviewed correctly by CBCT in 11 of 13 cases (85%) [4]. The position of a precurved electrode array was reported to be correctly assessed in the oblique sagittal plane [15] or using midmodiolar reconstruction even in multislice CT, with a radioanatomic correlation of 0.94 (0.89-0.98) after the consensus of two raters [16].

The identification of electrode position could be different using different kind of electrodes array and could result easier for precurved electrodes. Indeed, the perimodiolar position of the electrode array is more consistent than that of straight electrodes [8]. The presence of osseous spiral lamina clearly divides the medial portion of the cochlear lumen into two compartments and the electrode is firmly held by this bony structure either in a lower or higher position i.e., tympanic or vestibular ramp. In contrast, the lateral wall of the cochlear lumen has a rounded shape and the spiral ligament being less resistant is deformed or bended by the cochlear array that can assume an intermediate position close to the midline of the cochlear lumen even without damaging the basilar membrane or the spiral ligament, thus assuming a position that sometimes is difficult to be identified. For this reason, we adopted a third "intermediate" position for array location assessment that was never used in other studies. This third position increased the number of possible choices for the raters

Table II. Interrater agreement for electrode positioning assessment in patients and temporal bones.

	Electrode		
	180°	360°	Apical
	% Patients		
Mean pairwise agreement	92.5%	88.8%	70.3%
Fleiss' kappa	0.46	0.38	0.35
	Temporal bones		
Mean pairwise agreement	71.5%	61.9%	45.4%
Fleiss' kappa	0.48	0.35	0.13

making more difficult a high percentage of inter-observer agreement.

Inter-observer agreement for the imaging characteristics (scala implanted, number of contacts inserted into the cochlea and presence of kinking within the electrode array) was 100% among three reviewers in a temporal bone study where a straight electrode was implanted [5]. In this study, the authors only evaluated the presence or not of the translocation of the array and did not evaluate the location of three electrodes with three possible positions as in our study, and the implant used was different, which might also explain the different findings. Boyer et al. [10] found a very low translocation rate (3%) and high agreement between raters for the correct intracochlear localisation of the MEDEL flex electrodes; even in that study, the methodology for the evaluation of the position of the electrode was different to that used in our study and the results are not completely comparable.

Studies performed in temporal bones that evaluated the same electrodes array used in the present study reported a reliable postoperative control of the intracochlear position in the basal turn, but difficulties in the evaluation of the localisation in the medial and apical turns [6]. Diogo et al. [9] found a higher metallic artefact of the electrodes in temporal bone in comparison to the whole head, probably due to the lower absorption of radiation by soft tissue determining greater surface radiation of the metal, and thus a greater artefact. The amount of the metallic artefact was not considered in this study, but the different results in the identification of the apical electrodes between temporal bones and patients may be caused by the different intensity of the artefact. Indeed, CBCT has few artefacts, but is not an artefact-free method [6].

A possible drawback of the CBCT for analysis of submillimetre structures could be represented by the longer duration of the exam (18-36 sec) in comparison with MSCT (4-6 sec) that may result in possible artefacts due to the head movement [17]. Moreover, the higher the spatial resolution, the smaller the movement necessary to move the patient's structures out of the ''correct'' position. Nevertheless, in the eight CBCT images obtained from patients we did not observed any artefacts. The cone beam machine used in this study allowed the lying down position, and the use of a head holder helped to avoid artefacts.

Conclusions

With this study we validated a technique to identify the intracochlear position of straight electrodes array in the cone beam CT images using the 3D multiplanar reconstruction method. CBCT is confirmed to be a reliable imaging technique for the identification of scalar translocation even for straight and flexible arrays in adult implanted patients. In temporal bones, probably due to higher metallic artefacts, the position of the electrodes in the apical region of the cochlea were more difficultly assessed. For this reason, we suggest the use of histologic analysis for confirmation of electrode position in temporal bone studies.

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Audiology

Development of a novel Italian speech-in-noise test using a roving-level adaptive method: adult population-based normative data

Sviluppo di un innovativo test audiometrico vocale nel rumore in italiano che utilizza un metodo "roving-level" adattivo: dati normativi basati sulla popolazione adulta

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SUMMARY

In recent years the increasing development of hearing devices has led to a critical analysis of the standard methods employed to evaluate hearing function. Being too far from reality, conventional investigation of hearing loss based on pure-tone threshold audiometry and on mono/disyllabic word lists, presented in quiet conditions, has been shown to be inadequate. A speech-in-noise test using a roving-level adaptive method employs target and competing signals varying in level in order to reproduce everyday life speaking conditions and explore a more complete sound range. Up to now, only few roving-level adaptive tests have been published in the literature. We conducted a roving-level adaptive test in healthy Italian adults to produce new normative data on a language of Latin origin.

KEY WORDS: Speech-in-noise test • Roving-level adaptive test

RIASSUNTO

Negli ultimi anni, il crescente sviluppo di dispositivi acustici ha condotto a un'analisi critica dei metodi standard che sono stati impiegati per valutare la funzione uditiva. Gli esami audiologici tradizionali, basati sulla soglia audiometrica tonale e sulle liste di parole mono/bisillabiche nel silenzio, si sono nel tempo dimostrati inadeguati perché troppo distanti dalla realtà. Un test audiometrico vocale nel rumore, che utilizza un metodo "roving-level" adattivo, adopera segnali target e segnali competitivi modificabili con lo scopo di riprodurre le condizioni di eloquio della vita quotidiana, quindi esplorare un più ampio range uditivo. A oggi, solamente pochi test "roving-level" adattivi sono disponibili in letteratura. Gli autori hanno condotto un test "roving-level" adattivo in adulti italiani sani, al fine di ottenere nuovi dati normativi in una lingua di origine latina.

PAROLE CHIAVE: *Audiometria vocale nel rumore • Test "roving-level" adattivo*

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Introduction

In recent years the increasing development of hearing devices has led to a critical analysis of the standard methods employed to evaluate the hearing function. It is renowned that two main factors influence the outcomes of hearing aids: type and severity of hearing impairment and environmental acoustic characteristics. Clinical practice outlines that aid patients who are apparently homogeneous for anatomical and audiological features may report different hearing perception under the same fitting conditions [1 2]. Moreover, speech intelligibility involves complex perceptual processes that emphasise the need for audiological tests reflecting reality as much as possible [3]. Normal-hearing listeners show a natural and exceptional ability to select the target voice in a background of competing voices [4]. Being too far from reality, conventional investigation of hearing loss based on pure-tone thresholds and on mono/disyllabic word lists, presented in quiet conditions, has been shown to be inadequate [5]. In fact, the international diffusion of sentence-type speech-in-noise tests has witnessed the emerging necessity of a more accurate audiological assessment [3 6-16]. These tests have been conceived to explore speech communication in noisy settings at a fixed or varied signal-to-noise ratio (SNR) as an expression of two basic philosophies. Fixed SNR tests are easily adopted and are administered to assess performances at a specific SNR level established before the examination. The listener's abilities are evaluated in terms of percent intelligibility, thus showing meaningful results

not only for the clinician, but for the tested patient as well. Nevertheless, outcomes are influenced by the presentation levels of the target speech and the noise of competition. When clinicians select SNR parameters, the measured results not only depend on subjective hearing, but also on the fixed SNR. For example, a really challenging or an easy SNR may lead, respectively, to under- or overestimate the status of the patient [17 18]. The introduction of adaptive tests has overcome the described limitations by reversing the investigation perspective. No longer the tester, but the performance of the patient himself determines the SNR conditions. In particular, either the target signal level (e.g. speech) or the competing signal level (e.g. noise) increases/decreases by a set amount, according to the correct answers given by the patient [17 18]. The test starts with an easy SNR level, and subsequently the SNR conditions vary depending on the accuracy of the preceding response until the subject correctly repeats 50% of speech signals. The SNR presentation level, which is necessary for a listener to correctly recognise the speech messages 50% of the time, defines the speech reception threshold (SRT). In comparison to the fixed SNR tests, outcomes provided by the adaptive ones are expressed in decibels instead of percent intelligibility and show a reduced risk of bias arising from the limits of the method used [3]. Many adaptive tests have been developed and all are characterised by a varied SNR, but typically either the target signal or the competing signal is fixed [3 6-14 16 19]. It is self-evident that real life is much different: rarely do the speech signals or noise signals change while the other one remains unmodified, but all vary independently. Furthermore, each hearing device performs differently at different sound pressure levels in relation with its own specific input dynamic range. The effects of environmental noise and technical features of hearing aids on speech intelligibility should be detected as much as possible by hearing tests. A roving-level adaptive test employs target and competing signals varying in level in order to reproduce everyday life speaking conditions and to explore a more complete sound range. In particular, speech material is presented at a roving level and the noise is adapted depending on the number of correct words answered by the tester to obtain patients' SRT. Up to now, only few roving-level adaptive tests have been published [20]. The aim of our study was to introduce a novel Italian roving-level adaptive test to yield normative data in healthy Italian adults.

Materials and methods

We evaluated 50 native normal hearing Italian individuals (25 men and 25 women), aged between 23 and 50 years, showing a pure tone average (PTA) lower than 20 dB HL at the frequencies of 500, 1000, 2000 and 4000 Hz. To carry out the test, we employed the sentences developed by Cutugno, Prosser and Turrini [21], selecting only those made up of 5 words, establishing 6 lists piloted for equal difficulty and composed of 20 sentences each. Basically, some specific criteria were adopted for the construction of the sentence: choice of the lexical items, morphosyntactic structures and phrasal constituents order. The aim was to develop simple sentences that are easily understood by persons of different age groups, regional origins and cultural level. Therefore, enigmatic and abstract terms (e.g. solitude, height) or uncommon words (e.g. plausible) were avoided. With regard to the verb tenses, their usage frequency was taken into account, as well as their morphophonological structure in relation to perceptibility criteria. Considering the decreasing frequency, the most commonly used indicative verb tenses were: simple present, present perfect, imperfect tense, simple future and simple past. Sentences were short and understandable, made up of a number of syllables between 9 and 13 (Table I). Lists 1, 2 and 3 were used for the test (overall 60 sentences), while lists 4, 5 and 6 for the re-test (overall 60 sentences). The noise of competition applied was a cocktail party background. Sentences were separated by a 10-second pause while the noise of competition remained uninterrupted. The exam was performed in a soundproof booth; each sound was sent through a loudspeaker set in front of the subject, at eye-level and 1.2-meter distance. Each subject could reply by means of a microphone without any comments related to the correct answer. The procedure consisted of 60 sentences presented with a noise of competition. It lasted 14 minutes and was administered twice with a 30-minute break, in order to obtain an average result. Overall, each subject was submitted to a test and a re-test, and was instructed to repeat aloud completely or partially all the sentences heard or understood. During the test, speech material was randomly roved: sentences were casually organised in 20 groups of three sentences (overall 60 sentences) and each of the three sentences composing a triplet was casually presented at 55 dB HL, 65 dB HL, or 75 dB HL. Within each triplet all three levels were used once, the test started at +10 dB SNR with an easy competing signal and the noise level ("cocktail party" background) changed according to Table II and Table III. In particular, SNR varied across presentation levels and the SNR level was reduced progressively depending on the accuracy of the preceding response, until a conversion point that allowed calculation of the SRT value at which the subject was able to understand 50% of the sentences. The noise variation index ranged ± 5 dB HL from the 1st to the 5th triplet and ranged ± 2 dB HL from the 6th to the 20th triplet. The three presentation levels of the signal (speech) and the SNR conditions were selected to represent the range of speech levels that may typically be encountered in everyday life. In particular, 55 dB HL corresponds to a comfortable conversational speech level, while 75 dB HL represents the limit within which a proper hearing aid fitting can result beneficial in terms of auditory perception (hearing loss > 75 dB represents the selection criteria for cochlear implantation).

Table I. Lists of sentences used in the adaptive speech in noise test.

List 1*	List 2*	List 3*
È rimasto solo al mondo	È scappato ieri dalla prigione	La nave scivola sulle onde
Ieri hai comprato poco latte	Milano ha un clima freddo	L'aquilone vola alto nel cielo
Francesca è incinta di nuovo	Gli ospiti sono arrivati già	Certamente ha viaggiato in treno
L'acqua bolle a cento gradi	Il turista passeggia nel museo	Il ristorante ha cambiato gestione
Il giornale contiene cattive notizie	Il detersivo rovina la lana	Gli operai lavorano nel cantiere
La macchina funzionava con difficoltà	Le stelle brillano in cielo	Il fulmine ha colpito l'albero
Il tassista guida con prudenza	Oggi hanno camminato per ore	Tremava ancora per la paura
Stamattina sono andato in banca	Domani balleremo fino a tardi	I genitori sono molto apprensivi
Il recinto separa i giardini	La minestra bolliva in pentola	Prepariamo la colazione alla mamma
L'auto sbanda sempre in curva	Laura diceva bugie a tutti	Il ponte passava sul fiume
Il cameriere porterà le pizze	La signora leggeva un libro	Il vino invecchia nelle botti
Il mare era molto agitato	Le scale sono molto faticose	Il direttore convoca la riunione
Il compito è molto difficile	La partita inizierà in anticipo	Laura insegnava inglese ai bambini
Le ciliegie maturano a giugno	Il camino riscalda la stanza	Ha amato una sola donna
Il meccanico aggiusterà il motore	Il venditore mostra la merce	Il coro cantava una canzone
La ragazza aveva lunghi capelli	Dopo cena guardo la televisione	La ballerina danza con grazia
L'arrosto è cotto a puntino	A destra troverai un portone	Il parlamento discute le leggi
All'alba spegnevano le luci	La povera moglie piangeva sempre	Spesso mangiamo con troppa fretta
Pagherò il conto alla cassa	Il nostro amore sarà eterno	I cittadini pagano le tasse
Il nonno dormiva due ore	Il sole tramonta a occidente	Il fritto misto è pesante
List 4#	**List 5#**	**List 6#**
Il treno partirà in ritardo	Porteremo un regalo alla nonna	Porteremo un regalo alla nonna
Il vincitore avrà un premio	I guanti proteggono le mani	I pompieri spensero il fuoco
Domani andrò da mia madre	Le forbici tagliano la carta	Il frigorifero conserva i cibi
Il mese è iniziato oggi	Ha cercato lavoro a lungo	L'aeroplano volava fra le nuvole
Il vecchio era molto stanco	La posta arriva in ritardo	Il chirurgo ha operato d'urgenza
Manderemo un mazzo di fiori	Queste scarpe sono molto strette	L'acqua bolle a cento gradi
Lo spettacolo comincerà alle nove	La mamma abbraccia il bambino	Oggi hanno camminato per ore
Consegnerò il pacco alla posta	La fermata dista cento metri	L'aquilone vola alto in cielo
I genitori mantengono i figli	L'autobus partirà tra cinque minuti	Il treno partirà in ritardo
Il cameriere apparecchia il tavolo	Denuncia il furto alla polizia	Ha cercato lavoro a lungo
Il professore spiegava con chiarezza	Sveniva spesso per il caldo	Il recinto separa i giardini
Voglio un gelato alla panna	Le ragazze seguono la moda	Milano ha un clima freddo
Lo studente prepara gli esami	Le rose sbocciano a maggio	Il fritto misto è pesante
I tifosi vanno allo stadio	Dopo pranzo faccio un pisolino	La fermata dista cento metri
I pompieri spensero il fuoco	Il circo diverte i bambini	Il vecchio era molto stanco
La porta è appena socchiusa	La signora comprò una pelliccia	Il compito è molto difficile
Il cinema era molto affollato	La droga uccide molti giovani	Dopo cena guardo la televisione
Il tempo è passato velocemente	I pellegrini iniziarono il viaggio	Ha amato una sola donna
Il bidello sorveglia gli alunni	Il padre era molto malato	Le ragazze seguono la moda
Il postino consegnò la posta	Le patate crescono sotto terra	Il cameriere apparecchia il tavolo

** Sentences used during the test*

 # Sentences used during the re-test

Table II. Noise variation index from the 1st to the 5th triplet of sentences.

NUMBER OF CORRECT WORDS ANSWERED	NOISE VARIATION INDEX*
0	-5 dB HL
1	-3 dB HL
2	-1dB HL
3	+1 dB HL
4	+3 dB HL
5	+5 dB HL

**Noise variation index changed depending on the number of correct words answered (all employed sentences were composed of 5 words). For example, if the number of correct words answered was 0, then the noise presentation level of the next triplet was decreased of 5 dB HL.*

Table III. Noise variation index from the 6th to the 20th triplet of sentences.

NUMBER OF CORRECT WORDS ANSWERED	NOISE VARIATION INDEX*
0	-2 dB HL
1	-1 dB HL
2	0 dB HL
3	0 dB HL
4	+1 dB HL
5	+2 dB HL

**Noise variation index changed depending on the number of correct words answered (all employed sentences were made up of 5 words). For example, if the number of correct words answered was 0, then the noise presentation level of the next triplet was decreased of 2 dB HL.*

TRIPLET	SPEECH	NOISE	ANSWER	CORRECTION	SPEECH	NOISE	ANSWER	CORRECTION	SPEECH	NOISE	ANSWER	CORRECTION
1	0,1534911 55	45		-5	0,790503 65	55		-5	0,121552 75	65		-5
2	0,6865855 75	60		-5	0,65103 55	40		-5	0,160476 65	50		-5
3	0,0085683 75	55		-5	0,055349 55	35		-5	0,042109 65	45		-5
4	0,7952336 55	30		-5	0,93916 75	50		-5	0,445441 65	40		-5
5	0,7115584 75	45		-5	0,469677 55	25		-5	0,499572 65	35		-5

Fig. 1. Calculation sheet example from the 1st to the 5th triplet.
SPEECH: it refers to the speech material presentation intensities (55 dB HL, 65 dB HL, 75 dB HL)
NOISE: it provides the noise of competition level that changes depending on the accuracy of the preceding response
ANSWER: it represents the number of correct words answered
CORRECTION: it provides the noise variation index that is applied to the next corresponding noise level.

The technological setting was composed of two loudspeakers, a clinical audiometer Biomedica-Amplifon Interacoustics AC 40® and a power amplifier Interacoustics AP70®. To facilitate administration of the test, an automated computer controlled procedure was developed using an Excel calculation sheet (Fig. 1).

Statistical analysis

To determine the repeatability and consistency of SRTs measured over time, test-retest reliability was calculated, using Spearman`s Rho-correlation. To verify whether age has an influence on the overall measured mean SRT value, univariate analysis of variance (ANOVA) was performed.

Results

The mean results obtained through the test and re-test were calculated considering each employed intensity; subsequently, overall test + re-test outcomes were analysed (Table IV). The overall mean SRT value was -13.3 dB HL (standard deviation: 0.64; minimum value -14.6 dB HL; maximum value -12.1 dB HL) and was calculated at the end of both test and re-test, with respect to all SRT values for each intensity examined. The low standard deviation measured (close to 0) suggested that the mean SRT value was highly indicative of each listener's performance. Statistical analysis showed a significant relationship between the overall mean SRT of the test and the overall mean SRT of the re-test ($r = 0.496$; $p < 0.001$), confirming the repeatability and consistency of SRTs measured over time. However, when comparing the different levels between the test and the re-test, a significant relationship between the test and the re-test was found at 65 dB HL ($r = 0.366$; $p = 0.009$) and at 75 dB HL ($r = 0.362$; $p = 0.010$), but no significant relationship was found at 55 dB HL between the test and re-test ($r = 0.176$; $p = 0.223$). The results of univariate ANOVA showed that age significantly affected overall mean SRT ($F = 4.500$; $p = 0.039$) (Fig. 2).

Table IV. SRT Results.

	TEST				RE-TEST				TEST & RE-TEST*			
	SRT 55 dB HL	SRT 65 dB HL	SRT 75 dB HL	OVERALL TEST SRT	SRT 55 dB HL	SRT 65 dB HL	SRT 75 dB HL	OVERALL RETEST SRT	SRT 55 dB HL	SRT 65 dB HL	SRT 75 dB HL	OVERALL TEST-RETEST SRT
MEAN	-13.69	-14.97	-9.56	-12.74	-14.78	-16.00	-10.72	-13.84	-14.24	-15.49	-10.14	-13.29
MEDIAN	-13.65	-15.10	-9.58	-12.57	-14.90	-16.05	-10.75	-13.75	-14.20	-15.48	-10.10	-13.24
STANDARD DEVIATION	1.07	0.98	0.88	0.75	0.97	0.88	1.12	0.72	0.80	0.76	0.80	0.64
MINIMUN	-15.90	-17.15	-11.75	-14.38	-17.10	-17.65	-13.90	-15.45	-16.38	-17.28	-11.80	-14.61
MAXIMUM	-11.50	-12.85	-7.65	-11.65	-12.50	-13.10	-6.95	-12.58	-12.53	-13.43	-7.65	-12.13

** Final mean outcomes were calculated at the end of both test and re-test, with respect to all SRT values for each intensity examined.*

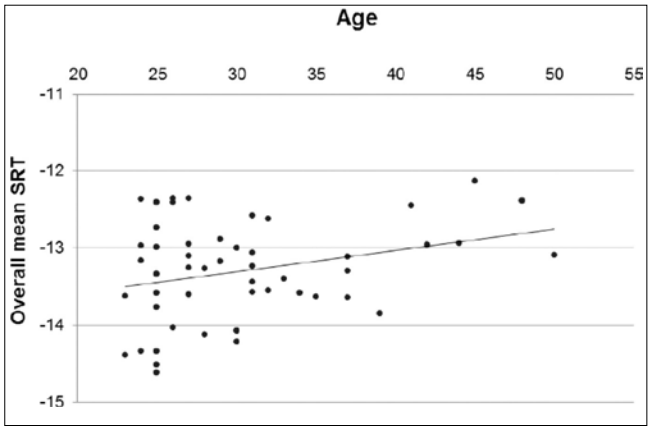

Fig. 2. Age influence on the overall mean SRT values.

Discussion

Over the past decades, advances in audiological research have improved to such an extent that they have considerably and truly changed patients' lives. Furthermore, the evolution of traditional hearing aids and the birth of total or semi-implantable hearing devices have led the clinician to re-evaluate the approach to clinical practice. The necessity to understand whether a certain patient could benefit from the current hearing technology, as well as quantitatively determining the functional improvement levels, has promoted the integration of better hearing diagnostic methods for the purpose of further exploration of the complexity of the auditory system functions. Being too far from reality, conventional investigations of hearing loss based on pure-tone threshold audiometry and on mono/disyllabic word lists presented in quiet conditions have been shown to be inadequate [5]. The lack of information derived from traditional test battery is typically relevant if we consider the "cocktail-party" problem, hence the loss of SNR score in patients with hearing disorders [4 22]. In particular, the loss of spectro-temporal acoustic resolution related to cochlear hair cell dysfunctions determines a reduction of speech intelligibility that is easily detectable in noisy environments [23]. Sentence-type speech-in-noise tests have been conceived to explore speech communication in noise at a fixed or varied SNR and currently have become part of the international basic audiological assessment [3 6-14 16 19]. Moreover, to avoid floor and ceiling effects that may influence the validity of results for fixed SNR tests, adaptive speech-in-noise tests have been applied [17 18]. The SNR score at which 50% of the sentences are repeated correctly (SRT) represents an alternative of percent intelligibility to measure speech intelligibility when the intensity level of either the speech or the noise is varied. Speech items are composed of daily sentences as the mono/disyllabic words lack information redundancy, which may not be adequate to trigger the signal processing features of hearing technologies [9]. The literature reports several studies that have been carried out to point out the real benefits related to hearing device rehabilitation. Bovo et al. [15] evaluated the effect of bone-anchored hearing aid simulators in subjects with acquired unilateral sensorineural hearing loss. In particular, the authors tested the SRT changes in relation to different speech source positions, with a background of diffuse noise. Outcomes highlighted a lack of efficacy of bone-anchored hearing aid simulators in discriminating speech sources located in different acoustic settings. Beltrame et al. [24] showed the auditory results of the Vibrant Soundbridge coupled with the round windows in patients with mixed hearing loss. The measurements of aided SRT in background noise of 55 and 70 dB SPL documented only a slight increase compared with normal reference data.

Among adaptive sentence-type speech-in-noise tests cited in literature, the introduction of roving-level tests may represent an additional and useful tool in speech intelligibility investigation [20]. It is notorious that each hearing device performs differently at different sound pressure levels in relation with its own specific input dynamic range. Furthermore, in everyday speaking conditions speech and noise signals change independently of one another. A roving-level adaptive test employs target and competing signals varying in level to mimic everyday life speaking conditions and to explore a more complete sound range. Haumann et al. recently analysed a relative homogeneous sample of 55 cochlear implant (CI) users with different CI systems submitted to fixed and roving-level adaptive level tests. When a fixed-level method was applied, the groups using different devices reached very similar outcomes. On the other hand, remarkable changes were recorded employing roving-level adaptive tests that are able to detect the effects of CI processors on everyday speech perception [20]. In our personal experience, the roving condition concerned three different speech material intensities (55 dB HL, 65 dB HL, 75 dB HL) and as a consequence three different mean SRT values were analysed. Speech messages were randomly roved while noise level varied depending on the accuracy of the preceding response until the subject repeated 50% of the speech signal correctly. The final mean value was -13.3 dB HL (standard deviation: 0.64; minimum value -14.6 dB HL; maximum value -12.1 dB HL) and was calculated at the end of both the test and re-test, with respect to all SRT values for each intensity examined. In particular, the population repeated 50% of the presented speech material correctly, when the confounding signal was overcoming the speech message of 13.3 dB HL. It is plausible that a normal hearing Italian adult submitted to the test obtains a result ranging from -14.6 dB HL to -12.1 dB HL, although Italian listeners with hearing impairment will probably show a SRT score worse than -12.1dB HL. As far as the literature is concerned, each of the 50 subjects evaluated achieved better results during the re-test probably due to the cognitive

gain achieved in the preceding test [25]. Statistical analysis showed a significant relationship between the overall mean SRT of the test and the overall mean SRT of the re-test ($r = 0.496$; $p < 0.001$), confirming the repeatability and consistency of SRTs measured over time. However, when comparing the different levels examined between the test and re-test, no significant relationship was found at 55 dB HL between the test and re-test ($r = 0.176$; $p = 0.223$). This result may be explained by a strong learning effect (much better performances during the re-test in comparison with the test) during the presentation level of 55 dB HL. The results of the univariate ANOVA showed that age significantly affected the overall mean SRT, despite the fact that this study did not include elderly subjects (age ranged between 23 and 50 years). Younger subjects achieved meaningfully better SRTs values demonstrating age as a relevant influencing factor on the hearing processing under conditions of noise (Fig. 2). Current literature describes the development of many adaptive SNR tests and their comparison is actually challenging because of several procedural aspects that may influence outcomes [25]:

- different language adoption with respect to a large number of speech audiological parameters: number of syllables/words, word frequency, sentence redundancy, understandable or meaningless sentences, list length, pronunciation, breaks between sentences;
- different noise presentation modes: noise masking type, continuous/fluctuating/synchronous noise delivering;
- different environment parameters: booth dimensions, type of soundproofing, use of headphones/speakers, number of speakers, distance between patient and speaker;
- different adaptive SNR test features: starting SNR presentation level, fixed element (speech or noise?), intensity of the fixed signal, adaptive method (signal change criteria according to tester answers), re-test execution, use of visual aids;
- different sample enrollment; number of listeners, nationality, age, education level, comorbidities.

In fact, despite the rather innovative aspects of adaptive speech intelligibility tests, they still have some limits:

- the extreme procedural variability does not allow an international comparison of SRT outcomes;
- paediatric age, education level and native language may highly influence correct performance of the test;
- the need for a relatively long execution time may condition the feasibility of adaptive tests during daily clinical practice.

Conclusions

We introduced a novel Italian roving-level adaptive test to obtain normative data in healthy Italian adults. The adoption of roving-level tests may represent an additional and useful tool in speech intelligibility investigation to quantify the actual benefits related to hearing rehabilitation devices (which hearing device? when to prescribe it?) in acoustic conditions simulating everyday life.

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Audiology

Cochlear implantation in post-lingually deafened adults and elderly patients: analysis of audiometric and speech perception outcomes during the first year of use

L'impianto cocleare nei soggetti ipoacusici postverbali adulti e anziani: analisi dei risultati audiometrici e logopedici nel primo anno di utilizzo

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SUMMARY

The aim of this study was to analyse audiometric and speech perception outcomes after cochlear implantation (CI) in adult and elderly patients in the first year post-CI activation. We evaluated 42 subjects who underwent CI at the Otorhinolaryngological Clinic of Padua Hospital. The subjects enrolled were post-lingually deafened patients who were unilaterally implanted for bilateral, severe-to-profound hearing loss. The overall sample was divided into three groups according to the age at the time of implantation: group A (35-49 years), group B (50-64 years) and group C (≥ 65 years). The subjects were assessed, both before and after surgery (at months 1, 3, 6 and 12), using pure tone audiometry, speech audiometry and speech perception tests and the CAP questionnaire. Statistical analysis of outcomes was using a Student's t-test for paired data. In all study groups a significant improvement was demonstrated in auditory performance examinations post-CI compared to the pre-operative scores. All subjects in all age groups obtained significant improvements in PTA scores before surgery and post-CI activation. Comparison of PTA values among the three age groups did not reveal any significant difference. Considerable improvement was obtained even in the speech audiometry thresholds in all groups at follow-up, with no significant differences between groups. The speech perception examination and CAP questionnaire showed good progress in all study groups, although younger patients tended to achieve more complex categories than older ones. In conclusion, CI is an effective treatment for severe-to-profound hearing loss with no significant differences in auditory performances between older and younger CI recipients. Even if somewhat slower, subjects older than 65 reached good performance and therefore are good candidates for a cochlear implant.

KEY WORDS: Cochlear implant • Hearing loss • Adults • Elderly • Speech perception

RIASSUNTO

Questo studio è volto alla valutazione degli outcomes audiometrici e logopedici dei pazienti anziani portatori di impianto cocleare durante il primo anno di utilizzo del dispositivo. Sono stati valutati 42 pazienti impiantati tra marzo 2010 e settembre 2014 presso l'UO ORL dell'Azienda Ospedaliera Universitaria di Padova. Sono stati inclusi nello studio pazienti affetti da sordità bilaterale postlinguale di grado severo-profondo impiantati unilateralmente. I soggetti sono stati divisi in tre gruppi in base all'epoca della chirurgia: 14 soggetti con impianto fra i 35 e i 49 anni, 14 fra i 50 e i 64 anni e 14 impiantati a un'età superiore di 65 anni. Tutti i pazienti sono stati valutati prima e dopo la chirurgia (a 1, 3, 6 e 12 mesi di follow-up) attraverso l'esecuzione di: audiometria tonale, audiometria vocale, test logopedici e somministrazione del questionario delle categorie percettive (CAP). L'analisi statistica è stata effettuata attraverso il Student's t-test. La totalità dei soggetti nei tre gruppi hanno dimostrato significativi miglioramenti all'audiometria tonale e vocale ai controlli post chirurgici rispetto alle performance ottenute precedentemente all'impianto. In particolare si sono verificati miglioramenti della soglia audiometrica media (PTA) senza differenze statisticamente significative tra i tre gruppi. risultati ottenuti nei test logopedici e dalla somministrazione del CAP hanno dimostrato evidenti miglioramenti in tutti i tre gruppi in studio. Abbiamo riscontrato, però, che i soggetti più giovani hanno raggiunto maggiori punteggi ai controlli post impianto rispetto a quelli più anziani. Concludendo, possiamo affermare che l'impianto cocleare è un trattamento efficace per soggetti affetti da ipoacusia severa-profonda senza differenze significative nelle performance audiologiche e logopediche in relazione all'età di impianto. Anche se più lentamente, i pazienti impiantati dopo i 65 anni di età raggiungono performance ottimali e possono essere ritenuti dei candidati ottimali all'intervento.

PAROLE CHIAVE: *Impianto cocleare • Ipoacusia • Adulti • Anziani • Percezione linguistica*

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Introduction

Hearing loss is one of the most frequent chronic disabilities with important medical and psychosocial implications. Recently, the World Health Organization (WHO) has estimated that approximately 15% of the world's adult population has some degree of hearing loss (HL) and 5.3% (360 million) suffer from disabling hearing loss (DHL) [1]. The ISTAT (Italian National Institute of Statistics) estimated that 12% (8 million) of Italians have hearing disorders and 1.2% suffer from severe to profound deafness [2]. The literature is in agreement that the magnitude of hearing impairment increases with age: according to WHO data, approximately one-third of the world's population above 65 years is affected by DHL. The number of people suffering from hearing disorders is also growing due to the increasing global population and extended life expectancies.

The interest on hearing impairment should expand beyond the epidemiological data to take into account the broad psychophysical and social factors that are likely to be impacted by hearing loss and which might lead to a significant decrease in quality of life [3 4].

In a longitudinal study by Li et al., it was shown that there is a significant association between HL and depression among US adults of all ages, and in particular the prevalence of depression is higher in woman aged 70 years or older [3].

A recent paper by Amieva et al. reported that HL has a significant impact on cognitive decline [4]. In particular, self-reported HL in individuals ≥ 65 years is related to a lower Mini-Mental-State Examination (MMSE) score and major cognitive decline over 25-years of follow-up. Furthermore, a difference in cognitive decline was observed between individuals with HL not using hearing aids (HA) and a control group, while there was no difference between deaf subjects with HA and controls.

When hearing loss progresses beyond the ability of a HA, cochlear implantation (CI) has been shown to be an effective treatment for individuals with severe-to-profound hearing loss.

In adults, CI is often used in case of sudden hearing loss after middle ear surgery [5] or deafness after acoustic or vestibular neuroma surgery [6].

It has been demonstrated that CI improves speech perception performances as well as the quality of life in both younger and older patients [7-11]. In a retrospective study, Lachowska et al. reported that the age of patients at the time of CI should not be a negative predictive factor of outcomes [7]. They demonstrated a significant improvement in pure-tone audiometry, speech audiometry, speech perception tests and in quality of life in the post-lingually deafened elderly (aged ≥ 65 years) assessed during a period of 2 years post-CI.

Castiglione et al. also showed the benefits of CI among patients ≥ 65 years, showing significant gains in hearing threshold and speech perception outcomes between pre-operative and post-operative assessment [8].

In agreement, in a retrospective study by Park et al., it was shown that age should not be a limitation for CI candidacy [9]. The authors reported that speech recognition and quality of life after CI improve significantly and to similar extents in all age groups examined (age < 50, 50-65, > 65).

In a work by Mancini et al., no significant differences were seen in speech perception outcome (both in quiet and in noise) between young and old patients with CI [10]. Even though younger individuals tended to achieve better scores, as far as the quality of life is concerned, both groups achieved a good level of personal autonomy after CI, even if patients > 65 were more satisfied with the use of CI.

Moreover, Hilly et al. showed that the audiometric outcome and quality of life of elderly CI patients remains stable over time (over a minimum of 5 years follow-up) [11].

The aim of our study was to assess audiometric and speech perception outcomes in implanted elderly subjects during the first year of CI use. In particular, we evaluated the difference between younger and older CI recipients (< 65 years and over 65 years) and the age of implantation as a predictive factor of CI efficacy.

Materials and methods

Patients

The medical records of 42 patients undergoing cochlear implant surgery from March 2010 to September 2014 at the ENT Clinic of University Hospital of Padua (Italy) were retrospectively examined in accordance with Italian privacy and sensible data laws (D.lgs 196/03) and to the ENT Clinic of University Hospital of Padua internal policies.

Patient selection criteria are reported in Table I. The 42 patients were divided into three groups according to the

Table I. Inclusion and exclusion selection criteria.

Inclusion criteria	Exclusion criteria
Post-lingual HL	Prelingual HL
Bilateral HL	Monolateral HL
Severe-to-profound HL	Mild-moderate HL
Time of implantation: > 35 years	Presence of neurodegenerative disorders or other pathologies associated with HL
Absence of neurodegenerative disorders or other pathologies associated with HL	Non-use of HA before implantation
Use of HA before implantation	Bilateral CI
Unilateral CI	Primary language: other languages
Primary language: Italian	Absence of speech and language therapy after CI
Speech and language therapy after CI	

Table II. Patient characteristics by group.

	Group A	Group B	Group C
No. of patients			
Female	9	8	6
Male	5	6	8
Total	14	14	14
Age	45.42 ± 5.41	61.42 ± 3.05	74.07 ± 4.15
CI age	42.28 ± 5.39	58.85 ± 3.32	71.14 ± 3.91
HL years	27.07 ± 11.22	28.14 ± 14.28	27 ± 14.42
Aetiology			
Otosclerosis	4	3	6
Cholesteatoma	3	3	1
Acoustic trauma	1	0	0
Unknown	6	8	7
Side implanted			
Right ear	10	7	6
Left ear	4	7	8
CI brand			
MED-EL	10	6	6
Cochlear	1	1	3
Advanced bionics	3	7	5

Age: mean age at present time expressed in years ± standard deviation (SD); CI age: mean age at the time of implantation expressed in years ± SD; HL years: mean duration of learing loss at the time of implantation expressed in years ± SD.

age of implantation: group A (35-49 years), group B (50-64 years) and group C (≥ 65years). Each group was composed of 14 subjects with monolateral cochlear implant (in worse ear) and contralateral HA. Patient characteristics are summarised in Table II.

Study design

Speech and auditory tests were performed pre- and post-surgery and follow-up evaluations were done after 1, 3, 6 and 12 months. Pre-surgical examinations were performed both with and without HA. Patients were assessed in quiet and without lip-reading using a set of audiometric and speech perception tests.

The auditory benefit of the CI was assessed in terms of free-field hearing threshold by measuring the Pure-Tone Average (PTA) expressed in decibels (dB HL) and corresponds to the average air-tonal threshold at the frequencies 500, 1000 and 2000 Hz.

The speech audiometry test was performed by of the Speech Audiometry, Disyllabic Words for Adults test [12], allowing us to verify the Speech Detection Threshold (SDT), the Speech Recognition Threshold (SRT) and patients' best discrimination score (PB). SDT corresponds to the lowest hearing level (expressed in decibels) at which the patient is able to distinguish the spoken word 50% of the time. SRT corresponds to the lowest hearing level at which the patient is able to correctly repeat 50% of a list of words. PB corresponds to the hearing level at which the patient is able to correctly repeat 100% of a list of words. Speech perception test was performed using the Cochlear Implantation Protocols for selection and evaluation of adults [13]. The evaluation was conducted employing live voice at the sound intensity of 60 dB, and the speech material selected were vowels and disyllabic words, while the results refer to three main categories: detection, identification and comprehension. Detection corresponds to the identification of vowels percentage score (idv%) < 80% and in disyllabic words percentage score (dsw%) < 50%. Identification correspond to idv% > 80% dsw% > 50%. Comprehension correspond to idv% > 80%, dsw% > 50% and the comprehension of the disyllabic words percentage score > 50%.

Patient performance was also classified by an evaluation questionnaire: Categories of Auditory Performance (CAP) [14]. CAP is composed of eight levels of skills that increase in difficulty, from no awareness of environmental sounds (category 0) to telephone use with a known speaker (category 7).

Statistical analysis

For speech or auditory tests, average values and standard deviations were calculated and divided by group age. Concerning outcomes evaluation among age groups, the Student's *t*-test for paired data was used. Statistically significant differences were considered with a $p < 0.05$. Statistica 7 (StatSoft s.r.l. Italy, 2005) software was used.

Results

In each study group almost half of patients had hearing loss of unknown causes: 43% in group A, 57% in group B and 50% in group C. The main HL aetiology was otosclerosis with an incidence of 29% in group A, 22% in group B and 43% in group C, while cholesteatoma and acoustic trauma were present to a lesser degree.

All patients, before surgery, were affected by profound HL in the worse ear (ear candidate for CI) and showed poor benefits from HA (PTA threshold shift = about 32 dB, respectively A = 36, B = 31 and C = 30 dB) (Fig. 1). Similar results were obtained evaluating the better ear (data not reported). All subjects according to age groups received significant improvement ($p < 0.001$) considering the PTA scores before surgery (both with and without HA) and those achieved at 1, 3, 6 and 12 months post-CI activation. Comparison of PTA values between the three age groups at all experimental times did not show any significant difference ($p > 0.05$) (data not reported).

Concerning speech audiometric examination, all patients reached SDT before and after CI (Table III). Comparing

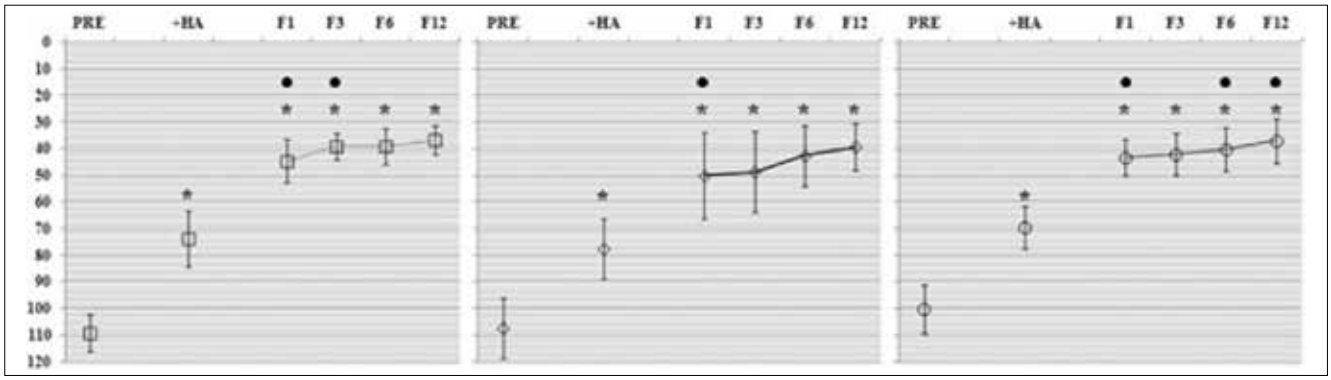

Fig. 1. Pure-tone average expressed in decibels hearing level (dB HL) ± standard deviation (SD).

*PRE= pre-surgery PTA without hearing aids; HA= pre-surgery PTA with hearing aids; F1= PTA at 1 month after activation; F3= PTA at 3 months after activation; F6= PTA at 6 months after activation; F12= PTA at 12 months after activation; *= p < 0.001, significant paired t test between PRE and other times; • = p < 0.001, significant paired t test between each follow-up time and the previous one.*

Table III. Pre-operative and post-operative speech audiometry thresholds expressed in dB of HL in the three age groups.

	Group A		Group B		Group C	
	dB HL	N	dB HL	N	dB HL	N
SDT						
PRE	99 ± 6.33	14	94 ± 5.25	14	98 ± 5.44	14
HA	75 ± 8.19 *	14	72 ± 5.78 *	14	79 ± 8.12 *	14
1 M	47 ± 12.65 *†	14	51 ± 9.75 *†	14	48 ± 14.39 *†	14
3 M	40 ± 9.61 *	14	46 ± 9.92 *	14	43 ± 16.10 *	14
6 M	38 ± 8.92 *	14	40 ± 12.47 *	14	40 ± 14.15 *	14
12 M	32 ± 8.93 *†	14	34 ± 10.08 *	14	34 ± 12.83 *	14
SRT						
PRE	/	0	/	0	/	0
HA	94 ± 2.50	4	94 ± 4.92	6	98 ± 2.89	3
1 M	66 ± 10.69 †	7	62 ± 12.77 †	9	75 ± 7.07 †	4
3 M	57 ± 8.45 †	11	65 ± 15.00	11	64 ± 10.83	9
6 M	55 ± 12.00	14	55 ± 14.91 †	11	59 ± 11.45	12
12 M	48 ± 7.78	14	51 ± 11.63	14	55 ± 11.84	14
PB						
PRE	/	0	/	0	/	0
HA	/	0	/	0	/	0
1M	/	0	/	0	/	0
3M	/	0	/	0	/	0
6 M	70	1	63 ± 5.77	3	75 ± 7.07	2
12 M	65 ± 5.47	5	65 ± 5.77	4	70 ± 0.00	2

*Speech audiometry thresholds expressed in decibels hearing level (dB HL) ± standard deviation (SD); PRE= pre surgery without hearing aids; HA: pre surgery with hearing aids; 1M= thresholds at the first month after activation; 3M= thresholds at the 3TH month after activation; 6M = thresholds at the 6TH month after activation; 12M= thresholds at the 12TH month after activation; *= p < 0.001, high significant paired t test between PRE and other times; †= p < 0.001, high significant paired t test between each time and the previous one.*

pre-operative performance scores (with and without HA) and post-activation outcomes after 1, 3, 6 and 12 months, all patients in the three groups showed significant improvement ($p < 0.05$). Comparisons of the SDT values reached after CI between groups revealed no statistically significant differences ($p > 0.05$) in performance.

No patient in the overall sample achieved SRT before surgery without HA; using HA, the SRT was achieved by 4 of 14 patients in group A, 6 patients in group B and 3 patients in group C. From qualitative analysis of outcomes, there was an upward trend in all three groups.

Among the youngest group of patients (35-49 years), 7 cases reached SRT in the first month after activation, 11 after 3 months of follow-up and the entire group after 6 months. SRT was achieved by 9 patients in group B and 4 in group C in the first month after activation; 11 patients in group B and 9 in group C after 3 months and 11 cases in group B and 12 in group C after 6 months. All patients reached SRT at 12 months of follow-up.

Statistical comparisons of performance scores showed no significant difference ($p > 0.05$) between groups.

Before CI, none of the subjects achieved a level of 100% of intelligibility (both with and without HA). The same result was achieved at the first and third month after activation. At 6 months post-CI activation, only 6 patients in the entire sample (1 in group A, 3 in group B and 2 in group C) were able to correctly repeat 100% of words. At 12 months post-CI activation, 100% of intelligibility was reached by 5 subjects in group A, 4 in group B and 2 in group C.

Figure 2 shows the speech perception evaluation before the cochlear implant and at 1, 3, 6 and 12 months after activation. Before CI in unaided conditions, none of the patients achieved detection, whereas with HA the results were reached by 7 individuals in group A, 8 in B and 6 in C. At the first month of follow-up, 2 patients in groups A and C and 5 in B achieved the best category (comprehension); identification was achieved in 6 cases in group A, 3 in group B and 2 in group C. Six patients in groups A and B

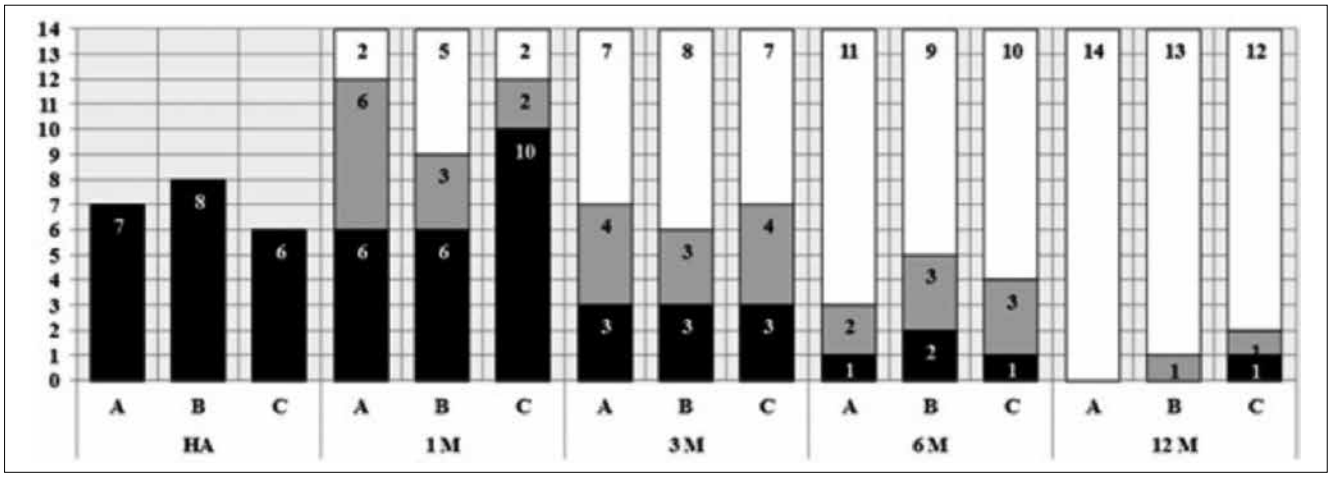

Fig. 2. Number of patients that achieved the three different speech perception categories according to age at the different experimental times.

HA= pre-surgery with hearing aids; 1M= 1 month after activation; 3M= 3 months after activation; 6M= 6 months after activation; 12M= 12 months after activation; black color= detection, grey color= identification, white color= comprehension.

and 10 in group C reached only the category of detection. At 3 months after activation, 7 patients in groups A and C and 8 in group B achieved comprehension; 4 patients in groups A and C and 3 in group B achieved identification. At 6 months post-activation, the number of patients who reached comprehension was: 11 subjects in group A, 9 in group B and 10 in group C. Eight subjects in the entire sample (2 in group A, 3 in group B and 3 in group C) achieved identification.

At 12 months of follow-up, the comprehension category was achieved by all patients in group A, 13 in group B and 12 in group C. Only 2 subjects (1 in group B and 1 in group C) reached the identification category and only one patient in group C achieved the detection category.

All patients were also evaluated by Categories of Auditory Performance (CAP) before and after surgery (Fig. 3). Before surgery, all groups were collocated in categories 0 and 1 if examined in unaided conditions and between categories 1 and 2 if assessed using HA. After 1 month, all patients in group C gained category 2 and few patients in groups A and B achieved category 4. Achievements increased significantly over time and no significant differences were found between groups: improved results were observed in both the youngest (group A) and elderly (group C) patients.

Discussion

The literature agrees that use of CI, both in adult and elderly subjects, leads to significant improvement in audiological tests and speech perception scores [7 8 10 11 15 16 19 21 22]. Furthermore, it is well known that cochlear implant improves the quality of life [7 9 15 23].

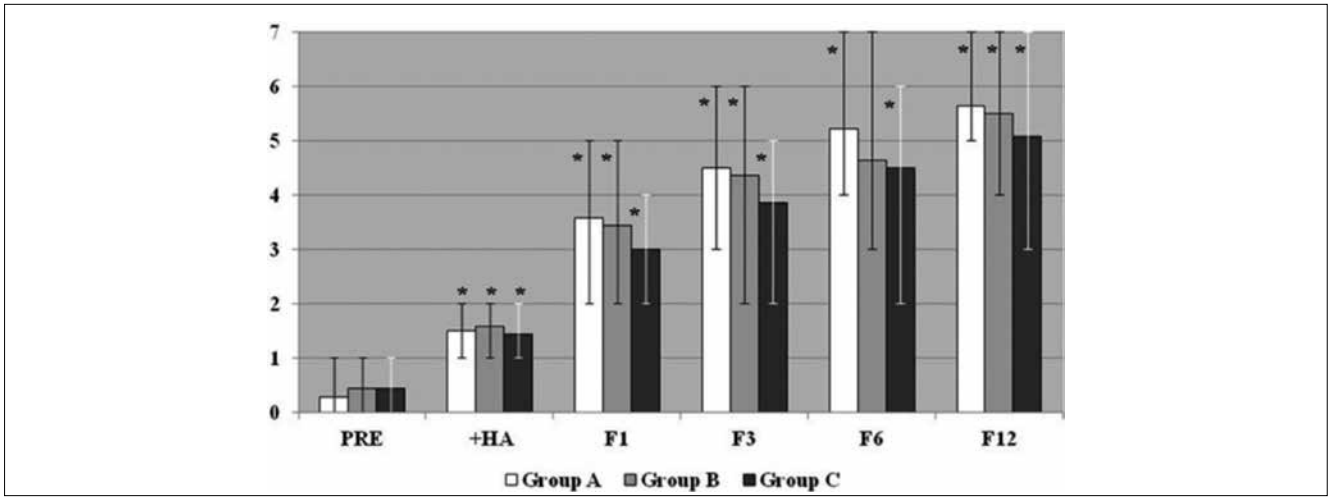

Fig. 3. Mean values obtained with the CAP questionnaire during post-operative follow-up.

*Bars indicated the min and max values. * paired t test, p-value < 0.01 between each follow-up time and the previous one by group.*

In agreement, in our study, since the first month post-activation, all implanted subjects showed improvements in audiological (hearing threshold and speech audiometry) and speech perception tests. In particular, when we evaluated PTA, SDT (speech audiometry) and CAP, a significant correlation was found between pre-surgery stage (with and without hearing aids) and different follow-up times in all three groups.

In the first month of CI use, all patients made good improvement in all tested categories (both audiological and speech score). Major progresses were reached in speech audiometry tests: most patients reached the categories of identification and comprehension, whereas before implantation, all subjects achieved only the detection category.

Differently from Budenz et al, the studies of Holden et al. and Lin et al., we can assert that the performance of our subjects in speech tests are not correlated to the age of implantation [16-18].

It is interesting to note that outcome improvement was seen in all our three groups, but to different degrees. The elderly group reached similar audiometrical and speech results as the other two groups, albeit slower. Looking at the outcomes of the elderly group at 12 months post-activation, patients reached the same PTA as the other two groups, but with persistent, small differences in performance in speech perception tests.

Different studies have analysed the factors affecting post-linguistic performance in implanted adults.

Some have shown that the use of a hearing aid before implantation influences auditory performance [19 20], whereas Park et al. have reported that the use of HA pre-implant had no substantial effect on patient performance or speech recognition [9].

In our study, since all subjects in the three groups used HA before implantation, we can suppose that the mild delay seen in performance in elderly patients was not correlated to the use of pre-surgery HA, in accordance with Park, but we cannot support this possibility due to the lack of comparison with a non-HA group.

Lazard et al. also reported that CI brand significantly influenced speech performance of implanted adults [20]. In our study, patients used three different CI brands (22 patients with Medel, 5 with Cochlear and 15 with Advanced Bionics), but the sample is too small and inhomogeneous to show any correlation between brand and other factors analysed.

Some authors affirmed that speech perception outcome in elderly implanted patients is significantly lower in difficult noisy conditions [18 19 21]. In our study, all speech perception tests were performed in quiet conditions.

Further prospective studies will be required to evaluate the performance of our subjects in noisy conditions.

Conclusions

In the present study, pure tone audiometry, speech audiometry, speech perception tests and CAP questionnaire revealed that there is a variability in auditory performances across study groups. In fact, no significant difference was seen in outcomes with CI between the three age groups. On the other hand, we observed that outcomes are achieved slower in older patients than in younger ones. Our results add additional support to the hypothesis that CI is an effective treatment for severe-to-profound HL and that the age of the subjects at time of implantation should not be considered as a limiting factor.

We can assert that, even if slower, subjects older than 65 years attain good performances and therefore are good candidates for a cochlear implant.

Acknowledgements

We are very grateful to Stella Montino and Prof. Alessandro Martini for their collaboration.

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VESTIBOLOGY

Nystagmus intensity and direction in bow and lean test: an aid to diagnosis of lateral semicircular canal benign paroxysmal positional vertigo

Intensità e direzione del nistagmo nel "bow and lean test": un contributo alla diagnosi nella vertigine parossistica da posizionamento benigna del canale semicircolare laterale

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SUMMARY

The objective was to evaluate nystagmus intensity and direction (NID) during bow and lean test (BLT) in subjects suffering from idiopathic lateral semicircular canal benign paroxysmal positional vertigo (LSC-BPPV), in order to differentiate between the geotropic and the apogeotropic form and to determine the affected ear before using classic diagnostic procedures. The BLT was performed in 32 subjects affected by LSC-BPPV. "Nystagmus intensity" evaluation allows distinguishing the geotropic variant from the apogeotropic one, while the "nystagmus direction" allows identification of the side. In particular, a more intense nystagmus in the bow position compared to the lean position indicates an ampullipetal flow caused by the presence of free-floating particles in the non-ampullary arm, and is suggestive of geotropic form. In this case, if the nystagmus in the bow position is left beating, the free-floating particles necessarily occupy the left LSC non-ampullary arm, while a right-beating nystagmus indicates the right LSC involvement. In contrast, a more intense nystagmus in the lean position compared to the bow position indicates an ampullifugal flow due to the presence of particles adherent to the cupula (cupulolithiasis) or free-floating in the ampullary arm (canalolithiasis), suggesting an apogeotropic form. In this situation, if the nystagmus in the lean position is left beating, the particles are in the left LSC ampullar arm or are coated on the left LSC cupula; vice versa, a right-beating nystagmus in the lean position is suggestive of the involvement of the right LSC. As a general rule, in both forms the direction of the more intense nystagmus points to the affected side. "NID-BLT" was effective in identifying the form and the side in 22/28 subjects (79% of the study population). The proper execution and interpretation of the "NID-BLT" helps to establish the form (geotropic versus apogeotropic) and side (right versus left) in most cases of LSC-BPPV. Unlike Choung's test, which requires knowing a priori if the form is geotropic or apogeotropic, our test enables fast and accurate diagnosis, or at least provides indispensable elements if the diagnosis of the affected side is doubtful, with the patient remaining in the sitting position.

KEY WORDS: Benign paroxysmal positional vertigo • Lateral semicircular canal • Vestibular system • Nystagmus

RIASSUNTO

L'obiettivo è stato valutare bed side l'intensità e la direzione del nistagmo (NID) nelle due differenti posizioni del "bow and lean test" (BLT) per differenziare la forma geotropa dalla forma apogeotropa e determinare il lato affetto in caso di vertigine parossistica da posizionamento benigna idiopatica da litiasi a carico del canale semicircolare laterale (LSC-BPPV), prima ancora di utilizzare le classiche manovre diagnostiche. Sono stati esaminati 32 soggetti affetti da LSC-BPPV, in ognuno dei quali sono state valutate l'intensità e la direzione del nistagmo nelle due posizioni del BLT. L'intensità del nistagmo consente di differenziare la forma geotropa della forma apogeotropa mentre la direzione del nistagmo consente di indentificare il lato affetto. Per le noti legge che governano la fisiopatologia del CSL, un nistagmo più intenso in flessione del capo (bow) rispetto all'estensione (lean) indica un flusso ampullipeto e quindi la presenza di materiale flottante nel braccio non ampollare, tipico della forma geotropa. In tal caso, se il nistagmo in flessione (bow) è diretto a sinistra, il materiale flottante deve necessariamente occupare il braccio non ampollare del CSL sinistro; viceversa se il nistagmo in flessione è diretto a destra. D'altro canto, un nistagmo più intenso in estensione del capo (lean) rispetto alla flessione (bow) indica un flusso ampullifugo e quindi la presenza di materiale aderente alla cupola (cupololitiasi) o flottante nel braccio ampollare (canalolitiasi), tipico della forma apogeotropa. In tal caso, se il nistagmo in estensione (lean) è diretto a sinistra, il materiale flottante deve necessariamente occupare il braccio ampollare del CSL sinistro; viceversa se il nistagmo in estensione è diretto a destra. Come regola generale, in entrambe le forme la direzione del nistagmo con maggiore intensità indica il lato affetto. Il "NID-BLT" è risultato efficace nell'identificare la forma ed il lato affetto in ventidue soggetti su ventotto (79% del campione). In caso di LSC-BPPV, la corretta esecuzione ed interpretazione del "NID-BLT" fornisce un importante aiuto nello stabilire la forma (geotropa versus apogeotropa) e la sede (destra versus sinistra) nella maggior parte dei pazienti, prima ancora di utilizzare le classiche manovre diagnostiche. A differenza del test di Choung, che richiede di conoscere a priori se il paziente ha una forma geotropa o apogeotropa, il nostro test consente di formulare direttamente la diagnosi o di fornire elementi indispensabili nei casi in cui la diagnosi di lato è dubbia, mentre il paziente è ancora in posizione seduta.

PAROLE CHIAVE: *Vertigine parossistica da posizionamentobenigna • Canale semicircolare laterale • Nistagmo*

Acta Otorhinolaryngol Ital 2016;36:520-526

Introduction

Lateral semicircular canal benign paroxysmal positional vertigo (BPPV) results from the movement of dense particles in the lateral semicircular canal (LSC). The diagnostic test is the supine roll test, also called Pagnini-McClure manoeuver [1 2], showing in the two positions a typical horizontal, paroxysmal bipositional bidirectional nystagmus which is apogeotropic in case of dense particles adherent to the cupula (cupulolithiasis) or free-floating in the LSC ampullary arm and geotropic in case of dense particles free-floating in the LSC non-ampullary arm (canalolithiasis) [3-5]. Indeed, the identification of the affected ear is fundamental, in order to perform the right repositioning manoeuvre.

In the apogeotropic form, the nystagmus is more intense when the affected ear is up, since this position provokes a direct (cupulolithiasis) or indirect (canalolithiasis, endolymph-mediated) excitatory deflection of the cupula, according to Ewald's 2nd law. Conversely, when the affected ear is down, the nystagmus is less intense since this position provokes an inhibitory deflection of the cupula, again according to Ewald's 2nd law. In contrast, the geotropic form is characterised by a nystagmus that is more intense when the affected ear is down, since this position provokes an indirect, endolymph-mediated excitatory deflection of the cupula, while the nystagmus is less intense with the affected ear up, since this position provokes an indirect, endolymph-mediated inhibitory deflection of the cupula. As a result, the affected ear can be determined as the side showing the more intense nystagmus in the geotropic form and the side showing the less intense nystagmus in the apogeotropic form [4 6].

However, it is sometimes difficult to identify the differences in nystagmus intensity, and consequently several tests for secondary signs of lateralisation, performed both in erect and supine position, have been described: "pseudo-spontaneous" nystagmus [6 7], "null-point" in the pitch plane [7 8], "bending nystagmus" [9], "bowing and leaning Choung's test" [10], "head shaking test-induced nystagmus" (HSIN) [7], sitting to supine position tests [11-14], null point in supine position [15 16].

However, these manoeuvre are often not well tolerated by the patient and are not always sufficient to identify the affected side. To reduce the discomfort to the patient and facilitate diagnosis, we have modified the execution and interpretation of Choung's test [10], developing a new method, called "nystagmus intensity and direction" bow and lean test (NID-BLT), which consists in the evaluation of different nystagmus directions, as in the original Choung's test [10], along with comparison of the different nystagmus intensity in the two positions.

Materials and methods

One hundred and six subjects with a history of recent, first and idiopathic episode of BPPV without any other associated labyrinthine disease were recruited from September to November 2015 and underwent vestibular examination using an infrared video-nystagmoscopic and video-nystagmographic instrument (VNG Ulmer; Synapsys S.A., Marseille, France) without fixation, according to the following procedure, designed to identify the subgroup with LSC-BPPV on which to evaluate the accuracy of NID-BLT.

Step 1: the patient, seated with the head in axis with the trunk (starting position), is assessed for a horizontal pseudo-spontaneous nystagmus or for a horizontal nystagmus induced by gentle lateral head rotations to either side. Such a horizontal nystagmus, which may be present in subjects suffering from LSC-BPPV, when present, is generated by the slow slide of the dense particles along the LSC. Since the LSC is anteriorly inclined by 30° forward relative to the horizontal plane, it behaves as a natural and true inclined plane along which the dense particles slowly slide, resulting in either an excitatory (dense particles adherent to the cupula or free-floating in the ampullary arm) or inhibitory (dense particles in non-ampullary arm) deflection of the cupula and nystagmus (Fig. 1).

Step 2: Choung's bow and lean test (BLT)10 is performed. As described by Choung et al. [10], the nystagmus direction reversal has been assessed, first when the patient bowed forward the head over 90° ("bowing nystagmus") and then leaned the head backward over 45° ("leaning nystagmus") in the sitting position. The nystagmus direction reversal, which occurs in most cases, is determined by the fact that, in the two different positions, the LSC plane radically reverses its inclination relative to the horizontal plane, thus causing an opposite sliding direction of the dense particles in the two positions.

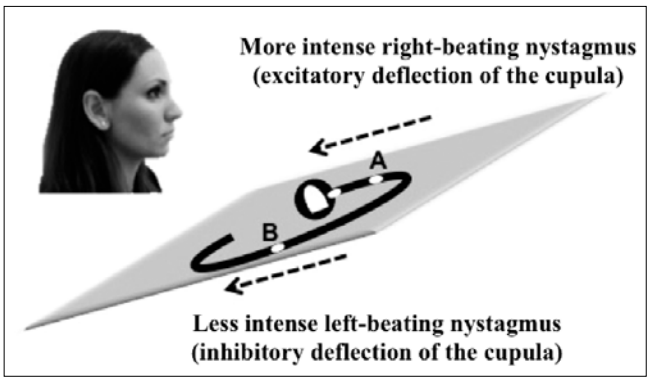

Fig. 1. The figure shows a right LSC-BPPV. In the patient seated with the head in axis with the trunk, the dense particles slide posteriorly and determine an excitatory (white dense particles adherent to the cupula or free-floating in the ampullary arm - A) or inhibitory (white dense particles in the non-ampullary arm - B) deflection of the cupula. The result is a horizontal pseudo-spontaneous nystagmus or a horizontal nystagmus induced by a gentle head rotation. Black arrows show ampullipetal and ampullifugal flow, respectively. Cupula, white.

In patients in which the presence of LSC-BPPV has been hypothesised, the NID-BLT was performed as follows.
First, the so-called "null point" was sought. The "null point" is the point of forward head tilt where the pseudo-spontaneous nystagmus or nystagmus generated by head rotation/BLT disappears: when the LSC lies on a horizontal plane, in fact, the spontaneous sliding of the particles disappears and so does the nystagmus (Fig. 2).
This preliminary phase is the first precondition for proper execution and interpretation of the test: by comparing the nystagmus intensity in the two BLT positions, only if the magnitude of the LSC tilt is identical in the two opposite positions can we be certain that the dense particles run through the affected LSC at the same speed and that the difference in nystagmus intensity is solely due to the Ewald's 2nd law. Once the null point is identified, which is slightly different in each subject due to the inevitable anatomical differences, we bow the head of 30° with respect to the null point itself and wait for about 30 seconds.
The next phase is the proper NID-BLT test: the head is leant 60° backward, and the nystagmus is evaluated; about 30 seconds later, the head is bowed 60° forward and the nystagmus intensity assessed again. This is the second, indispensable requisite to be followed when doing the NID-BLT. In fact, it would be a mistake just comparing the nystagmus generated by a forward head tilt of 30° from the null point (bow) with the one generated by a 60° backward head tilt (lean). Yet, the same principle is to be respected in the execution of the Pagnini-McClure manoeuvre when it is crucial to compare the nystagmus intensity generated by a 90° head rotation from right to left and vice versa and not by comparing the nystagmus generated by a head rotation from the supine to side (45°) with the nystagmus generated by a head rotation to the opposite side [19] (90°).
In order to assess the degree of operator dependence and the accuracy of the bed-side examination, two physicians were involved in the evaluation of the test results. The author evaluated bedside the nystagmus intensity and direction while another skilled physician analysed the video-nystagmographic recordings.
The different "nystagmus intensity" in the bow and in the lean positions was used to differentiate a geotropic form from an apogeotropic one and was evaluated as follows. After locating the null point, a more intense nystagmus in the bow position (head 30° forward) compared to the lean position (head 30° backward) is indicative of an ampullipetal, excitatory deflection of the cupula (according to Ewald's 2nd law). Consequently, more intense nystagmus must necessarily be generated by free-floating particles present in the LSC non-ampullar army, and this finding is suggestive of a geotropic form (Fig. 3).
Similarly, a more intense nystagmus in the lean position compared to the bow position is again indicative of an ampullipetal, excitatory deflection of the cupula. Consequently, more intense nystagmus must be necessarily generated by particles adherent to the cupula (cupulolithiasis) or by free-floating particles present in the LSC ampullary arm (canalolithiasis), and this finding is suggestive of an apogeotropic form.
"Direction nystagmus" evaluation allows identification of the affected side when associated with the "intensity nystagmus" evaluation. As already discussed, a nystagmus that is more intense in the bow position than in the lean position indicates the presence of free-floating particles in LSC non-ampullary arm, therefore suggestive of a geotropic form. Now, if the nystagmus in the bow position is left-beating, the free-floating particles must necessarily occupy the left LSC non-ampullary arm; in a similar way, if the nystagmus in the bow position is right-beating, the free-floating particles must necessarily occupy the right LSC non-ampullary arm (Fig. 3).
On the other hand, a more intense nystagmus in the lean position compared to the bow position indicates the presence of particles adherent to the cupula (cupulolithiasis) or free-floating in the ampullary arm (canalolithiasis), typical of an apogeotropic form. In such cases, if the nystagmus in the lean position is left beating, the particles are necessarily either in the left LSC ampullary arm or coated on the left LSC cupula; if the nystagmus in the lean position is right-beating, the particles occupy either the right LSC ampullary arm or are coated on the right LSC cupula (Fig. 4). We tested the accuracy index (AUC) of the modified BLT with SPSS software version 20 (IBM SPSS), which allowed us to depict ROC curve.

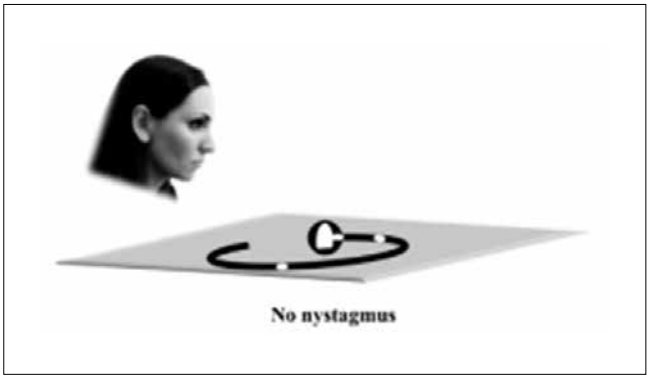

Fig. 2. When the LSC is no longer inclined relative to the horizontal plane, but parallel to it due to forward tilt of the head, the spontaneous sliding of the particles (white ovals) and the (pseudo-) spontaneous nystagmus disappears.

Results

Among the 106 subjects, 22 showed a pseudo-spontaneous nystagmus and 6 showed a horizontal nystagmus that appeared after lateral head rotations to either side, while 78 patients did not show any kind of horizontal nystagmus. These data strongly suggest the presence of LSC-

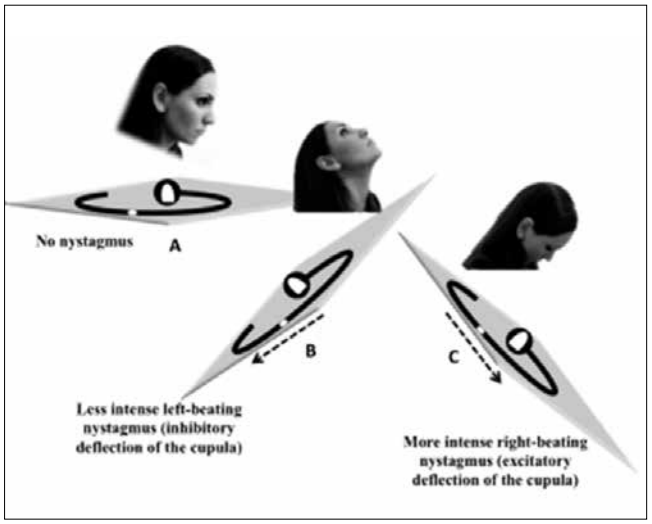

Fig. 3. In the "null point" position (A), the spontaneous sliding of the particles (white oval) and the (pseudo-) spontaneous nystagmus disappear. In the lean backward position (B), the particles slide posteriorly and demonstrate an ampullifugal inhibitory flow (black arrow) responsible for a left beating nystagmus. In the bow forward position (C), the particles slide anteriorly and demonstrate an ampullipetal excitatory flow (black arrow) responsible for a more intense right beating nystagmus. As a general rule, a more intense nystagmus in the bow position indicates a geotropic form (dense particles free floating in non-ampullary arm, canalolithiasis) and in this position the nystagmus direction indicates the affected side.

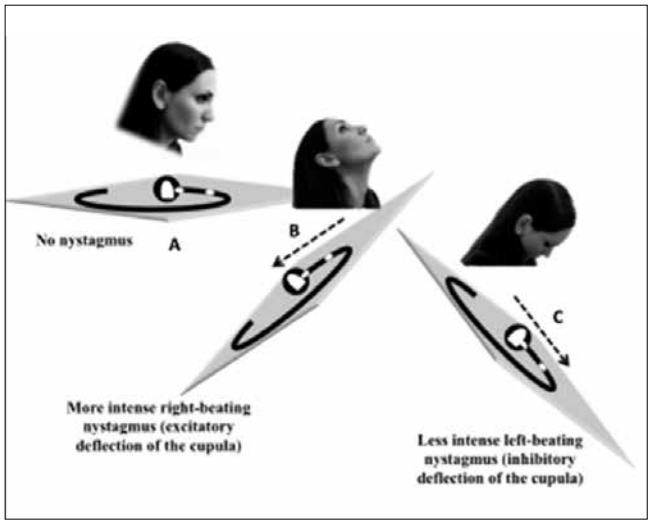

Fig. 4. In the "null point" position (A), the spontaneous sliding of the particles (white oval) and the (pseudo-) spontaneous nystagmus disappear. In the lean backward position (B), the particles slide posteriorly and demonstrate an ampullipetal excitatory flow (black arrow) responsible for a right beating nystagmus. In the bow, forward position (C), the particles slide anteriorly and demonstrate an ampullifugal inhibitory flow (black arrow) responsible for a less intense left beating nystagmus. As a general rule, a more intense nystagmus in the lean position indicates an apogeotropic form (dense particles free floating in ampullary arm or adherent to the cupula, respectively canalolithiasis or cupulolithiasis) and in this position the nystagmus direction indicates the affected side.

BPPV in 28/106 subjects (16 females, 12 males; mean age 45.96 +/- 5.45 years; duration of symptoms on average 11.57 +/- 4.18 days). Among these 28 subjects, the BLT reversed nystagmus direction in 24/28, while the direction of the nystagmus was not modified in 4/28 patients; these 4 patients (three females, one male; mean age 53.50 +/- 11.73 years; duration of symptoms on average 27.00 +/- 3.56 days) were excluded from the study. Among the remaining 78 subjects who did not show any nystagmus in the starting position, the BLT generated a horizontal nystagmus that reversed direction in the two positions in 4/78 subjects; in these four additional subjects the presence of LSC-BPPV was strongly hypothesised.

Overall, in 32 subjects we hypothesised the presence of LSC-BPPV.

In 28 out of 32 subjects, the "NID-BLT" results made us assume the presence of 22 geotropic forms (14 right-sided, 8 left-sided), and 6 apogeotropic forms, (4 right-sided, 2 left-sided). The Pagnini-McClure manoeuver confirmed the NID-BLT findings in 18/22 geotropic forms (82% of the sample) and in 4/6 apogeotropic forms (67% of the sample).

Overall, the "NID-BLT" proved effective in identifying the form and the side in 22/28 subjects (79% of the sample). All subjects affected by geotropic form were subjected to the liberatory Gufoni manoeuver, which was effective, as confirmed by a Pagnini-McClure manoeuver performed after three days. The 6 subjects affected by apogeotropic form were first subjected to the inverted Gufoni manoeuver, which transformed the apogeotropic form in the geotropic one, and then to the liberatory Gufoni manoeuver; again, a Pagnini-McClure manoeuver performed after three days confirmed the efficacy of the treatment. Table I shows the demographic data, duration of symptoms, features and SPAV of nystagmus in BLT, assumptions and treatment effectiveness. In the remaining 4/32 patients, the nystagmus direction did not change and, therefore, the NID-BLT did not offer any indication. However, the patients were further investigated, and the presence of a left, apogeotropic LSC-BPPV was hypothesised (see discussion). Statistical analysis was conducted with SPSS version 20 (IBM SPSS). The area under the ROC curve for BLT is 0.803 (p-value <0.001 ; 95% CI 0.69-0.91). The test had 81.8% sensitivity and 33.3% 1-specificity (Fig. 5).

Discussion

In cases of LSC-BPPV, the BLT ("Choung's test"10) is a simple method that may help to determine the affected ear; however, it is burdened by the major limitation that it is essential to know a priori which variant (geotropic vs.

Table I. Table I shows the demographic data, duration of symptoms, features and SPAV of nystagmus in BLT, assumptions and treatment effectiveness in 28 subjects who underwent the "NID-BLT".

Pt.	Sex	Age	Duration of symptoms in days	Horizontal nystagmus	Bow nystagmus intensity and direction	Lean nystagmus intensity and direction	Form hypothesis	Pagnini-McClure manoeuver	Inverse Gufoni manoeuver	Liberatory Gufoni manoeuver
1	F	44	6	Left Pseudo-Sp	14°/sec right	8°/sec left	Right geotropic	Confirmed	Not necessary	Effective
2	F	48	7	Left Pseudo-Sp	12°/sec right	6°/sec left	Right geotropic	Confirmed	Not necessary	Effective
3	M	39	9	Left After-LHR	10°/sec right	5°/sec left	Right geotropic	Confirmed	Not necessary	Effective
4	F	41	8	Left After-BLT	21°/sec right	12°/sec left	Right geotropic	Confirmed	Not necessary	Effective
5	M	59	12	Left Pseudo-Sp	18°/sec right	10°/sec left	Right geotropic	Confirmed	Not necessary	Effective
6	M	54	7	Left Pseudo-Sp	31°/sec right	8°/sec left	Right geotropic	Confirmed	Not necessary	Effective
7	F	44	6	Left Pseudo-Sp	14°/sec right	8°/sec left	Right geotropic	Confirmed	Not necessary	Effective
8	F	48	7	Left After-BLT	12°/sec right	6°/sec left	Right geotropic	Confirmed	Not necessary	Effective
9	M	43	9	Left Pseudo-Sp	9°/sec right	3°/sec left	Right geotropic	Confirmed	Not necessary	Effective
10	F	41	8	Left After-LHR	21°/sec right	12°/sec left	Right geotropic	Confirmed	Not necessary	Effective
11	M	59	12	Left Pseudo-Sp	18°/sec right	10°/sec left	Right geotropic	Confirmed	Not necessary	Effective
12	M	54	7	Left After-BLT	31°/sec right	8°/sec left	Right geotropic	Confirmed	Not necessary	Effective
13	M	43	13	Left Pseudo-Sp	12°/sec right	8°/sec left	Right geotropic	Not confirmed	Not necessary	Effective
14	M	43	13	Left Pseudo-Sp	10°/sec right	8°/sec left	Right geotropic	Not confirmed	Not necessary	Effective
15	F	45	14	Right Pseudo-Sp	18°/sec left	8°/sec right	Left geotropic	Confirmed	Not necessary	Effective
16	M	48	10	Right After-LHR	14°/sec left	8°/sec right	Left geotropic	Confirmed	Not necessary	Effective
17	F	45	14	Right Pseudo-Sp	19°/sec left	6°/sec right	Left geotropic	Confirmed	Not necessary	Effective
18	F	45	14	Right After-LHR	18°/sec left	8°/sec right	Left geotropic	Confirmed	Not necessary	Effective
19	M	48	10	Right Pseudo-Sp	14°/sec left	8°/sec right	Left geotropic	Confirmed	Not necessary	Effective
20	F	45	14	Right After-LHR	19°/sec left	6°/sec right	Left geotropic	Confirmed	Not necessary	Effective
21	F	42	9	Right Pseudo-Sp	13°/sec left	9°/sec right	Left geotropic	Not confirmed	Not necessary	Effective
22	F	39	9	Right Pseudo-Sp	9°/sec left	6°/sec right	Left geotropic	Not confirmed	Not necessary	Effective
23	F	43	16	Right After-LHR	9°/sec left	17°/sec right	Right apogeotropic	Confirmed	Effective	Effective
24	F	43	16	Right Pseudo-Sp	9°/sec left	14°/sec right	Right apogeotropic	Confirmed	Effective	Effective
25	F	51	17	Right After-BLT	7°/sec left	9°/sec right	Right apogeotropic	Not confirmed	Effective	Effective
26	M	51	17	Right Pseudo-Sp	9°/sec left	11°/sec right	Right apogeotropic	Not confirmed	Effective	Effective
27	F	41	20	Left Pseudo-Sp	12°/sec right	21°/sec left	Left apogeotropic	Confirmed	Effective	Effective
28	M	41	20	Left Pseudo-Sp	12°/sec right	21°/sec left	Left apogeotropic	Confirmed	Effective	Effective

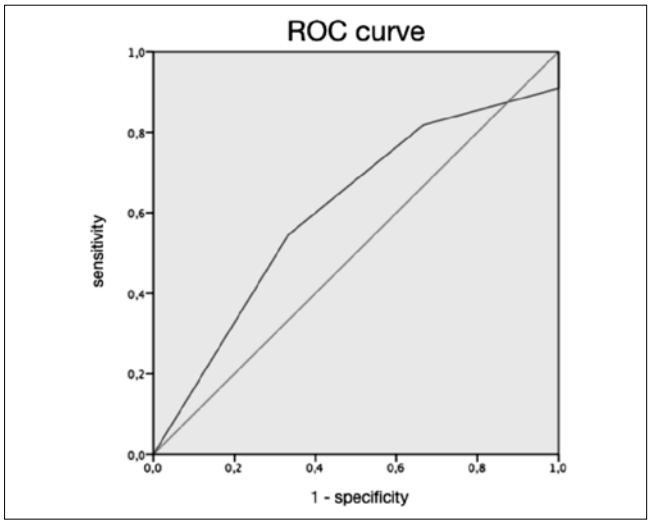

Fig. 5. ROC curve for Bow & Lean test (BLT): the area under theta ROC curve for BLT is .803 (p < 0.001; 95% CI 0.69-0.91). The test reported 81.8% sensitivity and 33.3% specificity. Statistical analysis was conducted with SPSS version 20 (IBM SPSS).

apogeotropic) the patient is suffering from. As reported by its authors, it is therefore essential to always integrate the BLT with the Pagnini-McClure manoeuvre.

In order to overcome this limitation, we decided to modify the BLT adding a "nystagmus intensity and direction" evaluation, which may provide information without necessarily having to resort to other tests.

As already reported, the different nystagmus intensity in the bow and in the lean position allow us to differentiate a geotropic form from an apogoetropic one, while the nystagmus direction allow us to determine the affected side. As a general rule, in both forms the direction of the more intense nystagmus points to the affected side.

The "NID-BLT" was effective in identifying the form and the side in the 79% of patients (81.8% sensitivity and 33.3% specificity, Fig. 5).

Particularly interesting are the indications offered by the 4 subjects in which the NID-BLT did not change the nystagmus direction. In these patients, the Pagnini-McClure manoeuvre revealed a left, apogeotropic LSC-BPPV. However, the presence of a left-beating, pseudo-spontaneous nystagmus that did not reverse its direction in the two BLT positions, the null point in supine position with head rotated about 20° on the left, the lack of response to the inverted Gufoni manoeuvere [18] to convert the apogeotropic form into the geotropic form were all suggestive of cupulolithiasis rather than canalolithiasis. Free floating particles in the ampullary arm should in fact necessarily change their direction in both positioning and determine a change in the nystagmus direction, as well. On the contrary, it may be that particles adherent to the cupula may not be mobilised enough during the BLT as they continue to exercise a certain fixed deflection of the cupula itself, in this case of excitatory type. Otherwise, the particles would determine a different cupula deflection with the patient in the supine position, as demonstrated by the presence of the null point in supine position with head rotated about 20° on the left. Therefore, this finding leads us to believe that, in the presence of LSC-BPPV, the non-reversal of the direction of horizontal nystagmus in the two positions of the BLT can be suggestive of cupulolithiasis. All patients then performed the Brandt-Daroff exercises [20] and the inverted Gufoni manoeuvre converted the apogeotropic form into the geotropic form after 15 and 20 days, respectively. Subsequently, both patients were subjected to the liberatory Gufoni manoeuvre, which was immediately effective [21]. The effectiveness of the Brandt-Daroff exercises excludes the possibility of a light or heavy cupola [22].

From the above, it is evident that the most delicate phase in the execution of the NID-BLT is to distinguish the nystagmus intensity in the two different positions at the bedside, whereas no difficulties are encountered in the evaluation of the direction of the nystagmus. This represents the real limitation of our test. Failure to evaluate the different nystagmus intensity in the two different BLT positions does not allow the form to be identified correctly (geotropic vs. apogeotropic) and consequently the identification of the side: only if the form is known is it possible to identify the side.

Undoubtedly, the lack of identification of the form, and consequently of the side, in 6 of 28 patients was due to our inability to correctly identify whether the nystagmus was more intense in the bow rather than in the lean position. In particular, the video-nystagmographic recordings of these 6 patients showed an almost undetectable nystagmus and a very minimal difference between the intensities in the two positions, thus misleading us. Another limitation is the occurrence of mixed forms in which some otoconia are aderent to the cupula, but others are free-floating within the semicircular canal. Another limitation is represented by the fact that an identical flexion and extension head angle from the null point is necessary because different angles may produce different accelerations in the canal: in this case, the different nystagmus intensity may be due to ampullifugal or ampullipetal endolymph flow, but also to a slight difference in head angle.

Conclusions

Determining the affected ear in LSC-BPPV is the first and fundamental step for the diagnosis and therapy. We modified the BLT supplementing it with "nystagmus intensity and direction" bedside assessments in order to provide additional elements for diagnosis. The NID-BLT was effective in identifying the form and the correct side in 22 of 28 subjects (79%). Because of its rapidity and ease of execution, the remarkable effectiveness in identifying form

and affected side and despite the mentioned limitations, we believe that the bedside NID-BLT should be included routinely in the diagnostic strategy when a LSC-BPPV is suspected as a complementary test to classic manoeuvres.

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CASE SERIES AND REPORTS

Free flap loss caused by heparin-induced thrombocytopenia and thrombosis (HITT): a case report and literature review

Trombocitopenia eparino-indotta e trombosi (HITT): una causa sottostimata di fallimento di lembi liberi: case report e revisione della letteratura

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SUMMARY

Heparin-induced thrombocytopenia and thrombosis (HITT) represents a dramatic condition that is difficult to diagnose because of nuanced clinical presentation. Therefore, in every case of microvascular thrombosis during heparin-therapy prompt suspicion about HITT is necessary to avoid flap necrosis. We present a case of HITT which, as the 8 other articles reviewed, clearly shows that HITT is difficult to diagnose and complex to manage. Microvascular reconstruction is the first choice in head and neck reconstruction; unfortunately, dramatic outcomes in free flap surgery due to unpredictable thrombotic events are still reported in the English literature. More knowledge is required about HITT and reaching a consensus about thrombotic prevention in microsurgery could be helpful. Furthermore, a careful anamnesis can help minimise unexpected situations.

KEY WORDS: Microsurgical free flap • Thrombosis • Blood coagulation disorder • Drug-related side effects and adverse reactions

RIASSUNTO

La trombocitopenia eparino-indotta con trombosi rappresenta una complicanza che può portare a esiti drammatici nella chirurgia ricostruttiva microvascolare, tanto più che il suo riconoscimento non è sempre semplice. In ogni caso di trombosi microvascolare, in corso di terapia eparinica, il sospetto di HITT deve subito insorgere, così da poter intercettare e trattare la catena di eventi che porterebbe alla necrosi del lembo ricostruttivo. Presentiamo un caso che dimostra quanto possa essere difficile la diagnosi di HITT, così come appare negli altri reports reperibili in letteratura internazionale. I lembi microvascolari sono il gold standard nella chirurgia ricostruttiva cervico-facciale: purtroppo però il successo della metodica può essere inficiato da eventi trombo-embolici imprevedibili. Crediamo che una maggior divulgazione e la formulazione di domande anamnestiche specifiche possano essere utili nel limitare le conseguenze devastanti della HITT.

PAROLE CHIAVE: *Lembi liberi microchirurgici • Trombosi • Disordini della coagulazione • Reazioni avverse ai farmaci*

Acta Otorhinolaryngol Ital 2016;36:527-533

Introduction

Microvascular tissue transfer is the first choice in the oral cavity reconstruction, especially in oncological resection [1]. The efficacy of this technique has progressively increased during years [2 3]: improvements in optical technologies, surgeons' attitudes and confidence with head and neck microvascular reconstruction and all its anatomical variations [4], in association with accurate patient selection have led to a global survival rate of 95-99% [5].

Despite this enormous success, there are still some unpredictable causes of failure: among thrombotic events, heparin-induced thrombocytopenia and thrombosis (HITT) represents a dramatic condition that is frequently misrecognised and consequently, very difficult to treat in a timely manner [6-12]. HITT has devastating outcomes and greater information and understanding are needed about the condition: until now, only 8 papers have been published in the English literature: herein we report our experience on HITT through presentation of a case report.

We conducted a research on PubMed focusing on 2 keywords "HITT/HIT + microvascular free flap reconstruction" and we found 6 publications and 1 systematic review reporting a total of 9 cases of HITT in microvascular surgery (Table I), confirming that HITT is not a widely documented condition in the medical literature. In 2008, Tremblay et al. [6] described 2 cases of HITT in heparin naïve patients, both confirmed by positive anti-heparin antibody tests. They both suffered from venous congestion within hours following the intervention (respectively at 26 and 48 hours) af-

Table I. Literature review.

Author, year	Number of patients	Clinical manifestation (arterious, venous)	Onset time	Time to hitt diagnosis	Pre-hitt therapy	Post-hitt therapy	Hitt therapy	Previous herapin exposure	Confirmation of Hitt by antibody test
Tremblay, 2008	2	Case 1: venous congestion Case 2: venous congestion	Case 1: 26 hours Case 2: 48 hours	Case 1: 12 days Case 2: 11 days	Case 1: Heparin 5000 U sc twice daily Case 2: Heparin 5000 U sc twice daily, ASA 80 mg daily	Case 1: heparinised gauzes, Leeches, Heparin perfusion Case 2: continuous heparin infusion, Heparin 6000 U boluses, Leeches	Case 1: Heparin discontinued, Argatroban Case 2: Heparin discontinued, Orgaran for 17 days	Case 1: no Case 2: unknown	Case 1 & 2: yes
Schleich, 2008	1	Venous thrombosis, decreased doppler sign	6 hours	6 hours	Systemic herapinisation	IV derapi perfusion	Heparin discontinued, Argatroban for 5 days, long term Warfarin for 3 months	Unknown	Yes
Busch, 2009	2	Case 1: malperfusion Case 2: arterial thrombosis	Case 1: 12 hours Case 2: referred from another hospital	Case 1: unknown Case 2: unknown	Case 1: unknown Case 2: unknown	Case 1: unknown Case 2: unknown	Case 1: Heparin discontinued, Lepirudin Case 2: Heparin discontinued, Lepirudin	Case 1: unknown Case 2: yes	Case 1 & 2: yes
McCleave, 2010	1	Venous congestion and thrombosis, venous and arterial thrombosis	5 days	6 days	LMWH preop, Heparin 5000 U	Heparin infusion	Heparin discontinued, Lepirudin, long term Warfarin	No	Antibody test negative, but platelet aggregation assay positive
Medina, 2010	1, 2 flaps	1st flap: venous congestion, necrotic tissue 2nd flap: venous congestion	st flap: 4 days 2nd flap: 1 day	12 days	ASA, Lovenox	Heparin 5000 U boluses	Heparin discontinued, Leeches, Argatroban, long term Coumadin	Unknown	No. HITT confirmed by hypercoaguable workup
Tessler, 2013	1, 2 flaps	1st flap: venous congestion, decreased doppler sign 2nd flap: arterial thrombosis	Immediately compromised, 1st flap failure: 2 days 2nd flap failure: 6 days	6 days	Heparin drips, leeches	tPA 6 mg in a close loop circuit, Enoxaparin 40 mg sc daily	Heparin discontinued, fondaparinux, long term Warfarin	Unnown	Yes
Zaman, 2014	1	Arterial thrombosis	6 hours	Unknown	Unknown	Heparin 5000 U iv, Heparin 5000 U twice daily	Heparin discontinued, Danaparoid infusion	Unknown	Yes

ter having received unfractioned heparin (UFH). The first case was treated with leeches and anticoagulation therapy (argatroban) for about 1 month until he had a total free flap loss. In the second case, heparin was stopped promptly and danaparoid sodium was started, which worked adequately.

Schleich et al.[7] reported a case of HITT in a patient treated with a latissimus dorsi flap with an unknown story of heparin exposure. Six hours after surgery a decreased arterial Doppler signal, platelet count drop and positive antibody test confirmed a suspicion of HITT. Heparin was inter-

rupted and anticoagulation was switched to argatroban. Warfarin was mandatory as long term therapy.

In 2009, Busch et al. [8] published 2 cases of HITT with a total flap loss with early onset, recurrent arterial thrombosis and no significant decrease in platelets. In the first case, HITT was diagnosed 12 hours post-operatively and was confirmed by positive antibody test in a patient with previous heparin exposure. Microvascular anastomoses were unsuccessfully revised 12 times. The second case reported was a flap failure due to HITT that occurred at an unknown period after surgery. HITT antibodies were positive and heparin was immediately stopped and changed into lepirudin; the defect was reconstructed with a second free flap 10 days after heparin suspension.

McCleave et al. [9] published a paper in 2010 describing the case of a heparin naïve patient which had both an arterial and a venous congested flap 5 days after surgery with a negative antibody test and a positive platelet aggregation assay. He was unsuccessfully treated with exploration, heparin was interrupted and lepirudin was initiated. Warfarin was also mandatory as long-term therapy in this case.

In 2010 a paper by Medina et al. [10] reported the failure of 2 free flaps due to HITT in the same patient with unknown prior heparin exposure. Four days after performing the 1st flap, a second one was done. Venous congestion was noted immediately in the 2nd flap, which was successfully treated with leeches and argatroban. HITT was diagnosed thanks to a hypercoagulability workup.

Tessler et al. [11] in their review in 2013 analysed the literature by dividing papers in 3 groups: prior heparin exposure, heparin naive and prior heparin status not discussed. In each group, the number of patients, HITT flap characteristics, time until flap failure, treatment of HITT and confirmation of HITT by antibody test were analysed. They also reported a case of an ALT flap failure 2 days after surgery in a patient with a chronic right malleolus wound and no story of previous heparin exposure. Anastomosis were revised twice and a therapy with tPA in the operating theatre and leeches afterward was used, and starting on the 4th day RFFF was performed and persisted with good perfusion for 4 days. Thrombosis manifested again: thrombolysis with tPA and attempt of re-anastomosis were done unsuccessfully; the final decision was positioning a vacuum assisted closure therapy. HITT was diagnosed afterwards using an ELISA test and heparin was immediately stopped in favour of fondaparinux. Despite anticoagulant therapy, a trans-tibial amputation was needed because of deep venous thrombosis (DVT).

Zaman et al. [12] wrote a letter to the editor in 2014 to expose a case of a free gracilis flap partial failure 6 hours after surgery due to an arterial thrombosis, so the arterial anastomosis was revised. Post-operatively over the next few days the flap again showed signs of failure. At re-exploration, both the artery and vein were thrombosed and it was impossible to re-establish flow. The flap was removed, the wound debrided and a negative pressure dressing was applied. The platelet count was trending downward prior to the gracilis free flap. A diagnosis of HITT was considered and anti-heparin antibody assays were positive. Heparin was ceased and the patient was started on danaparoid infusion. The platelet count returned to normal limits within 3 days following cessation of heparin. Because of platelet count stability, his lower limb defect was reconstructed with a right latissimus dorsi free muscle flap. This second flap had an unremarkable post-operative course.

Case report

A 40-year-old non-smoking man, F.M., with no co-morbidities presented. He reported a fracture of the right knee, occurring 20 years ago; we after discovered that on this occasion he had had anti-thrombotic prophylaxis with sub-cutaneous heparin.

The patient came to our attention for squamous cell crcinoma (SSC) of the lateral border of the tongue (cT2N0), diagnosed in September 2015. We performed the usual pre-operative assessments (blood exam, ECG, chest radiograph, anaesthesiological evaluation) and no surgical contraindications were found. We performed partial glossectomy, selective neck dissection level I-III, and the defect was reconstructed with a left anterolateral thigh (ALT) flap. As per our routine, before cutting the descending branch of the deep circumflex artery, a heparin bolus was administered (2500 I.U.). The arterial and the two venous microanastomoses were performed on the superior thyroid artery and on the thyreolinguofacial trunk and on the superior thyroid vein, respectively. During the microsurgical time, the vessels were washed only with heparinised solution. Intra-operative angiography with indocyanine green was negative. The surgery was carried out unremarkably, and no surgical or anaesthesiological problems were seen. As per routine, we prescribed nadroparin 4000 I.U. daily. About 24 hours after surgery the flap appeared mildly congested, and application of medical leeches was initiated. We continued with hourly flap monitoring, but the clinical suspicion of mild-to moderate congestion persisted. On the morning of the 2nd post-operative day the flap colour had turned to blue, the temperature was decreased and the blood color, at the puncture, was quite dark: the patient was thus returned to the operating theatre. As expected, multiple venous thrombi were detected while the arterial flow was still valid. We attempted to remove the thrombi with direct administration of fibrinolytic drugs (6 mg of tissue plasminogen activator [tPa]) and by mechanical thrombolysis with a Fogarty catheter. Both maneuvers were relatively ineffective: the artery was still working, but without venous drainage. The flap appeared to be irrecoverable, so we removed the ALT flap and reconstructed the tongue defect with a left radial

forearm free flap (RFFF): the microvascular anastomoses were performed again on the superior thyroid artery and the internal jugular vein, in a termino-lateral fashion. Vessel patency was tested with indocyanine green. The RFFF showed a good perfusion for about 24 hours; unfortunately, impairment of the venous drainage was noted on post-operative day 3. The patient was returned to the operating theatre again. At surgical exploration, we discovered the left internal jugular vein completely occluded by thrombi. We tried once again to remove the thrombi, but they continued to reform intraoperatively and it was not possible to re-establish venous flow. The flap appeared still alive and so we performed a second venous anastomosis on the superior thyroid vein (Fig. 1). At the end of this third surgery, the flap perfusion was good and continuous heparin infusion had been started to contrast thrombophilia. During these 72 hours, blood exam, coagulation test and platelet counts did not show significant alterations (Fig. 2), and the patient's general conditions were good. After about 24 hours of intravenous heparin (3000 I.U./day), haematomas formed in each surgical site (left thigh, left forearm, left neck): we evacuated the cervical and the antebrachial haematomas in the operating room. The flap perfusion continued well, the forearm skin was pink and no stasis was detected (Fig. 3). The situation worsened on the 5th post-operative day: the RFFF started to suffer, it became blue (Fig. 4) and, in addition to the local problem, systemic manifestations showed: venous accesses, both peripheral and central, did not work and the blood in drainage sack coagulated very quickly. We performed another surgery: the forearm flap appeared very congested, we tried once again to restore venous flow, but

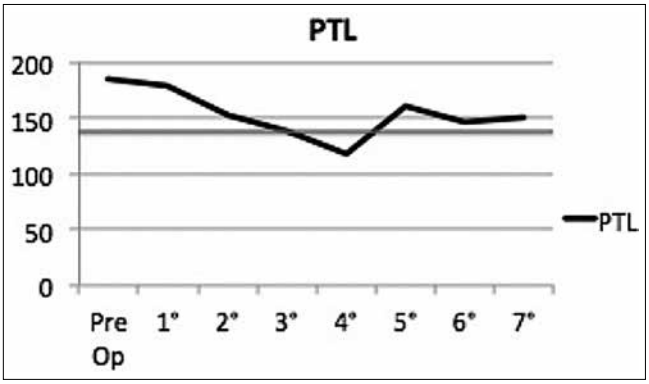

Fig. 2. Platelet profile during post-op days.

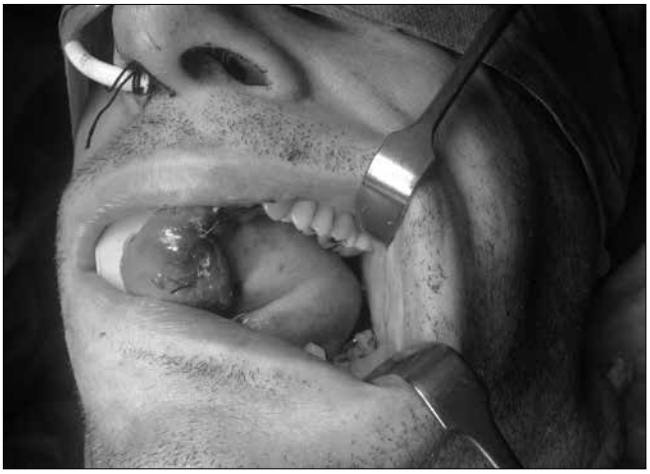

Fig. 3. Radial forearm free flap, after the second re-exploration.

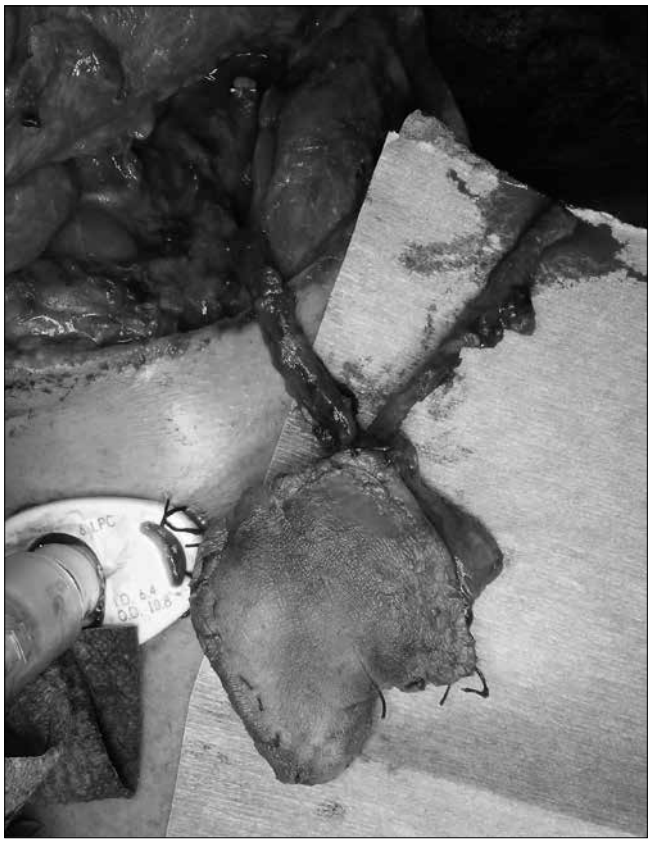

Fig. 1. Radial forearm free flap well perfused.

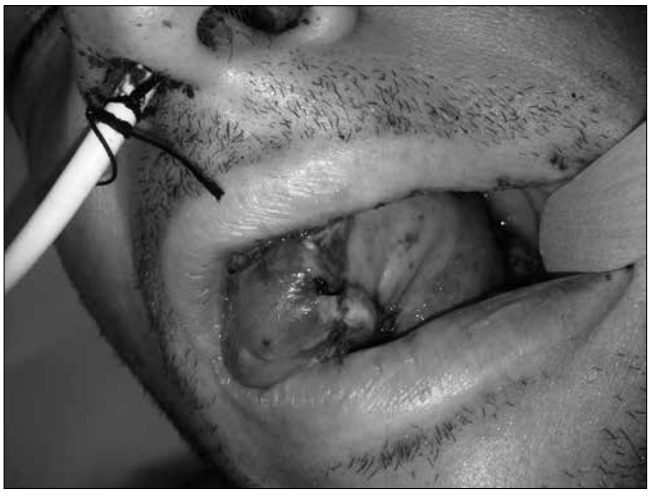

Fig. 4. Venous stasis of the radial forearm free flap.

every attempt was unsuccessful. We finally decided to remove the flap and to change the reconstructive technique: the wound was closed with a facial artery myo-mucosal (FAMM) flap.
A haematologist was consulted and specific coagulation tests were performed: on the morning of the 6th postoperative day we received the results: heparin-PF4 antibodies resulted positive by enzyme-linked immunoassay (ELISA). The haematologist rendered a diagnosis of HITT. We promptly substituted low body weight heparin (LBWH) with fondaparinux, a synthetic heparin-like polysaccharide targeting only the coagulation factor Xa and without affinity for PF4, avoiding the formation of heparin/PF4 antibody complexes. In the following days, the platelet count, which had dropped at least at $120x10^9$ at the apex of the manifestations on the 5th day, increased to 483-529 x 10^9, further supporting a diagnosis of HITT. The patient's recovery continued without complications, and the fondaparinux dose was increased up to 7.5 mg/day. He was discharged on the 21th day after the first surgery; 3 weeks later the autonomization of the pedicled flap was accomplished without further complications.

Discussion

HITT is a syndrome caused by the presence of antibodies linked to complex platelet factor 4 (PF4), which are exposed after heparin linkage. Among all antibodies, IgG are those that provoke platelet activation and aggregation, leading to thrombocytopenia and, in 50% of cases, thrombotic events. A diagnosis of thrombocytopenia is made when the platelets count is less than 150,000/mm^3 or when the decrease is more than 50%; the thrombotic events usually involve veins, with a venous:arterious ratio of 4:1 [13].
HITT manifests in two different forms. Type 1 depends on the direct activation of platelet heparin-mediated and is asymptomatic: thrombocytopenia resolves spontaneously in 1-2 days, normally without thrombotic events, and no intervention is usually required [14]. HITT type 2 is platelet activation mediated by immuno-complex [15]: it manifests later, usually in 4-10 days after heparin exposure and thrombotic events are co-existing, usually involving organs or tissues with pre-existing endothelial injury [16]; there is also a so-called "local-form" characterised by flap loss occurring very early in the post-operative course, with no drop in platelet counts [8]. The risk of developing HITT is correlated to the type of heparin: the major risk is with bovine heparin and with LBWH. The antibodies completely disappear in 100 days [17]. Rapid diagnosis of HITT is challenging: it manifests in unexpected ways, it's hard to recognise and unfortunately the consequences of diagnostic delay can be dramatic: flow impairment to the flap can result in flap loss, nullifying the efficacy of the surgery [18]. Typically heparin prophylaxis is administered to prevent venous flow impairment; when venous suffering is recognised, leech therapy is usually introduced, and can gradually resolve the situation. If leeches do not work, surgical revision is required: during surgery it is possible to directly see anastomosis, remove thrombi and locally administer fibrinolytic drugs, such as t-PA.
There is no general consensus about thrombosis prevention [19], but heparin therapy still remains a cornerstone during postoperative microsurgery: the paradox is that the therapy is the cause of the thrombosis, and this explains the difficulty in diagnosing HITT. Laboratory tests typically show thrombocytopenia after clinical manifestations that could be referred to other causes; systemic manifestations of thrombosis do not manifest, sustaining the probability of a local problem. Furthermore, routine anamnesis does not investigate prior heparin therapy, and even if well investigated, prior assumption of heparin is not an essential diagnostic information because it could occur even in heparin naive patients [9].
When the microsurgeon has to face venous drainage complications the first doubt is technical error [20]. In routine surgical activity, local problems are more easily believed to be the cause of venous congestion, more than a misdiagnosed systemic condition. All these aspects clarify the problems in HITT diagnosis: the time gap between the first clinical sign and diagnosis is usually enough to lead to irrecoverable damage (Table I). Hypercoagulability state, hereditary or acquired, is quite frequent in the general population and unrecognised coagulopathies represent a significant cause of flap failure [21]. We also have to consider the typology of patient undergoing reconstruction in head and neck surgery: the patient is usual oncological, as in our case, and frequently is a heavy smoker: both these factors increase propensity to clot formation. Furthermore, microsurgery itself may concur to thrombosis: the handling of vessels, with micro-damage on the endothelium, and the long surgical time, with prolonged immobilisation, may play a role in thrombotic aetiology. Dramatic outcomes in free flap surgery due to unpredictable thrombotic events are reported in the literature: from the experience with unknown coagulopathic patients the importance of specific anamnesis can be recognised, investigating about thrombophilia, not only in the patient but also in the family [22]; differently, the patient at risk for HITT cannot be recognised previously: the search for antibodies cannot be routinely performed and is not useful because they disappear at about 100 days after the manifestations; perhaps the only useful anamnestic data is previous exposure to heparin but, as already mentioned, is not specific for HITT diagnosis. Diagnosis is assessed only with a laboratory test that should be requested as soon as possible in order to break the chain of events: a prompt suspicion of HITT may be helpful in reducing negative outcomes. Warkentin and Heddle suggested a

Table II. 4T score.

4T's	0 POINT	1 POINT	2 POINT
Thrombocytopenia	< 30% platelet count fall or < 10 x 10^9/L platelet nadir	A 30-50% decrease in platelet count or platelet nadir 10-20 x 10^9/L	> 50% fall in platelet count or nadir 2-100 x 10^9/L
Timing of platelet count fall	Early drop (< 4 days) in platelet count in never exposed	Onset after 10 days, or some platelet count data missing	Clear onset between 5-10 days after initiation of heparin, or platelet fall 1 day
Thrombosis _ other sequela	None	Progressive or recurrent thrombosis	New thrombosis (confirmed), skin necrosis present, systemic reaction to heparin bolus
Other causes of thrombocytopenia	Definite	Possible	No alternative explanation

pre-lab test score ("4T score") [23]: clinical data and lab exam determine the grade of risk for HITT (Table II): evidence of a low score demonstrates unlikely HITT (< 5%), an intermediate score (4-5) has a clinical profile of HITT, but alternative explanations may still be relevant, and finally a high score representing a likely case of HITT (> 80%). This clinical score has been evaluated by both prospective and retrospective studies and has been demonstrated to have a predictive negative value (PNV) of 100% [24]. Whenever thrombotic complications occur HITT diagnosis should be considered, and this clinical test should be kept in mind as it allows addressing suspicions toward intrinsic alterations in coagulation.

Conclusions

In reconstructive microsurgery unexpected thrombosis is a very serious complication that, if untreated, can lead to flap necrosis. A prompt and correct diagnosis followed by appropriate therapy is mandatory. The microsurgeon usually suspects technical error or some other local problem; systemic alterations are considered as a possible cause of thrombosis secondarily, also because routine coagulation tests are considered sufficient to discriminate coagulopathic patients. Furthermore, the absence of a general consensus about post-operative anticoagulation therapy complicates the management of thrombotic manifestations. The case presented summarises very well as diagnosis of HITT is difficult: a healthy young patient, non-smoker, silent anamnesis, platelet count and PT and PTT in normal range and the onset of haemorrhagic problems: all these aspects contribute to deviating one's attention. The result was devastating: four re-exploration surgeries and two free flap failures. The 4T test could be a valid aid for HITT diagnosis because clinical evaluation alone is insufficient and laboratory confirmation requires cost and time. At present, the most useful and feasible tool for HITT suspicion is complete anamnesis investigating not only coagulopathic risk, as proposed by Friedman et al. [22], but also investigating prior heparin exposure (Table III).

Table III. Pre-operative assessment.

Pre-op questionnaire
1. Have you or anyone in your family have had a blood clot?
2. Have you or anyone in your family ever been on blood thinners?
3. Have you or anyone in your family ever been diagnosed with a blood clotting disorder?
4. Has anyone in your family had a disease called "*purpura fulminans*"?
5. Have you ever been diagnosed with Lupus or anyother autoimmune disease?
6. For female patients: Have you ever had a miscarriage?
7. Have you ever been exposed to heparin?

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In Memoriam of Prof. Renato Fior

It is with much emotion and sadness that I would like to remember Professor Renato Fior, who passed away a few months ago in his beloved Trieste.
Renato was a good friend, and together we had many enjoyable and stimulating days at numerous conferences in Italy and around the world.
Without a shadow of doubt, he is considered as the father of paediatric ENT in the entire world, and its founder in Italy together with Gatti Manacini, Stelio Crifò, Virgilio Pinelli and Giulio Pestalozza.
It was Renato who organised the first paediatric ENT meeting in Sirmione in 1977 with the participation of scholars and clinicians from around the world. It was at Sirmione, in the magical atmosphere typical of a lake in the spring, that the foundations were placed for a paediatric ENT study group, which was the starting point for the present day ESPO (European Society of Paediatric Otorhinolaryngology) of which Renato was General Secretary for many years.
Careful scholar, thorough researcher, capable clinician and wise master, he directed the ORL division of "Burlo Garofolo" Paediatric Institute in Trieste for many years since its foundation in 1968. Thanks to his excellent organisational skills and clinical skills, he brought the specialist department to a high level of efficiency, making it a reference centre for many parents of small, suffering children. Shy and reserved, but not introverted or unsociable, he dedicated his life to paediatric ENT, meeting Italian and foreign colleagues, and sharing scientific and cultural interests; he deeply loved his wife Sandra and his daughters, sharing their passion for music and visual arts.
The recognition and appreciation that he gave me when I was appointed the Paediatric ENT chair in L'Aquila and the affection that united us in recent years, when he was retired, will always remain in mind as were the carefree moments we shared in Venice together with our wives.

Desiderio Passali

Calendar of events – Italian and International Meetings and Courses

Acta Otorhinolaryngol Ital 2016;36:535-536

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JANUARY-DECEMBER 2017

CORSO DI DISSEZIONE OTOLOGICA, OTONEUROLOGICA E IMPLANTOLOGIA UDITIVA, DISSEZIONE ENDOSCOPICA DELL'ORECCHIO MEDIO E INTERNO • ***January 10-12, 2017 • Paris – France***

Directors: Olivier Sterkers and Daniele Bernardeschi

VIII INSTRUCTIONAL WORKSHOP "EUROPEAN ACADEMY OF OTOLOGY AND NEURO-OTOLOGY" – *EAONO 2017 • January 18-21, 2017 • Izmir – Turkey*

Website: www.eaono2016.org/

XVIII CONGRESSO NAZIONALE AOICO – L'impatto dell'innovazione tecnologica sulla diagnosi e trattamento delle affezioni cervico-facciali • ***January 27-28, 2017 • Rome – Italy***

Website: http://www.aoico.it/blog/

TRAINING DI CHIRURGIA IMPLANTOLOGICA DELLA SORDITÀ – V Edizione
February 1-3, 2017 • Pavia – Italy

Website: www.bquadro-congressi.it

12th SURGICAL ANATOMY IN HEAD & NECK CANCERS PROCEDURES • ***March 1-3, 2017 • Arezzo – Italy***

Course Directors: M. Benazzo, F.G. Chiesa – Website: www.iclo.eu

CURSO DE MICROCIRUGÍA DEL OÍDO Y DISECCIÓN DEL HUESO TEMPORAL
TEMPORAL BONE SURGICAL DISSECTION COURSE
March 1-3, 2017 • Barcelona – Spain

Sra. Conchi Castilla – Tel. 93 205 02 04 – Fax 93 205 43 67 – E-mail: entsecretaria@hotmail.es – info@iogi.org

CORSO DI ANATOMIA CHIRURGICA ENDOSCOPICA DEI SENI PARANASALI
March 5-7, 2017 • Arezzo – Italy

Responsabili Scientifici: Enzo Emanuelli, Fabio Pagella, Stefano Pelucchi – Website: www.iclo.eu

PREMIMA HANDS-ON COURSE, ADVANCED – Extended endoscopic transnasal surgical approaches to the skull base • ***March 21-23, 2017 • Varese – Italy***

Course Directors: Paolo Castelnuovo, Davide Locatelli, Manfred Tschabitscher – Website: www.milanomasterclass.it

9th MILANO MASTERCLASS • ***March 24-28, 2017 • Milan – Italy***

Charimen: Paolo Castelnuovo and Pietro Palma – Website: www.milanomasterclass.it

THE 13th INTERNATIONAL NETHERLANDS CANCER INSTITUTE HEAD AND NECK SYMPOSIUM – Diagnosis and treatment of sinonasal cancer and nasopharyngeal cancer
April 6-7, 2017 • Amsterdam – The Netherlands

E-mail: kno@nki.nl – Website: http://www.hoofdhalskanker.info/symposium-head-and-neck-cancer/

2nd WORLD CONGRESS ON ENDOSCOPIC EAR SURGERY • *April 27-29, 2017 • Bologna – Italy*

Chairmen: Livio Presutti, Muaaz Tarabichi, Daniele Marchioni – http://www.eesworldcongress2017.com/

XXV INTERNATIONAL EVOKED RESPONSE AUDIOMETRY STUDY GROUP (IERASG) BIENNIAL SYMPOSIUM • *May 21-25, 2017 • Warsaw – Poland*

Website: ierasg2017.com/

104° CONGRESSO NAZIONALE SIO – SOCIETA ITALIANA DI OTORINOLARINGOLOGIA E CHIRURGIA CERVICO-FACCIALE • *May 24-27, 2017 • Sorrento – Italy*

President: Carlo Antonio Leone – Website: www.sioechcf.it

HANDS-ON COURSE, BASIC - SINUS & SKULL BASE SURGERY: ANATOMICAL DISSECTION, DIAGNOSTICS AND OPERATIVE TECHNIQUES • *June 12-14, 2017 • Varese – Italy*

Website: www.attingo-edu.it

IFOS PARIS 2017 - ENT WORLD CONGRESS • *June 24-28, 2017 • Paris – France*

Website: www.ifosparis2017.org

SWISS ENDOSCOPIC EAR SURGERY COURSE SEES – HANDS-ON ENDOSCOPIC EAR AND LATERAL SKULL BASE SURGERY • *September 4-5, 2017 • Bern – Switzerland*

Website: http://sees.swiss-meeting.org

ENDOSCOPIC PARANASAL SINUS & SKULL BASE HANDS ON COURSE PSSB *September 7-8, 2017 • Bern – Switzerland*

Website: http://paranasal.swiss-meeting.org

XXXVI CONGRESSO NAZIONALE DELLA SOCIETÀ ITALIANA DI AUDIOLOGIA E FONIATRIA *September 27-30, 2017 • Siena – Italy*

Website: www.congresso-siaf2017.it/

XVI CONGRESSO NAZIONALE AIOLP • *October 6-7, 2017 • Venice – Italy*

Website: www.aiolp.it/

4th CONGRESS OF THE EUROPEAN ORL-HNS • *October 7-11, 2017 • Barcelona – Spain*

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CORSI PRATICI DI VIDEOCHIRURGIA ENDOSCOPICA NASO-SINUALE E DEL BASICRANIO *November 13-17, 2017 • Milan – Italy*

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17th ASEAN ORL HNS CONGRESS • *November 16-18, 2017 • Myanmar*

Website: www.entnet.org/content/17th-asean-orl-hns-congress

JANUARY-DECEMBER 2018

15th INTERNATIONAL CONFERENCE ON COCHLEAR IMPLANTS AND OTHER IMPLANTABLE AUDITORY TECHNOLOGIES • *June 13-16, 2018 • Antwerp – Belgium*

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6th WORLD CONGRESS OF THE INTERNATIONAL FEDERATION OF HEAD AND NECK ONCOLOGIC SOCIETIES • *September 1-5, 2018 • Buenos Aires – Argentina*

Website: http://ifhnos2018.org/

JANUARY-DECEMBER 2019

14th ASIA-OCEANIA ORL-HNS CONGRESS 2019 • *January 9-13, 2019 • Hyderabad – India*

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Villa Maria Pia
Visocchi Massimiliano
Zampino Giuseppe
Zanetti Diego
Zanoletti Elisabetta
Zenner Peter