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REVIEW

# Anterior palatoplasty in the treatment of obstructive sleep apnoea - a systemic review

## *La palatoplastica anteriore nel trattamento delle apnee ostruttive del sonno: una revisione sistematica*

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### SUMMARY

This study seeks to determine the objective and subjective success rates of anterior palatoplasty and its variants for the treatment of obstructive sleep apnoea (OSA). A systematic review with two independent searches of Medline, PubMed, Cochrane Library and Evidence Based Medicine Reviews was performed to identify publications relevant to OSA and anterior palatoplasty. All relevant studies published before 30 June 2015 were included. Six studies were included in the systematic review. The numbers of patients in each paper ranged from 13 to 77 (total = 240), and mean age ranged from 21 to 51 years. Substantial and consistent improvement in polysomnography (PSG) outcomes were observed in patients after the anterior palatoplasty, with or without multilevel surgery. The results showed that the anterior palatoplasty technique provides significantly improvement in the post-operative Apnoea-Hypopnea Index. The mean pre-operative AHI (in the 6 papers) improved from 16.3 to 7.1, the snore visual analogue scale improved from 7.5 to 3.1 and the Epworth score reduced from 11.3 to 7.3 post-operatively. The overall pro-rated pooled success rate for all the patients was 72.5%, with a mean follow-up of 17.3 months. Anterior palatoplasty is an effective option in the management of patients with mild to moderate OSA.

KEY WORDS: Anterior palatoplasty • Obstructive sleep apnoea • Systemic review • Level of Evidence: 2a

### RIASSUNTO

*Obiettivo di questo studio è determinare il tasso di successo, oggettivo e soggettivo, della palatoplastica anteriore e delle sue varianti nel trattamento delle apnee ostruttive del sonno. È stata quindi effettuata una revisione sistematica attraverso due ricerche indipendenti utilizzando Medline, PubMed, Cochrane Library and Evidence Based Medicine Reviews al fine di identificare le pubblicazioni di rilievo in merito alle apnee ostruttive del sonno e alla palatoplastica anteriore. Sono stati considerati tutti gli studi importanti pubblicati prima del 30 giugno 2015. Sono stati inclusi sei studi nella revisione sistematica. Il numero di pazienti in ciascun lavoro variava da 13 a 77 (per un totale di 240 pazienti), e l'età media variava da 21 a 51 anni. Dopo la palatoplastica, con o senza "chirurgia multilivello", è stato osservato un netto e consistente miglioramento dei parametri della polisonnografia. I risultati hanno mostrato che con la palatoplastica anteriore si ottiene un significativo miglioramento dell'Indice di Apnea/Ipopnea (AHI) postoperatorio. Il valore medio (dei 6 lavori) di AHI preoperatorio è migliorato da 16,3 a 7,2 e la scala visuo-analogica del russamento da 7,5 a 3,1, la scala di Epworth, infine, si è ridotta da 11,3 a 7,3. Il tasso di successo globale per tutti i pazienti è risultato pari a 72,5%, considerando un tempo di follow-up medio di 17,3 mesi. In conclusione, la palatoplastica anteriore è un'opzione efficace nella gestione dei pazienti con apnee ostruttive del sonno, di grado lieve e moderato.*

PAROLE CHIAVE: *Palatoplastica anteriore • Apnee ostruttive del sonno • Revisione sistematica • Livello di evidenza: 2a*

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### Introduction

Snoring is considered a social nuisance and an objectionable social problem. It is caused by the vibration of the structures in the oral cavity and oropharynx – namely the soft palate, uvula, tonsils, base of tongue, epiglottis and pharyngeal walls. Many sleep authorities believe that it

may represent an alarm to alert one to the possibility of obstructive sleep apnoea (OSA). OSA is a common sleep disorder; Young et al. studied 602 state employees with attended overnight polysomnography and found that the incidence of sleep disordered breathing (SDB) was 24% in men and 9% in women <sup>1</sup>. Most of these patients are

undiagnosed. It is estimated that up to 93% of females and 82% of males with moderate to severe OSA remain undiagnosed<sup>2</sup>. OSA is due to the collapsibility of the upper airway during sleep. These collapsible soft tissues, when subjected to negative pressure within the upper airway, may lead to complete or partial obstruction of the upper airway leading to cessation of breathing, increased sympathetic activity, increased blood pressure and hypoxaemia. Collapse of the upper airway is often multilevel, at the level of the palate/velopharynx, the base of tongue and/or the lateral pharyngeal walls. Patients with OSA have either a thick redundant soft palate and/or bulky lateral pharyngeal walls that contribute to the collapse and obstruction of the upper airway in these patients. These areas of collapse should be addressed, if one is aiming to relieve the patient of the apnoeas.

Many techniques that have been introduced to treat snoring and OSA, mainly aimed to create scar tissue, in order to incite fibrosis and stiffen the palate. With the stiffened palate, the vibration of the palate diminishes, and hence snoring is reduced. An anterior palatal stiffening operation was first introduced by Ellis in 1994<sup>3</sup> (this involved stripping of a small area of uvular and palatal mucosa) and modified by Mair in 2000<sup>4</sup>. Both techniques had promising results, although they produced a stellate and puckered scar on the soft palate that resulted in tenting and pulling of the lateral pharyngeal walls medially, and therefore narrowing of the lateral distance between the tonsillar pillars laterally. These anatomic manifestations might explain why some patients did not experience much benefit from the procedure. Pang et al. described the modified cautery assisted palatal stiffening operation (CAPSO) technique done under local anaesthesia (LA)<sup>5</sup>. This technique had showed encouraging results for patients with snoring and mild OSA<sup>5</sup>. The modified CAPSO technique was renamed as the anterior palatoplasty in 2009, as the technique involved the anterior surface of the soft palate primarily<sup>6</sup>. We present a systemic review of anterior palatoplasty and its variants since its introduction 8 years ago.

## Materials and methods

We performed a systematic literature search using Medline, Google Scholar, Cochrane Library and Evidence Based Reviews (up to June 30, 2015) databases for procedures that included anterior palatoplasty and its variants, mainly the modified CAPSO and the barbed anterior palatoplasty<sup>7</sup>. The overall search strategy combined search terms of anterior palatoplasty, palate surgery, uvulopalatopharyngoplasty, sleep apnoea, obstructive sleep apnoea and outcomes.

### *Selection criteria*

All relevant studies published prior to June 30, 2015 were included. All included studies had to be published in English and/or another language but with English translation. We included case control studies and/or cohort studies, with or without any form of comparison with the traditional treatment method for snoring and/or OSA. We included both adult and paediatric studies. The selection criteria for individual patients were based on patients with or without nasal obstruction, with mainly retro-palatal obstruction/narrowing and no hypo-pharyngeal collapse.

### *Data extraction*

For studies that met inclusion criteria, data was extracted into a standardised worksheet. Extracted data included the name of the first author, year of publication, study design, number of study subjects in each treatment group, the age and gender of subjects, description of the surgical procedure, pre-operative and post-operative apnoea-hypopnea index (AHI) and success rates.

The primary effectiveness outcome measure was pre-operative and post-operative AHI values following the anterior palatoplasty with or without any comparison with the traditional uvulopalatopharyngoplasty and/or other surgical method like uvulopalatal flap (UVF). The secondary outcome was surgical success rate defined as a reduction of post-operative AHI by 50% (compared to pre-operative AHI) and an AHI value below 20. Means with standard deviations (SD) were summarised for the major outcome, and the AHI change before and after surgical intervention was evaluated as for the treatment effect. Other outcomes taken into consideration include, snoring visual analogue scale (VAS) reduction, Epworth sleepiness scale (ESS), snoring reduction (as a percentage), pain levels (as a VAS), pain duration (number of days) and two-year satisfaction (based on patient and bed partner reports).

### *Statistical methods*

Data was analysed using a generic inverse method and  $p < 0.05$  was regarded as statistically significant. Combined summary statistics of the standardised (STD) paired difference in mean for the individual studies are shown. Combined STD paired differences in means were calculated and a 2-sided  $p$ -value  $< 0.05$  was considered to indicate statistical significance.

### *Procedural technique*

Most of the papers had the anterior palatoplasty technique done under general anaesthesia, however, the anterior palatoplasty technique can be done under local anaesthesia in

the office as well. General anaesthesia would be the standard choice if the patient had relatively larger sized tonsils (tonsil size 2, 3 or 4) and a tonsillectomy was needed.

The procedure may be done under local anaesthesia in the office as an out-patient. The patient was seated in an examination chair with the mouth open. Topical lidocaine (10%) was used to anaesthetise the palatal region. A total of 2 to 4 ml of 1:80,000 adrenaline and 2% xylocaine was injected into 3 sites of the soft palate. A partial uvullectomy (usually using diathermy/radiofrequency/coblation) may be performed, followed by supero-lateral cuts (para-uvular cuts) on either side of the uvula (especially if there were very prominent posterior and/or anterior palatal arch webbing), through both soft palatal arches. A horizontal rectangular strip of mucosa was removed from the soft palate (about 40 mm to 50 mm in length by 7 mm to 10 mm in width); down to the muscle layer. Haemostasis was achieved with electrocautery. The horizontal stripped area on the soft palate would be sutured with Vicryl 4/0 round body curved needle. A minimum of 10 to 20 sutures are used to appose the wound edges (while suturing, the entire soft palate would be transposed anteriorly and superiorly). All patients were prescribed anaesthetic gargles (Difflam) and lozenges (Difflam), non-steroidal anti-inflammatory agents (Naproxen Sodium), narcotics (e.g. codeine) and/or cyclo-oxygenase-2 inhibitors.

The same procedure may be carried out under general anaesthesia with the patient supine using the Boyle-Davies mouth gag with an oral intubation. Tonsillectomy was first performed followed by anterior palatoplasty (in the same fashion as described above). The anterior and posterior tonsillar pillars may or may not be sutured together, depending on the author/surgeon's preference.

Barbed anterior palatoplasty is a variant or evolved technique of the anterior palatoplasty<sup>7</sup>. The technique is similar to the anterior palatoplasty, and the barbed thread

would be the addition in order to allow the suture to suspend the different mucosa and muscular planes without the need to tie knots. The authors used the double needle QUILL® knotless tissue closure device, Angiotech Pharmaceutical Inc., Vancouver, Canada<sup>7</sup>. After the standard anterior palatoplasty, the barbed suture is passed from the pterygoid hamulus, pterygo-mandibular raphe from both sides, and passed through the rectangle box superiorly and inferiorly in a zig-zag fashion. The authors conclude their description of the procedure by including the Roman Blind technique proposed by Mantovani et al.<sup>8,9</sup>.

## Results

From the Medline and PubMed search, with the keywords "sleep apnoea" and "palatoplasty" search yielded 20 papers; after narrowing the search down to specific "anterior palatoplasty" in "sleep apnoea" only 10 papers were retrieved, which had included palatoplasty for cleft palates. The refined database search only identified six studies potentially eligible for review (specific to sleep apnoea and the anterior palatoplasty method) and analysis (Tables I, II)<sup>5-7,10-12</sup>. Two studies had a comparison group with either the uvulopalatal flap<sup>10</sup> or the modified uvulopalatopharyngoplasty<sup>11</sup>, this is illustrated separately in Table III. The other studies had reported the various result outcomes in terms of AHI, lowest oxygen desaturation, Epworth sleepiness scale, snore VAS, snoring reduction, and/or pain score and pain duration (Tables I, II). Five studies reported the ages, the mean body mass index (BMI) and pre/post-operative AHI; only 2 papers reported their pre/post-operative lowest oxygen values, while four papers reported their overall post-operative success rates, defined as a reduction of post-operative AHI by 50% (compared to pre-operative AHI) and an AHI value below 20<sup>5-7,10-12</sup>. The numbers of patients in each paper ranged from 13 to

**Table I.** Pre-operative and post-operative AHI, LSAT and success rates of the six papers included.

	N	Age	BMI	AHI		LSAT		% Success	F/U
				Pre	Post	Pre	Post		
Pang 2007 <sup>5</sup>	13	35.7	28.4	12.3	5.2	88.3	92.5	75	3
Pang 2009 <sup>6</sup>	39	39.3	24.9	25.3	11.0	81.4	92.0	71.8	33.3
Marzetti 2013 <sup>10</sup>	38	> 20	26.7	22.0	8.6			86	2
Ugur 2013 <sup>11</sup>	50	43	28.8						24
Ugur 2014 <sup>12</sup>	42	39.2	35.3	13.2	7.3			57.1	24
Salamanca 2014 <sup>7</sup>	24	46	28.6	8.9	3.8				
<i>Overall</i>	<i>206</i>		<i>28.6</i>	<i>16.3</i>	<i>7.1</i>	<i>84.5</i>	<i>92.0</i>	<i>72.5</i>	<i>17.3</i>

*N* = total number in study; *Age* = mean age of patients; *BMI* = mean body mass index of patients; *AHI* = Apnoea-hypopnea index; *LSAT* = Lowest oxygen saturation; *Success rate* in %; *F/U* = mean follow up in months.

*Note:* Success rates (in all articles) defined as 50% reduction of pre-operative AHI and an AHI < 20.

**Table II.** Illustrating the pre-operative and post-operative ESS, snore VAS and pain scores of the six papers included.

	N	Age	BMI	ESS		Snore VAS		Pain score	Pain duration
				Pre	Post	Pre	Post		
Pang 2007 <sup>5</sup>	13	35.7	28.4	12.2	8.9	8.3	3.3	Mild	10 days
Pang 2009 <sup>6</sup>	39	39.3	24.9	16.0	7.9	8.4	2.5	Mild	10 days
Marzetti 2013 <sup>10</sup>	38	> 20	26.7	8.5	4.9		80%↓	5.1	7 days
Ugur 2013 <sup>11</sup>	50	43	28.8	8.4	6.5	5.3	3.4	6	
Ugur 2014 <sup>12</sup>	42	39.2	35.3	11.5	8.3	6.2	3.4		
Salamanca 2014 <sup>7</sup>	24	46	28.6			9.2	2.9	Mild-mod	
Overall	206		28.6	11.3	7.3	7.5	3.1		

N = total number in study; Age = mean age of patients; BMI = mean body mass index of patients; ESS = Epworth Sleepiness Scale; VAS = Visual Analogue Scale.

**Table III.** Demonstrating the comparative results between the Anterior Palatoplasty (AP) with the respective traditional techniques of the Uvulopalatal Flap (UPF) and the modified Uvulopalatopharyngoplasty (ModUPPP).

	N	Age	BMI	ESS		AHI		Snore VAS		Success%	F/U	Pain VAS	Pain (d)	2 yr satisfaction
				Pre	Post	Pre	Post	Pre	Post					
Marzetti 2013 <sup>10</sup>	AP	15	48.3	26.5	8.5	4.9	22.0	8.6	80%↓	86	2	5.1	7	
	UPF	19	46.3	26.6	8.1	5.2	23.0	9.6	70%↓	84	2	6.8	10.8	
Ugur 2013 <sup>11</sup>	AP	26	43.2	28.1	8.4	6.5			5.3	3.4		24	6.0	85%
	ModUPPP	24	42.1	29.8	9.8	7.3			6.8	4.6		24	8.0	70%

N = total number in study; Age = mean age of patients; BMI = mean body mass index of patients; AHI = Apnea-hypopnea Index; LSAT = Lowest Oxygen Saturation; ESS = Epworth Sleepiness Scale; VAS = Visual Analogue Scale; Pain (d) = Duration of pain in days; Success rate in %; F/U = mean follow up in months.

Note: Success rates (in all articles) defined as 50% reduction of pre-operative AHI and an AHI < 20.

77 (total = 206), and mean age range from 21 to 51 years. Mean BMI was 28.6. Substantial and consistent improvement in PSG outcomes were observed in patients after the anterior palatoplasty, with or without multilevel surgery. The results showed that the anterior palatoplasty technique is associated with significant improvement in post-operative AHI. The mean pre-operative AHI (in the 6 papers) improved from 16.3 to 7.1 postoperative, the lowest oxygen saturation improved from a mean of 84.5% to 92% (in the 2 papers that reported); the snore visual analogue scale (in the 5 papers) improved from 7.5 to 3.1, the Epworth score (in the 5 papers) reduced from 11.3 to 7.3, post-operatively (Tables I, II). One study by Marzetti et al. reported an overall snoring reduction of 80% in their 34 patient cohort.

The overall pro-rated pooled success rate for patients (in the 4 studies that reported, n = 132) was 72.5%, with a mean follow-up of 17.3 months (Table I).

Two of these six articles had included a comparison group, other than the anterior palatoplasty technique<sup>10-11</sup> (Table III). Marzetti et al. had compared the anterior palatoplasty technique with the traditional uvulopalatal flap technique<sup>10</sup>. They found that the respective AHI and ESS

had significant improvement in the anterior palatoplasty group compared to the uvulopalatal flap group (p < 0.05) (Table III). Of interest, Marzetti et al. reported that both pain intensity and duration was lower in the anterior palatoplasty compared to the uvulopalatal flap group. Ugur et al. also reported similar results with the anterior palatoplasty group showing greater improvements in both ESS and snoring reduction compared to the modified uvulopalatopharyngoplasty group<sup>11</sup> (Table III). Ugur et al. also showed that the 2 year overall satisfaction rate was significantly higher in the anterior palatoplasty group than in the modified uvulopalatopharyngoplasty group (85% vs. 70%, respectively)<sup>11</sup> (Table III).

## Discussion

In 2000, Mair et al.<sup>4</sup> reported a promising 77% success rate for snoring reduction in 206 patients, at one year follow up, who underwent the cautery-assisted palatal stiffening operation (CAPSO). Pang et al.<sup>5</sup> modified the CAPSO technique and had showed encouraging results in a small group of patients with snoring and mild OSA. The modified CAPSO technique had combined the laser assisted uvulopalatoplasty (LAUP)<sup>13</sup> technique first de-

scribed by Kamami and simple horizontal stripping of the soft palatal mucosa. Kamami et al. studied 417 snorers who underwent LAUP and found a reduction of snoring in 95% of patients after one year. Most authors report modest improvement after LAUP for patients with mild OSA<sup>3,4,13</sup>. By combining the use of cautery with the principles of the laser palatoplasty and the creation of a horizontal denuded mucosal strip on the soft palate, with the suturing/closure of this horizontal strip, this technique is able to move the soft palate anteriorly and superiorly, while opening up the anterior-posterior velopharyngeal space. This technique opens up the retropalatal area by transposing the soft palate anteriorly; this is similar to advancing the entire palate forwards, as in Woodson's transpalatal advancement pharyngoplasty<sup>14</sup> but without bone surgery, with less resulting morbidity and a lower risk of oro-nasal fistula.

The 3-year follow-up of 77 patients (38 snorers and 39 patients with OSA) reported by Pang et al. showed that AHI improved in patients with OSA, from  $25.3 \pm 12.6$  to  $11.0 \pm 9.9$  ( $p < 0.05$ )<sup>6</sup>. The overall success rate (reduction of at least 50% of the pre-procedure AHI and post-procedure AHI below 20) for this OSA group was 71.8% (at mean 33.5 months, median follow-up at 31 months and a range of 29 to 39 months). The mean snore scores (VAS) improved from 8.4 to 2.5 (for all 77 patients) ( $p < 0.05$ )<sup>6</sup>. Lowest oxygen saturation also improved in all OSA patients, from a mean pre-operative  $81.4 \pm 19.2$  to  $92.0 \pm 16.9$  ( $p < 0.05$ )<sup>6</sup>. All patients had improvement in their snoring, and patients and their sleep partners were satisfied with the result at a mean of over 30 months postoperatively. The VAS showed gradual reduction in the snoring intensity with time, ranging from a preoperative level of 8.4 (range 7.5 to 9.1) to a low of 2.5 (range 1.0 to 4.6) at about 30 months postoperative<sup>6</sup>. Similar improvements were seen in the Epworth scale which decreased from 16.2 (range 8 to 20) to 7.9 (range 5 to 13) postoperatively ( $p = 0.05$ )<sup>6</sup>.

Marzetti et al. demonstrated the highest success rate in their 34 selected patients with mild to moderate OSA, with an impressive 86% success<sup>10</sup>, while Ugur et al. produced only a 57.1% success rate in 42 patients with mild to moderate OSA after a 24 month follow-up<sup>12</sup>. Salamanca et al. introduced the improved "barbed Roman blinds" technique with promising reductions in both AHI and snoring VAS, even if, unfortunately, they did not report on the success rate in their study of 46 patients<sup>7</sup>.

Of great interest are the two papers comparing the anterior palatoplasty technique with the uvulopalatal flap (Marzetti et al.<sup>10</sup>) and the modified uvulopalatopharyngoplasty (Ugur et al.<sup>11</sup>). Both studies had shown improvements in both techniques compared, but greater impressive improvements in both AHI, ESS and snoring reduction VAS

score were consistently demonstrated in the anterior palatoplasty group of patients.

It was also highlighted in 4 of the 6 papers reviewed here-in that the overall pain intensity and duration post-operatively in the anterior palatoplasty technique was lower than with other traditional palatoplasty techniques<sup>5,6,10,11</sup>. These six investigations demonstrated subjective and objective improvements in the 240 patients studied; this may suggest that the palatal fibrotic scar achieved by this anterior palatoplasty technique is superior over other techniques described, and appears to be able to maintain the encouraging results in the long term. Pang et al. hypothesised a number of advantages of this procedure<sup>6</sup>. It is anatomically sound (as it causes fibrotic scarring superiorly and anteriorly) and it can be done as an office-based procedure on an out-patient basis or part of a tonsillectomy (with or without preservation of the uvula) under general anaesthesia. The procedure is also fairly quick, low-cost and does not require expensive equipment.

## Conclusions

This systematic review has shown that anterior palatoplasty has comparably favourable results in relation to other methods of palatal surgery in adults. The procedure is simple to perform, is anatomically sound and has minimal complications.

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## HEAD AND NECK

# Nerve and vein preserving neck dissections for oral cancers: a prospective evaluation of spinal accessory nerve function and internal jugular vein patency following treatment

*Preservazione del nervo accessorio spinale e della vena giugulare interna durante dissezione del collo per carcinoma del cavo orale: valutazione prospettica della funzione del nervo e della pervietà della vena dopo trattamento*

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## SUMMARY

Nerve and vein preserving modification of the radical neck dissection is commonly used in the management of oral squamous cell cancers. There is limited literature addressing nerve function and vein patency following treatment. We prospectively analysed 65 patients with nerve conduction study using surface electromyography at baseline, 1 month and 6 months post-surgery and colour Doppler of the internal jugular vein at baseline and 1 month post-surgery. We also studied functional outcomes of nerve sparing with arm abduction test and Neck Dissection Quality of Life questionnaire. There was a statistically significant increase in mean latency of motor action potential and decrease in the mean amplitude of the motor action potential following surgery, suggesting nerve dysfunction. Following surgery, there was a significant decrease in the diameter of the vein as well as an increase in the velocity of blood flow; there was partial thrombus in 5% of individuals. In conclusion, even though nerve dysfunction compromised shoulder abduction, vein dysfunction rarely resulted in any significant clinical impact.

KEY WORDS: Neck dissection • Mouth neoplasms • Accessory nerve • Jugular veins • Quality of life

## RIASSUNTO

*La preservazione del nervo accessorio spinale e della vena giugulare interna durante la dissezione del collo è una pratica comune nella gestione del carcinoma squamoso del cavo orale. Tuttavia, la letteratura riguardante la funzione del nervo e la pervietà della vena è limitata. Pertanto, abbiamo analizzato retrospettivamente 65 pazienti e abbiamo studiato tramite elettromiografia superficiale la funzione del nervo spinale basale e dopo 1 mese e dopo 6 mesi dall'intervento e tramite color doppler la pervietà della vena giugulare interna basale e dopo 1 mese dall'intervento. Abbiamo inoltre studiato i risultati funzionali mediante il test di abduzione del braccio e il questionario "Neck dissection Quality Of Life". È risultato un aumento statisticamente significativo della latenza media del potenziale d'azione motorio e un decremento dell'ampiezza media del potenziale d'azione motorio in seguito a trattamento chirurgico, suggerendo quindi una disfunzione del nervo. Inoltre, in seguito all'intervento, c'è stato un decremento altrettanto significativo del diametro della vena, e, parallelamente, un incremento della velocità del flusso sanguigno e nel 5% dei pazienti è stata documentata una trombosi parziale. In conclusione, da una parte la disfunzione nervosa ha compromesso il movimento di abduzione del braccio, dall'altra la disfunzione venosa raramente ha avuto un impatto clinico.*

PAROLE CHIAVE: Dissezione del collo • Carcinoma del cavo orale • Nervo accessorio • Vena giugulare • Qualità della vita

Acta Otorhinolaryngol Ital 2018;38:7-12

## Introduction

Squamous cell carcinomas of the head and neck (HNSCC) account for 90% of all malignant diseases of the head and neck region <sup>1</sup>. The oral cavity lined by stratified squamous

epithelium is the most common site of HNSCC. The highest incidence of carcinomas of oral cavity and oropharynx are in South East Asia, where chewing tobacco with betel quid (paan) is a common practise. According to GLOBOCAN 2012, the estimated 5 year prevalence of lip and oral

cavity malignancies worldwide is 2.2% with a male preponderance (3.1% vs. 1.4%)<sup>2</sup>.

The single most important factor affecting prognosis in HNSCC is the status of cervical lymph nodes at presentation, and more than 40% of patients with oral and pharyngeal squamous cell carcinomas present with regional spread<sup>3</sup>. The management of the neck in oral cancers depends on whether the nodes are clinically involved, and if not then on the risk of occult metastasis. For oral cancers, the estimated incidence of subclinical disease in a clinically N0 neck is 15 to 20%. When regional metastasis is clinically detected, comprehensive clearance of all regional lymph nodes is recommended, whereas for a cN0 neck, selective neck dissection is performed. The understanding that optimal lymph nodal clearance can be achieved with conservative surgical procedures such as preservation of the spinal accessory nerve (SAN) and internal jugular vein (IJV) without the added risk of recurrences has shifted the focus to so-called modified radical neck dissections<sup>4</sup>. Among the various modifications, modified neck dissection (MND) type-II preserving SAN and IJV is popular, with the preservation being thought to reduce the morbidity of neck dissection<sup>5</sup>. Though MND type II preserves two of the most important non-lymphatic structures, few studies have shown that the function of the preserved nerve as well as the patency of the vein may be suboptimal<sup>6,7</sup>. There is paucity of published data on the functionality and quality of life after these non-radical surgeries at present, and hence the present study was undertaken to look at the overall impact of MND type II surgery with specific reference to function of the SAN and patency of the IJV together with the postoperative quality of life.

## Materials and methods

This was prospective study of consenting patients with biopsy proven oral squamous cell cancer (OSCC) of operable cT (T1 to T4a, AJCC/TNM 2010) stage undergoing primary surgery with modified neck dissection type II (defined as preservation of both the SAN and IJV) over a period of one year from June 2014 to May 2015. The main exclusion criteria included cN2 or N3 disease, prior treatment (surgery, radiotherapy or chemotherapy), gross invasion of XI nerve or internal jugular vein either preoperatively or at surgery, previous or intra-operative injury to the nerve or vein, cardiac pacemaker (contraindication for nerve conduction studies), patients on anticoagulant therapy and patients who developed postoperative complications that prevented evaluation at 3 to 4 weeks.

All eligible patients were subjected to nerve conduction

study (NCS) for measurement of amplitude and latency of Motor Action Potential (MAP) of the Spinal Accessory Nerve and colour Doppler study for calibre, patency and velocity of the IJV preoperatively. Patients underwent appropriate surgery including nerve and vein sparing neck dissection (MND type II). Following surgery, a repeat NCS was done at one and 6 months postoperatively and colour Doppler evaluation of the vein was done at one month postoperatively. The angle of arm abduction was measured with a goniometer pre-and post-operatively, and the quality of life after neck dissection was assessed by a Neck Dissection Quality of Life (NDQOL) questionnaire as described previously by Giordano et al.<sup>8</sup> (Table I) and the results were compared using a chi square test. Postoperatively, the use of adjuvant chemoradiation or radiotherapy was based on standard guidelines.

### *Nerve conduction study*

The nerve conduction study was done by MEDELEC synergy 10 channel machine using surface electrodes to obtain electrophysiological readings from the nerve and muscles. The test was carried out in a sitting position as per the recommendations of Surface Electro MyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) project group<sup>9</sup>. The nerve was stimulated at one end and recorded at other end near the muscle for 0.2 msec with three times the supramaximal stimulus. The amplitude and latency of the MAP were measured and compared.

### *Colour Doppler of the IJV*

In the supine position, after applying coupling gel over the neck, the ultrasound probe was placed over the IJV

**Table I.** Arm abduction test and NDQOL questionnaire<sup>8</sup>.

Angle of arm abduction	Score
Up to less than 90°	1
Up to more than 90° but less than 150°	2
Up to more than 150° but less than 180°	3
Up to 180° but with pain or effort	4
Up to 180° but without pain or effort	5
NDQOL questionnaire	Score
Are you bothered by shoulder or neck stiffness?	1-5
Are you bothered by shoulder or neck pain?	1-5
Are you bothered by numbness of your neck?	1-5
Are you bothered by constriction of your neck?	1-5
Do you think the shoulder dropped?	1-5
Do you have difficulty in reaching objects above your neck?	1-5
Are you bothered by appearance of your neck?	1-5
Total	7-35

to look for signs of thrombus (internal echoes and non-compressibility). The differential flow of blood in veins was detected by sound waves by measuring the calibre, velocity and phasic variation.

#### Statistical analysis

All data were recorded in a pre-designed Performa and were managed using Microsoft Excel 2007; data were presented as mean  $\pm$  SD. The paired t test and repeated measure ANOVA were used for qualitative data and the chi square test was used for quantitative data. Statistical analysis was performed using SPSS (statistical package for social sciences) Version 21 software, and a p value less than 0.05 was considered significant.

## Results

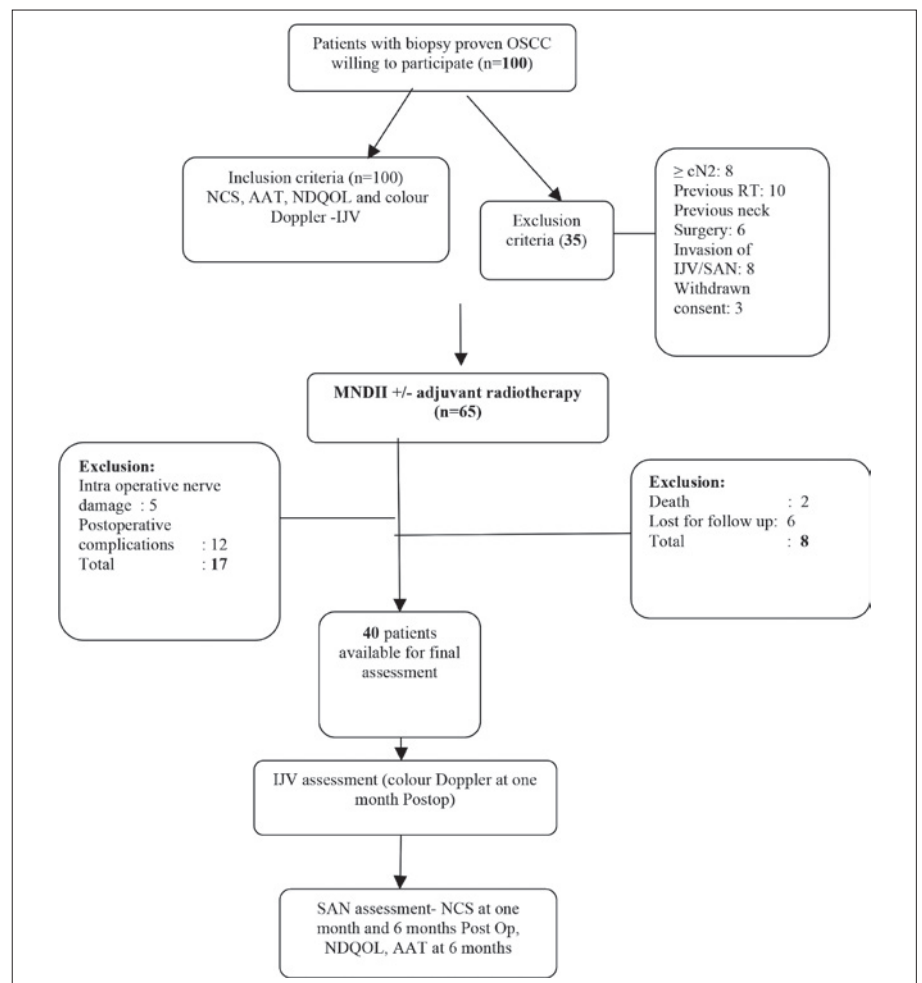
Over a period of one year, of the 100 consenting patients with biopsy proven OSCC, 35 did not meet the selection criteria for various reasons (Fig. 1). All 65 eligible patients, following pre-operative baseline NCS and colour Doppler of the IJV, underwent neck dissection with preservation of the SAN and IJV. Five patients with intra-operative injury to the nerve and 12 patients with post-operative wound complications were also excluded from the final analysis. Of the remaining 48 patients, 6 patients were lost to follow-up and two patients died of malignancy (Fig. 1). The mean ( $\pm$  SD) age of patients was 55.86 ( $\pm$  10.22) years, the majority were female (50 of 65, 77%) and most had left side lesions (45, 69%). A total of 42 of the 65 patients were less than 60 years of age and 37 patients received postoperative adjuvant neck irradiation.

#### Nerve conduction study

**Latency:** The mean ( $\pm$  SD) preoperative, at 1 months and at 6 months latency of the MAP of the spinal accessory nerve were 2.13 ( $\pm$  0.79), 2.75  $\pm$  1.16 and 3.01 ( $\pm$  1.51) msec respectively. The differences were sta-

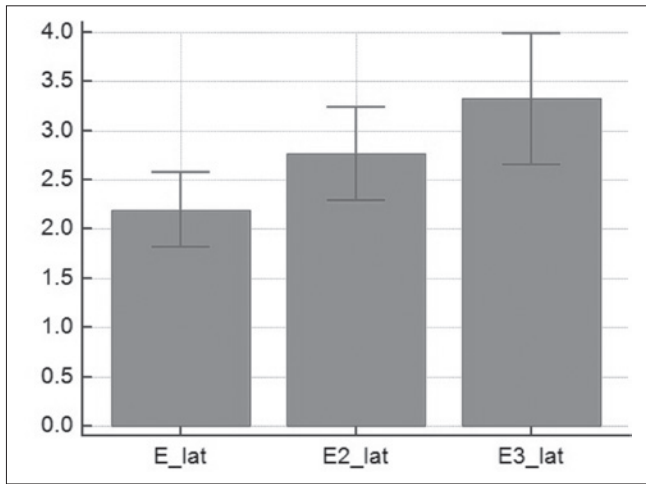
tistically significant ( $p < 0.001$ ). The latency (Figs. 2, 3) showed an increasing trend at one month and at 6 months postoperatively in most subjects except in 6, who showed an increase in latency at one month and decrease in latency at 6 months, but the value never fell below the pre-operative value. Interestingly, 5 of these 6 patients did not receive any postoperative neck irradiation.

**Amplitude:** The mean ( $\pm$  SD) amplitude of MAP expressed in mV at baseline, 1 month and 6 months postoperative were 8.06 ( $\pm$  0.35), 5.02 ( $\pm$  0.51) and 4.67 ( $\pm$  0.48) respectively. The amplitude of individual subjects (Figs. 4, 5) decreased at one month and 6 months progressively (ANNOVA,  $p < 0.001$ ) except in 6 patients, who showed an increase in amplitude at 6 months, but this never reached the pre-operative value. Again, 5 of these did not receive any neck irradiation. Though there was a decrease in mean amplitude at one month (2.2  $\pm$  0.8

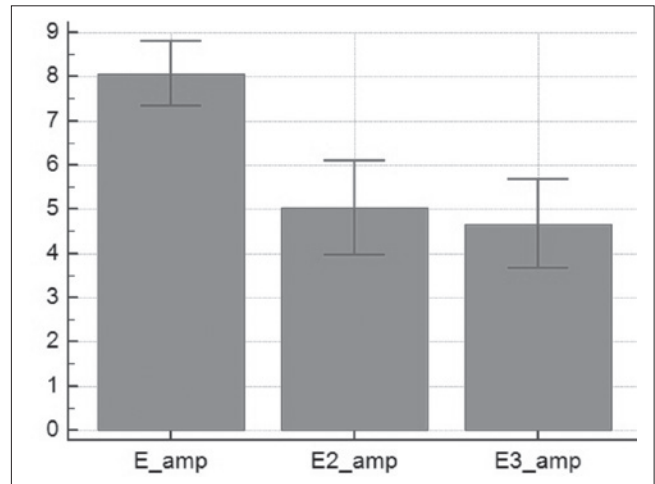


**Fig. 1.** Consort diagram.

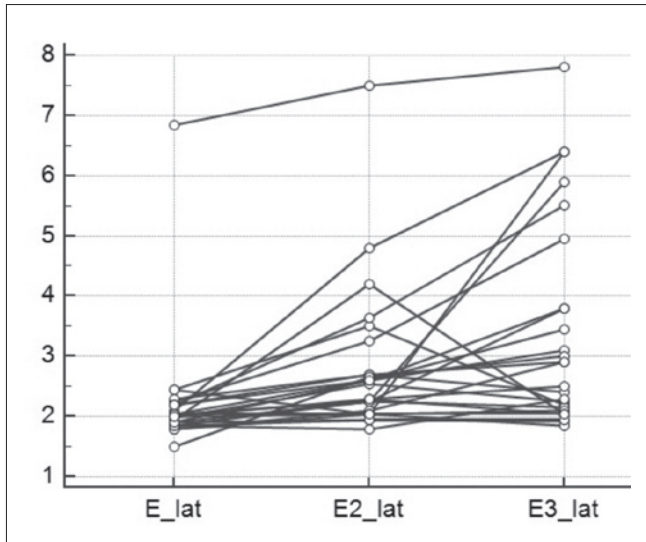
OSCC: oral squamous cell carcinoma; NCS: nerve conduction study; AAT: arm abduction test; NDQOL: neck dissection quality of life questionnaire; IJV: Internal jugular vein; RT: radiotherapy.



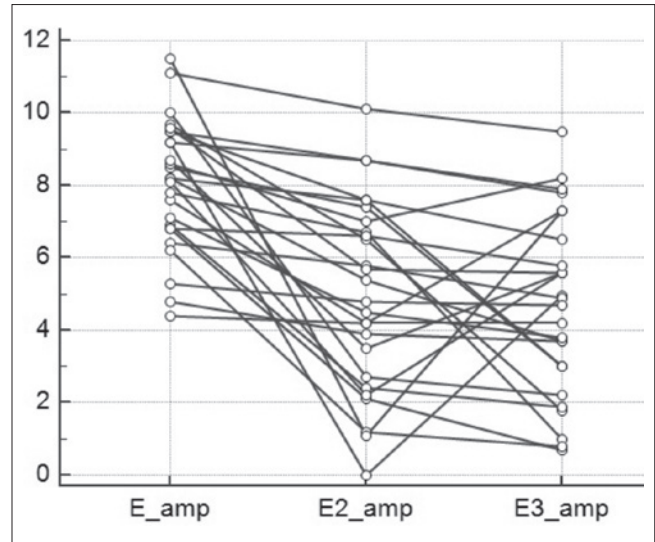
**Fig. 2.** The mean latency of SAN at different time intervals of the study (msec± SD). E\_lat: pre-operative value; E2\_lat: 1 month post-operative; E3\_lat: 6 months post-operative.



**Fig. 4.** The mean amplitude (mV ± SD) at different time intervals. E\_amp: pre-operative value; E\_2 amp: one month post-operative; E\_3 amp: 6 months post-operative.



**Fig. 3.** Latency of SAN (msec) of individual subjects (n=40) at different time intervals. E\_at: pre-operative value; E2\_lat: 1 month post-operative; E3\_lat: 6 months post-operative.



**Fig. 5.** The amplitude (mV) of study population (n = 40) at different time intervals. E\_amp: pre-operative value; E\_2 amp: one month post-operative; E\_3 amp: 6 months post-operative.

mV) compared to pre-operative value ( $8.12 \pm 0.41$  mV,  $p < 0.01$ ), this increased at 6 months ( $6.15 \pm 1.43$  mV). In comparison to the value at one month, this increase in amplitude was statistically significant ( $p < 0.001$ ). The values for latency and amplitude at different periods for postoperative neck irradiation and surgery alone group are summarised in Table II.

**Arm abduction test and NDQL questionnaire:** On goniometric analysis, the mean ( $\pm$  SD) preoperative and postoperative scores were  $4.9 (\pm 0.04)$  and  $3.23 (\pm 0.53)$ , respectively, indicating a decrease in arm abduction postoperatively (chi square test,  $p < 0.001$ ). The

mean pre-and post-operative scores for the questionnaire were  $7.05 \pm 0.03$  and  $11.05 \pm 0.33$ , respectively, indicating there was a marginal decrease in the quality of life postoperatively that was statistically significant (chi square test,  $p < 0.001$ ).

*Venous study*

The results of venous study (diameter and velocity) are summarised in the Table III. The results were compared by paired t test and the differences were statistically significant. Two patients showed partial occlusion of the vein by thrombus at 1 month postoperatively.

**Table II.** NCS in adjuvant neck radiation and surgery alone groups (mean + SD).

NCS Parameters	Adjuvant irradiation (n = 35)	Surgery alone (n = 5)	P value
Mean pre operative latency (msec)	2.12 ± 0.7	2.11 ± 0.32	0.4
Mean latency at one month (msec)	2.78 ± 1.07	2.65 ± 1.38	0.8
Mean latency at 6 months (msec)	3.07 ± 1.16	2.66 ± 1.34	0.4
Mean pre operative amplitude (mV)	8.01 ± 0.32	8.12 ± 0.41	0.3
Mean amplitude at one month (mV)	5.60 ± 1.03	2.20 ± 0.80	< 0.01
Mean amplitude at 6 months (mV)	3.07 ± 1.16	6.15 ± 1.43	0.28

**Table III.** Results of the venous Doppler study at different time intervals.

Vein diameter (mm)	Mean ±SD	p value
Preoperative	11.43 ± 0.35	
Postoperative at 1 month	9.65 ± 0.46	< 0.001
Vein velocity (cm/sec)		
Preoperative	28.05 ± 2.07	
Postoperative at 1 month	31.05 ± 2.32	0.0544

## Discussion

The modified radical neck dissection in association with resection of the primary tumour has been the standard of care for clinically node positive operable OSCC owing to the complications resulting from sacrifice of SAN and IJV as well as the comparable outcomes as with the classical radical neck dissection. However, MND may also be associated with disability secondary to the surgical technique itself, or proximity of the lymphatics to neurovascular structures. The reported nerve dysfunction rates following MND ranges from 28% to 45%<sup>8,10,11</sup>. The possible reasons can be surgical technique of excessive handling with traction injury, microtrauma due to electrodiathermy, devascularisation and adjuvant treatments such as cisplatin based chemotherapy and radiotherapy<sup>12</sup>. Also, the forced immobilisation of the nerve resulting in shoulder stiffness may contribute to shoulder dysfunction postoperatively, which can be managed by aggressive physiotherapy. Some refinements in surgical techniques such as early identification of the nerve, preservation of the level IIb nodes, especially in cN0 neck, minimising the manipulation of the SAN and IJV and avoidance of electrodiathermy near neurovascular structures may minimise disability.

In the present study, there was a statistically significant increase in mean latency of MAP and decrease in the mean amplitude of the MAP following surgery, suggesting nerve dysfunction. These results are in line with earlier studies<sup>8,13-15</sup>. Though the impact of adjuvant radiation was not assessed separately, even in 5 of the patients

who did not receive any postoperative neck irradiation, the values at 6 months were less than preoperative values. Furthermore, the mean amplitude at one month in the adjuvant RT group (5.6 ± 1.03 mV) was more than the mean amplitude in the surgery alone group (2.2 ± 0.8 mV, Table II), which was statistically significant. One interesting finding with respect to mean latency and amplitude in the no radiation group was that the 6 month postoperative values improved from those at 1 month suggesting progressive nerve recovery following surgery. This calls into question whether adjuvant neck irradiation interferes with postoperative neurological recovery, which can only be answered by larger or preferably randomised studies. With respect to arm abduction, which indirectly assess SAN function, the mean score of 3.23 corresponded to an angle between 150° to 180° and there was a significant reduction in arm abduction both pre-and postoperatively. Though there was a statistically significant reduction in quality of life following treatment as assessed with the questionnaire, this did not translate into any meaningful clinical effect. The reason for this discrepancy can be explained by the high neurological reserve and the decreased action of the trapezius muscle being compensated by other arm abductors like supraspinatus, teres major and deltoid. Furthermore, all patients, as per protocol, received post-operative shoulder and neck physiotherapy which also could have contributed favourably to the quality of life scoring.

The patency of the IJV following preservation ranges from 74% to 100% and the prevalence of thrombus ranges from 5% to 26%<sup>16-18</sup>. The possible reasons could be surgical technique of neck dissection with ligation of small branches and the external compression by the myocutaneous flaps used for reconstruction<sup>8,19</sup>. In the present study, only 5% of the veins developed partial thrombus (p > 0.4). The studies by Xing et al.<sup>20</sup> and Maria et al.<sup>12</sup> showed similar results, whereas the study by De Bree et al.<sup>18</sup> showed a significant change in patency caused by surgery. Following surgery, there was a significant decrease in the diameter of the vein as well as an increase in the velocity of blood flow, which could be due to luminal narrowing because of extrinsic compression by the myocutaneous flap used in these patients for oral reconstruction.

## Conclusions

In conclusion, the present study highlights nerve and vein dysfunction following MND type II in patients undergoing surgery for OSCC. Although nerve dysfunction compromised shoulder abduction, vein dysfunction rarely resulted in any clinical impact.

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HEAD AND NECK

# Cancer of the head and neck: a set of indicators based on register and administrative data

## *Indicatori di aderenza nel percorso di cura nei tumori del distretto cervico-facciale ottenuti da dati del registro tumori e flussi informativi sanitari*

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### SUMMARY

Head and neck (H&N) tumours are a heterogeneous group of neoplasms with 5-year relative survival ranging from about 25% for the hypopharynx to 60% for the larynx in Europe. To improve survival rates, along with therapeutic improvements, it is important to standardise and optimise care received by patients with H&N tumours across different healthcare providers. To reach this goal, it is necessary to evaluate adherence to standards of received care at a population level. Published guidelines can serve as the basis to develop indicators, which can be computed from administrative health databases, measuring the adherence to specific recommendations at the individual level in unselected H&N cancer patients, identified from a population cancer register. We developed a set of indicators and calculated them in a cohort of 2007-2012 incident cases of H&N tumours in the cancer register of the Milan province (n = 1441 cases). The study cohort was mainly composed of men (77%) and patients older than 50 years (89%). Surgery was the most frequently employed treatment (66%). Ten percent of patients had no recorded treatment. Timing between cyto-histological assessment and first therapy for those having a recorded microscopic verification procedure was ≤ 60 days for 90.4% of patients undergoing surgery, 86.3% of those undergoing radiotherapy, and 90.7% of patients receiving chemotherapy. Eighty-three percent of patients underwent cyto-histological assessment in the 180 days before the first treatment. Evaluation by a pain therapist, opioid therapy or hospitalisation for palliative therapy in the 90 days before death was performed in 51% of patients who eventually died of cancer. This is the first Italian study defining and calculating quality indicators to monitor adherence to standards of care received by H&N cancer patients at a population level.

KEY WORDS: Quality indicators • Head and neck neoplasms • Health care evaluation • Guideline adherence

### RIASSUNTO

*I tumori della testa e del collo (T&C) sono un gruppo eterogeneo di neoplasie che presentano ancora un elevato tasso di mortalità, con una sopravvivenza relativa a cinque anni che va da circa il 25% per l'ipofaringe al 60% per la laringe in Europa. Per incrementare ulteriormente i tassi di sopravvivenza, congiuntamente ai progressi diagnostici e terapeutici, è importante standardizzare e rendere aderente alle linee guida internazionali il percorso di diagnosi e cura a cui sono sottoposti i pazienti con tumore della T&C. Per raggiungere questo obiettivo, è necessario valutare il percorso di cura a livello dell'intera coorte dei pazienti con tumore della T&C di una determinata area geografica, determinata tramite un registro tumori di popolazione e quindi non selezionata. Le linee guida, nazionali ed internazionali, basate su evidenze scientifiche aggiornate possono servire da punto di partenza per sviluppare degli indicatori di aderenza calcolabili a partire dal registro tumori stesso e da database sanitari amministrativi correnti. Abbiamo sviluppato una serie di indicatori in grado di misurare, a livello individuale, l'adesione a raccomandazioni specifiche relative alla diagnosi ed al trattamento dei tumori della T&C. Li abbiamo poi calcolati nei pazienti con tumore della T&C individuati dal registro tumori della provincia di Milano (n = 1441 casi incidenti nel periodo 2007-2012). La coorte in studio è principalmente composta da uomini (77%) e pazienti di età superiore ai 50 anni (89%). Il dieci per cento dei pazienti non ha alcun trattamento registrato. Nei restanti pazienti, la chirurgia è stata il trattamento più frequentemente utilizzato (66%). Per quanto riguarda il tempo di attesa tra la valutazione cito-istologica e l'inizio della prima terapia, per i pazienti per cui è presente una verifica microscopica della neoplasia, esso è stato uguale o inferiore a 60 giorni per il 90,4% dei pazienti sottoposti come primo trattamento a chirurgia, per l'86,3% di quelli che hanno fatto radioterapia e per il 90,7% dei pazienti che hanno ricevuto chemioterapia. L'83% dei pazienti trattati ha effettuato una valutazione cito-istologica nei 180 giorni precedenti il primo trattamento. Tecniche di radioterapia ad intensità modulata (IMRT) sono state impiegate nel 37% dei pazienti trattati con radioterapia. Il 51% dei pazienti poi deceduti è stato valutato da un terapeuta del dolore, ha ricevuto oppiacei o è stato ricoverato nei 90 giorni precedenti l'exitus. Questo è il primo studio italiano che definisce e calcola un insieme di indicatori di aderenza, allo scopo di monitorare a livello di popolazione differenti aspetti del percorso di cura dei pazienti affetti da tumore T&C e potrebbe essere utilizzato come punto di partenza per monitorare l'aderenza alle linee guida a livello nazionale.*

PAROLE CHIAVE: Indicatori di qualità del processo di cura • Neoplasie della testa e del collo • Valutazione delle cure • Aderenza alle Linee Guida



## Introduction

Head and neck (H&N) tumours are a heterogeneous group of relatively infrequent neoplasms, with a worldwide age-standardised incidence rate of 14.3 per 100,000 in men and 4.4 per 100,000 in women<sup>1</sup>. Mortality rates have been slowing decreasing in the last decades in western countries<sup>1,2</sup>, presumptively due to advances in diagnosis and treatment<sup>3-5</sup>, but also to the increase in the proportion of less aggressive HPV-related tumours<sup>6</sup>. However, there is still a high local recurrence rate (40-60%) in patients with locally advanced tumours<sup>5</sup>, i.e. stages III and IV according to American Joint Commission of Cancer – AJCC – classification 7<sup>th</sup> ed.<sup>7</sup> and 5-year relative survival across Europe ranges from about 25% for hypopharyngeal to 60% for laryngeal cancers<sup>8</sup>. To further improve survival, it is important to deliver the best available care, optimising and standardising diagnosis and treatment received by patients with H&N tumours across different healthcare providers. An evaluation of adherence to standards of the care received, at a population level and in recent years, is necessary to detect deviations from international recommendations and take actions to improve the delivered care.

A recently published study has investigated the causes of deviation from guidelines in patients with H&N tumours, and found that patients not receiving standard treatment have a lower 3-year survival rate<sup>9</sup>. Among factors associated to non-adherence to guidelines there are gender, age, socio-economic conditions and the presence of comorbidities<sup>9</sup>. Concurrent chronic diseases are frequent in patients with H&N tumours, both because of advanced mean age at diagnosis and the high prevalence of tobacco smoking and alcohol consumption<sup>9,10</sup>. In this group of tumours there are different entities, both in terms of aetiology (i.e. alcohol and tobacco vs. human papilloma virus) and site-related histology (i.e. salivary gland tumours vs. squamous cell carcinoma in the upper aerodigestive tract). According to this heterogeneity, recently developed guidelines such as those of the UK National Institute for Health and Care Excellence (NICE) and the Associazione Italiana di Oncologia Medica (AIOM) include recommendations common to all sites and aetiologies, and others that are specific for tumour site, stage and histology<sup>11,12</sup>.

Indicators used in public health are measures, often proportions, meant to describe the quality of care for a group of patients. They can be compiled from either clinical or administrative data that has been recorded about particular aspects of care. They may evaluate structures, processes or outcomes of care, and are usually aimed at evaluating the quality of the delivered care to inform improvement activities<sup>13,14</sup>.

Evidence-based guidelines can serve as the basis to develop process indicators, which can be computed from administrative health databases, measuring adherence to specific recommendations at the individual level in unselected H&N cancer patients, identified from a population cancer register. We decided to use NICE and AIOM guidelines<sup>11,12</sup> as they both cover the different aspects of care and provide documentation of the applied methodology, for selected indicators we also used additional guidelines (Appendix: Supplementary Table I). To implement a set of indicators capable of monitoring different aspects of care, we linked information included in the cancer register with administrative databases, stratifying for tumour site, age, gender and Charlson comorbidity index<sup>15</sup>. Our aim is to describe the developed set of indicators and discuss their values as calculated in the cohort of the 2007-2012 incident cases of H&N tumours in the cancer register of the Milan province (Lombardy region, Italy).

## Materials and methods

### *Selection and description of the cohort*

The cohort included all patients resident in the Milan province and registered with the regional health service developing an H&N cancer (ICDO-3 topographic codes<sup>16</sup>: C00-06 oral cavity, C07-08 salivary glands, C09-13 pharynx, C32 larynx; C14 other and ill-defined sites in lip, oral cavity and pharynx) in the period 2007-2012. Nose and paranasal sinuses tumours were not included, as it is usual practice in tumour registry reports, because they are rare and often occupational cancers<sup>17</sup>. The Milan province includes 14 municipalities around Milan in Northern Italy and had a population of 1,546,237 inhabitants on 1 Jan. 2013, 754,821 males and 791,416 females<sup>18</sup>. The cancer register is nationally accredited and partially automated, using multiple sources of information (i.e. inpatient, histopathology and death certificate databases) and a record linkage algorithm to match all information at the individual level. The date of incidence was defined, according to international cancer registration rules<sup>19</sup>, as the first available date among those of pathological examination, clinical diagnosis or death. Exclusion criteria were: previous malignant tumour (from 1996 to 3 months before diagnosis, excluding non-melanoma skin cancers), tumours identified only through death certificate and distant metastases at diagnosis. The latter were identified through the register and the inpatient database, searching in records of hospitalisation – occurred from 45 days prior to 180 days after H&N cancer diagnosis – ICD-9 codes 197 and 198 in any of the diagnosis fields.

**Table I.** Patient and tumour characteristics from the cohort of head and neck 2007-2012 incident cancers, non-metastatic at diagnosis (N = 1441), from the nationally accredited cancer register of the Milan province, Italy.

	No.	%
<b>Year of incidence</b>		
2007	246	17.1
2008	266	18.5
2009	252	17.5
2010	195	13.5
2011	261	18.1
2012	221	15.3
<b>Age class</b>		
≤ 40 years	43	3.0
41-50	120	8.3
51-55	131	9.1
56-60	190	13.2
61-65	230	15.9
65-70	246	17.1
71-75	203	14.1
> 75	278	19.3
<b>Gender</b>		
Male	1110	77.0
Female	331	23.0
<b>Charlson index</b>		
0	865	60.0
1-2	448	31.1
≥ 3	128	8.9
<b>Site</b>		
Oral cavity (C00-06)	469	32.5
Salivary glands (C07-08)	79	5.5
Oropharynx (C09-10)	167	11.6
Nasopharynx (C11)	65	4.5
Hypopharynx (C12-13)	82	5.7
Larynx (C32)	567	39.4
Other and ill-defined sites (C14)	12	0.8
<b>Histology</b>		
Malignant tumour, not specified	60	4.2
Squamous cell carcinoma	1245	86.4
Adeno, muco, acinar, cystic carcinomas	81	5.6
Others*	55	3.8
<b>First treatment</b>		
No recorded treatment	142	9.9
Surgery	852	59.1
Radiotherapy	396	27.5
CT alone	51	3.5
<b>Total number of patients</b>	<b>1441</b>	

\*Including mixed and undifferentiated.

Abbreviations: RT = radiotherapy; CT = chemotherapy.

#### Identification of the set of indicators and calculation at patient level

Referring mainly to the comprehensive NICE and AIOM guidelines<sup>11,12</sup>, but also to specific guidelines reported in Supplementary Table I, a group of epidemiologists and a multidisciplinary team of surgeons, medical and radiation oncologists, which are members of the *Associazione Italiana di Oncologia Cervico-Cefalica*, *Associazione Italiana di Radioterapia Oncologica*, *Associazione Italiana di Oncologia Medica*, and *Società Italiana di Otorinolaringologia e Chirurgia Cervico Facciale*, developed a set of process indicators. All indicators, each measuring adherence to a selected guideline, had to be computable from the available administrative data. In order to calculate the indicators at the patient level, we used all available computerised sources of health information of the Lombardy region from January 2006 to December 2014. These sources included: inpatient database (SDO), prescription databases, database of outpatient diagnostic and therapeutic procedures. The aim was to trace different facets of care, from organisational aspects, to diagnosis and treatment, and to use multiple independent sources of information to improve the reliability of the indicators. Vital status was updated at 30 Dec. 2015, using the database of the people registered with the Regional Health Service (Nuova Anagrafe Regionale), where an update is performed every 6 months covering at least 95% of deaths. We derived gender and age at diagnosis from the register. On the available administrative databases, both in and outpatients, we also calculated the Charlson comorbidity index<sup>15,20</sup>. From the administrative databases, we also derived type and date of the first administered therapy and hospital where it was administered. First therapy, as used in the calculation of the indicators, does not consider combined therapies and was defined as following: we identified all therapeutic events i.e. surgery, radiotherapy (RT) or chemotherapy (CT) in the 180 days preceding and following the date of diagnosis recorded in the register. We then assigned the patient to the surgery category if he/she had undergone, in the defined time-window, any of the following procedures (ICD-9 codes) irrespective of RT or CT: oral cavity, 24.31, 25.1-25.4, 27.3x, 27.42, 27.43, 27.49, 27.72; salivary glands, 26.29 26.3x; pharynx, 28.2-28.6, 29.3x; larynx, 30.1-30.4, 30.09; facial bones: 76.2x-76.6x, 76.9x; soft tissues 83.49. If the patient had not received surgery but RT (from inpatient database: V58.0, 92.2; from outpatient treatment database: 92.23.1 to 92.27.5, 92.29), we assigned him/her to the RT category regardless of having performed also CT. If the patient had not received surgery nor RT but CT only, we assigned him/her to CT (from inpatient database: V58.1, 99.25; from outpatient treatment database: 99.25, MAC01,

MAC02, MAC04; from database of prescription ‘file F’, ATC code: LO1).

To assess the cyto-histological confirmation of the tumour, we searched for the codes reported in Table II, footnote \*. In a sample of revised medical records, we noticed that the biopsy performed during an endoscopy was not always coded. Consequently, we calculated two versions of the indicators involving cyto-histological evaluation (S1, S2, S4, D1): one using biopsy codes only (Table II, footnote \*) and the other assuming that endoscopies of the pharynx and larynx (ICD-9 codes 29.11 and 31.42) were concomitant with a non-coded cyto-histological assessment. The true value of the S1, S2, S4, and D1 indicators is expected to be between the two versions of the indicator. Two indicators, T1 and T2, are technically outcome indicators by they are commonly used as quality indicators for surgery<sup>21,22</sup>, even if they need to be interpreted with caution. Deterministic record linkage on a unique key was used to match all information at the patient level. Record linkage was performed at the local health authority of Milan, according to the national legislation on sensitive data<sup>23</sup>.

### Statistical analysis

The characteristics of the included patients and tumours are described using percentages. For all indicators, we calculated the proportion of patients who received the procedure,

in the defined time window, among those eligible. Indicators of diagnosis and treatment are presented overall and stratified for tumour site. All indicators were also stratified by: gender, age (< 60, 60-70 and > 70 years), and comorbidities (Charlson index 0 vs  $\geq 1$ ). Overall survival was estimated using the Kaplan-Meier method<sup>24</sup>. To investigate the association between respecting each guideline and survival, we fitted a separate Cox model for each indicator (indicators measuring proportion of death were excluded), first without covariates and then adjusting for gender, age, Charlson index and tumour site. This analysis does not aim to establish causal relationships, as important confounders as stage at diagnosis and socioeconomic status are not accounted for. Results are presented as hazard ratio (HR) of death for not fulfilling vs. fulfilling the guideline with its 95% confidence interval (CI). All analyses were performed with SAS software (v.9.4, SAS Institute, Cary NC).

## Results

### Population

From 1<sup>st</sup> January 2007 to 31<sup>st</sup> December 2012 there were 1,650 incident cases of invasive H&N cancers in the register (Fig. 1). After exclusions (DCO, n = 7; multiple primary cancers n = 108; patients with distant metastasis at diagnosis, n = 94), the analysed cohort included 1,441 cases, whose characteristics are reported in Table I.

The study cohort was mainly composed of men (77.0%). Eighty-nine percent of patients were 51 years or older and 40% had at least one comorbidity. Concerning site, the most frequent were laryngeal (39.4%) and oral (32.5%) cancers. By far the most frequent histological type was squamous cell carcinoma (86.4%). Ten percent of patients (n = 142) had no recorded treatment. However, this figure includes those patients having a clinically believed benign tumour, which then resulted malignant at pathological examination, and was completely excised during the diagnostic procedure and consequently required no further treatment. Among treated patients, surgery was the most frequently employed treatment (65.6%).

Considering the hospitals delivering surgery, the number of any head and neck therapeutic surgical procedures in H&N patients per provider in a year, calculated on 2015, varied from 1 to 78. RT treatments were performed in centers with an annual volume of procedures for all cancers varying from 7,580 to 64,198 (measured for 2016).

### Identified set of indicators

The identified indicators were organised into three groups:

**Table II.** Definition and values of the indicators evaluating time between diagnosis and treatment, and between treatments.

Indicator code	Description Proportion of patients having an:	No. of eligible pts	Value (%)
S1	Interval between cyto-histological assessment* and surgery as the first treatment $\leq 60$ days	665 <sup>†</sup>	90.4
S2	Interval between cyto-histological assessment* and RT as the first treatment $\leq 60$ days	357 <sup>†</sup>	86.3
S3	Interval between discharge from primary surgery and postoperative RT $\leq 60$ days	302	69.9
S4	Interval between cyto-histological assessment* and CT as the first treatment $\leq 60$ days	43 <sup>†</sup>	90.7

\*ICD-9 codes. Biopsies: cranial nerves, 04.11, 04.12, 05.11; oral cavity, 24.11, 25.01, 25.02, 27.21-27.24; salivary glands, 26.11, 26.12; pharynx, 28.11, 29.12; larynx, 31.43, 31.45; facial bones, 76.11; soft tissues, 83.21; lymph-nodes, 40.11. Microscopic examination of specimen from: ear, nose, throat, and larynx, 90.3; lymph-nodes, 90.7. Pharyngoscopy: 29.11; Laryngoscopy: 31.42.

<sup>†</sup>The eligible patients where those having a procedure of those included in note \* in the 180 days before the first treatment, i.e. patients for whom there was no record of a cyto-histological assessment were not included. Also the 9 patients undergoing surgery after adjuvant RT or CT were excluded from the denominator of S1.

Abbreviations: RT = radiotherapy; CT = chemotherapy.

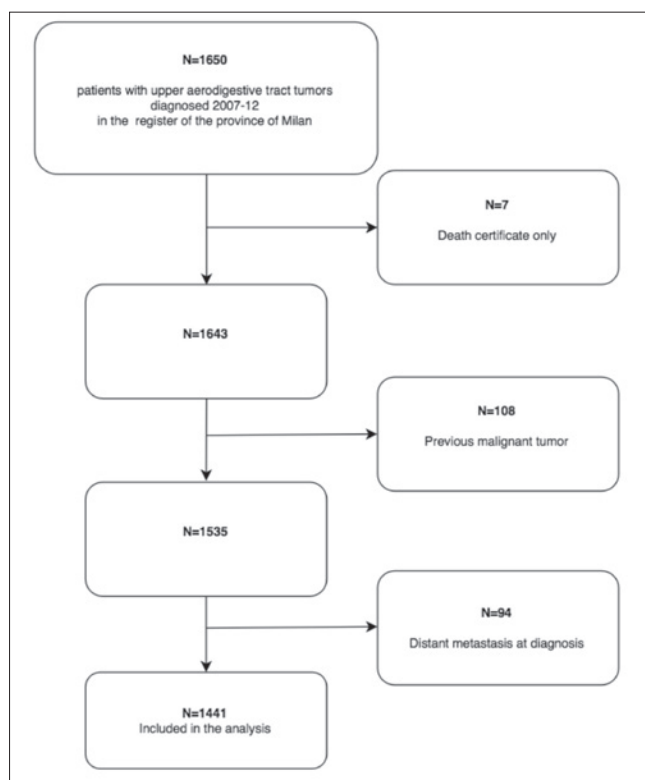


Fig. 1. Sample selection flow-chart.

1) indicators measuring the time between diagnosis and relevant procedures or treatments (Table II), 2) indicators evaluating diagnostic procedures (Table IIIa) and 3) indicators evaluating therapeutic procedures (Table IIIb). No follow-up indicators were calculated because of the absence of high level evidence on the type and timing of follow-up<sup>11</sup>. Concerning timing between diagnosis and surgery as the first treatment (Table II), 90.4% of patients having a cyto- or histological examination record (n = 665) had an inter-

val between the two events shorter than or equal to 60 days (S1, when calculated not including fibroscopy only codes: 73.8%), and 68.9% shorter than or equal to 30 days (when calculated not including fibroscopy only codes: 55.3%). For patients receiving radiotherapy as the first treatment, 86.3% of patients having a cyto- or histological examination record (n = 357) had an interval between the two events shorter than or equal to 60 days (S2, when calculated not including fibroscopy codes: 78.7%), and 48.7% shorter than or equal to 30 days (when not including fibroscopy codes: 37.0%). When RT was performed after surgery (n = 302), the interval between discharge after the surgical intervention and RT was lower or equal than 60 days in 69.9% of patients (S3). For those undergoing CT, 90.7% of patients having a cyto- or histological examination record (n = 43) had an interval between the two events shorter than or equal to 60 days (S4, when calculated not including fibroscopy codes: 83.7%), and 32.6% shorter than or equal to 30 days (when calculated not including fibroscopy codes: 25.6%). Variations across gender, age and comorbidity level (Table IV) were negligible for the interval between cyto-histological assessment and surgery (S1). For RT (S2), the proportion was lower for patients with comorbidities (80.6% for Charlson index  $\geq 1$  vs. 90.9% for patients with 0). Concerning CT (S4), the proportion was lower for older patients (92.3% for over 70 year olds vs 100% for 60 year olds or younger).

Regarding indicators measuring diagnostic procedures (Table IIIa), 82.6% of patients underwent cyto-histological assessment in the 180 days before first treatment (D1, when calculated not including fibroscopy codes: 71.8%): 78.9% of those undergoing surgery, 90.1% of those receiving RT, and 84.3% of patients submitted to CT. The percentage varied from 77.1% for salivary glands to 90.6% for pharyngeal tumours, and it was fairly stable across gender, age and Charlson index (Table IV).

Forty-one percent of patients with a tumour site at high

Table IIIa. Definition and values of the indicators evaluating diagnostic procedures, overall and across tumour types.

Indicator code	Description <i>Proportion of patients:</i>	No. eligible overall	Value (%)				
			Oral cavity N = 469	Salivary glands N = 79	Pharynx N = 314	Larynx N = 567	Overall
D1	Having performed a cyto-histological assessment* of the primary tumour in the 180 days before the first treatment	1299	77.7	77.1	90.6	82.7	82.6
D2	With distant metastasis risk tumour type <sup>†</sup> undergoing systemic staging with PET-CT or whole body computed tomography	249			41.0		41.0

\*ICD-9 codes. Biopsies: cranial nerves, 04.11, 04.12, 05.11; oral cavity, 24.11, 25.01, 25.02, 27.21-27.24; salivary glands, 26.11, 26.12; pharynx, 28.11, 29.12; larynx, 31.43, 31.45; facial bones, 76.11; soft tissues, 83.21; lymph-nodes, 40.11. Microscopic examination of specimen from: ear, nose, throat, and larynx, 90.3; lymph-nodes, 90.7. Pharyngoscopy: 29.11; Laryngoscopy: 31.42.

<sup>†</sup> rhino and hypo-pharynx.

**Table IIIb.** Definition and values of the indicators evaluating treatment procedures, overall and across tumour types.

Indicator code	Description <i>Proportion of patients:</i>	No. eligible overall	Value (%)				Overall
			Oral cavity N = 469	Salivary glands N = 79	Pharynx N = 314	Larynx N = 567	
T1	Deceased in perioperative period (≤15 days from surgery)	852	1.6		1.1	0.3	0.8
T2	With a second hospital access ≤ 30 days from discharge for primary surgery	852	15.1	10.2	19.1	27.1	20.8
T3	Treated with IMRT*	706	32.4	37.2	51.1	26.4	36.8
T4	Deceased and evaluated by pain therapist, under opioids or hospitalised for palliation in the 90 days before†	606	56.5	67.9	53.3	40.9	51.0

\*IMRT codes 92.24.6, 92.29K e 92.29L.

†ICD9 codes 89.01.1, 89.70.1, 92.28.6 in the outpatient procedures, ATC code N02A\* in prescription database, V66.7 in inpatient database.

Abbreviations: PET-CT = Positron Emission Tomography-Computed Tomography, IMRT = Intensity Modulated Radiotherapy, CT = chemotherapy.

**Table IV.** Values of the indicators stratified for gender, age group and Charlson index.

Indicator code	Description	Value (%)						
		Gender		Age group			Charlson index	
		Male N = 1110	Female N = 331	≤ 60 N = 484	61-70 N = 476	> 70 N = 481	0 N = 865	≥ 1 N = 576
S1	Interval between cyto-histological assessment and surgery as the first treatment ≤ 60 days	91.2	87.4	87.9	94.6	88.6	90.8	89.8
S2	Interval between cyto-histological assessment and RT as the first treatment ≤ 60 days	85.2	90.4	87.6	86.7	84.3	90.9	80.6
S3	Interval between discharge from primary surgery and postoperative RT ≤ 60 days	69.8	70.0	69.6	67.8	72.9	70.6	68.8
S4	Interval between cyto-histological assessment and CT as the first treatment ≤ 60 days	87.5	100.0	100.0	81.3	92.3	91.3	90.0
D1	Having performed a cyto-histological assessment of the primary tumour in the 180 days before the first treatment	82.9	81.5	83.5	83.1	81.1	81.3	84.6
D2	With distant metastasis risk tumour type undergoing systemic staging with PET-CT or whole body computed tomography	40.6	41.9	41.8	50.6	29.3	35.2	49.0
T1	Deceased in perioperative period (≤ 15 days from surgery)	0.6	1.5	0.4	0.4	1.7	0.8	0.9
T2	With a second hospital access ≤ 30 days from discharge for primary surgery	22.5	14.9	19.8	22.4	20.1	19.7	22.5
T3	Treated with IMRT	36.2	39.1	47.4	36.3	24.9	34.3	40.2
T4	Deceased and evaluated by pain therapist, under opioids or hospitalised for palliation in the 90 days before	50.7	51.9	61.6	52.1	44.2	55.4	46.5

**Table V.** Hazard ratio (HR) of death for indicator not fulfilled vs. fulfilled. The adjusted model includes gender, age, Charlson index and tumour site as covariates.

Indicator		Unadjusted model			Adjusted model		
		HR	95% CI		HR	95% CI	
S1	Interval between cyto-histological assessment and surgery as the first treatment $\leq$ 60 days	0.99	0.64	1.54	0.97	0.62	1.51
S2	Interval between cyto-histological assessment and RT as the first treatment $\leq$ 60 days	1.57	1.05	2.34	1.25	0.81	1.92
S3	Interval between discharge from primary surgery and postoperative RT $\leq$ 60 days	0.81	0.55	1.19	0.79	0.53	1.18
S4	Interval between cyto-histological assessment and CT as the first treatment $\leq$ 60 days	1.01	0.31	3.36	0.70	0.20	2.43
D1	Having performed a cyto-histological assessment of the primary tumour in the 180 days before the first treatment	1.01	0.80	1.26	1.00	0.80	1.27
D2*	With distant metastasis risk tumour type undergoing systemic staging with PET-CT or whole body computed tomography	0.97	0.68	1.38	0.93	0.65	1.33
T2	With a second hospital access $\leq$ 30 days from discharge for primary surgery	1.01	0.76	1.34	0.99	0.74	1.32
T3	Treated with IMRT	1.26	0.99	1.59	1.20	0.94	1.54

\*not adjusted for tumour site.

Abbreviations: HR = hazard ratio, CI: = confidence interval.

risk of distant metastasis (nasopharyngeal cancers) underwent systemic staging (D2) before treatment, less frequently (29.3%) patients over 70 years and more frequently those with comorbidities (49.0%, Table IV).

Concerning treatment indicators (Table IIIb), 0.8% of patients died in the perioperative period ( $\leq$  15 days from curative surgery, T1); 28.8% of patients had a second hospital access within 30 days from discharge after surgery as the first treatment (T2), excluding hospitalisations for RT and CT, plastic surgery, prosthesis positioning, stoma checking and palliative care. Women had a second hospital access less frequently (14.9%, Table IV). In the cohort of patients that underwent RT, intensity modulated RT (IMRT) techniques were used in 36.8% of patients undergoing RT (T3). Fifty-one percent of deceased patients were evaluated by a pain therapist, under opioids or hospitalised for palliation in the 90 days before death (T4), less frequently if they had comorbidities (46.5%) or were over 70 years (44.2%, Table IV).

Five-year overall survival was 60.6% (95% CI, 57.9-63.1%). Median follow-up time was 6.1 years (95% CI, 5.8-6.2 years). An interval between RT and cyto-histological assessment of the primary tumour longer than 60 days (S2) was significantly associated with a higher risk of death only in the unadjusted model (HR, 1.57; 95% CI, 1.05-2.34, Table V).

## Discussion

In the last decade there has been much work intended to evaluate the quality of care delivered to oncologic patients using administrative databases<sup>13,25</sup>, although H&N cancers have seldom been considered<sup>26</sup>. This is the first study aiming at identifying quality indicators for H&N cancer from routinely available administrative health data and a cancer registry in Italy. Those indicators have been designed and interpreted together by epidemiologists and health professionals directly involved in the care of patients, and may serve as the basis to define quality standards both in Lombardy region and Italy. The relative rarity and heterogeneity of H&N tumours creates additional problems in determining guidelines common to all sites and consequently in developing indicators to evaluate adherence to guidelines. We implemented a set of indicators to collectively monitor adherence to important diagnostic and therapeutic guidelines for H&N tumours, using data included in a cancer register and administrative health databases, and tested it on the cohort of 2007-2012 incident cases of the Milan province.

In this cohort, 54% of treated patients received a single treatment modality, which was surgical intervention in 40% of cases. The remaining 46% of patients received a multimodal treatment. This remarks the importance of a multidisciplinary approach, especially in patients with more advanced stages<sup>27,28</sup>. Multidisciplinary evaluation

is recommended in guidelines<sup>11 12</sup> and is an important quality indicator to measure. However, for the analysed years, it could not be monitored reliably using administrative data. Surgery was characterised by a short waiting time, lower than 30 days from diagnosis for almost 70% of patients receiving it as first treatment. The indicator measuring a second hospital access within 30 days from discharge after surgery (21%) needs to be interpreted with caution, as it does not distinguish between unplanned, i.e. radicalisations or complications, and planned readmissions such as a programmed second surgical procedure as a part of the primary intervention e.g. neck dissection after transoral glossectomy, second-look cordectomy after laser microresection of glottic carcinoma involving the anterior commissure.

When RT was the first therapy, only 49% of patients started it within 30 days from diagnosis. A multidisciplinary approach could also lower this waiting time, because patients are almost always referred to RT by other specialists (e.g. surgeon, medical oncologists) and this implies a delay between diagnosis and the start of RT<sup>27-30</sup>. Similar considerations apply when interpreting that about 70% of patients started the postoperative RT within 60 days from discharge after surgery. According to international guidelines<sup>11</sup>, RT should start as soon as possible ideally within 6 weeks from surgery. However, some clinical factors such as postoperative complications as well as logistic challenges (e.g. limited number of RT unit, arrangements for concomitant CT) could explain our finding. Regarding the type of radiation treatment, considering the period analysed in this study (i.e. from 2007 to 2012) it is not surprising that only 39% of patients were treated with more recent and advanced approaches like IMRT, which have diffused in recent years<sup>31</sup>. Almost 20% of patients, even assuming that pharyngoscopy and laryngoscopy close to the diagnosis included a non-coded cyto-histological assessment, had no recorded microscopic verification procedure before treatment. These cases would need a more detailed ascertainment of clinical records, as there may be patients undergoing a single diagnostic-therapeutic procedure, i.e. very small lesions on which a biopsy would produce macroscopic changes, tumours in sites that would require general anaesthesia for both biopsy and treatment, such as glottis erythroleukoplakia. Also, as in all studies using administrative databases, there could be a minimal loss of information due to private healthcare providers.

We are well aware of the limitations of our study that derive from the use of the administrative data. Not all the indicators judged to be important to monitor the care process can be calculated because of lack of information in the routinely collected health data of a particular health system. In this case, the availability of stage at diagnosis would have al-

lowed to calculate additional stage-specific indicators, to better monitor the therapeutic process. In addition, the relatively small number of cases does not allow to investigate predictors of adherence to guidelines in a multivariate model in order to evaluate the impact of the hospital case volume, year of diagnosis and other factors that most probably are associated with treatment outcome.

This type of approach on a larger cohort of patients could also allow evaluation of the relationship between time from diagnosis to treatment, or among different treatments, and outcome.

## Conclusions

This is the first study in Italy defining and calculating from a cancer register and administrative health data indicators of adherence to guidelines in H&N cancer patients, and could be the starting point to propose indicators to inform health policies at the national level.

## Acknowledgements

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**APPENDIX: Supplementary Table I.** Evidence of the recommendations evaluated by the developed indicators.

Indicator code	Description <i>Proportion of patients having an:</i>	Recommendation	Evidence type and strength (grade)
S1	Interval between cyto-histological assessment and surgery as the first treatment ≤ 60 days	Cancer care needs to be timely <sup>1</sup>	Meta-analysis <sup>2</sup> Moderate
S4	Interval between cyto-histological assessment and CT as the first treatment ≤ 60 days		
S2	Interval between cyto-histological assessment and RT as the first treatment ≤ 60 days	Cancer care needs to be timely <sup>1</sup>	Meta-analysis <sup>3</sup> Strong
S3	Interval between discharge from primary surgery and postoperative RT ≤ 60 days	Time between surgery and start of radiotherapy should be less than 6 weeks <sup>4</sup>	Observational studies <sup>5,6</sup> Week
D1	Having performed a cyto-histological assessment of the primary tumor in the 180 days before the first treatment	A clinically suspected diagnosis of malignancy should be confirmed by biopsy or cytology before operation <sup>7</sup>	No specific studies Week
D2	With distant metastasis risk tumor type undergoing systemic staging with PET-CT or whole body computed tomography	Offer systemic staging to all people with cancer of the upper aerodigestive tract except those with T1N0 or T2N0 disease. Offer FDG PET-CT to people with T4 cancer of the hypopharynx or nasopharynx. Offer FDG PET-CT to people with N3 cancer of the upper aerodigestive tract <sup>8</sup>	RCTs and observationals <sup>8</sup> High
T1	Deceased in perioperative period (≤ 15 days from surgery)	Used as a proxy for adequate pre-surgical evaluation and quality of surgery <sup>9</sup>	Expert opinion <sup>10</sup> Week
T2	With a second hospital access ≤ 3 days from discharge for primary surgery	Used as a proxy for adequate pre-surgical evaluation and quality of surgery <sup>11,12</sup>	Observational studies <sup>13</sup> Week
T3	Treated with IMRT	IMRT therapy is recommended for pharyngeal cancer <sup>4</sup>	Observational studies <sup>14,15</sup> Week
T4	Deceased and evaluated by pain therapist, under opioids or hospitalized for palliation in the 90 days before	Patients with advanced cancer, whether patient or outpatient, should receive dedicated palliative care services, early in the disease course, concurrent with active treatment <sup>16</sup>	Systematic review <sup>17</sup> Strong

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## LARYNGOLOGY

# Impact of resection margin status on oncological outcomes after CO<sub>2</sub> laser cordectomy

## *Impatto sui risultati oncologici dei margini di resezione dopo cordectomia laser CO<sub>2</sub>*

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## SUMMARY

The management of positive resection margins in micro-endoscopic glottic laser surgery remains a controversial and critical point. This study aims to assess the impact of margin status after transoral laser surgery on local control, survival and organ preservation rates; the decision-making process and treatment options in cases with positive margins are also discussed. We retrospectively reviewed the clinical and histological records of 308 consecutive patients with primary early glottic carcinoma (T1a, T1b, selected T2) and treated with endoscopic laser cordectomy. Recurrence rates and survival related to margin status were analysed using the Kaplan-Meier method. Local relapses and disease-free-survival rates were significantly related to excision margin status ( $p < 0.001$ ). In the T1a category ( $n = 228$ ) no significant differences were observed in disease-free-survival ( $p = 0.889$ ) and overall survival ( $p = 0.426$ ) between patients submitted to further treatment (revision endoscopic surgery or radiotherapy) for positive excision margins and patients who were left untreated. In 20 of 24 (83%) patients with positive margins that were surgically re-excised, no residual carcinoma was detected. Margin status (mainly multifocal and deep positive margins) at first surgery was significantly related to the final organ preservation rate ( $p < 0.001$ ). Margin status during laser cordectomy in early glottic cancer has a prognostic impact on local control of disease without compromising survival. Patients with multifocal and deep positive borders should be surgically retreated and strictly monitored to increase the organ preservation rates. Careful preparation and mapping of the surgical specimen enhances the accuracy of pathological examination by reducing the risk of overestimate positive margins.

KEY WORDS: CO<sub>2</sub> laser • Cordectomy • Early glottic carcinoma

## RIASSUNTO

*Le modalità di trattamento dei margini positivi dopo cordectomia endoscopica con laser CO<sub>2</sub> presentano aspetti critici e ancora controversi. Questo lavoro si propone in primo luogo di analizzare l'impatto dello stato dei margini positivi dopo cordectomia endoscopica sul controllo di malattia, sulla sopravvivenza e sulle percentuali di preservazione d'organo; secondariamente di discutere le strategie operative e le opzioni di trattamento nei pazienti con margini positivi. Sono stati analizzati retrospettivamente i dati clinici ed istologici di 308 pazienti consecutivi trattati per carcinomi glottici in stadio iniziale (T1a, T1b e T2 selezionati) mediante cordectomia endoscopica laser CO<sub>2</sub>. Per l'analisi dei tassi di recidiva e di sopravvivenza è stato impiegato il metodo di Kaplan-Meier. Le recidive locali di malattia e la sopravvivenza libera da malattia correlavano in modo statisticamente significativo con lo stato dei margini di resezione ( $p < 0,001$ ); le percentuali di sopravvivenza globale a 60 mesi risultavano essere pari al 90% per i margini negativi e all'81,4% per quelli positivi ( $p = 0,27$ ). Nei casi con margini di resezione positivi appartenenti al gruppo T1 ( $n = 228$ ) non sono state riscontrate differenze statisticamente significative, in termini di sopravvivenza libera da malattia ( $p = 0,889$ ) e globale ( $p = 0,426$ ), fra pazienti sottoposti a ulteriore trattamento (revisione chirurgica endoscopica o RT) e pazienti non trattati. In 20 dei 24 (83%) pazienti con margini positivi trattati mediante revisione chirurgica endoscopica non è stato riscontrato carcinoma residuo. Lo stato dei margini (principalmente di quelli profondi) dopo il primo intervento chirurgico risultava correlare significativamente con le percentuali di preservazione finale d'organo ( $p < 0,001$ ). Lo stato dei margini dopo cordectomia laser CO<sub>2</sub> nei carcinomi glottici in stadio iniziale ha un impatto prognostico sul controllo locale di malattia senza compromettere la sopravvivenza. I pazienti con margini positivi multifocali e profondi devono essere sottoposti a revisione chirurgica e stretto follow-up per incrementare le percentuali di preservazione d'organo. È necessario allestire e mappare in modo molto scrupoloso gli specimen chirurgici al fine di ottimizzare la valutazione istopatologica e ridurre il rischio di sovrastimare i margini positivi.*

PAROLE CHIAVE: Laser CO<sub>2</sub> • Cordectomia • Stadi iniziali del carcinoma glottico

## Introduction

Transoral laser microsurgery (TLM) represents a minimally invasive approach that is widely accepted in early glottic cancer<sup>1</sup>. Moreover, this endoscopic procedure can be easily repeated when positive margins are detected postoperatively or, in many cases, when local relapses occur<sup>2</sup>.

While surgical margin status significantly impacts local control and survival in head and neck cancer<sup>3</sup>, the prognostic significance of positive resection margins after endoscopic laser surgery for early stage glottic cancer remains controversial. The high incidence (up to 50%) of positive neoplastic margins after laryngeal laser microsurgery reported in the literature may be due to the modality of laser dissection performed in narrow free tissue, especially in the glottic area, which is justified by anatomic and functional reasons<sup>2,4</sup>.

The results of the several series reported up to now have not led to univocal interpretation on the significance of margin status since, in some of these, positive margins seem to determine a negative impact on local relapses, whereas in most studies they do not influence survival. The incidence of local recurrence after endoscopic laser cordectomies has been reported to range from 0 to 9.3% and from 14 to 50%, respectively, for negative and positive resection margins<sup>5-9</sup>.

In many series of TLM with positive/close margins at pathological examination, a high incidence (up to 80-90%) of cases with no residual disease in revision specimen has been reported<sup>1,9,10</sup>. Neoplastic cells in revision specimen represent a prognostic factor for poor local control, rather than positive margins in the initial specimen<sup>1</sup>. The low concordance between positive margins after primary laser cordectomy and pathological findings after revision surgery may be due to postoperative artifacts of surgical specimen. For all these conditions, the tissue specimens after TLM may be not fully representative of real extent of resection<sup>1,5</sup>.

On these bases, herein we have retrospectively reviewed our series of 308 patients with primary early glottic cancer treated by TLM. The main aims were to correlate the status of resection margins with local control rate, survival and organ preservation, and to discuss the decision-making process and further treatment options in cases with positive margins. The methodological procedures and the pitfalls of pathological diagnosis are also analysed.

## Materials and methods

### *Patients*

Between 1990 and 2010 a total of 308 consecutive patients with early glottic carcinoma (T1a, T1b, selected T2) were

treated at the Department of Otorhinolaryngology, Head and Neck Surgery, University of Eastern Piedmont, Novara (Italy). All clinical and surgical records and histopathological reports were collected from the department's tumour registry and retrospectively reviewed. Demographics, tumour T stage, types of laser cordectomy and resection margin status were collected. There were 291 men and 17 women, with a mean age of 65.2 years (range 32-91).

### *Technique*

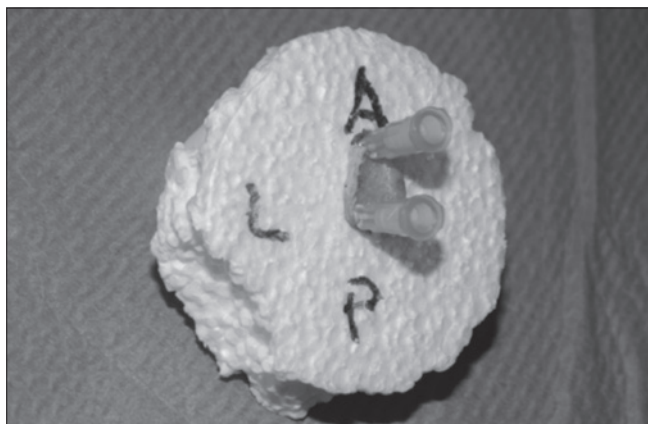
All patients underwent TLM under general anaesthesia using a Sharplan CO2 laser (Acublade system) mounted on a Zeiss surgical microscope. A Mallinckrodt laser-flex tracheal tube with a double cuff was employed. Endoscopic laser cordectomy were graded according to the classification system proposed by the European Laryngological Society (ELS)<sup>11</sup>, as follows: type I subepithelial (n = 9), type II subligamental (n = 32), type III transmuscular (n = 107), type IV total (subperichondral) (n = 102), type V extended (n = 58). Most glottic cancers were removed "en bloc", and a multi-bloc procedure was utilised in bulky tumours on rare occasions.

Inclusion criteria were: no previous curative laryngeal treatment and good endoscopic glottic exposure at micro-laryngoscopic examination. In many cases, tumour diagnosis was previously confirmed by biopsy; however, in recent years an excision-biopsy was systematically planned in superficial and favourable limited lesions (selected T1) in order to spare a surgical procedure and to avoid treatment delay. In the latter cases, an extensive and informed consensus on this type of diagnostic and therapeutic procedure was obtained. We excluded all cases with pT0 postoperative staging ("curative biopsy") from the study. A preoperative CT scan was systematically obtained in all glottic cancers except for early and superficial lesions limited to the middle third of the vocal fold. Intraoperative diagnostic examination included rigid endoscopy with 0° and 70° angles of view and, recently, a narrow band imaging system (NBI) for planning the extension of surgical resection.

Surgical specimens were three-dimensionally oriented and opportunely fixed on a plastic slab with fine needles to avoid excessive tissue contraction and distortion that could interfere with pathological assessment. The superficial and deep resection margins were marked with different coloured inks before formalin fixation (Fig. 1).

Resection margins were defined as positive if they were infiltrated by neoplastic tissue, and close if < 1 mm of free tissue between margins and tumour was present.

All surgical specimens with close or positive margins included in this study were systematically reassessed by an experienced pathologist to confirm margin status.



**Fig. 1.** Surgical specimen from laser cordectomy prepared for pathological examination: the deep (lateral) margin has been stained by yellow ink; A: anterior margin; P: posterior margin; L: lateral margin.

Follow-up ranged from 12 to 243 months (median, 68.3 months). Patients were examined with flexible video-laryngoscopy or rigid video-laryngoscopy every 1-2 months the first year and subsequently every 2-6 months depending on staging and margin status. During endoscopic follow-up, microlaryngeal examination was routinely planned if suspicious areas were observed.

Indications for adjuvant therapy in patients with positive surgical margins have changed over the years: until 2008 postoperative radiotherapy was performed in some cases ( $n = 20$ ). At present, a second look laryngoscopy is preferred and planned within 4-6 weeks in deep and/or multifocal positive margins, whereas monthly endoscopic follow-up is proposed if a close margin or a single superficial margin is involved, under the condition that an intraoperative satisfactory excision is obtained.

#### Statistical analysis

Disease-free survival (DFS) was calculated from the date of cordectomy to the date of relapse or last follow-up. Overall survival (OS) was considered from cordectomy to death or last follow-up. Larynx survival was estimated from the date of cordectomy to the date of laryngectomy or last clinical examination. Observations were censored at 60 months. Survivals were calculated considering as variables the presence of positive/close margins at cordectomy and, in these cases, the site of margin involved (superficial vs deep), additional treatment performed on these patients, TNM staging and type of cordectomy.

Kaplan-Meier analysis was used to describe disease-free survival and overall survival in different clinical groups (Tis, T1 and T2 categories were analysed separately). Comparison of groups was carried out using the Log-rank

test, and a two-sided  $p$  value  $< 0.05$  was considered statistically significant.

## Results

According to the AJCC TNM staging system (2002), T clinical categories of the 308 endoscopic laser cordectomies were distributed as follows: 29 Tis (9.4%), 228 T1a (74%), 29 T1b (9.4%) and 22 T2 (7.2%). Most T1 lesions were treated with either a type III or a type IV cordectomy (110 and 107, respectively).

Of 102 primary cases (33.1%) with non-negative surgical margins detected at definitive pathological examination, 85 were clearly positive (both superficial and/or deep margins) and 17 were defined as close margins. Endoscopic revision surgery was performed in 24 of 85 cases (28.2%), all with multifocal and/or deep positive margins: in 20 of 24 of these, no residual carcinoma was detected (83%), whereas in the other 4 cases (17%) positivity was confirmed (Table I). In the other 20 cases (23.5%), postoperative radiotherapy was performed. In the remaining 41 of 85 cases in which a satisfactory resection was achieved and only one superficial positive margin was histologically detected, we used a “wait and see” strategy; accordingly, in these patients no further treatment but only strict follow-up was planned.

Local recurrences were diagnosed in 39 of 308 cases of TLM, and the overall recurrence rate was 12.6%; 23 of these relapses were found in patients with positive margins at first surgery and 16 in negative ones. Twenty-three of 102 primary cases with positive margins (22.5%) and 16 of 206 with free surgical margins (7.8%) relapsed.

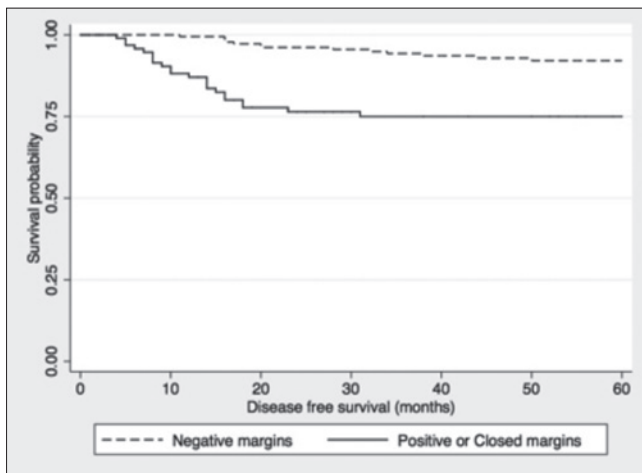
Resection margin status was significantly associated with local recurrence and lower DFS ( $p < 0.001$ ) for T1a, T1b and T2 categories, whereas OS at 60 months for negative and positive/close margins was 90% and 81.4% ( $p = 0.27$ , 95%CI), respectively (Fig. 2). The site of positive margins (deep vs. superficial) did not show significant differences in the rate of recurrence ( $p = 0.99$ ) or OS ( $p = 0.98$ ); at 60 months, OS was 72% and 85% for superficial and deep positive margins, respectively. On the contrary, a significant difference emerged between close/single superficial margins and multifocal/deep margins ( $p < 0.001$ ). In the group

**Table I.** Histological findings of revision surgery cases ( $n = 24$ ).

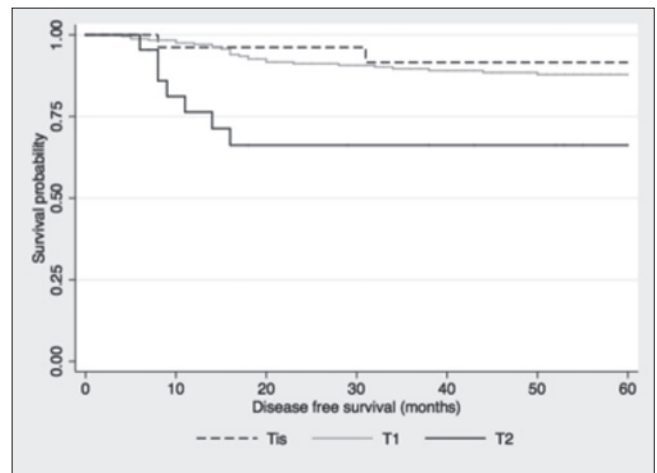
	Negative	Positive	Total
All margins	20	4	24
Deep margins *	11	3	14
Superficial margins **	9	1	10

\* at least one deep margin involved at first surgery.

\*\* only superficial margins involved at first surgery.



**Fig. 2.** Disease-free survival (DFS) according to margin status; the presence of positive and/or closed margins is negatively related to disease-free survival ( $p < 0.001$ ). Kaplan-Meier method.



**Fig. 3.** Disease-free survival (DFS) according to T stage (Tis vs. T1 vs. T2); patients with T2 stage show worse prognosis ( $p < 0.002$ ). Kaplan-Meier method.

of T1a patients ( $n = 228$ ), no significant differences in rate of recurrences, DFS ( $p = 0.889$ ), or OS ( $p = 0.426$ ) were observed between patients submitted to further treatment (revision endoscopic surgery or RT) for positive excision margins at first surgery and patients who were left untreated. The type of laser cordectomy for T1 stage was not significantly related to either DFS ( $p = 0.39$ ) or OS ( $p = 0.0617$ ). TNM stage was significantly related to the rate of recurrence ( $p = 0.002$ ), but did not negatively impact overall survival ( $p = 0.316$ ) (Fig. 3). Distribution of recurrences by T stage is shown in Table II.

Recurrences were treated conservatively by repeated endoscopic laser surgery in 9 subjects and by supracricoid laryngectomy in one patient. Local control with laser alone was 89%. Twenty-four patients underwent salvage total laryngectomy for recurrence: in this group, surgical margins at first laser surgical procedure were positive in 15 cases (11 deep and 4 superficial) and negative in 9. In these patients, salvage treatment with chemo-radiotherapy was jointly discussed, but was decided against. The laryngeal preservation rate at 60 months was 90% (95.6% in negative margins group and 85% in close/positive margin

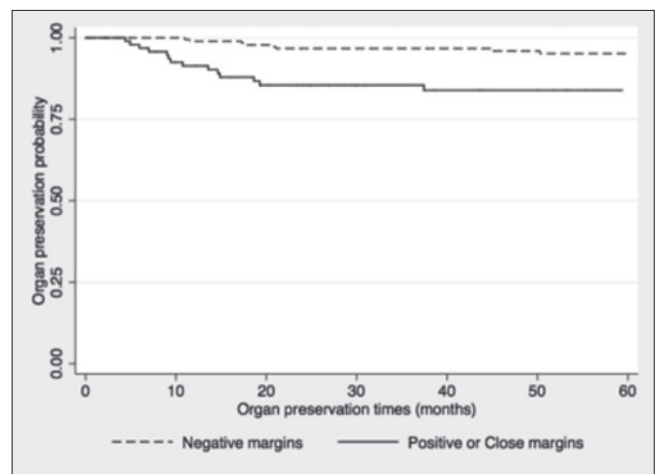
group, respectively). Margin status (mainly deep positive margins) at first surgery was significantly related to the final organ preservation rate ( $p < 0.001$ ) (Fig. 4). Of four cases with confirmed residual carcinoma after second-look surgery, 2 are alive without disease (one patient was submitted to a further endoscopic intervention for a local relapse) and 2 died for unrelated causes. In our series, 58 patients died, 7 of local recurrences (5 with positive and 2 with negative excision margins at first laser surgery) and 51 of unrelated causes; 14 patients were lost to follow-up.

### Discussion

The presence of neoplastic tissue in resection margins is

**Table II.** Distribution of recurrences per T stage ( $n = 308$ ).

	Cases (n)	Recurrences (n)	Recurrences %
Tis	29	3	10.3
T1a	228	25	11.0
T1b	29	4	13.8
T2	22	7	31.8
TOT	308	39	12.7



**Fig. 4.** The presence of positive margins is significantly related to failure in organ preservation ( $p < 0.001$ ). Kaplan-Meier method.

usually known to be a negative prognostic factor in HN-SCC<sup>10</sup>. Anatomic and embryologic specificity of the glottic area and microsurgical magnification allows obtaining a successful oncological outcome even in cases of early laryngeal cancer with limited free margins. In fact, whereas for other head and neck surgical specimens clear margins of at least 5 mm are considered oncologically adequate, a 3 mm space of free tissue from the neoplastic front is enough to achieve good oncological results in conservative laryngeal surgery<sup>12,9</sup>. The superficial and exophytic growth pattern of most glottic cancers, often sparing muscle, and the absence of lymphatic drainage in the glottic area justifies this surgical approach.

The type of TLM and extension of muscle resection should be tailored to the individual patient in relation to site and depth of neoplastic infiltration, in order to spare most healthy tissue and obtain better phonatory results. Thus, especially in superficial early glottic cancers, the laser excision can be adapted individually in respect of the oncological criteria<sup>8</sup>. An excisional biopsy, with diagnostic and therapeutic purpose, should be recommended in suspected superficial, limited glottic cancers to avoid additional surgical procedures and to limit the risk of overtreatment. Indeed, after performing a laser cordectomy for glottic cancer histologically confirmed by biopsy, the pathologist sometimes does not find any residual cancer in the surgical specimen. Such negative cordectomies were identified in 32.6% of early glottic cancers treated by TLM and previously biopsied<sup>4</sup>.

In our series, we evaluated the margin status of specimens by strictly applying the pathological criteria described above, and found clearly positive margins in 27.6% of cases, whereas close margins were present in another 5.5%; this result is similar to other studies, since in the literature positive margins after TLM are reported in 10-50% of cases<sup>112-14</sup>. The clinical significance of positive or close margins in surgical specimens of laser cordectomy is still debated: local relapses after TLM in early glottic cancer have been reported in many studies, ranging from 6% to 22%<sup>13-18</sup>. However, overall survival does not seem to be affected by either margin status at first surgery or by modality of treatment of positive margins (revision surgery vs. radiotherapy). These observations may be explained by the fact that local recurrences after TLM are frequently detected in relative early stages and can be successfully treated, thereby achieving high survival rates. However, margin status of surgical margins can negatively impact the laryngeal preservation rate<sup>1</sup>. For our patients, local relapses and DFS were significantly correlated with the margin status, as well as with the organ preservation rate. Similar results were obtained by Ansarin et al. who analysed, in a multivariate model, the results of 8-year follow-up in relation to margin status (n = 274); pa-

tients with close and positive margins, not further treated with a second resection nor adjuvant RT, had a greater risk of recurrence (hazard ratio, 2.53; p = 0.06) than patients with negative margins<sup>19</sup>. In contrast, Michel et al., in a series of 64 patients retrospectively analysed after TLM for T1a glottic carcinoma, did not observe any significant difference in recurrence-free or OS in relation to the status of resection margins<sup>9</sup>.

The site of positive resection margins (deep or superficial) may also influence surgical outcome, as reported in a large series of 595 glottic cancers treated with TLM. The authors emphasised the importance of a meticulous preoperative examination and complete removal of the tumour at the first surgical procedure because endoscopic revision for positive deep margins may be not sufficient to obtain an adequate local control<sup>8</sup>. Recently, a retrospective study has demonstrated that post-resection CO2 laser photocoagulation of surgical close or positive superficial margins significantly decreases the rate of local recurrences after endoscopic cordectomy<sup>20</sup>.

In other series, an intraoperative procedure on frozen sections has been applied to evaluate resection margins: by this technique it has been demonstrated that involvement of the margins during the primary resection was predictive for poor OS in 75 consecutive patients<sup>21</sup>. A high negative predictive value (95%) of frozen sections in a series of 97 patients treated by TLM with the Acublade system has also been reported<sup>22</sup>. However, this method is burdened with a high false negative rate<sup>23</sup>. The application of frozen sections to evaluate the status of resection margins is debatable and has not been applied by all groups<sup>19</sup>. In our experience, this tool was not too effective because of the thermal effects on the specimen, leading to difficult interpretation of morphologic findings even if, more recently, the Acublade system has reduced this problem.

On the other hand, no residual carcinoma was found in 83% of our patients (24 cases) submitted to revision surgery for positive margins. In many series of TLM a high incidence of cases with no residual disease in specimen at second look surgery has been reported: for instance, Jackel demonstrated that only 70 of 382 patients (18%) had confirmed positive neoplastic margins at revision surgery<sup>1</sup>. The definition of false positives for these cases may be inappropriate, as the immune system of the host is functionally able to attack and destroy small fields of neoplastic cells<sup>24</sup>. This may also explain the relatively high frequency of cases with a diagnosis of squamous carcinoma on biopsy, and the absence of tumour on the subsequent TLM<sup>4</sup>.

Nonetheless, it should be assumed that the presence of residual tumour on the margins of TLM is due, at least in a proportion of cases, to postoperative modifications and

artifacts of the surgical specimen, such as shrinkage, inadequate orientation and mapping and thermal effects of tissue coagulation. Since these pitfalls may result in pathological misinterpretation and in over-diagnoses of positive margins, we have applied a standard procedure to treat the surgical specimen for pathological analysis: a mild stretching with needles on a rigid frame and tridimensional mapping with inks is useful to reduce post-resection shrinkage of excised tissues. Of course, strict cooperation between surgeons and pathologists is mandatory.

The management of positive or close resection margins in endoscopic cordectomy remains a controversial and critical point. The options discussed in the literature vary from planned early revision endoscopic surgery to complementary radiotherapy or only strict endoscopic surveillance. According to most authors, whenever retreatment is planned, revision surgery should be preferred<sup>8,20</sup>. Deep recurrences are difficult to detect early even with close endoscopic follow-up, and negatively impact on chances for conservative treatment in case of relapses. For this reason, systematic re-excision in all positive or suspected deep positive margins should be suggested. If a single superficial margin is positive and laser excision was satisfactorily achieved, a strict endoscopic follow-up may be proposed, reserving revision surgery only in case of suspected neoplastic persistency, as previously reported<sup>25,26</sup>.

## Conclusions

The present study shows that positive margins after TLM for early glottic cancer has a prognostic impact on local control and organ preservation without compromising survival. Careful preparation and mapping of the surgical specimen enhances the accuracy of pathological examination by limiting over-diagnoses of positive margins. Decision-making process in positive margins cases (revision surgery, radiotherapy, or no further treatment) should also be based on the surgeon's experience and intraoperative judgment. Multifocal and deep positive margins after endoscopic laser cordectomy should be surgically verified and subsequently strictly monitored in order to increase local control and organ preservation rates.

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LARYNGOLOGY

# Neutrophil-to-lymphocyte ratio as a prognostic factor for pharyngocutaneous fistula after total laryngectomy

## *Rapporto neutrofili-linfociti come fattore prognostico per le fistole faringocutanee dopo laringectomia totale*

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### SUMMARY

The role of systemic inflammatory response as a prognostic factor has been proposed in a variety of cancers. The purpose of this study was to investigate the prognostic value of the pretreatment neutrophil-to-lymphocyte ratio (NLR) in the incidence of pharyngocutaneous fistula (PCF) in patients who underwent total laryngectomy. We conducted a retrospective cohort analysis of 141 patients with squamous cell carcinoma of larynx who underwent total laryngectomy from 2009 to 2015. The incidence of PCF was 49.6%. A higher risk of 23% was observed among patients with NLR > 2.5 for the occurrence of PCF ( $p = 0.007$ ). Patients with laryngeal squamous cell carcinoma who present elevated values in the ratio  $> LR > (> 2.5)$  presented a higher risk of developing pharyngocutaneous fistula in the postoperative setting of total laryngectomy.

KEY WORDS: Laryngeal neoplasms • Squamous cell carcinoma • Postoperative complications • Cutaneous fistula

### RIASSUNTO

*Il ruolo della risposta infiammatoria sistemica come fattore prognostico è stato già proposto per molti tipi di tumore. Lo scopo di questo studio è stato quello di definire il valore prognostico del rapporto neutrofili-linfociti (NLR) pretrattamento come fattore di rischio per la fistola faringocutanea (PFC) in pazienti sottoposti a laringectomia totale. Abbiamo quindi analizzato retrospettivamente 141 pazienti con carcinoma squamoso della laringe trattati con laringectomia totale tra il 2009 e il 2015. L'incidenza di PCF è stata pari a 49,6%. In particolare, è stato osservato un rischio maggiore di sviluppare PFC, di circa il 23%, nei pazienti con NLR > 2,5 ( $p = 0,007$ ). In conclusione, i pazienti con carcinoma squamoso della laringe con un elevato rapporto neutrofili-linfociti ( $> 2,5$ ) presentano un maggiore rischio di sviluppare fistole faringocutanee nel post-operatorio della laringectomia totale.*

PAROLE CHIAVE: Tumore laringeo • Carcinoma squamocellulare • Complicanze postoperatorie • Fistola cutanea

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## Introduction

Smoking and alcohol consumption are the most important risk factors for laryngeal cancer <sup>1</sup>. Traditional prognostic factors, such as tumour staging, lymph node extracapsular spread and surgical margins have been commonly used to predict outcome for laryngeal cancer patients <sup>2,3</sup>. However, those factors are often insufficient in determining prognosis, and the role of novel markers have been investigated. It has been progressively recognised that oncological

outcomes do not depend exclusively of tumour features, but also on the patient's response, mainly regarding the immunologic condition <sup>4</sup>. Some proinflammatory elements can strongly influence immunologic status by inhibiting apoptosis and promoting angiogenesis and DNA damage <sup>5,6</sup>.

The role of inflammation in cancer pathogenesis has been extensively studied <sup>5</sup>. The production of proinflammatory cytokines facilitates the proliferation and survival

of tumour cells <sup>7</sup>, whereas the increased release of these cytokines produces a systemic inflammatory response reflected in changes in circulating markers of inflammation, including white blood cells <sup>8</sup>. Peripheral blood leukocyte count is a marker closely related to inflammation in patients. Increased leukocyte count can reflect an individual's immune response to infection, inflammation and possibly cancer.

Counts of total white blood cells and its related components count can predict survival in a variety of malignancies, although a limited number of studies have evaluated the role of haematologic markers of inflammation as predictors of outcome in head and neck cancer patients. Recently, some studies have demonstrated a significant correlation between the neutrophil-to-lymphocyte ratio (NLR) and nasopharyngeal <sup>9-11</sup>, oral <sup>12-14</sup> and laryngeal <sup>15 16</sup> cancer outcomes. Elevated NLR has been demonstrated to be associated with tumour progression and metastasis, with increased rates of mortality. Pharyngocutaneous fistula (PCF) is the most common surgical complication after total laryngectomy. It is due to a failure in the pharyngeal repair resulting in salivary leak and is associated with a higher incidence of morbidity, hospital stay and cost. Its incidence varies around 20-25%. In a recent meta-analysis, chronic obstructive pulmonary disease (COPD), previous haemoglobin < 12.5 g/dL, blood transfusion, previous radiotherapy or chemoradiotherapy, advanced primary tumour, supraglottic subsite, hypopharyngeal tumour site, positive surgical margins and the performance of neck dissection were risk factors for PCF <sup>17</sup>. Elevated NLR was associated with tumour progression, although it has not been correlated to the rates of surgical complications.

The objective of this study is to evaluate the value of pretreatment NLR in predicting the incidence of PCF in patients who underwent total laryngectomy for larynx cancer treatment.

## Materials and methods

### *Study design*

This is a retrospective and observational cohort study with evaluation of clinical charts among patients who underwent total laryngectomy for treatment of larynx squamous cell carcinoma at the Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil, from July 2009 to June 2015.

### *Inclusion and exclusion criteria*

All consecutive patients with larynx squamous cell carcinoma and confirmed through histopathological analysis of the biopsy who underwent total laryngectomy were includ-

ed. All surgical procedures had curative intent with radical resection of the tumour and without any evidence of distant metastasis or macroscopic residual lesion. Patients with comorbidities that could influence the serum levels of neutrophils, platelets and/or lymphocytes (infectious, inflammatory or autoimmune diseases) were excluded.

### *Data collected*

A form was elaborated containing the following data collected from each chart: gender, age, tumour site (supraglottic, glottic, infraglottic or transglottic level), tumour extension (to hypopharynx), regional lymph node spread, histological differentiation (grades I, II or III), perineural and angiolymphatic invasion and preoperative serum values of neutrophils and lymphocytes at an interval of less than 1 month after surgery. The main outcome evaluated was the occurrence of PCF.

### *Statistical analysis*

The NLR was calculated through the simple division of the absolute count of neutrophils by the absolute count of lymphocytes. The optimal cutoff value for defining a high NLR rate was established by an ROC curve (receiver operating characteristic). The cutoff value was the point closest to both maximum sensitivity and specificity for both measures. The measures of the main outcomes were expressed in absolute numbers and univariate analysis of the data was performed using a 2 x 2 table (risk difference) and compared using a chi-square test. Continuous variables were analysed considering the difference between the averages and standard deviations using a Student's t test. A p value < 0.05 was considered as statistically significant.

## Results

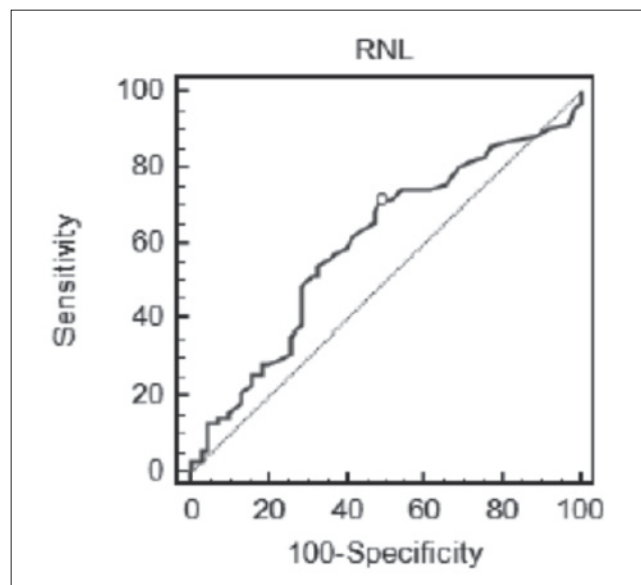
A total of 157 patients were eligible for the study. After applying inclusion and exclusion criteria, 141 patients with larynx squamous cell carcinoma who underwent total laryngectomy were selected, including 117 men (83%) and an age varying from 41 to 83 years (mean 61.6 ± 9.1). Five patients were excluded because they had been operated on another department with a lack of access to preoperative leucogram; 4 patients had a histological diagnosis different from squamous cell carcinoma; 4 patients due to the presence of macroscopic residual tumour after surgery; and 3 patients due to the presence of comorbidities that could change laboratory values.

Clinical and demographic data and the NLR values are shown in Tables I and II, respectively. In general, patients with more advanced clinical staging and worse pathological findings, representing poorer prognosis, presented higher NLR val-

**Table I.** Clinical and demographic data.

Data	n (%)
<b>Gender</b>	
Men	117 (82.9%)
Women	24 (17.0%)
<b>Age</b>	
≤ 60	73 (51.8%)
> 60	68 (48.2%)
<b>Tumour site</b>	
Glottic	14 (9.9%)
Supraglottic	9 (6.4%)
Glottic + supraglottic	11 (7.8%)
Glottic + Subglottic	7 (4.9%)
Supraglottic + hypopharynx	13 (9.2%)
Transglottic	53 (37.6%)
Transglottic + hypopharynx	28 (19.9%)
Hypopharynx	6 (4.3%)
<b>T stage</b>	
T2	10 (7.1%)
T3	36 (25.5%)
T4	95 (67.4%)
<b>N stage</b>	
N0	72 (51.1%)
N1	17 (12.1%)
N2	48 (34.0%)
N3	4 (2.8%)
<b>Histological differentiation grade</b>	
I	24 (17.2%)
II	96 (68.1%)
III	21 (14.7%)
<b>Perineural invasion</b>	
Present	60 (42.7%)
Absent	81 (57.3%)
<b>Angiolymphatic invasion</b>	
Present	47 (33.3)
Absent	94 (66.7%)

ues. The overall incidence of PCF was 49.6%. Gender, age, tumour extension and neck metastasis did not influence the incidence of PCF (Table III). Patients who underwent salvage laryngectomy presented a higher risk for PCF of about 25% (70.8% x 45.3%,  $p = 0.02$ ). Primary closure, flaps (supraclavicular, pectoralis major or microsurgical free flaps) and linear stapler were employed for pharyngeal closure in 52.5%, 17.7% and 29.8% of cases, respectively. Compared to primary closure, the linear stapler reduced the risk for PCF by 22% ( $p = 0.02$ ), whereas there was no difference when free flaps were employed ( $p = 0.39$ ).

**Fig. 1.** ROC curve related to NLR and PCF incidence.

A value of 2.5 [sensitivity = 71.4%, specificity = 51.4%, area under the curve (AUC) = 0.600; Fig. 1] was established as a cutoff value for defining the NLR before surgery. Thus, patients with  $NLR > 2.5$  presented a higher absolute risk of 23% for the occurrence of PCF compared to those with  $NLR \leq 2.5$  ( $p = 0.007$ ). Among patients who presented PCF in the postoperative period, 48 (68.6%) had resolution in the first month under conservative measures, whereas in 11 patients (15.1%) the fistula was permanent and in 9 patients (12.8%) a surgical approach was necessary to correct the dehiscence. The mean NLR among patients who presented conservative resolution of the PCF during the first postoperative month was  $3.0 \pm 1.4$  compared to  $4.2 \pm 3.3$  of those who had resolution after the first month and those who continued with the PCF ( $p < 0.001$ ). The variables that presented significant difference in the incidence of PCF at univariate analysis were included in the logistic regression model (Table IV).  $NLR > 2.5$  was the only risk factor associated with the incidence of PCF (OR = 2.44; 95% CI 1.18 to 5.03;  $p = 0.01$ ).

## Discussion

The cytokine network of several tumours is rich in inflammatory cytokines, growth factors and chemokines. Inflammatory cytokines and chemokines, which can be produced by the tumour cells and/or tumour-associated leucocytes and platelets, may contribute directly to malignant progression. Many cytokines and chemokines are inducible by hypoxia, which is a major physiological difference between tumour

**Table II.** Correlation between inflammatory markers and pathological findings.

Data	n	Neutrophils	p	Lymphocytes	p	NLR	p
<b>T stage</b>							
T2-T3	46	5043 ± 2466	0.11	1941 ± 687	0.4	3.1 ± 2.1	< 0.001
T4	95	6130 ± 3047		1802 ± 769		4.3 ± 3.6	
<b>N stage</b>							
N-	72	5583 ± 3104	0.25	1811 ± 608	0.01	3.1 ± 1.6	< 0.001
N+	69	5985 ± 2702		1968 ± 820		3.8 ± 2.9	
<b>N stage</b>							
N1	17	5696 ± 2861	0.68	2140 ± 735	0.55	3.1 ± 1.9	0.03
N2-N3	52	6079 ± 2670		1911 ± 845		4.0 ± 3.1	
<b>Histological differentiation grade</b>							
I	24	5446 ± 1859	0.23	2102 ± 511	0.26	2.8 ± 1.1	< 0.001
II / III	117	5544 ± 2304		1831 ± 626		3.6 ± 2.2	
<b>Perineural invasion</b>							
Present	60	5255 ± 1833	0.01	1871 ± 697	0.04	3.6 ± 2.6	< 0.001
Absent	81	5739 ± 2476		1882 ± 547		3.3 ± 1.5	
<b>Angiolymphatic invasion</b>							
Present	47	5240 ± 1526	< 0.001	1724 ± 603	0.96	3.9 ± 2.8	< 0.001
Absent	94	5675 ± 2504		1956 ± 609		3.2 ± 1.5	

**Table III.** Risk factors associated with PCF.

Variables	Without PCF (n = 71)	With PCF (n = 70)	Difference of absolute risk (95% CI)	p
<b>Gender</b>				
Men	62	55	15.5% (-5.88 to 36.87%)	0.18
Women	9	15		
<b>Age</b>				
< 60	31	32	2.1% (-14.52 to 18.67%)	0.81
≥ 60	40	38		
<b>T stage</b>				
T2-T3	26	20	9.2% (-8.34 to 26.65%)	0.31
T4	45	50		
<b>N stage</b>				
N-	41	31	13.5% (-2.89 to 29.82%)	0.11
N+	30	39		
<b>Spread to hypopharynx</b>				
Yes	29	30	2.1% (-14.66 to 18.79%)	0.81
No	42	40		
<b>Pharynx closure</b>				
Primary	31	43	-	-
Stapler	27	15	22.4% (4.06 to 40.73%) <sup>a</sup>	0.02a
Flap	13	12	10.1% (-12.47 to 32.69%) <sup>b</sup>	0.39b
<b>Previous radiotherapy</b>				
Yes	7	17	25.5% (5.24 to 45.83%)	0.02
No	64	53		
<b>NLR</b>				
≤ 2.5	36	20	23.1% (6.77 to 39.45%)	0.007
> 2.5	35	50		

<sup>a</sup> Primary x stapler; <sup>b</sup> Primary x flap.

**Table IV.** Multivariate analysis of the risk factor for PCF.

Variable	Coefficient	Standard error	OR	95% CI	p*
Previous radiotherapy	0.5186	0.4938	1.68	0.64 to 4.42	0.29
RNL $\geq$ 2.5	0.8901	0.3700	2.44	1.18 to 5.03	0.01

OR = Odds ratio; \* = logistic regression.

and normal tissue<sup>5</sup>. Chronic inflammation associated with infection or autoimmune disease precedes tumour development and can contribute to it through induction of oncogenic mutations, genomic instability, early tumour promotion and enhanced angiogenesis. This inflammatory response can enhance neoangiogenesis, promote tumour progression and metastatic spread, cause local immunosuppression and further augment genomic instability. Cancer-related inflammation causes suppression of antitumour immunity by recruiting regulatory T cells and activating chemokines, which results in tumour growth and metastasis. The presence of both neutrophilia and thrombocytosis tends to represent a nonspecific response to cancer-related inflammation. Cancer has been shown to produce myeloid growth factors, such as granulocyte colony-stimulating factor, tumour necrosis factor- $\alpha$ , interleukin-1 and interleukin-6, which may influence tumour-related leukocytosis and neutrophilia<sup>18</sup>. Cancer therapy can also trigger an inflammatory response by causing trauma, necrosis and tissue injury that stimulate tumour re-emergence and resistance to therapy. However, in some cases, therapy-induced inflammation can enhance antigen presentation, leading to immune-mediated tumour eradication<sup>19</sup>. Chronic inflammation caused by infection, autoimmune disease and exposure to irritants as well as tumour-associated inflammation contribute to tumour promotion, progression and metastatic spread. Whereas in inflammation-associated cancer inflammation can be viewed as a causative agent affecting either tumour initiation or early promotion, tumour-elicited inflammation acts as a late tumour promoter to enhance progression and metastasis<sup>20</sup>.

The NLR is a nonspecific marker of systemic inflammation. An elevated preoperative NLR ( $\geq$  5) may correlate with an increased risk of recurrence and death in patients who undergo hepatic resection for colorectal liver metastases and for primary hepatocellular carcinoma<sup>21,22</sup>. Clinically, peripheral blood leukocyte count is a marker closely related to inflammation in patients. Increased leukocyte count usually reflects an individual's immune response to infection and inflammation, and perhaps malignancies. Elevation of NLR in cancer patients indicates a decrease of antitumour activity, implying that tumour development may be related to NLR imbalance in cancer patients. Elevated NLR has been demonstrated to be associated with tumour progression and metastasis<sup>6</sup>.

A total of 295 patients underwent oesophagectomy with

56 patients (18.9%) presenting elevated NLR preoperatively. In multivariable analysis, elevated NLR was associated with significantly poorer disease-free (hazard ratio [HR] 2.26, 95% CI 1.43-3.55) and overall survival (HR = 2.31, 95% CI 1.53-3.50). Thus, an elevated preoperative NLR was associated with a nearly 2-fold increased risk of recurrence and death, independent of other patient and tumour characteristics associated with poor outcomes. NLR reflected systemic inflammation and may serve as a composite "score" that reflects the degree of host inflammatory cell activity that promotes tumour growth and progression<sup>23</sup>. In a series of 483 patients who underwent oesophagectomy for oesophageal squamous cell carcinoma, high preoperative NLR ( $\geq$  3.5 vs.  $<$  3.5,  $p = 0.039$ ) and platelet lymphocyte ratio PLR ( $\geq$  150 vs  $<$  150,  $p < 0.001$ ) were significantly associated with poorer overall survival in multivariate analysis. In a group of patients diagnosed with locally advanced oesophageal cancer, compared with the low ( $<$  2.0) NLR group ( $n = 43$ , 31.2%), the high ( $\geq$  2.0) NLR group ( $n = 95$ , 68.8%) exhibited significant decreases in both progression-free and overall survival. Multivariate analysis showed similar findings<sup>24</sup>.

One of the reasons for the differences observed in the association of NLR with survival may be due to the different methods that have been used to identify and categorise NLR cutoff values. The two methods most commonly used are receiver operating characteristic (ROC) curves and comparison of medians and quartiles<sup>16</sup>.

Pretreatment NLR and percentages of lymphocyte and neutrophil were found to be independent prognostic factors and clinically useful biomarkers for survival in 1410 patients with nasopharyngeal carcinoma<sup>10</sup>. Eight independent prognostic factors were identified in 3237 patients with nasopharyngeal carcinoma who underwent radiation therapy, including anaemia or thrombocytosis during radiotherapy, continuous reduction in haemoglobin and high NLR before radiotherapy<sup>11</sup>.

In a retrospective study of 226 patients with oral squamous cell carcinoma, preoperative C-reactive protein CRP level  $\geq$  5.0 mg/L was significantly associated with NLR  $\geq$  2.44 (linear regression,  $p < 0.001$ ). Elevated CRP and NLR were significantly associated with pathological tumour status ( $p < 0.001$ ), pathologic nodal metastasis ( $p < 0.001$ ), tumour depth ( $\geq$  10 mm vs  $<$  10 mm,  $p < 0.001$ ), disease-

free survival ( $p < 0.001$ ) and overall survival ( $p < 0.001$ ). CRP was considered an independent prognostic factor, and incorporating NLR into CRP level had significant potential as a biomarker for risk stratification of oral cancer<sup>14</sup>. A cohort of 97 patients with locally advanced oral squamous cell carcinoma receiving preoperative chemoradiotherapy was retrospectively evaluated. In multivariate analysis, advanced pathologic TNM stage after neoadjuvant therapy, positive perineural invasion and high pretreatment NLR (HR = 10.37,  $p = 0.029$ ) were independent factors associated with poor disease-specific survival<sup>13</sup>. In a group of 273 retrospectively evaluated patients with head and neck cancer, higher pretreatment NLR ( $> 4.27$ ) was associated with higher rates of recurrence (35% compared to 7%;  $p < .0001$ ). In addition to inflammatory cells, tumour stroma consists of new blood vessels, connective tissue and a fibrin-gel matrix. Wound healing is usually self-limiting whereas tumours secrete vascular endothelial growth factor (VEGF) which can lead to persistent extravasation of fibrin and fibronectin and continuous generation of extracellular matrix. Platelets in wounds are a critical source of cytokines and VEGF. Platelet release of such factors may also be important in tumour angiogenesis<sup>25</sup>. In addition, malignant cells also secrete proinflammatory cytokines<sup>5</sup>. Tumours interact both directly and indirectly with host inflammatory cells. The NLR is a nonspecific marker of systemic inflammation. Regarding laryngeal tumours, the optimal cutoff values of the NLR have been reported to be 2.17<sup>26</sup> and 2.46<sup>27</sup>. We found that a cutoff value of 2.5 for a higher risk of PCF as a complication. The NLR is a simple and effective marker of the patient's inflammatory and immunity status. Patients with elevated NLR usually have relative lymphocytopenia, and this may reflect a deficient immune response to tumours<sup>26</sup>. This is also a possible factor for increasing PCF rates.

## Conclusions

Patients with laryngeal squamous cell carcinoma who present elevated values in the NLR ( $> 2.5$ ) have a higher risk of developing pharyngocutaneous fistula in the postoperative period following total laryngectomy.

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OSAS

# Transoral glossoepiglottopexy in the treatment of adult obstructive sleep apnoea: a surgical approach

## *Glossoepiglottoplastica con approccio trans-orale nel trattamento delle apnee ostruttive notturne nell'adulto*

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### SUMMARY

The treatment of obstructive sleep apnoea syndrome (OSAS) is still a matter of debate; among the different therapeutic alternatives, both surgical and conservative, treatment with continuous positive airway pressure (CPAP) is considered the “gold standard”. The recent scientific literature reports that even if CPAP represents an effective solution for sleep apnoeas, 12% of patients do not benefit from its use. In most cases, primary collapse of the epiglottis is responsible for failure. We developed a surgical technique that provides a stable support to the epiglottis without influencing its function during swallowing while preserving laryngeal anatomy and physiology. The procedure we propose is based on that conceived by Monnier for children affected by laryngomalacia. We analysed a group of 20 patients who underwent glossoepiglottopexy between January 2015 and September 2016 and compared data (AHI, ODI, t90, ESS, EAT10, etc.) collected before and 6 months after surgery to demonstrate the safety and effectiveness of our glossoepiglottopexy (GEP). The results allow us to consider GEP as a valid choice to treat adults who suffer from sleep apnoeas.

KEY WORDS: OSAS • Epiglottis • Transoral laser microsurgery (TLM)

### RIASSUNTO

*I dati della letteratura scientifica internazionale stabiliscono che almeno il 10% della popolazione adulta sia affetto da Sindrome delle Apnee Ostruttive nel Sonno (OSAS). Nonostante le numerose proposte terapeutiche, chirurgiche e non, che si sono susseguite negli anni, la ventiloterapia con C-PAP rappresenta ad oggi il gold standard per il trattamento di questi pazienti. Esiste comunque una percentuale di pazienti, stimata attorno al 12%, che non trae beneficio dalla terapia ventilatoria o che, addirittura, peggiora in corso di C-PAP; il collasso primario dell'epiglottide, ovvero quello dipendente esclusivamente da un'eccessiva lassità della cartilagine, verso l'aditus laringeo rappresenta la causa più frequente di insuccesso in questi soggetti. Sulla base di queste osservazioni abbiamo deciso di sviluppare una tecnica chirurgica volta unicamente alla stabilizzazione dell'epiglottide che fosse conservativa e potenzialmente reversibile. La procedura che proponiamo prende spunto dall'epiglottoplastica proposta da Monnier per i pazienti pediatrici affetti da laringomalacia. Lo studio comprende 20 pazienti sottoposti a glossoepiglottoplastica tra Gennaio 2015 e Settembre 2016; diversi parametri (tra i quali AHI, ODI, t90, ESS, EAT10 ed altri) sono stati confrontati tra quelli registrati nel per operatorio e dopo 6 mesi di follow-up per valutare l'efficacia dell'intervento chirurgico. I risultati evidenziano come la glossoepiglottopexy rappresenti una valida possibilità di trattamento delle epiglottidi primarie responsabili della sindrome delle apnee ostruttive notturne nell'adulto.*

PAROLE CHIAVE: OSAS • Epiglottide • Microchirurgia laser transorale (TLM)

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### Introduction

Obstructive sleep apnoea (OSA) is a disorder caused by repetitive collapse of the upper airway during sleep, resulting in either partial or complete airflow obstruction<sup>1,2</sup>. In the adult population, the prevalence of OSA is 22% in men and 17% in women<sup>3</sup>. The morphology of upper-

airway structures plays a major role in the pathogenesis of OSA.

Treatment of OSA with continuous positive airway pressure (CPAP) is currently considered as the “gold standard”. Despite its proven efficacy, a significant number of patients cannot tolerate the device and require therapeutic

alternatives such as surgery, oral appliances and/or positional devices.

In the past, the prevalence of epiglottis collapse evaluated by clinical examination was estimated to be 12% in OSAS patients, although nowadays thanks to the introduction of drug-induced sedation endoscopy (DISE) it is possible to show that the prevalence of epiglottis collapse in determining the airway obstruction is actually much higher<sup>4,6</sup>, and also allows for stratification of OSAS into different levels of obstruction. Nonetheless, the role of the epiglottis in airway collapse still remains a matter of debate in the medical community<sup>17</sup>.

The laxity of the epiglottis is widely discussed in the paediatric literature as one of the possible presentations of congenital laryngomalacia; however, laryngomalacia in adults is a rare entity that has not been clearly described. Primary collapse of the epiglottis represents a challenging situation because CPAP treatment may aggravate airway obstruction by further pushing the epiglottis down into the laryngeal aditus<sup>8</sup>, and up to now no standardised surgical procedures have been described.

Herein we describe a new surgical procedure, obtained by modifying Monnier's glossoepiglottopexy, used in malacic epiglottis in children<sup>9</sup>, with the aim to resolve the collapse of the epiglottis in adults without interfering with its fundamental functions.

## Materials and methods

From January 2015 to September 2016, 20 patients (16 males and 4 females), aged between 35 and 65 years old (mean 49.2) affected by OSAS underwent glossoepiglottopexy at the Department of Otorhinolaryngology and Head and Neck Surgery of the University of Genoa. All patients were submitted to multilevel surgery (nasal-pharyngopalatal-laryngeal) performed by a senior surgeon. If tonsils were still in place a tonsillectomy was performed<sup>10</sup>, sparing the palatoglossus and palatopharyngeus muscles and as much as possible the mucosal covering both pillars<sup>11</sup>. Septoplasty and turbinoplasty<sup>12</sup> was performed if needed<sup>13</sup>.

All patients were evaluated in a preoperative setting and after 6 months after surgery by clinical, polysomnographic and endoscopic assessment. All data were extracted from a single database<sup>14</sup>.

Inclusion criteria were: OSA confirmed by sleep study (with an apnoea hypopnoea index (AHI)  $\geq 15$  episodes/h, BMI  $< 35$  kg/m<sup>2</sup>; primary epiglottic collapse evaluated by drug-induced sedation endoscopy (DISE) and Laryngoscore  $< 6$ <sup>15</sup>.

Major comorbidities, severe tongue base hypertrophy,

secondary epiglottis, cranio-facial malformations and laryngeal dysfunction were considered exclusion criteria.

The study was approved by our institutional review board.

### *Clinical evaluation*

Clinical evaluation included a complete head and neck examination as well as body mass index (BMI) calculation. Moreover, all patients were evaluated by a comprehensive history that covered sleep habits and sleep disturbances. Excessive daytime sleepiness was estimated by the Epworth sleepiness scale (ESS)<sup>16</sup>, while swallowing by the Eating Assessment Tool (EAT 10)<sup>17</sup> and the penetration aspiration scale<sup>18</sup>. EAT 10 is a self-administered, symptom-specific outcome survey that was investigated before and one week after surgery, while the penetration aspiration scale is an endoscopic finding that expresses the accidental loss of food or liquid into the airway while eating or drinking.

The possibility to have an adequate exposure of the larynx by a trans-oral approach was evaluated by the Laryngoscore<sup>15</sup>.

### *Polysomnographic study*

Polysomnographic study was performed with a cardiorespiratory monitor (Vital night, Vital aire, Milan Italy) to record the following variables simultaneously: nocturnal snoring sound, arterial oxygen saturation measured by finger oximetry, body position, nasal and mouth airflow, thoracic and abdominal respiratory movements recorded by inductive plethysmography and heart rate. The entity of sleep apnoea was evaluated by: AHI; oxygen desaturation index (ODI); T  $< 90\%$  (average desaturation and the percentage of total time with oxygen saturation level lower than 90%); mean oxygen saturation (SpO2 mean).

### *Endoscopic evaluation*

Flexible video nasopharyngoscopy (V-NFL) was used for endoscopic evaluation. To perform this procedure, we used a transnasal flexible endoscopy using an ENF-V2 videoendoscope connected to an EvisExera II CLV-180B light source (Visera Elite OTV-S190, Olympus Medical Systems Corporation, Tokyo, Japan), integrated with high-definition television (HDTV). Upper airway and digestive tract morphology was examined. The Muller manoeuvre was performed in a sitting position to determine the extent of retropalatal (Muller RP) and retrolingual (Muller RL) obstruction; it was considered significant when the percentage of collapse of the airway was at least 50%.

### *Drug-induced sedation endoscopy (DISE)*

DISE was performed in a supine position without neck extension. The entire exam was recorded. No local anaesthesia was used in the nasal cavity according to the Eu-

ropean position statement on DISE<sup>19</sup>. Sleep was induced with a bolus of 1.3 mg of midazolam in pre-anaesthesia and intravenous propofol in target controlled infusion (TCI) (1.1-1.6 µg/ml according Schnider's model)<sup>20</sup>. The degree of obstruction was evaluated at the level of the nasal cavity, nasopharynx, oropharynx, hypopharynx and larynx using the NOHL classification<sup>21</sup>.

#### *Surgical technique*

During microlaryngoscopy, the patient lies supine in Boyce-Jackson's position with the eyes protected by wet bandages and the superior teeth by a silicone device. The smallest efficient tube (Laser Shield®II Endotracheal Tube, Medtronic Xomed, Jacksonville, FL USA) for trans oral-intubation was chosen. Exposure of the supraglottis and the base of the tongue was obtained by a Sataloff laryngoscope (Microfrance Sataloff Laryngoscopes 124, Medtronic ENT, Jacksonville FL USA) to achieve adequate exposure of both the base of the tongue and the entire valleculae and epiglottis. The position of the hyoid bone was marked on the skin as a landmark.

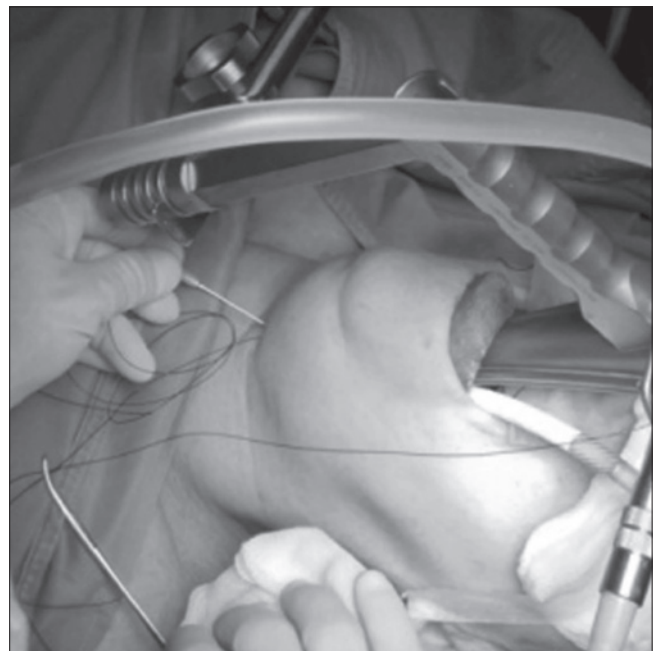
A CO<sub>2</sub> laser (Ultrapulse Dualpro Laser CO<sub>2</sub>, Lumenis, Yokneam, Israel), set on ultrapulse mode, at 3 watts of delivered power at a 400 mm working distance, was used to vaporize the mucosa overlying the valleculae and the base of the tongue and outlining two raw areas leaving a rim of 2-4 mm of healthy mucosa along the entire profile of the supra-hyoid epiglottis. The cicatricial retraction during the healing process determined an iatrogenic synechia attracting the epiglottis to the tongue base<sup>14</sup>. The surgical field was mostly bloodless thanks to the ability of the CO<sub>2</sub> laser to coagulate vessels with a diameter less than 0.5 mm. For larger vessels, cauterising monopolar forceps was routinely adopted and surgical clips are also strongly recommended. In case of hypertrophy of the lingual tonsils, resection of the lymphatic tissue may be combined. A cottonoid, soaked in saline solution, was applied intraoperatively to remove char and clean the raw surface for detection of any residual intact mucosal island as a cause of possible retention cysts when the two surfaces adhere to each other.

To ensure complete sealing of the pexy, two Premilene® sutures number 1 (Premilene, Braun, Melsungen Germany) embraced the hyoid bone guided by means of two 16 gauge catheters. The first suture was bent in the middle to form a loop and was inserted inside the first needle to exit from the tip. Later, the catheter was passed through the skin, in a supra-hyoid position, along the midline to avoid vascular injuries, until reaching the glosso-epiglottic vallecula. This procedure was monitored under microscopic control (Fig. 1). The needle was then pushed through the epiglottis and retrieved out of the mouth.

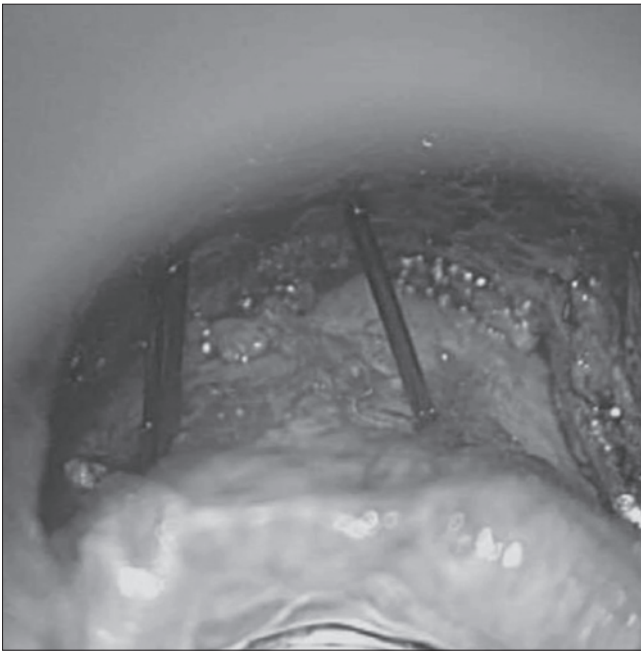
The second suture was inserted into the second catheter and penetrated soft tissues beneath the hyoid (Figs. 2, 3). Finally, the surgeon inserted the proximal end of the wire



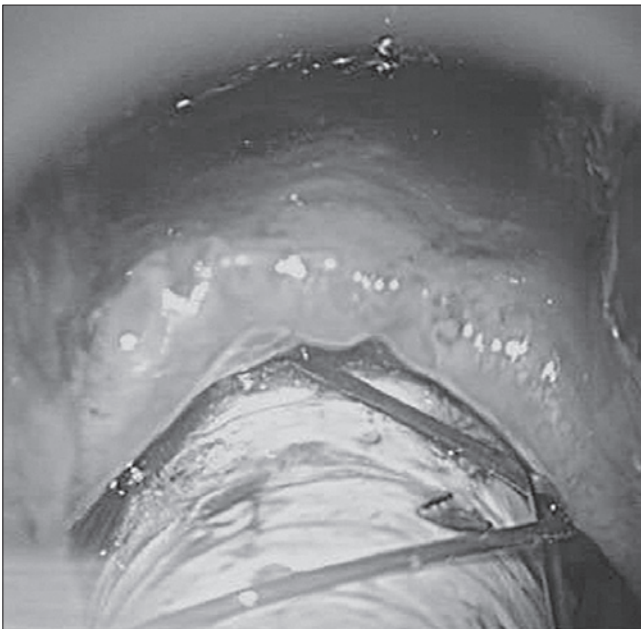
**Fig. 1.** The first needle penetrates the skin of the neck in a suprahyoid position. This needle contains a suture bent to form a loop. In MLS the first surgeon controls that the needle penetrates the epiglottis in a correct position and he then retrieves the loop out of the mouth.



**Fig. 2.** The second suture was inserted into the second catheter and penetrated soft tissues beneath the hyoid.

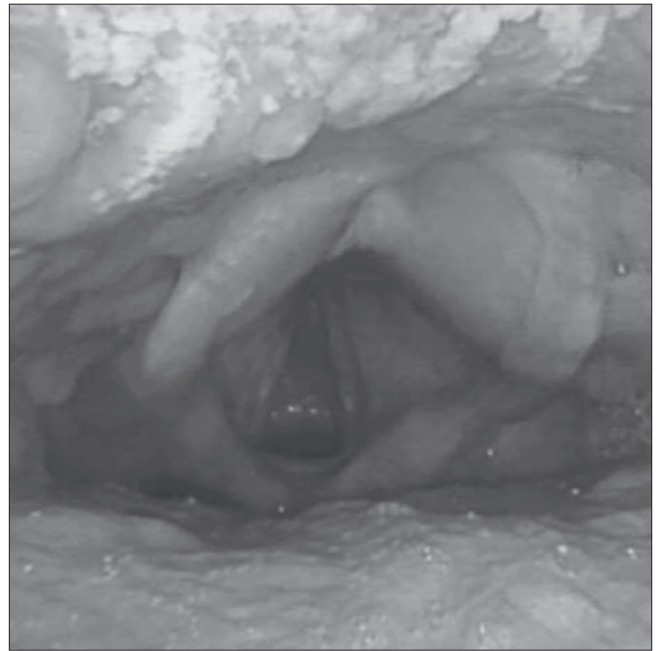


**Fig. 3.** Endoscopic view after the insertion of the second suture.



**Fig. 4.** The proximal end of the wire is inserted within the loop that is used as a guide to make the free suture exit the neck.

within the loop while holding it with one hand (Fig. 4). The second surgeon retracts the distal part of the loop, with a firm movement, allowing the second suture to exit from the skin. Both wires are then fixed anteriorly to the larynx using a Silastic sheet, on the anterior neck, to protect the skin from local trauma. Before tying the suture, a small amount of



**Fig. 5.** The suture is removed after 4 weeks under endoscopic control. The epiglottis results perfectly stabilised.

Tisseel® (Baxter, Westlake Village, CA USA) is spread in the glosso-epiglottic vallecula using a Duplocath® (Baxter, Westlake Village, CA USA) catheter.

#### *Postoperative care*

The patient was extubated at the end of the procedure. A clinical swallow evaluation was obtained on the first postoperative day. In case of normal scores, the patient was allowed to resume oral intake, including thin liquids, and was placed on a soft diet for 1 week. Intravenous antibiotics were administered for 24 hours. The patient was discharged after 48 hours of observation. Oral antibiotics and analgesics were recommended for one week.

The stitch was removed endoscopically after 4 weeks (Fig. 5); neither general or local anaesthesia is required.

Flexible laryngoscopy was performed after 1 week, testing the penetration-aspiration scale, and was repeated 3 weeks postoperatively. All patients filled in the EAT 10. All subjects also underwent an additional polysomnography testing 6 months after the procedure, while postoperative views were recorded at the time of control polysomnography.

#### *Statistical analysis*

Statistical analysis was performed with IBM SPSS Statistics version 24.0. Data were collected on a paired sample basis and comparisons were done using a nonparametric Wilcoxon Signed Rank Test. The Wilcoxon Signed Rank

Test was used to test for statistically significant differences between pre- and post-operative parameters.  $P < 0.05$  was accepted as statistically significant.

## Results

Twenty patients affected by OSAS with primary epiglottic collapse were included in this study. All patients (100%) underwent glossoepiglottopexy and pharyngoplasty, according to the palatal conformation: 10 (50%) Barbed Reposition Pharyngoplasty (BRP)<sup>11</sup>, 6 (30%) Functional Expansion Pharyngoplasty (FEP)<sup>22</sup>, 4 (20%) Barbed Roman Blinds Technique (BRB)<sup>23,24</sup>. Tonsillectomy was performed in 11 (55%) patients and septoplasty and turbino-plasty in 4 (20%) patients (Table I).

Transoral glossoepiglottopexy was associated with a significant decrease in ESS scores ( $p < 0.001$ ) evaluated at 6 months after surgery ( $16.5 \pm 4.3$  vs.  $3.1 \pm 2.5$ ).

Clinical swallow evaluation and EAT-10 score was normal in all the patients; in particular, only one patient reported that extra effort was needed to swallow pills, with a total score of 2. All patients received a score of 1 on the penetration-aspiration scale in their first swallows.

Mean  $\pm$  sd AHI values were  $23.6 \pm 6.5$  and  $5.2 \pm 3.2$  events/hour, before and six months after surgery respectively, and this difference was statistically significant ( $p < 0.001$ ). ODI

presented a significantly lower value at 6 months after surgery ( $19.3 \pm 6.1$  vs.  $4.8 \pm 2.7$ ,  $p < 0.001$ ). There was a significant decrease of  $T < 90\%$  values, which decreased from  $9.7 \pm 3.4$  to  $1.4 \pm 2.0$  ( $p < 0.001$ ). Mean oxygen saturation (mean SpO2) showed an increase at final evaluation vs. pretreatment levels  $86.9 \pm 2.3$  vs.  $94.7 \pm 2.3$  ( $p < 0.001$ ) (Table I).

## Discussion

A positive correlation between high BMI and OSA is well known in the literature; the pressure of the parapharyngeal fat pads and chronic collapse of the retroglottal airway during sleep create deformity of the epiglottis observed in patients with OSA. Thus, the shape of the epiglottis reflects the degree of the chronic airway obstruction. In patients suffering from OSAS, primary collapse of the epiglottis is due to the high negative intrathoracic pressure generated during obstructive events, in contrast to that which characterises laryngomalacia.

However, even when the epiglottis represents a cause of obstruction, its function in protecting the upper airway must be taken into account. The role played by the epiglottis in preventing inhalation of bolus is two-fold: on one hand, it offers a physical closure of the laryngeal aditus, while on the other its sensitive receptors (distributed on the laryngeal surface, ariepiglottic folds, arytenoids and posterior commissure)

**Table I.** Comparison of data collected before and 6 months after surgery.

Age	Sex	Surgery			Questionnaires						Polysomnography							
		Pharyngoplasty	Tonsillectomy	Septoplasty and turbino-plasty	ESS pre	ESS post	EAT10 pre	EAT10 post	PAS pre	PAS post	AHI pre	AHI post	ODI pre	ODI post	T90% pre	T90% post	mean SpO2 pre	mean SpO2 post
50	M	BRP	Yes	No	16	8	0	0	1	1	25	10	20	10	10	2	88	93
45	M	FEP	Yes	No	11	3	0	0	1	1	17	5	10	5	5	0	92	92
63	M	FEP	No	Yes	15	3	0	0	1	1	20	4	15	3	10	0	89	98
45	M	BRP	No	No	20	6	0	0	1	1	30	8	30	8	20	8	86	95
51	M	BRB	No	No	18	0	0	2	1	1	18	0	10	2	5	0	88	93
38	M	BRB	Yes	No	24	0	0	0	1	1	38	10	25	5	10	3	86	92
42	M	FEP	No	No	12	5	0	0	1	1	22	5	15	5	8	3	89	97
46	M	BRP	Yes	No	10	2	0	0	1	1	28	8	19	7	10	0	86	95
50	M	BRP	Yes	No	20	4	0	0	1	1	26	6	15	6	10	1	84	96
56	F	FEP	Yes	Yes	20	5	0	0	1	1	40	10	35	8	15	2	83	93
53	F	BRP	No	No	10	3	0	0	1	1	18	8	18	8	5	0	89	98
48	M	BRB	Yes	No	11	0	0	0	1	1	22	1	20	1	12	0	86	97
35	M	BRP	Yes	No	13	4	0	0	1	1	25	6	21	6	10	2	88	95
46	M	BRP	No	No	15	0	0	0	1	1	17	1	15	2	8	0	89	95
49	M	FEP	No	Yes	20	5	0	0	1	1	20	3	20	2	5	0	88	97
53	M	BRB	Yes	No	20	0	0	0	1	1	18	2	16	2	5	0	87	95
65	M	BRP	Yes	No	23	5	0	0	1	1	27	7	25	7	9	3	85	96
49	M	BRP	Yes	No	20	3	0	0	1	1	22	5	20	2	10	0	86	94
55	F	BRP	No	Yes	16	6	0	0	1	1	21	3	20	2	16	0	83	92
45	F	FEP	No	No	15	0	0	0	1	1	18	2	16	5	11	3	85	90

stimulate the so-called “glottis closure reflex”. This reflex is coordinated by the vagal nerve, and more precisely by its superior laryngeal branch, which provides the abduction of the vocal folds during deglutition thus avoiding the entrance of bolus in the airways. To maintain these two functions, two technical precautions must be taken into consideration: 1) it is necessary to leave a 3-4 mm rim of healthy cartilage and mucosa along the entire profile of the epiglottis to address food to the piriform sinuses; 2) the mucosa of the supraglottis (except the lingual aspect of the epiglottis) and the glottis should be preserved to allow the activation of reflexes.

Since the advent of DISE, the indications for the laryngeal surgery for OSAS have significantly changed, due to the fact that the awake endoscopy with Muller manoeuvre alone underestimates the obstructive component at this level by 40%<sup>25</sup>.

To date, surgical approaches in this region are technically complex, significantly invasive and associated with a high rate of complications, such as bleeding, oedema, persistent dysphagia, dysgeusia, etc.<sup>26</sup>. New technologies (diathermy, CO2 laser and co-blation) have allowed the introduction of innovative surgical techniques aimed at modifying the epiglottis and negatively interfering with its sphincter function<sup>27</sup>.

## Conclusions

The surgical technique described herein is able to preserve laryngeal anatomy and physiology, and is safe and reversible in case of unexpected complications. Moreover, it provides stable support to the epiglottis without interfering with its function during swallowing and reinforces the wall of the airway by creating a type of landslide barrier for posterior falling of the tongue base.

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All procedures 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.

Informed consent was obtained from all individual participants included in the study.

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## RHINOLOGY

# The hump columellar strut: a reliable technique for correction of nasal tip underprojection

## *Lo strut columellare ricavato dal gibbo nasale: una tecnica affidabile per la correzione di deficit di proiezione della punta*

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## SUMMARY

Nasal tip under projection is often found in rhinoplasty cases both for congenital or post-traumatic deformity. Nasal trauma may result in alteration of the external and internal nasal structures with following aesthetic impairment and difficulties in breathing. Post-traumatic surgery is frequent, but restoration of pre-traumatic form and function remains a challenge. The present paper describes a new method to increase tip projection by a columellar strut harvested from the autologous nasal bone and cartilage of the resected hump. A total of 15 cases (11 women/4 men, mean age  $32.6 \pm 12.3$  years) of major tip projection/misalignment abnormalities to be corrected by increased nasal tip projection were drawn, and all underwent closed or open rhinoplasty with the placement of a bony columellar strut harvested from the resected hump of the patient. Short and long-term advantages of this procedure are to be underlined. Harvesting is routinely performed during dorsal resection and preparation of the graft is easy. Differently from bone of the vomer or the inferior turbinate, this is cortical bone straight in shape and rigid in framework, and therefore ideal to gain reliable tip support overtime. No additional harvesting areas are needed. Placement of this bony strut is carried out in the standard fashion without additional dissection or further procedures. Long-term follow-up shows maintained projection over time. This graft can be combined with various grafting or suturing techniques usually applied according to each surgeon's experience and the needs of each patient.

KEY WORDS: Columellar strut • Nasal hump • Bony graft

## RIASSUNTO

*Molti casi di alterazioni della proiezione della punta nasale, sia per deformità congenita che post-traumatica, sono trattati con intervento chirurgico di rinoplastica. Un trauma nasale può causare alterazioni delle strutture nasali esterne e interne con conseguente compromissione estetica e difficoltà respiratoria. Spesso si tratta di una chirurgia post-traumatica, ma il recupero della forma prima del trauma e della funzione rimane tuttora una sfida. Tale studio ha lo scopo di descrivere un nuovo metodo con il quale trattare deficit di proiezione della punta tramite uno strut columellare proveniente da osso nasale autologo e cartilagine del gibbo asportato. Sono stati esaminati 15 casi (11 donne/4 uomini, età media  $32,6 \pm 12,3$  anni) con gravi anomalie della proiezione/disallineamento della punta, i quali sono stati sottoposti a rinoplastica chiusa o aperta e con posizionamento di uno strut columellare osseo raccolto dal gibbo resecato dal paziente stesso. Sono stati ottenuti risultati a breve e a lungo termine. Durante la resezione dorsale, la raccolta dell'innesto viene fatta di routine. A differenza dell'osso del vomere e dei turbinati inferiori, tale osso corticale è dritto e rigido ed è, quindi, ideale per ottenere un supporto utile alla punta. Non sono, pertanto, necessarie altre preparazioni di innesti. Il posizionamento dello strut osseo avviene in maniera standardizzata senza dissezione supplementare o ulteriori procedure. Tale trapianto può essere combinato con varie tecniche di innesto o di sutura solitamente in base all'esperienza di ciascun chirurgo e in base alle esigenze di ogni singolo caso.*

PAROLE CHIAVE: Strut columellare • Gibbo nasale • Trapianto osseo

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## Introduction

Nasal tip under projection is often found in rhinoplasty cases both for congenital or post-traumatic deformity.

Nasal trauma may result in alteration of the external and internal nasal structures with subsequent aesthetic impairment and difficulties in breathing. Post-traumatic surgery is frequent, but restoration of pre-traumatic form and



function remains a challenge<sup>1,2</sup>. Recurrence is very common because of cartilage memory and scar contracture so that permanent support is needed to prevent relapse and maintain the correction over time. Various kinds of structural grafts have been proposed in order to reinforce/replace the traumatised or missing structures<sup>3,4</sup>.

Specifically, in the case of under projected and ptosis tip often medial crura support is reduced and real or pseudo-hump of the dorsum is part of the deformity. These alterations are frequently combined with weak and distorted nasal septum. Columellar strut grafting is required in these cases to gain re-positioning of the tip, but the availability of grafting material from the septum may be jeopardised by the above-mentioned deformities.

Options to recruit additional material include autologous cartilage/bone from the auricle, rib, calvarium, or iliac crest<sup>5-11</sup>, or alloplastic implants e.g. high-density polyethylene, silicone etc.<sup>12-15</sup>. A neglected source of autologous grafting material lies within the operative field and obviates the need for a second operative graft harvesting site: the resected dorsal hump<sup>3</sup>.

The resected hump may be trimmed to harvest bone tissue to be fashioned and placed properly as columella strut with no added patient morbidity to provide nasal tip realignment and support. Our experience and long-term follow-up of functional and aesthetic results of this technique are reported.

## Materials and methods

A total of 265 unselected, consecutive primary rhinoplasties treated from January 2007 to December 2012 were retrospectively analysed. A Goode ratio less than 0.55 was considered as a feature of hypo-projected tips, while a normal nasal tip projection was defined ranging from 0.55 to 0.61<sup>16</sup>.

15 cases (11 women, 4 men; mean age  $32.6 \pm 12.3$  years) of major tip projection/misalignment abnormalities to be corrected by increased nasal tip projection were drawn, and all underwent closed or open rhinoplasty with the placement of a bony columellar strut harvested from the resected hump of the patient. Five patients were also given an unilateral spreader graft made from the same bone for re-alignment of the caudal-dorsal septum. A minimal two years follow-up available was considered as selection criteria.

A closed approach with alar cartilage delivery exposure and sub-periosteal hump resection through intercartilaginous and transfix incisions was used in 10 cases. An open approach with inverted V columellar incision was preferred in 5 cases with severe tip deformities. Hump

removal was always performed by using a # 10 and 12 Rubin osteotome. Standard septoplasty was always carried out with minimal resection of the quadrangular cartilage and conservative repositioning of the vomer bone. Tip shape and projection were then addressed by cephalic resection of the lower lateral cartilage with interdomal suturing.

The hump columellar strut was trimmed from the nasal bone using a Mayo scissor: the cephalocaudal dimension equalling the high of the existing medial crura (Fig. 1). Excessive thickness of the hump was corrected by drilling to obtain a flat graft. The cartilaginous part of the hump was left attached to the bone graft and trimmed according to the individual needs. To avoid risks of fracture while driving a curved needle through the implant, one or two preliminary holes are developed by a straight cutting needle or 2 mm round burr (Fig. 2). The next step is the placement between the medial crura (Fig. 3) and fixation of the strut to the medial crura using one trough-and-trough 4-0 polyglactin or polydioxanone suture. Two mattress stitches run in the inferior and superior membranous septum to prevent posterior dislodging and upward rotation of the columellar complex. An additional one or two stabilising sutures can be placed between the cartilaginous septum and the caudal margin of the medial crura.

In cases of osteocartilaginous hump graft, the bony portion is placed towards the nasal spine and the cartilage is put between the dome in order to have better flexibility of the tip. Moreover, suturing of the strut to the medial crura is easier and the stiffness of the tip is reduced.

Should additional projection be required, a tip cartilaginous onlay graft in a T fashion may be placed. The nose is taped and cast in standard fashion. Packing (3 × 18-inch petroleum-impregnated gauze for 48 hours) is not mandatory, but was used in case of concomitant turbinate surgery.

Oral and written informed consent for participation in this study was obtained from each subject.

The follow-up ranged from 12 to 60 months (mean: 12 months).

Preoperative and postoperative photographs were taken with a digital camera with flash lighting, postoperative subjective satisfaction (surgeons) was measured by visuo-analogue scale (scores 0-5). Post-operative patient satisfaction was measured by the Roe Validated Questionnaire<sup>17</sup>.

Comparisons were made of the change in the tip position with regards to lateral deviation and upward rotation. Photo documentation and measurements of nasal tip projection using the Goode ratio were obtained at least 12 months after surgery.

Evaluations were carried out by a physician uninvolved in patient care to avoid possible bias. Statistical evaluation



Fig. 1. Hump Graft shaped.

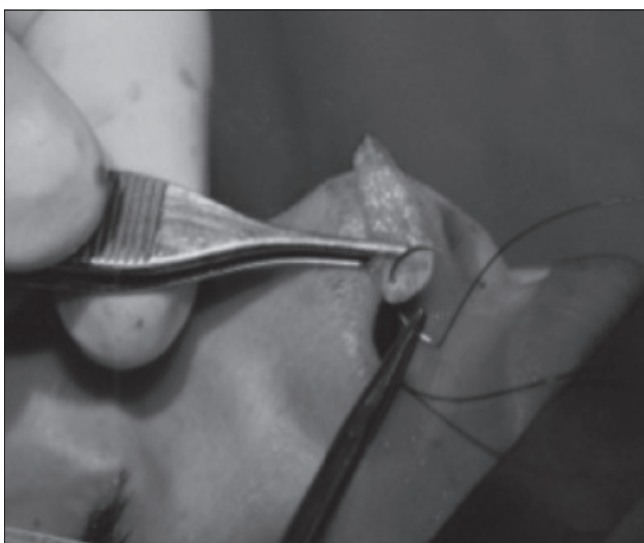


Fig. 2. Graft carving.

was carried out by computer-assisted (Microsoft-Excel, USA) mean + SD comparisons by 2-tail/paired data Student's T-test ( $p < 0.05$ ).

## Results

In all patients tip projection improvement was gained and demonstrated by means of visual (Fig. 3) and Goode ratio analysis (Table I). Follow-up showed maintained result overtime. No graft reabsorption (Fig. 4), infection or extrusion were observed and no other complications were recorded in this series.



Fig. 3. Graft positioning.

The alar cartilage misdirection observed preoperatively in 6 patients (40%) was corrected without recurrence overtime. In 2 (13%) more patients with absence of the caudal septum, the columellar retraction was significantly improved by using this type of graft.

Surgeon's judgment of results ranked an overall 3.1 score. Patient's aesthetic judgment of his/her nose improved markedly at Roe Self Valuation (Table II).

Adjunctive revisions or refinements of the first operation were needed in 1 case (6%) of under-projecting tip; cause of revision was tip asymmetry not linked to the graft, but to the outcome of suturing.

Two typical cases are shown in Figures 4 and 5. Correction of tip under projection was performed using the hump bone graft columellar strut technique.

## Discussion

The modification of the projection of nasal tip requires a thorough understanding of the anatomy and physiology of its components. The framework is made by the alar cartilages that act as a tripod based on medial and lateral crura: muscles and gliding areas allow the movements of the rigid structures loosely inter-connected. The biodynamics of this functional unit have been reviewed by focusing on

Table I. Measures of tip projection improvement by and Goode ratio analysis.

Measurement	Mean ratio
Pre-operative	0.50 ± 0.25
Post-operative 3 months	0.58 ± 0.12
Post-operative 12 months	0.57 ± 0.15



Fig. 4. CT scan: graft in place at 5 years follow-up.

the importance of length, thickness and resistance of the alar cartilage on determination of nasal tip projection<sup>18-20</sup>. It must be underlined that a correct morphological-functional result may be obtained with the re-shaping of the tip framework with careful respect of the alar muscular and ligament structures that allow the alar cartilages to act as a dynamic “spring” that keeps the nasal valve patent. Specifically, we feel that the relationship between lateral and medial crura length is a key point that must be evaluated and corrected to obtain the desired result. Additionally, the shape of the dome may influence the medial/lateral crura length ratio, thus influencing both tip projection and shape. It follows that a sound surgical correction must recreate the right proportions of these cartilages as well as a physiological function of the same. An important aspect seen in long-term follow-up of a consistent series of cases treated is the importance of maintaining or re-enforce the medial crura-caudal end of the septum relationship to support the tip projection. Our initial enthusiasm for alar car-

Table II. Roe patient satisfaction evaluation.

Measurement	Mean ratio
Pre-operative	26.5 ± 9.1
Post-operative 3 months	78.1 ± 12.3
Post-operative 12 months	78.5 ± 10.1

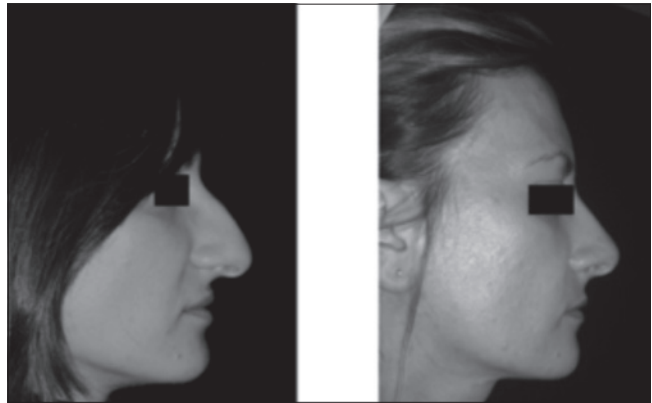


Fig. 5. Case # 1, Pre- and post-operative pictures.

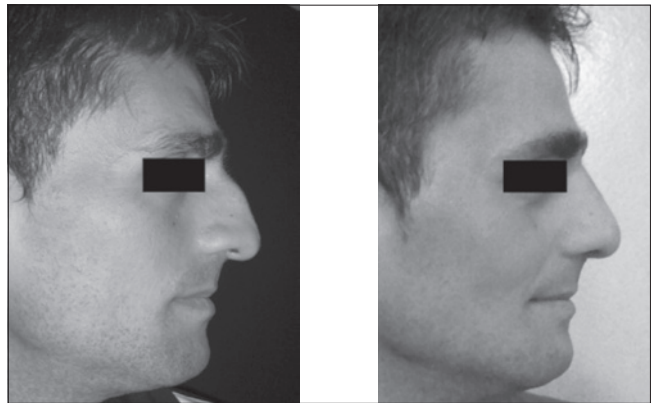


Fig. 6. The hump columellar strut: a reliable technique for correction of nasal tip underprojection.

tilages cephalic trimming procedures has been replaced by a cautious approach to the same. The reason for this lies on the experience that the mere resection of a prominent dome gives satisfactory immediate post-operative results for shape, rotation and definition, but under projection needs to be specific addressed.

The simplest way to eliminate under projection may be a Goldmann procedure, which combines dome division with medial crura suturing in higher position. Several pitfalls have been described in detail, the most important of which are the loss of tip projection and distortion. A possible alternative to the interrupted-strip procedures are inter/intradomal sutures to re-project the tip by dome re-positioning/re-orienting, but these techniques generally do not allow a major improvement and sometimes the result is temporary. Another option is the use of onlay grafts (Peck type) alone or combined with sutures to correct slight under projections or to camouflage irregularities. The safest way to achieve strong and durable tip support is with a columellar strut. This graft is effective

to supplement the medial crura, which are the main pillar of the tripod structure of the tip<sup>20</sup>. All the described techniques useful in projection improvement can take advantage of the adjunctive and pivotal reinforcing effect of the columellar strut. Patients who have undergone previous trauma or rhinoplasty or submucous septal resection and those who require extensive onlay grafting may not have sufficient material for creating an adequate columellar strut. Alternative harvesting (e.g. ears or rib) mandates another operative site, lengthens surgery and increases morbidity. Alloplastic material is doomed by higher risks of infection/extrusion. Autologous local nasal bone like demucosalised inferior turbinate as a columellar strut shows good promise in terms of strength and persistence in time, but forced resection of the turbinates is demanded with potential for further complications such as bleeding, crusting, fracturing and increased surgical time<sup>21</sup>. The resected hump has been proposed as useful grafting material for closure of perforation and septal reconstruction and also for different reconstruction purposes of the nasal framework<sup>22</sup>. The use of hump columellar strut gives substantial advantages in rhinoplasty when hump removal is planned, no septal cartilage is sufficiently available and a tip projection improvement is needed. In these instances, the material is already present, its carving and shaping are easy and the quality of bone and cartilage are good. A further advantage in comparison with other grafting materials is the naturally straight and robust framework of this graft, and therefore very effective to support the tip overtime. No additional operative sites are needed. Placement requires little or no additional dissection. Long-term follow-up shows maintained projection. Packing is not mandatory since no turbinate resection is needed. Every other procedure can be utilised together with hump graft<sup>4-15 23 26</sup>. Its disadvantages are the potential for intraoperative fracture and mild nasal tip stiffness similar to conventional strut or tongue-in-groove procedures.

## Conclusions

In conclusion, the use of the resected nasal bone is a possible alternative autologous strut graft to increase and maintain nasal tip projection, the described procedure requires little and further surgical manoeuvres to be shaped and positioned without extra incision or donor site.

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AUDIOLOGY

# Correlation between musical aptitude and learning foreign languages: an epidemiological study in secondary school Italian students

## *Correlazione fra attitudine musicale e apprendimento delle lingue straniere: studio epidemiologico su studenti italiani della scuola media secondaria di primo grado*

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### SUMMARY

The aim of this study was to assess if a correlation exists between language learning skills and musical aptitude through the analysis of scholarly outcomes concerning the study of foreign languages and music. We enrolled 502 students from a secondary Italian school (10-14 years old), attending both traditional courses (2 hours/week of music classes scheduled) and special courses (six hours). For statistical analysis, we considered grades in English, French and Music. Our results showed a significant correlation between grades in the two foreign languages and in music, both in the traditional courses and in special courses, and better results in French than for special courses. These results are discussed and interpreted through the literature about neuroanatomical and physiological mechanisms of foreign language learning and music perception.

KEY WORDS: Musical aptitude • Foreign aptitude • English • French

### RIASSUNTO

*Scopo di questo studio è stato lo studio della relazione fra l'apprendimento delle lingue e le abilità musicali attraverso l'analisi dei risultati scolastici ottenuti da studenti della scuola secondaria nelle materie linguistiche e nello studio della musica. Sono stati inclusi nello studio 502 alunni (età 10-14 anni) di una scuola media secondaria di primo grado, divisi in classi tradizionali (2 ore settimanali di insegnamento della disciplina musicale) e classi "speciali musicali" (6 ore settimanali di insegnamento musicale). Sono stati considerati per l'analisi statistica i voti riportati nelle tre discipline: Inglese, Francese ed Educazione Musicale. I nostri risultati mostrano una correlazione statisticamente significativa fra i voti riportati nelle due lingue straniere e nella disciplina musicale sia nelle classi tradizionali che nelle classi speciali. Inoltre, nel confronto fra classi speciali "musicali" e classi tradizionali l'analisi statistica ha evidenziato una differenza statisticamente significativa per la lingua francese. I risultati vengono discussi ed interpretati sulla base della letteratura riguardante i meccanismi neuroanatomici e fisiologici che sottostanno all'apprendimento delle lingue straniere e della percezione musicale.*

PAROLE CHIAVE: *Attitudine musicale • Apprendimento delle lingue straniere • Inglese • Francese*

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## Introduction

The present study is based on the hypothesis that there may be a relationship between musical aptitude and language learning ability <sup>1</sup>. Several studies have shown that foreign language learning skills are based on rhythm, singing and musical perception and that musical training enhances the acquisition of phonological skills required for foreign language learning <sup>2-5</sup>. In addition, there are studies on the role of music in specific learning disorders,

especially dyslexia: it seems that patients with learning disabilities, in addition to the well-known deficiencies in visual-spatial skills, present an alteration in the perception of rhythm <sup>6</sup>. In these children, musical training may facilitate the achievement of better results in spelling and phonological segmentation tests <sup>7-9</sup>.

To our knowledge, there is only one published paper concerning foreign languages learning skills and possible related disorders in Italian children. That study focused only on Italian seventh and eighth grade students with

low (LA) or high achievements (HA) in learning English. Foreign language abilities were assessed through an ELT (English Learning task) and a PMA (Primary Mental Aptitude Battery) test previously validated. Students were tested in two different experiments with batteries of tests analysing native language reading skills, comprehension of text, calculation, attention and self-regulation control (from parents and teachers point of view). The results showed that LA students performed poorly in native language reading comprehension tests, and had attentional control problems. The authors hypothesised that students with foreign language learning difficulties were at risk for attention-deficit disorders, but not for learning disorders<sup>10</sup>.

Neurophysiological aspects related to perception of music have been the subject of major studies over the years. Interesting investigations have examined the correlation between linguistic and musical components. According to these studies, music can be considered the equivalent of language, and also consists of discrete elements and specific rules. In fact, it has been shown that language and music share some brain circuits, thus excluding the theory of the two independent areas: the right hemisphere for music and the left for language<sup>11</sup>. Also, the pathological patterns of aphasia and amusia have confirmed these neuro-anatomical and physiological data<sup>12</sup>.

The aim of the present study was to assess if a correlation exists between language learning skills and musical aptitude through the analysis of scholarly outcomes concerning the study of foreign languages and music.

## Materials and methods

After an investigation, and the request to different schools for collaboration in our study, we chose a school for the feasibility of the project, which was related to the adequate number of students, the foreign languages studied (French and English) and the presence of special courses with 6 hours/week of music classes scheduled.

We enrolled all students ( $n = 585$ ) of a secondary school (Italian middle school) for the project. Exclusion criteria were the presence of disabilities related to or directly concerning learning skills (30 children), and the possibility of interference from another language (the same or different than the languages learned at school). We excluded 53 bilingual children resulting from parents with different native language or emigrated to avoid contamination of the results arising from external factors.

We included in the study the remaining 502 students, aged between 10 and 14 years old.

Twelve teachers were involved in the study. Regarding the

methodology of the school program, the school and teachers follow the national guidelines for the curriculum of the secondary school level. It should be noted that the data, obtained directly from the school, with the approval of the Headmaster, were not sensitive data, as the students were listed numerically and the classes encoded with random letters.

The students were divided by school grade (from 6<sup>th</sup> to 8<sup>th</sup>): the first group included 173 students, while the second 159 and the third 170. The weekly timetable concerning foreign languages scheduled 3 hours for English and 2 for French. Foreign language teachers were Italian. The hours for musical discipline are usually two per week in Italian school. 70 of the 502 students belonged to “special courses” with 6 music classes/week. In fact, students have as an optional choice the possibility to attend additional music classes during the afternoon. We considered this as a separate group of students, and we took in account the different grade attended for statistical purposes (6<sup>th</sup> grade 24 students, 7<sup>th</sup> 24 and 8<sup>th</sup> 22).

In order to evaluate learning abilities, we considered the final grade for each discipline considered (English, French and music). In this specific school, grades are given in a standardised way according to parameters established at the beginning of the school year by teachers from different departments. We collected all the final marks for each subject and each student, and we performed statistical analyses to assess whether a correlation existed between language learning abilities and music skills.

The  $\alpha$  level was fixed at 0.05 for all statistical tests. The sample size was computed using the software STATA 10.0, StataCorp LP, TX USA. To detect a difference in the means of 0.3 with a 0.9 power and with a 0.05  $\alpha$  value, we estimated an overall sample size of 468 students (assuming two equally numerous groups). Other statistical analyses were performed using the JMP software, release 7.0.1, from the SAS institute. For comparisons among means (continuous variables) according to categorical variables (independent variable), we performed the analysis of variance using one-way ANOVA, and in case of statistical significance, we compared each pair using a student's T test. We first evaluated the correlations among the numeric variables through a multivariate approach, obtaining scatterplot and covariance matrices, both in the whole population and after stratifying the children according to the type of course attended (nominal variable). When the  $r$  coefficient at scatterplot analysis for a pair of variables was above 0.4, we evaluated the correlation through logistic regression and checked the linear fit through analysis of variance.

**Table I.** Marks in the traditional courses (mean ± SD).

	6 <sup>th</sup> grade	7 <sup>th</sup> grade	8 <sup>th</sup> grade
English	7.05 ± 1.27	6.93 ± 1.2	6.85 ± 1.3
French	7.03 ± 1.12	7.1 ± 1.28	6.7 ± 1.1
Music	6.98 ± 0.91	7 ± 1.02	6.88 ± 1.02

**Table II.** Marks in the special courses (mean ± SD)

	6 <sup>th</sup> grade	7 <sup>th</sup> grade	8 <sup>th</sup> grade
English	6.79 ± 0.88	6.66 ± 1.12	6.63 ± 0.9
French	7.75 ± 0.89	7.12 ± 1.11	7.45 ± 0.91
Music	7.37 ± 1.24	6.75 ± 1.18	7.54 ± 0.96

## Results

Tables I and II describe mean marks achieved by 6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup> grade students in French and English classes, and are shown separately for students attending traditional and special courses with more music classes scheduled.

Statistical analysis showed that final marks in French classes were significantly different among students attending different grades, and showed a significant (at one-way ANOVA  $p = 0.0166$ ) even if modest decrease along the 3 different grades, being significantly higher (at Student’s T test) in the 6<sup>th</sup> than in the 8<sup>th</sup> ( $p = 0.0095$ ) and in the 7<sup>th</sup> than in the 8<sup>th</sup> grade ( $0.0194$ ). Final marks for English and music classes achieved by students attending different grades did not show any significant difference. When evaluating separately traditional vs. special courses, we observed that only traditional classes showed an even more evident decrease in French marks ( $p = 0.0101$  at ANOVA), while in special courses a significant increase of marks in music was observed ( $p = 0.049$ ), with an improvement between the 7<sup>th</sup> and the 8<sup>th</sup> grades ( $p = 0.021$  at student’s T test).

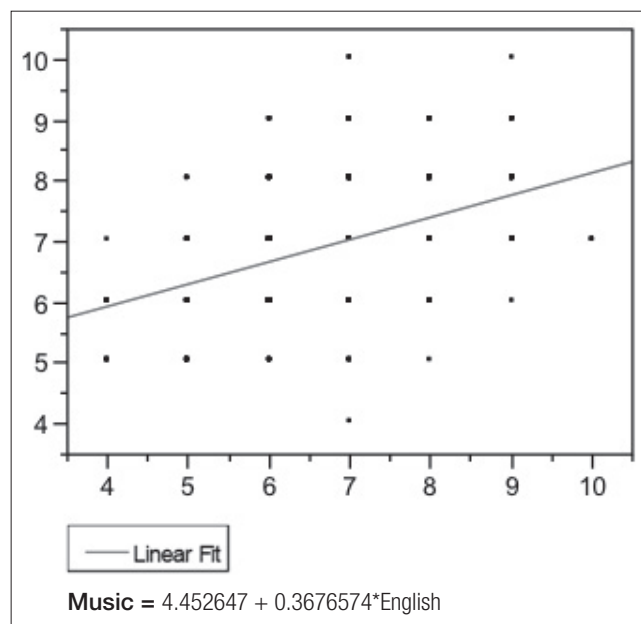
Generally, we observed a significant correlation between the marks in the two different languages ( $r = 0.623$  in scatterplot matrix,  $r = 0.897$  in covariance matrix,  $p < 0.0001$  at analysis of variance for the linear fit), and between the marks in both the languages and in music (English and music:  $r = 0.443$  in scatterplot matrix,  $r = 0.556$  in covariance matrix,  $p < 0.0001$  at analysis of variance for the linear fit; French and music:  $r = 0.488$  in scatterplot matrix,  $r = 0.583$  in covariance matrix,  $p < 0.0001$  at analysis of variance for the linear fit) (Figs. 1, 2). Such correlations were all confirmed even when separately evaluating “special courses” and traditional ones.

Finally, the comparison between special courses and traditional ones showed no statistically significant differences for English and music, while there was a statistically

significant difference for French language ( $p = 0.0003$  at t test) (Fig. 3).

## Discussion

Our results strengthens the hypothesis of a close correlation between language learning skills and musical aptitude. In fact, we demonstrated a significant statistical correlation between the marks obtained by the student in music versus English and French both in traditional and special courses. Moreover, comparison between two groups (traditional and special courses) showed that the agreement is more relevant in special courses: students with musical disposition, or exposed to specific musical



**Fig. 1.** Bivariate Fit of Music (Y) by English (X) shows a statistically significant correlation ( $p < 0.0001$ ).



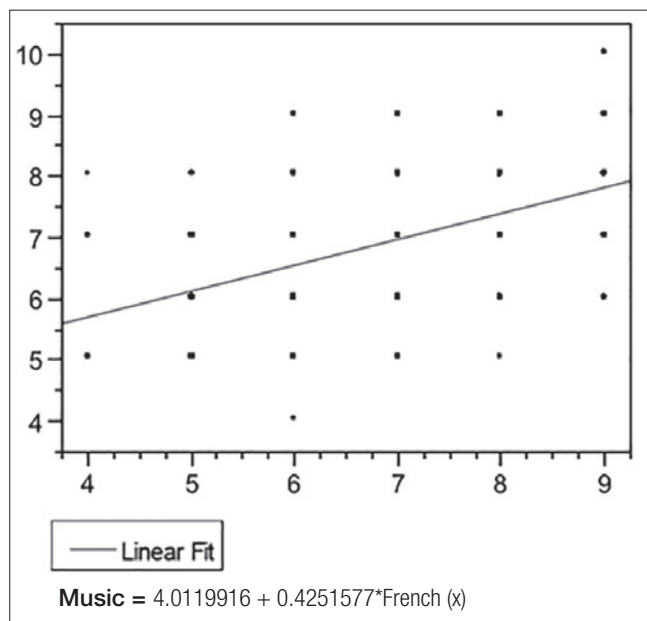


Fig. 2. Bivariate Fit of Music (Y) by French (X) shows a statistically significant correlation ( $p < 0.0001$ ).



Fig. 3. Comparison of the French marks demonstrates significantly better results in special courses than in traditional courses ( $p = 0.0003$ ).

training appear to have a greater success in foreign language learning. Our results are in agreement with Finnish studies by Milovanov et al.<sup>13</sup> about this subject. In a recent review, these authors analysed the neuropsychological and electrophysiological aspects related to music in relation to second language linguistic abilities<sup>14</sup>. They assumed that a better ability to discriminate sounds, typical of individuals with a greater propensity to musicality, predisposition to a better recognition and offering a greater possibility to acquire foreign languages with correct pronunciation. The same authors carried out a study

on students undergoing special musical training that led to a modulation effect in the cerebral organisation of language centre, altering hemispheric functioning with an interesting improvement of foreign language learning<sup>15</sup>. Recently, Christener and Reiterer<sup>2</sup> demonstrated in adults that good singers benefit from vocal and motor flexibility, both productively and cognitively. In particular, motor flexibility and the ability to sing can improve both language and musical function, acting on the memory span of the auditory working memory.

These results could be interpreted as the neuroanatomical and physiological basis of the behind the shared neurological pathways between central auditory processing of musical and linguistic information. Preliminary studies proposed by Mackenzie Beck in 2003<sup>16</sup> showed that musical ability was a useful predictor of general phonetic skills. Afterwards, Dankovicová et al in 2007<sup>17</sup> demonstrated a significant relationship between musical training and intonation task scores, and between music test scores and intonation test scores.

Regarding comprehension of foreign languages, a French study on adult musicians, exposed to sentences spoken in Portuguese, showed that musical expertise increases discrimination of pitch, facilitating the processing of pitch variations not only in music but also in language<sup>18</sup>.

To our knowledge, the present study is the first of this type conducted in the Italian school system. Our results show that students attending traditional courses tend to achieve lower marks in French classes during subsequent grades. This finding is in contradiction with an apparent easiness of the French language learning, due to the common Latin origin. Anyway, the difficulty could be related to grammatical and syntactical aspects of the French language rather than phonological and lexical ones.

On the other hand, students attending special courses showed better French learning skills: we suppose that better results could be justified by the greater musicality of French than English, resulting in better learning of French by students with a more marked musical aptitude.

This retrospective study has some limitations: marks, even if assigned according to standardised parameters, cannot be considered objective, if not for the presence of multiple evaluators. Moreover, the analysis of data from more schools would have been much more representative, but would have brought even more confounding factors, including different programs, a wider range of textbooks and probably different standards for marks. Of course, this should be considered just the first step towards more ambitious study designs. It would be very interesting, for example, to carry out a more detailed examination of foreign language learning skills evaluating separately writ-

ing skills, conversation and pronunciation, as well the knowledge of musical theory and ability in music practice. We believe that our findings, reflecting the impact of the discussed neurophysiological theories on real life, will give some momentum to this interesting research field.

## Conclusions

In conclusion, our results are interesting under multiple points of view. First of all, even if not conclusive and with the discussed points of weakness, they do reflect the potential impact of the neurophysiological theories connecting music and language processing pathways. If confirmed by further studies, these findings will prove useful both in the research field and as actual teaching tools. In a clinical setting, assessing the role of musical aptitude in learning disabilities involving foreign language studies may offer us both a testing tool and a therapeutic aid<sup>19 20</sup>. However, before any actual application, more data and more evidence, possibly interpreted by interdisciplinary teams constituted by musicians, hearing and speech therapists, psychologists and physicians will be needed to improve our understanding of the relations between both comprehension and production of written and spoken foreign languages and the study and practice of music. We hope that this initial retrospective work will be a prompt both for our and other research groups to further explore this field, possibly through electrophysiological analysis and specific phoniatric tests.

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OTOLOGY

# Cochlear obliteration following a translabyrinthine approach and its implications in cochlear implantation

## *Ossificazione cocleare dopo l'approccio translabirintico e le sue implicazioni per l'impianto cocleare*

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### SUMMARY

The most frequent sequelae following a translabyrinthine approach for vestibular schwannoma resection is complete hearing loss on the affected side. Such patients could benefit from a cochlear implant, provided that two essential requisites are met before surgery: a preserved cochlear nerve and a patent cochlea to accommodate the electrode array. The goal of our study is to determine the prevalence and extent of cochlear ossification following a translabyrinthine approach. Postoperative MRI of 41 patients were retrospectively reviewed. Patients were classified according to the degree of cochlear obliteration into three groups (patent cochlea, partially obliterated cochlea and totally obliterated cochlea). The interval between surgery and the first MRI was studied as well as its relationship with the rate of cochlear ossification. At first postoperative MRI (mean interval of 20 months), 78% of patients showed some degree of cochlear ossification. Differences were found in the time interval between surgery and first MRI for each group, showing a smaller interval of time the patent cochlea group ( $p > 0.05$ ). When MRI was performed before the first year after surgery, a larger rate of patent cochlea was found ( $p > 0.05$ ). The present study suggests that cochlear ossification is a time-depending process, whose grounds are still to be defined.

KEY WORDS: Cochlear obliteration • Translabyrinthine approach • Vestibular schwannoma • Cochlear implant

### RIASSUNTO

*La conseguenza più frequente dopo un approccio translabirintico per uno schwannoma vestibolare è la completa perdita uditiva dal lato affetto. Questi pazienti possono trarre beneficio da un impianto cocleare, qualora però vengano soddisfatti due importanti requisiti prima della chirurgia: un nervo cocleare intatto e una coclea permeabile per accomodare l'elettrodo. L'obiettivo del nostro studio è quello di determinare la prevalenza e l'estensione dell'ossificazione cocleare dopo l'approccio translabirintico. Pertanto, sono state rivisitate retrospettivamente le immagini della risonanza magnetica (RM) post-chirurgica di 41 pazienti. I pazienti sono stati classificati secondo il grado di oblitterazione cocleare in tre gruppi (coclea permeabile, coclea parzialmente oblitterata e coclea completamente oblitterata). È stato studiato l'intervallo tra la chirurgia e la prima RM post-chirurgica ed anche la sua relazione con il tasso di ossificazione cocleare. Alla prima RM post-chirurgica (intervallo medio: 20 mesi), il 78% dei pazienti ha mostrato un certo grado di oblitterazione cocleare. Sono state trovate differenze nell'intervallo di tempo tra la chirurgia e la prima RM per ogni gruppo, mostrandosi l'intervallo di tempo più breve nel gruppo con la coclea permeabile ( $p > 0,05$ ). Questo studio suggerisce, quindi, che l'ossificazione cocleare è un processo tempo-dipendente, rimanendo, però, i motivi di ciò ancora sconosciuti.*

PAROLE CHIAVE: Ossificazione cocleare • Approccio translabirintico • Schwannoma vestibolare • Impianto cocleare

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## Introduction

A translabyrinthine approach (TLA) for the resection of a vestibular schwannoma (VS) results invariably in complete hearing loss. This symptom is the most common complaint after VS surgery<sup>1</sup>. Hearing rehabilitation of these patients

has traditionally relied on crossover or bone conduction hearing aids. In 1988, Chen et al.<sup>2</sup> demonstrated the presence of survival spiral ganglion after a labyrinthectomy in a comparable number to those found in patients with a CI. More recently, several studies have shown that these pa-

tients can be good candidates for cochlear implantation provided that the cochlear nerve has been anatomically and functionally preserved<sup>3</sup>. However, another requisite for cochlear implantation is the presence of a patent cochlea, capable of accommodating an electrode array. Cochlear ossification depends on different phenomenon of fibrosis or ossification derived from the violation of the otic capsule<sup>4</sup>. The surgical insult to this structure may produce either a vascular compromise or an inflammatory process such as a labyrinthitis that derives in a cochlear degeneration.

The lack of cochlear patency limits hearing rehabilitation with cochlear implants (CI), especially when there is a notable delay between the VS removal and the CI surgery. Even though a CI insertion in an obliterated cochlea is achievable, it becomes a more challenging surgery and hearing outcome may be less than expected<sup>5,6</sup>; this is the reason why the presence of an obliterated cochlea is generally considered as a contraindication to implantation. Some authors advocate for simultaneous implantation or sequential cochlear implantation soon after the TLA to prevent this problem. Computerised tomography scan (CT) has demonstrated to be useful to study cochlear anatomy and electrode position in cochlear implantation, although it has important limitations to assess the cochlear patency<sup>7</sup>.

In order to study this phenomenon, magnetic resonance imaging (MRI) is the best imaging modality to determine cochlear patency and fibrous or osseous changes on it<sup>8,9</sup>. It possesses a sensitivity of almost 100% in predicting cochlear obstruction and is routinely used for this reason preceding a CI insertion<sup>10,11</sup>. However, the number of studies determining the rate of cochlear obliteration after TLA are scarce, and their results are contradicting. Furthermore, no study has been able to establish a “safe” time interval between the TLA and the cochlear obliteration to date; nonetheless, it is widely accepted that the sooner the CI is inserted, the better the hearing outcomes to be expected.

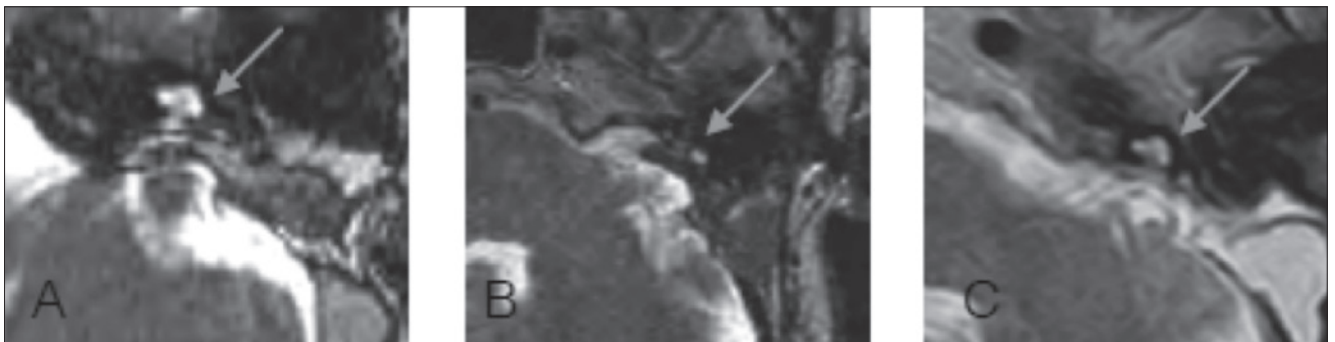
The aim of this study was to determine the prevalence and extent of cochlear obliteration after a TLA for VS removal, examining routine follow-up MRI studies performed as part of postoperative monitoring.

## Materials and methods

This study was conducted according to the principles stated in the Declaration of Helsinki of 1983.

Sixty-nine patients that underwent a TLA for removal of a unilateral sporadic VS between April 2008 and June 2014 at the Department of Otolaryngology of the Hospital Universitario Ramón y Cajal were retrospectively reviewed. Patients that underwent other type of approach for tumour removal (retrosigmoid (RSG) approach or middle fossa (MF) approach) were excluded. Surgical approach was elected based on tumour characteristics, such as size and extension within the internal auditory canal, and factors related to the patient, such as age and preoperative hearing. In this case, the follow-up protocol of our centre includes MRI at 1, 3 and 5 years postoperatively<sup>11</sup>.

Patients were classified into 3 groups depending on the intensity of the cochlear signal of the surgical side compared to the contralateral cochlea. A patent cochlea (Fig. 1A) was considered when its T2-hyperintensity was homogeneous to the contralateral side. When there was no T2-hyperintensity signal of the cochlea, it was considered as a totally obliterated cochlea (Fig. 1B). Those cases that presented T2-hyperintensity signal, but in a lower fashion than the normal cochlea, with or without filling defect, were considered as partially obliterated cochlea (Fig. 1C). The relation between the degree of cochlear ossification in these three categories and the interval between surgery and the first MRI was studied. A secondary analysis was performed dividing the patients into 3 categories according to the time interval between surgery and the first MRI (< 1 year, 1-2 years and > 2 years).



**Fig. 1.** T2 weighted temporal bone MRI, axial cuts at the level of the cochlea showing normal cochlear patency (A), totally obliterated cochlea (B) and partially obliterated cochlea (C).

### Statistical analysis

Data was analysed with a statistical software program (SPSS Statistics for Windows version 20, Chicago, IL). Continuous data was summarised as mean  $\pm$  95% confidence interval (CI95). Categorical data was presented as frequencies and percentages. Kolmogorov-Smirnov test demonstrated non-parametric distribution of the sample. The relation between cochlear patency and the interval between surgery and first MRI was studied with Kruskal-Wallis test and Fisher's exact test. P values  $<$  0.05 were considered significant.

## Results

Of the initial 69 patients, MRI examination was available for 41 patients. The mean age of the patients at the time of the surgery was 52.73 years, ranging from 24 to 80 years. 24 patients were women (58.5%) and the remaining 17 were male (41.5%). There was a predominance of left VS 27 (65.9%) versus right VS 14 (34.1%). The mean interval from surgery to the first MRI scan was 20 months (IC 95% 16-23).

Of the 41 cochleae examined at the first MRI, 32 (78%) presented some degree of obliteration; 14 (34%) of them were totally obliterated cochleae and 18 (44%) of them were partially obliterated cochleae. The remaining 9 cases (22%) showed a T2-hyperintensity homogenous to the contralateral side and were considered as patent cochleae. No statistically significant differences were found between groups ( $p >$  0.05).

In order to establish whether the interval between surgery and the first MRI has any impact on the cochlear obliteration rate, we calculated the mean interval between surgery and the first radiological image of the 3 different groups of cochlear patency previously described. The mean interval was 690 days (95% CI 417-962) for the total obliteration group, 622 days (95% CI 490-753) for the partial obliteration group and 434 days (95% CI 271-596) for the patent cochlear group (Fig. 2). No statistically significant differences were found ( $p >$  0.05).

When the patients were divided according to the interval between surgery and the first MRI, a tendency can be distinguished. Those who underwent the first MRI before completing the first year after surgery, 12 patients, tended to present a higher percentage of patent cochlea, whether those patients who underwent the first MRI after the first year, 29 patients, showed some degree of obliteration of the cochlea with a higher frequency (Fig. 3). In that sense, we can infer that the obliteration of the cochlea may be a time-depending process even though no statistically significant differences were found ( $p >$  0.05).

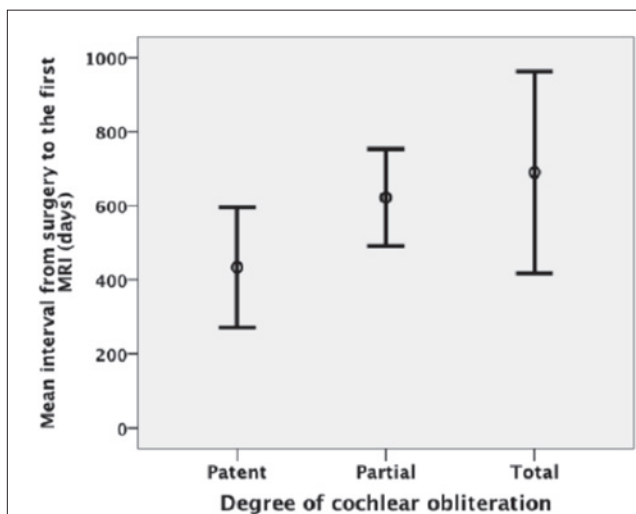


Fig. 2. Error bar diagram showing the mean interval of time from surgery to first MRI according to the clarification of cochlear patency.

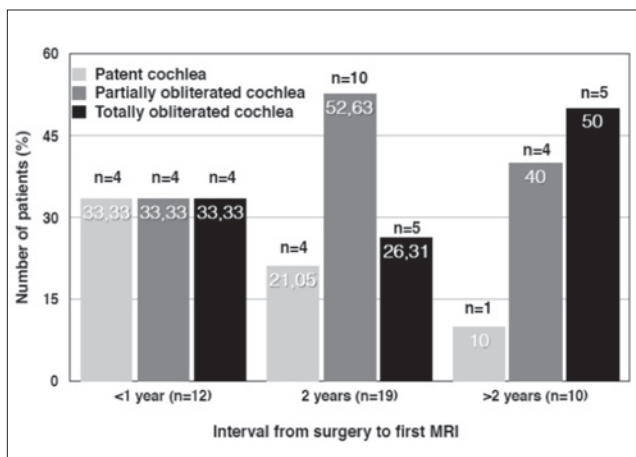


Fig. 3. Bar diagram showing the cochlear status depending on the time interval between surgery and first MRI.

## Discussion

Surgical treatment of VS has evolved considerably over the past decades. Today, life-threatening complications secondary to surgery are rare; nevertheless, patients may experience different physical impairments that have a negative impact on their quality of life, such as facial palsy, vestibular disorders, persistent operative headache or more frequently, profound hearing loss<sup>12,13</sup>. Moreover, some surgical approaches invariably entail specific sequelae, such as complete hearing loss for the TLA. In case of a RSG or MF approaches, no insult to the otic capsule is encountered, and therefore hearing function can be theoretically preserved without any morphological changes within this structure. However, if hearing loss takes place after hearing preservation surgery, CI has been reported to be successful after retrosigmoid approach<sup>14</sup>.

Cochlear implantation is the standard hearing rehabilitation procedure in cases of profound hearing loss, offering excellent results regardless of the age of subjects<sup>7</sup>. CI indications have progressively expanded over the years, from both the audiological and surgical points of view. More recently, new surgical approaches have been introduced in combination with CI, such as subtotal petrosectomy or skull base approaches, which allow implantation in cases formerly considered as non-candidates<sup>15 16</sup>. Hearing rehabilitation with a CI simultaneously to a VS resection was first described in 1995 by Arriaga and Marks<sup>17</sup>. Since then, publications of CI after VS resection have been increasing progressively, either simultaneously to tumour resection<sup>18 19</sup> or delayed implantation<sup>20</sup>, and more recently in cases of single sided deafness (SSD)<sup>21 22</sup>. CI has also been employed for hearing rehabilitation after labyrinthectomy for Meniere's disease with different degrees of success, either simultaneously to labyrinthectomy or in a second procedure<sup>23</sup>. In both clinical scenarios, those who are prone to simultaneous implantation allege the risk of cochlear ossification after labyrinthectomy as one of the main reason to support this attitude. Since CI insertion depends on the feasibility of the electrode insertion and the integrity of the neural pathway, both conditions should be present to obtain useful hearing in any case.

However, the relation between cochlear ossification and time after the surgical procedure is not well defined in the literature, and there is not an established time frame to perform the CI insertion. To ensure cochlear patency, some authors suggest placing an intracochlear placeholder to avoid cochlear obliteration following the TLA<sup>22</sup>. This approach also permits radiological follow-up with MRI in case that residual tumour or tumour recurrence is suspected, which is estimated in up to 9%<sup>24</sup> in some series.

Currently, only two studies have attempted to determine the time in which the cochlear obliteration occurred after TLA, with different results. Beutner et al.<sup>25</sup> determined the rate of cochlear obliteration presented on 14 patients who underwent a TLA. This study found that the rate of cochlear obliteration increased to 88.9% of patients at 1 year after surgery. Interestingly, some degree of cochlear obliteration was found in 66.7% of the sample as soon as 3 months after surgery.

On the contrary, the obliteration rate found by Charlett et al.<sup>26</sup> was significantly lower. In this study, 65 cochlear were examined based on T2-weighted images one year after the TLA. On 44 cochleae (68%) no sign of obliteration was found. The remaining 21 cochleae presented either complete (14%) or partial obliteration (18%).

Since the aetiology of cochlear obliteration is yet to be revealed, it is difficult to determine the circumstances to explain the difference in the obliteration rate of both studies. In our series, 78% of patients presented some degree

of cochlear obliteration in the first follow-up MRI, and this rate is more similar to that presented by Beutner et al. However, our mean interval from surgery to MRI was longer than in studies described previously (20 months with 95% of the patients between 16 and 23 months). This longer interval could definitely influence the high degree of cochlear ossification found in the present study. Additionally, in our series there is a relation between the interval from surgery to the first MRI and cochlear obliteration rate, with a higher interval in cases showing a total obliteration, followed by the group with partial obliteration. The group with complete cochlear patency presented the lower time interval. Although these differences were not statistically significant, a temporal pattern can be identified. This supports the theory that cochlear obliteration is a time-dependent process that hampers CI insertion but that may be avoided with early CI placement or an intracochlear placeholder.

CI has been demonstrated to be a successful method for hearing rehabilitation after labyrinthectomy and TLA VS removal, being an effective alternative to the most classical auditory rehabilitation devices for SSD<sup>27</sup>. Even though the cases illustrated in the literature to date are scarce, auditory outcomes are promising when appropriate selection and counseling is performed<sup>21 28 29</sup>. In this sense, it becomes critical to determine the time frame between the surgery and the beginning of the degenerative process. The present study found a rate of 78% in a sample of patients with an MRI obtained at a mean interval of 20 months after surgery, showing a temporal tendency to a higher degree of cochlear ossification with longer time interval. However, prospective studies are needed to clearly establish a "safe" time interval for cochlear implantation.

## Conclusions

Surgical labyrinthectomy generates changes in cochlear histology that drive oblitative process. The interval between the surgery and the occurrence of the obliteration is still unknown, and so, the aetiology behind it also remains unclear. The present study found a rate of 78% in a sample of patients with an MRI obtained in a mean interval of 20 months after surgery, showing a temporal tendency to a higher degree of cochlear ossification with longer time interval. This fact limits the auditory rehabilitation process in cases when a CI is to be considered in a second surgery. Since a "safe" frame time between surgery and cochlear implantation has not yet been established, simultaneous cochlear implantation or an intracochlear placeholder is recommended.

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OTOLOGY

# Treatment of cholesteatoma with intact ossicular chain: anatomic and functional results

## *Il trattamento chirurgico del colesteatoma a catena ossicolare integra: risultati anatomici e funzionali*

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### SUMMARY

In case of cholesteatoma with intact ossicular chain, the primary aims of surgery are complete removal of the cholesteatoma matrix and reconstruction of a dry and safe middle ear; if possible, ossicular chain continuity and therefore the preoperative hearing must be preserved. The aim of this retrospective study is to present the experience of the U.O.C. Otorinolaringoiatria Universitaria of University of Bari "Aldo Moro" in treatment of intact ossicular chain cholesteatoma with Bondy modified radical mastoidectomy (BMRM) and canal wall up tympanoplasty (CWUT). The study group was composed of 65 subjects affected by cholesteatoma with intact ossicular chain. Mean age was 40.7 years (range 6-79), with 42 males and 23 females. 30 patients were treated by a BMRM and 35 by CWUT, in 22 cases without mastoidectomy and in 13 cases with mastoidectomy. Mean follow-up was 24.25 months. In the BMRM group, no cases of residual cholesteatoma located in the middle ear space were detected; at follow-up, 1 patient developed a retraction pocket (3.33%), 1 patient showed a small epidermal cysts of the tympanic membrane (3.33%) and 3 patients (10%) experienced otorrhea. In CWUT, residual cholesteatoma was detected in 2 cases (5.7%); at follow-up, 3 patients presented recurrent cholesteatoma (8.57%; 2, 6 and 8 years after surgery), 3 cases a retraction pocket (8.57%) and one case otorrhea (2.86%). Statistical analysis showed a significant higher number of residual cholesteatoma in CWUT ( $p < 0.005$ ) and differences in terms of long-term complications. No significant changes in hearing occurred post-operatively or at 1 year follow-up in either group. The current trend in our centre is to perform BMRM when indicated and CWUT preferably without mastoidectomy in case of mesotympanic cholesteatoma with normal OC.

KEY WORDS: Cholesteatoma • Intact chain • Modified bondy mastoidectomy • Canal wall up tympanoplasty

### RIASSUNTO

*L'obiettivo primario del trattamento chirurgico del colesteatoma a catena integra è la completa eradicazione della patologia, la creazione di un orecchio asciutto e se possibile il mantenimento della funzione uditiva pre-operatoria. L'obiettivo di questo studio retrospettivo è di presentare i risultati ottenuti nel trattamento del colesteatoma a catena integra trattati mediante Radicale Modificata secondo Bondy e timpanoplastica chiusa presso U.O.C. Otorinolaringoiatria Universitaria Dell'Università di Bari "Aldo Moro". Il gruppo di studio è composto da 65 pazienti affetti da colesteatoma a catena integra. L'età media era di 40 anni (range 6-79 anni), 42 maschi e 23 femmine. 30 pazienti sono stati sottoposti a Radicale Modificata secondo Bondy e 35 a timpanoplastica chiusa (22 senza e 13 con mastoidectomia). Il follow-up medio è stato di 24,25 mesi. Nei pazienti trattati con radicale modificata secondo Bondy in nessun caso si è verificato un colesteatoma residuo, due pazienti (6,66%) hanno presentato complicanze precoci (3,33% vertigine, 3,33% acufeni) e 5 pazienti (16,67%) hanno manifestato complicanze tardive (3,33% tasca di retrazione, 3,33% cisti epidermica della MT, 10% otorrea). Nel gruppo trattato con timpanoplastica chiusa, 2 pazienti hanno presentato colesteatoma residuo al secondo tempo (5,7%) e 7 pazienti (20%) hanno presentato complicanze tardive (8,75% colesteatoma ricorrente, 8,75% tasca di retrazione, 2,86% otorrea). L'analisi statistica ha dimostrato un numero significativamente più alto di colesteatoma residuo in pazienti sottoposti a timpanoplastica chiusa ( $p < 0,005$ ) e nessuna differenza nelle complicanze a lungo termine. La capacità uditiva in entrambi i gruppi non si è modificata nel post-operatorio e ad un anno di follow-up. Entrambe le tecniche si sono dimostrate efficaci da un punto di vista anatomico e funzionale nel trattamento del colesteatoma a catena integra. La tecnica di Bondy trova indicazione in caso di colesteatoma epi-timpanico laterale alla catena ossicolare, mentre la timpanoplastica chiusa è la nostra tecnica di scelta in caso di colesteatoma mesotimpanico.*

PAROLE CHIAVE: Colesteatoma • Catena integra • Bondy • Timpanoplastica



## Introduction

The erosion of the ossicular chain (OC) in the course of cholesteatoma is a common condition found in over 85% of cases <sup>1</sup>. In recent decades, cases of advanced cholesteatoma have been significantly reduced because of the use of antibiotics and improved diagnostics; this has also led to an increased number of patients with intact OC and good hearing at presentation <sup>2</sup>.

In case of cholesteatoma with intact OC, the primary aims of surgery are complete removal of the cholesteatoma matrix and reconstruction of a dry and safe middle ear; if possible, OC continuity and therefore the preoperative hearing must be preserved.

All these aims can be fulfilled using two surgical techniques, namely Bondy modified radical mastoidectomy (BMRM) <sup>3</sup> and canal wall up tympanoplasty (CWUT) with or without mastoidectomy <sup>4</sup>. BMRM is an extremely effective operation when practiced on carefully selected patients <sup>5</sup>. This technique is indicated in case of patients affected by epitympanic cholesteatoma spreading laterally to an intact OC, normal pars tensa and good preoperative hearing (air bone gap, ABG, < 25 dB) <sup>3,6</sup>. CWUT with or without mastoidectomy is a conservative technique that can be performed in all cases of cholesteatoma with intact OC. In case of cholesteatomas involving only the middle ear, CWUT can be performed through a postauricular microscopic approach <sup>7</sup> or an exclusive endoscopic transcanal approach <sup>8</sup>.

The aim of this retrospective study is to present the experience of the U.O.C. Otorinolaringoiatria Universitaria of University of Bari "Aldo Moro" in the treatment of intact OC cholesteatoma with BMRM and CWUT.

## Materials and methods

Between November 2000 and December 2014, 673 subjects affected by a previously untreated middle ear and mastoid cholesteatoma were operated on and among these subjects all patients in whom the OC was kept intact during surgery were selected. The study group was therefore composed of 65 consecutive subjects. Mean age was 40.7 years (range 6-79), with 42 were males and 23 females. 30 patients were treated by a BMRM and 35 by CWUT, in 22 cases without mastoidectomy and in 13 cases with mastoidectomy. CWUT was staged in 8 cases (23%). The location and the extension of the cholesteatoma were evaluated as well as the anatomical and functional postoperative results and complications. In particular, the location of the cholesteatoma was recorded in the following anatomical sites: epitympanum, antrum, mastoid, mesotympanum and protympanum.

The guidelines of the Committee on Hearing and Equilib-

rium of the American Academy of Otolaryngology Head and Neck Surgery <sup>9</sup> were followed and the pure-tone average (PTA) was calculated as the mean of 0.5, 1, 2 and 4 kHz thresholds. Air-Bone Gaps (ABG) were calculated from air conduction (AC) and bone conduction (BC) thresholds determined in each study. Mean follow-up was 24.25 months (range 6-210); in BMRM, average follow-up was 25.83 months and in CWUT it was 22.8 months. All patients signed an informed consent and the work was performed in accordance with the principles of the 1983 Declaration of Helsinki.

### *Surgical technique*

BMRM was performed as described by Sanna et al. <sup>10</sup> with some technical differences. Conchal cartilage was not removed and the meatoplasty was obtained through a full thickness incision along the superior wall of the external auditory canal with posterior-inferior displacement of the flap obtained. The sinodural angle was obliterated with bone paté and covered with connective tissue, as previously described <sup>11</sup>. Particular care was taken to avoid contact between bone paté and the short process of the incus in order to prevent fixation.

CWUT was performed through a retroauricular incision in all cases under microscopic magnification. In case of cholesteatoma located only in the middle ear spaces, the surgery was performed through a postauricular transcanal approach. When needed, atticotomy was performed and the scutum reconstructed with tragal cartilage. In case of cholesteatoma involving the posterior epitympanum and spreading towards the antrum, a CWUT with posterior tympanotomy was performed. Scutum defect was reconstructed with bone paté. The tympanic membrane was always reconstructed with temporalis fascia.

### *Statistical analysis*

Anatomical results are presented as percentiles and comparison between the two groups was done by Chi-square test. Statistical analysis of functional results was performed by ANOVA test for comparison between the two groups and by paired samples t-test for comparison between preoperative and postoperative values for each group of patients. The statistical software STATA\_MP11 was used. Significance was set for  $p < 0.05$ .

## Results

### *Anatomical results*

In Table I the anatomical subsites involved by cholesteatoma are reported. Epitympanum (100% vs. 42.86% of the CWUT group;  $X^2 = 24.76$ ;  $p$ -value = 0.000001) and antrum

**Table I.** Anatomical sites involved by cholesteatoma are reported. BMRM; Bondy modified radical mastoidectomy. CWUT; canal wall up tympanoplasty.

Sites	BMRM	CWUT	p-value
Antrum	66.67%	17.14%	p < 0.001
Epitympanum	100%	42.86%	p < 0.001
Mesotympanum	0	74.28%	p < 0.001
Mastoid	13.33%	5.71%	p > 0.01
Protympanum	0	0	1

(66.67% vs. 17.14% of the CWUT group;  $X^2 = 16.51$ ; p-value = 0.00048) were most commonly involved in case of BMRM compared to CWUT (p < 0.001). Otherwise, the involvement of the posterior mesotympanum was significantly higher in case of CWUT (p < 0.001).

In Table II the number of anatomical sites involved are reported. In both groups, the cholesteatoma involved one or two sites in a large proportion of cases. In case of CWUT, cholesteatoma involved only one site in significantly more cases (p-value = 0.002).

Dehiscence of the tympanic portion of the facial nerve was observed in 2 patients treated with BMRM (6.67%). A lateral semicircular canal fistula was detected in 2 cases (6.67%) of the BMRM group, while in the CWUT group a fistula of the stapes footplate was found in 1 case. Partial erosion of the long process of the incus was observed in 8 patients submitted to BMRM (26.67%) and 3 patients to CWUT (8.57%). No significant differences were found in terms of intra-operative findings.

Anatomical complications were grouped into three categories: early post-operative, at second-look and at follow-up. In the early post-operative period, 1 patient treated with BMRM experienced dizziness and one reported post-operative tinnitus; analogous symptoms were reported by 2 patients treated with CWUT (5.7%). Second-look procedures were performed in 8 cases operated by CWUT where complete removal of the disease was doubtful. In two cases (5.7% of total and 25% of second look procedures) a residual cholesteatoma was found, in one case adherent to the stapes superstructure and in one case to the long process of the incus. In BMRM, no cases of residual cholesteatoma located in the middle ear space were detected at follow-up. Statistical analysis showed a significant difference (p 0.005) between

**Table II.** Number (and %) of anatomical sites involved in the two groups.

	1 site	2 sites	3 sites	4 sites
BMRM	10 (33.33%)	16 (53.33%)	4 (13.33%)	0
CWUT	23 (65.71%)	8 (22.86%)	0	1 (2.86%)
TOTAL	33 (50.77%)	24 (36.92%)	4 (6.15%)	1 (1.54%)

BMRM, Bondy modified radical mastoidectomy; CWUT, canal wall up tympanoplasty.

the two techniques. At follow-up in the BMRM group, 1 patient developed a mesotympanic retraction pocket (3.33%), 1 patient showed a small epidermal cysts of the tympanic membrane (3.33%) and 3 patients (10%) experienced otorrhoea. In patients treated with CWUT, long-term complications occurred in 20% of cases: 3 patients presented recurrent cholesteatoma (8.57%; 2, 6 and 8 years after surgery), 3 cases a retraction pocket (8.57%) and one case otorrhoea (2.86%). Statistical analysis did not show a significant difference between the two techniques in terms of long-term post-operative complications.

### Functional results

In Table III the pre-operative, immediate post-operative and 1 year follow-up average AC, BC and ABG thresholds ( $\pm$  standard deviation) of the two groups are reported. Statistical analysis showed that, pre-operatively, patients submitted to CWUT presented significantly worse hearing compared to BMRM group in terms of AC (p = 0.008), BC (p = 0.04) and ABG (p = 0.02). No differences were encountered in the post-operative period. No significant changes in hearing occurred post-operatively and at 1 year follow-up in both groups.

One patient in the BMRM group presented a decline of bone conduction > 20 dB and one patient submitted to BMRM underwent a revision surgery because of a post-operative increase in the ABG at 6 months after surgery. During revision, bone dust was found at the level of the incudo-malleolar joint that impeded the normal vibration of the OC; after removal of the bone dust the ABG returned to 8 dB HL.

## Discussion

The aim of this study was to analyse the results of our experience in the surgery of cholesteatoma with intact OC by BMRM or CWUT.

**Table III.** Postoperative hearing results at follow-up. PTA-AC; pure tone average air conduction at 0.5, 1, 2 and 4 kHz. PTA-BC; pure tone average bone conduction at 0.5, 1, 2 and 4 kHz.

		Preoperative	Postoperative	1 year follow-up
PTAAC	BMRM	27.72 $\pm$ 11.46	32.66 $\pm$ 13.77	23.18 $\pm$ 12.41
	CWUT	41.2 $\pm$ 20.58	42.55 $\pm$ 22.19	35.19 $\pm$ 22.33
PTABC	BMRM	15.92 $\pm$ 9.14	18.8 $\pm$ 10.29	15.91 $\pm$ 9.92
	CWUT	23.75 $\pm$ 16.07	23.02 $\pm$ 13.13	22.21 $\pm$ 16.83
ABG	BMRM	11.79 $\pm$ 6.48	13.86 $\pm$ 9.03	7.27 $\pm$ 4.87
	CWUT	17.45 $\pm$ 9.18	19.53 $\pm$ 13.62	12.98 $\pm$ 10.40

ABG, air bone gap; BMRM, Bondy modified radical mastoidectomy; CWUT, canal wall up tympanoplasty.

It is clear from this series that the two surgical techniques have different indications. BMRM has very strict indications, namely epitympanic cholesteatoma lateral to an intact OC. The involvement of the posterior mesotympanum was, in fact, never encountered in the present series, while involvement of the antrum and mastoid was not a contraindication of the technique as well as the partial erosion of the OC. CWUT with or without mastoidectomy was instead used in cases of limited cholesteatomas involving only one or two sites in 97.14% of cases, with the posterior mesotympanum involved in 74.28% and the epitympanic spaces in 42.86% of cases. Surgery was performed exclusively through a postauricular transcanal approach in 2/3 of cases and with mastoidectomy and posterior tympanotomy in the remaining.

It should be noted that the present series includes only patients where the OC was maintained intact during surgery; in fact, all subjects in whom the intact OC was not maintained during surgery were excluded. We usually try to preserve an intact OC only when the cholesteatoma sac does not involve the medial surface of the body of the incus and/or of the incudo-malleolar joint. In these cases, even with the use of angled endoscopes and angled instruments the likelihood to radically remove the cholesteatoma and preserve the OC has been reported to be around 15%<sup>9</sup>.

In case of patients with intact OC, the indications of the two techniques overlap only in case of limited cholesteatoma involving the epitympanum without medial extension, while the involvement of the posterior mesotympanum represents a contraindication to the use of BMRM. In case of a pure epitympanic cholesteatoma, both an atticotomy and a BMRM can be performed, although a higher risk of recurrence is possible with the former technique.

In the present series, patients treated with CWUT presented residual cholesteatoma in 5.37% of cases (25% of patients undergoing second look), tympanic membrane retraction pocket in 8.57% of cases and recurrent cholesteatoma in 8.57% of cases, while patients treated with BMRM presented no cases of residual disease medial to the tympanic membrane, one case (3.3%) of tympanic membrane retraction pocket and no cases of recurrent cholesteatoma.

Similar results are reported by other authors in patients with an intact OC. In a large series of 258 patients affected by epitympanic cholesteatoma and intact OC treated by BMRM with at least 5 years follow-up, Prasad et al.<sup>12</sup> reported the occurrence of residual cholesteatoma lateral to the tympanic membrane in 8.1% of patients, no cases of residual cholesteatoma medial to the tympanic membrane and 3.1% of retraction pocket and no recurrent cholesteatoma. Berrettini et al.<sup>5</sup> in a series with at least 5 years of follow-up reported that 84.5% of patients were free of

complications. Marchioni et al.<sup>8</sup> presented a series of 20 patients affected by epitympanic cholesteatoma with intact OC treated with exclusive endoscopic surgery. They reported a recurrence rate of 8.7%, and, as in the present series, they were able to preserve the OC only in cases of limited cholesteatoma not involving the medial attic<sup>8</sup>. Tarabichi<sup>13</sup> in a series of 73 cases affected by limited attic cholesteatoma treated with endoscopic surgery reported OC preservation in 69.8% of cases, tympanic membrane retraction pocket in 38% of cases and recurrent disease in 6.8% of cases. Smouha and Javidfar<sup>14</sup> in series of 39 patients affected by mesotympanic and epitympanic cholesteatoma with normal hearing and intact OC treated with microscopic CWUT reported OC preservation in 77% of cases and a recidivism rate of 26%, being 6% residual cholesteatoma and 20% recurrent cholesteatoma.

In terms of post-operative hearing in the present series, maintenance of the OC was associated with a not significant change in the post-operative ABG with either technique. Similar results were reported by Prasad et al.<sup>12</sup> in case of BMRM; no significant change in hearing was reported by Tarabichi<sup>13</sup>, while Smouha and Javidfar<sup>14</sup> were able to preserve hearing in 78% of cases where the OC was maintained intact.

In case of epitympanic cholesteatomas, in our experience MRBM represents the technique of choice, since it gives the best results in terms of recidivisms as well as hearing. One of the problems that have been associated with “open cavities” such as BMRM is the poor quality of life reported by patients because of the cavity itself and a large meatoplasty. Our group has, however, recently demonstrated that with the obliteration of the sinodural angle and a “cosmetic meatoplasty”, the reported quality of life in these patients is not worse than that reported by patients submitted to CWUT<sup>11</sup>.

The real challenge for the surgeon is therefore treatment of patients affected by mesotympanic cholesteatomas with intact OC. In these cases, the creation of a cavity may represent an overtreatment considering the pure involvement of the middle ear spaces. In our opinion, in cholesteatomas with intact OC localised in the posterior mesotympanum with or without involvement of the epitympanum and antrum a CWUT is indicated. The main complications associated with this technique are residual and recurrent cholesteatoma. Residual cholesteatoma originates from epidermal cells that are left behind during surgery, while recurrent cholesteatoma derives from a newly formed retraction pocket or a perforation of the reconstructed tympanic membrane<sup>15</sup>. Two recent papers have evaluated disease recurrence after CWUT and canal wall down tympanoplasty (CWDT)<sup>16 17</sup>; the

authors performed a systematic review in one case<sup>16</sup> and a meta-analysis in the other<sup>17</sup>; in both papers, the relative risk of recurrent or residual disease was 2.87 after CWUT compared to CWDT. The higher risk of residual disease has been correlated with poorer visualisation of the hidden recesses of the middle ear in CWUT such as the tympanic sinus and medial wall of the attic<sup>20</sup>. Use of endoscopes in middle ear surgery increase visualisation of middle ear spaces<sup>21</sup> and has the potential to reduce the risk of residual disease<sup>8 13 18 19</sup>. Recurrent disease is caused in most of the cases by retraction of the tympanic membrane and formation of a cholesteatoma sac. An everted mastoid behind an intact canal wall has been proposed as a precondition for recurrence, together with the presence of fibrous tissue and adhesions in mastoid and middle ear that impair normal mucosal function<sup>22-26</sup>. In the present series, two of the three patients who developed a recurrent cholesteatoma and one of the three patients who developed retraction pockets underwent mastoidectomy. The maintenance of the middle ear mucosa, reconstruction of any scutum defect and ventilation of middle ear spaces are the mainstay in prevention of recurrences<sup>10</sup>.

## Conclusions

It is clear from the literature that there is no single procedure that can be used in all cases of cholesteatoma, and therefore the surgeon should be able to choose the right technique for the individual patient. The high percentage of complication-free cases, associated with excellent functional results, lead us to consider that both BMRM and CWUT are extremely effective when performed correctly and following the right indications. The advantages of the Bondy technique are good short- and long-term functional results and a low risk of residual and recurrent cholesteatoma. The downside is the risk of cochlear trauma, with a consequent deterioration of bone conduction and the limited indications. The current trend in our centre is to perform BMRM when indicated and CWUT preferably without mastoidectomy in case of mesotympanic cholesteatoma with normal OC. In these cases, the use of endoscopes can help the surgeon in dealing with cholesteatoma in hidden areas.

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MAXILLO FACIAL AND PLASTIC SURGERY

# Is it possible to define the ideal lips?

## *È possibile definire le labbra ideali?*

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### SUMMARY

The lips are an essential component of the symmetry and aesthetics of the face. Cosmetic surgery to modify the lips has recently gained in popularity, but the results are in some cases disastrous. In this review, we describe the features of the ideal lips for an individual's face. The features of the ideal lips with respect to facial anatomy, important anatomical landmarks of the face, the facial proportions of the lips and ethnic and sexual differences are described. The projection and relative sizes of the upper and lower lips are as significant to lip aesthetics as the proportion of the lips to the rest of the facial structure. Robust, pouty lips are considered to be sexually attractive by both males and females. Horizontal thirds and the golden ratio describe the proportions that contribute to the beauty and attractiveness of the lips. In young Caucasians, the ideal ratio of the vertical height of the upper lip to that of the lower lip is 1:1.6. Blacks, genetically, have a greater lip volume. The shape and volume of a person's lips are of great importance in the perception of beauty by humans. The appearance of the lips in part determines the attractiveness of a person's face. In females, fuller lips in relation to facial width as well as greater vermilion height are considered to be attractive.

KEY WORDS: Lip • Ideal lip • Horizontal thirds • Golden ratio • da Vinci's classic proportions

### RIASSUNTO

*Le labbra sono una componente essenziale per la simmetria e l'estetica del viso. La chirurgia estetica delle labbra ha recentemente ottenuto grande popolarità, tuttavia i risultati in alcuni casi sono disastrosi. In questo lavoro di revisione, noi descriviamo le caratteristiche delle labbra ideali, quindi vengono elencate le caratteristiche delle labbra ideali nel rispetto dell'anatomia del viso, i punti di riferimento anatomici del viso, le giuste proporzioni delle labbra e le differenze in base al sesso e all'etnia. Le proiezioni e le relative misure del labbro superiore e inferiore sono importanti non solo per l'estetica delle labbra in sé, ma anche per le proporzioni del viso. Le labbra carnose sono considerate sensuali sia dal genere maschile sia da quello femminile. Le linee orizzontali (con le quali si può dividere un volto) e la "golden ratio" descrivono le proporzioni che contribuiscono alla bellezza e all'attrattività delle labbra. Nei giovani caucasici, il rapporto ideale tra l'altezza del labbro superiore e quella del labbro inferiore è di 1:1,6. Gli individui di razza nera hanno, geneticamente, delle labbra molto grandi. La forma e il volume delle labbra di una persona sono di notevole importanza per la percezione di bellezza da parte degli altri individui. Le labbra pertanto sono determinanti per l'attrattività di una persona. Nelle donne, le labbra carnose, in relazione alla larghezza del viso, così come l'altezza del vermiglio, sono considerate attraenti.*

PAROLE CHIAVE: Labbra • Labbra ideali • Proporzioni orizzontali • Golden ratio • Proporzioni classiche di da Vinci

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### Introduction

Beauty is defined as “a state of harmony – a balance of facial proportions – a balanced relationship among skeletal structures, teeth, and soft tissue”<sup>1</sup> or as the relative measure of balance and harmony<sup>2</sup>. Aesthetics is “the study of beauty and to a lesser extent, its opposite, the ugly”<sup>3</sup>. The main factor defining an individual's attractiveness is his or her face<sup>4</sup>. An attractive appearance has a strong influence on that person's everyday life<sup>5</sup>. Beautiful people are con-

sidered friendlier, more intelligent, more interesting and more socially competent<sup>6-9</sup>.

The lips are an essential component of the symmetry and aesthetics of the face (Fig. 1). Anthropometric studies have shown that wider and fuller lips in relation to facial width as well as greater vermilion height contribute to defining female attractiveness<sup>10</sup>. Gonzalez-Ulloa<sup>11</sup> described the changes of the lip with aging, including a less exposed vermilion and a relative loss of vermilion bulk.

The projection and relative sizes of the upper and lower lips are as significant to lip aesthetics as the proportion of the lips to the other facial structures. Additional important dimensions include the relative vertical length of the upper “red” lip to the length of the philtrum, or upper “white” lip. This is clearly demonstrated in the lips of the elderly, which are characterised by relative philtral excess and an atrophic upper red lip. On anterior view, the height of the upper red lip should be less than that of the lower red lip, and the upper lip should project approximately 2 mm over the lower lip on profile <sup>12</sup>.

In virtually all females since the beginning of recorded history, full lips have been associated with youth, beauty and voluptuousness. Robust, pouty lips are considered to be sexually attractive by both males and females <sup>13</sup>. Recently, cosmetic surgery to modify the lips has gained in popularity, with the goal of increasing facial attractiveness, but the results are in some cases disastrous. In this review, we consider the features of the ideal lips for an individual’s face.

## Anatomy of the lips

### Muscles of the lips

The **orbicularis oris** acts as a sphincter around the mouth. Its fibers interlace with those of all the other facial muscles that act on the mouth. The buccal and marginal mandibular branches of the facial nerve provide the motor supply to the orbicularis oris, whose actions include *pursing, dilation and closure of the lips* <sup>14</sup>.

The **depressor anguli oris** arises from the periosteum of the mandible, along the oblique line lateral to the depressor labii inferioris. Its fibers converge on the modiolus, together with fibers of the orbicularis oris, risorius and, in some individuals, levator anguli oris muscles. The marginal mandibular branch of the facial nerve supplies the depressor anguli oris, which *depresses the corners of the mouth on contraction* <sup>14</sup>.

The **depressor labii inferioris** arises from the oblique line of the mandible in front of the mental foramen, where it is covered by fibers of the depressor anguli oris. It passes upward and medially to insert into the skin and mucosa of the lower lip and into fibers of the orbicularis oris <sup>14</sup>.

The **mentalis** arises from the incisive fossa of the mandible and descends to insert into the dermis of the chin. Contraction elevates and protrudes the lower lip and creates the characteristic “peach-pit” dimpling of the skin over the chin. The motor supply arises from the marginal mandibular nerve <sup>14</sup>.

The **levator labii** lies deep to the orbicularis oculi at its origin from the maxilla, just above the infraorbital foramen.

It passes downward to insert into the upper lip and orbicularis oris. A smaller slip of medially located muscle, the **levator labii superioris alaeque nasi**, originates from the frontal process of the maxilla and inserts into the nasal cartilage and upper lip. Both of these muscles are supplied by branches of the zygomatic and buccal branches of the facial nerve. Their function is to *elevate the upper lip* <sup>14</sup>.

The **levator anguli oris** arises deeply from the canine fossa of the maxilla, below the infraorbital foramen, and inserts into the upper lip. It is innervated on its superficial aspect by the zygomatic and buccal branches of the facial nerve. This muscle *elevates the corners of the mouth* <sup>15</sup>.

The **risorius** is often underdeveloped. This muscle arises from a thickening of the platysma muscle over the lateral cheek, the parotidomasseteric fascia, or both. It inserts into the corners of the mouth and *pulls them laterally* <sup>14</sup> (Fig. 2).

### Important anatomical landmarks of the lips

The upper lip extends from the base of the nose superiorly to the nasolabial folds laterally and to the free edge of the vermilion border inferiorly. The lower lip extends from the superior free vermilion edge superiorly to the commissures laterally and to the mandible inferiorly. Around

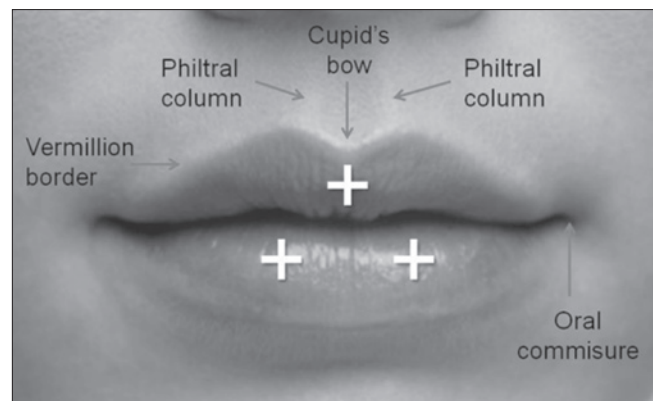


Fig. 1. The lips.



Fig. 2. Muscles of the lips (Adapted from Prendergast, 2013 <sup>14</sup>).

the circumferential vermilion-skin border, a fine line of pale skin accentuates the colour difference between the vermilion and normal skin. Along the upper vermilion-skin border, two paramedian elevations of the vermilion form Cupid's bow. Two raised vertical columns of tissue form a midline depression called the philtrum, which is located between the paramedian elevations of the vermilion and the columella above (Fig. 3). The labiomental crease passes horizontally in an inverted U-shape across the lower lip, which intraorally corresponds to the depth of the gingivolabial sulcus<sup>15</sup>.

## Facial proportions for the lips

### *Horizontal thirds*

The face is divided into horizontal thirds. The upper third extends from the hairline to the glabella, the middle third from the glabella to the subnasale and the lower third from the subnasale to the menton. These facial thirds are rarely equal in size. In Caucasians, the middle third is often smaller than the upper third and the middle and upper thirds are smaller than the lower third<sup>16</sup>. In East Asians, the middle third of the face is often larger than the upper third and equal to the lower third, and the upper third is smaller than the lower third<sup>17</sup>. The lower third is also divided into thirds; these define the upper lip, lower lip and chin (Fig. 4)<sup>18</sup>.

### *The golden ratio*

Beauty and facial attractiveness are easily identified but difficult to quantify. Despite its subjective nature, we can attempt to define, measure and explain the captivating phenomenon of beauty by describing it numerically and geometrically<sup>19</sup>. The golden ratio, denoted by the symbol  $\Phi$  (phi), is an irrational number of the order 1.618033988. It is obtained when a line  $a + b$  is sectioned such that  $a + b/a = a/b$  (Fig. 5)<sup>18</sup>. Although Indian mathematicians studied the golden ratio over 2,000 years ago, it first appeared in written documentation in Euclid's elements in ~ 300 B.C.<sup>20</sup>. The golden ratio, also known as the divine proportion, is considered by many to be the key to the mystery of aesthetics, attraction and human beauty<sup>21</sup>. The width of the mouth is  $\Phi$  times the width of the nose. The distance between the lateral canthi is  $\Phi$  times the width of the mouth. The height of the face from the pupils to the chin is  $\Phi$  times the height from the hairline to the pupils. The volume and, therefore, the vertical height of the vermilion of the upper and lower lips should ideally fit within the golden ratio (divine proportion), that is, yielding the value of  $\Phi$ , 1:1.618. This is first seen with da Vinci's classic proportions of the lips relative to the rest of the face.

These basic artistic principles, first practiced hundreds of years ago, still apply today<sup>13</sup>.

On frontal view, the ideal upper lip: lower lip ratio is 1:1.6. The vertical height of the upper lip should be less than that of the lower lip. Females will often request augmentation of the upper lip alone, without considering the balance between the upper and lower lips. Thus, it is incumbent upon the physician to educate the patient regarding the ideal ratio. "Sausage" or "duck" lips do not merely occur from over-correction, but also from a poor understanding of the delicate contours of the normal lip anatomy. On lateral view, if a straight line is drawn from the subnasion to the pogonion, the upper lip should project 3.5 mm anterior to the line and the lower lip 2.2 mm; the upper lip should project slightly more than the lower lip again about 1.6:1 (Fig. 6)<sup>13</sup>. An exaggeration of these proportions or the wrong ratio can lead to a "duck-like" or "trout-pout" appearance. Under no circumstances should the lips enter the room before the individual. The proportions of the lower thirds as applied by da Vinci further help to position the gnathion. A vertical reduction in chin height will help to achieve lip competence and correct the facial index. In contrast to the facial index, the lower third rules may be violated in females. The chin may be reduced more than indicated by the ideal proportion of 70% or even the 66% indicated by the classical canon<sup>22</sup>. Marquardt devised a mathematical model that used  $\Phi$  as the central measurement to map out facial proportions and aesthetically "ideal" shapes and sizes<sup>23</sup>. Despite general enthusiasm for the thesis that  $\Phi$  is the Holy Grail in defining the beauty and harmony of the human form, Holland<sup>24</sup> reminds us that several studies have not found a relationship between facial attractiveness and the golden ratio.

## Historical overview of beauty and facial proportions

Long before scientists first attempted to appraise beauty, artists in the 4th century B.C. attempted to formulate rules for the ideally proportioned face. Greek artists were the first to execute their works according to these rules. For example, Aphrodite's head and body exhibit ideal proportions based on the concept of the golden section<sup>25</sup>, an allegedly ideal ratio between the lengths of two lines of 0.6180<sup>26</sup>. The Romans later postulated their own rules, but following the Greek example. Thus, the Roman architect Vitruvius devised a famous threefold partition of the face, a concept adhered to even today in orthodontics and in oral and maxillofacial surgery. During the Renaissance, renowned painters (da Vinci, Dürer, della Francesca) proposed rules for establishing ideal proportions to achieve optimum aesthetics and harmony. These rules, later adopted also by



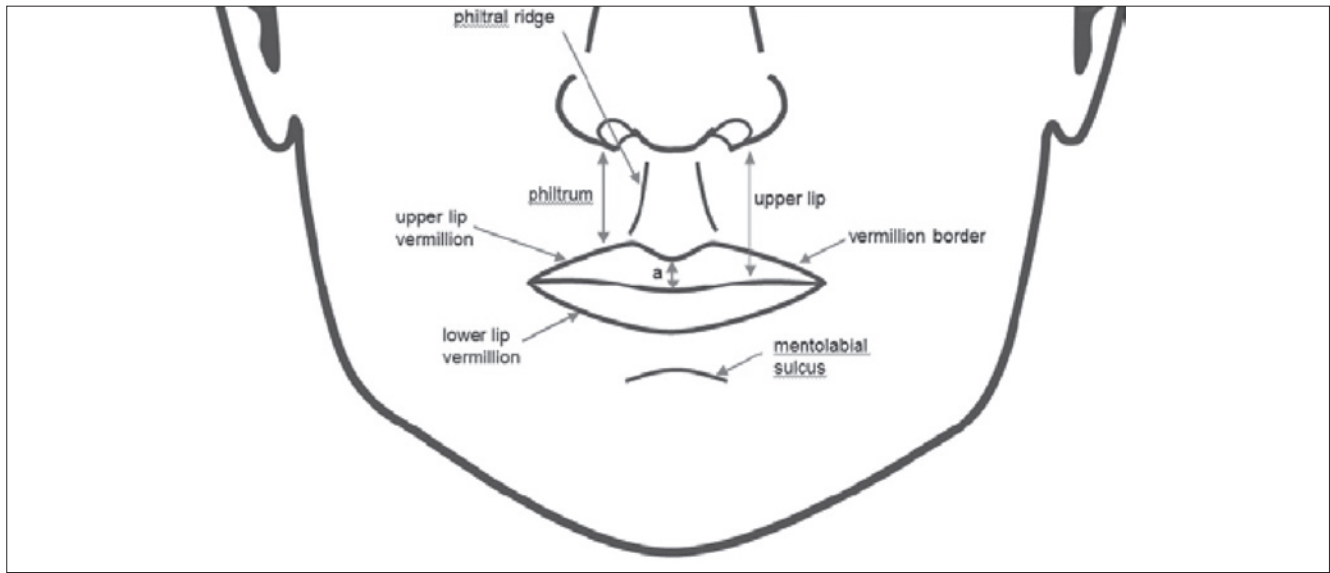


Fig. 3. Important anatomical landmarks of the lips.

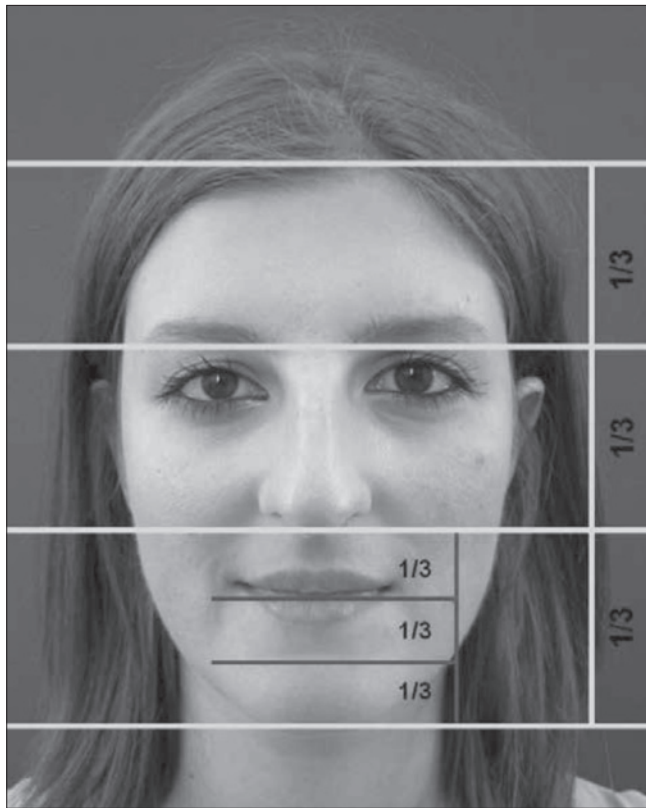
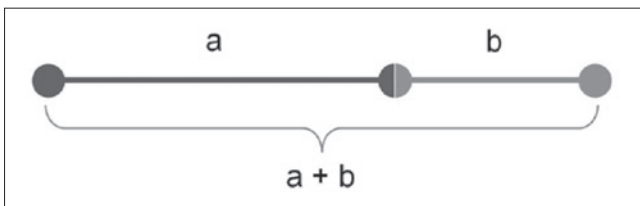


Fig. 4. Horizontal facial thirds. The upper third extends from the hairline to the glabella, the middle third from the glabella to the subnasale and the lower third from the subnasale to the menton. The lower third is also divided into thirds: the upper third extends from the subnasale to the stomion, the middle third from the stomion to the labiomental crease and the lower third from the labiomental crease to the menton. These thirds define the upper lip, lower lip and the chin (adapted from Prendergast, 2012<sup>18</sup>).

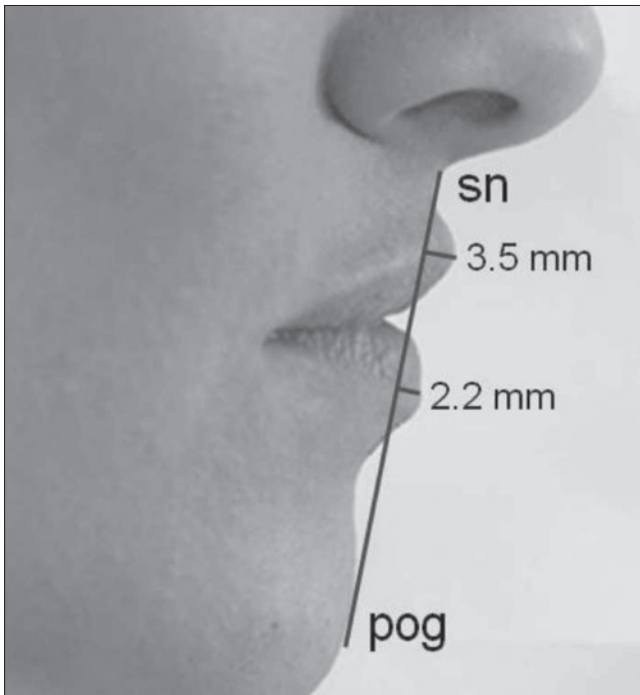
orthodontists and surgeons, were generally based on average values<sup>27</sup>.

### Ethnic differences in the lips

In youthful Caucasians, the ideal ratio of the vertical height of the upper lip to that of the lower lip is 1:1.6<sup>28</sup>. The fundamental proportions of the lips change as a person ages, with lengthening of the cutaneous portion of the upper lip and volume loss and thinning of the upper lip vermillion. Gravity, osteoporosis, dental changes, maxillomandibular bony resorption and further soft-tissue volume loss at the oral commissures cause the commissures to turn downward in a perpetual frown. While aging Caucasian males and females have similar hard and soft-tissue volume loss, with thinning of the vermillion and cutaneous portions of the lips, males generally do not develop rhytides of the upper and lower lips. This is because their skin is thicker, with more subcutaneous fat surrounding the terminal hair follicles (as opposed to the fine vellus hairs in females)<sup>13</sup>. Certain ethnic groups, especially Blacks, genetically have greater lip volume. Because the increased melanin in their skin is protective throughout their lifetimes, the skin of Blacks is less prone to solar elastosis. Consequently, they rarely develop radial rhytides in the lips and their vermillion tends to retain its volume even subsequent to aging<sup>13</sup>. Hwang K and Hwang SH reported that the ratio of vermillion size to mouth width was greater according to the Japanese than to the Korean ideals of beauty in the late 18<sup>th</sup> and early 19<sup>th</sup> centuries<sup>29</sup>.



**Fig. 5.** The golden proportion. A line  $(a + b)$  is sectioned such that  $(a + b)/a = a/b = 1.618033988^*$ .



**Fig. 6.** In lateral view, an analysis according to the golden ratio.

### Gender differences in the lips

Anic-Milosevic et al.<sup>30</sup> compared the proportions of the lower facial third segments in males and females. The chin accounted for the largest segment and the lower lip height the smallest in both sexes. Although the vermilion heights of the upper and lower lips did not differ between males and females, upper and lower lip heights were larger in males. In both sexes, the height of the upper vermilion was smaller than that of the lower vermilion. The height of the vermilion of the upper lip relative to the upper lip itself was significantly greater in females than in males. The width of the lips should be about 40% of the width of the lower face and generally equal to the distance between the medial limbi. The width-to-height ratio of the face is typically 3:4, with an oval-shaped face being the aesthetic ideal.

Hier et al.<sup>31</sup> reported that females prefer fuller lips to a greater degree than do males. Czarniecki et al.<sup>32</sup> created androgyn-

nous facial silhouettes and asked 545 professionals to evaluate the profiles constructed with various lips, chin and nose relations. The authors found that a slightly convex profile was desirable for females and a straighter profile for males. The index of the lower facial thirds was unchanged for 2500 years, without differences between males and females. However, in the average contemporary ideal, the female face is shorter than the male face, although the interpupillary distances are similar. The harmonious male face is longer than its counterpart during antiquity. The ideal lower facial height in contemporary idealised females and males is 45% and 48% of the total facial height, respectively. During antiquity, it was 50% for both. The ideal ratio chin height/total lower facial height is 70% on average, with no differences between the sexes, whereas it was 66% in the classical canon. In the lower face, the Vitruvian thirds should be adjusted so as to yield a proportion corresponding to 30% upper lip and 70% lower lip-chin. The contemporary ideal ratios are suitable for use in orthofacial planning<sup>22</sup>.

According to Baudouin and Tiberghien<sup>33</sup>, full lips contribute to the attractiveness of a female face, together with large eyes, prominent cheekbones, thin eyebrows and a small nose and chin. The centre of the face thus consists of baby-like features, while the periphery implies sexual maturity. In the opinion of those authors, males find this type of female face particularly alluring.

Michiels and Sather<sup>34</sup> attempted to describe the essentials of facial beauty in Caucasian females. They concluded that the chin, upper lip and nose were particularly important factors in the perception of attractiveness.

### Conclusions

The lips are of great importance for the perception of beauty by humans. The appearance of the lips in part determines the attractiveness of a person's face. Fuller lips in relation to facial width and greater vermilion height are perceived as attractive in females. Horizontal thirds and the golden ratio provide the proportions for beauty and attractiveness, also of the lips. The golden ratio has been used since da Vinci's time and has been applied to describe the classic proportions of the lips relative to the rest of the face. In youthful Caucasians, the ideal ratio of the vertical height of the upper lip to that of the lower lip is 1:1.6. Blacks genetically have greater lip volume.

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CASE SERIES AND REPORTS

# Intraparotid facial nerve schwannoma: two case reports and a review of the literature

## *Schwannoma del nervo facciale intraparotideo: due casi clinici e review della letteratura*

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### SUMMARY

Schwannomas are rare benign tumours that arise from Schwann cells. The most known and studied is the intracranial vestibular schwannoma, even if it is not the most frequent. More often schwannomas arise from peripheral sensitive nerves, and the vagous is most involved among the cranial nerves. Intraparotid schwannomas account for just 10% of all facial involvement, so they are an extremely rare localisation. At present, there are less than 100 cases described in the literature. We performed a retrospective analysis of parotidectomy in two Italian hospitals and present two cases of intraparotid schwannoma and a review of the literature. In the first case, we performed a parotidectomy with a stripping of tumour from the nerve. In the other case, a hypoglossal-facial neuroorrhaphy was performed. Follow-up was 24 months in the first (House-Brackmann II degree in temporal-ocular and III in facial-cervical branches) and 30 months in the second case (House-Brackmann III degree in both temporal-ocular and facial-cervical branches). Preoperative diagnosis of facial nerve schwannoma is a challenge; however, it is extremely important since post-operative palsy is common and often higher grade. Unfortunately, schwannoma has similar radiologic finding as more common pleomorphic adenoma and often FNAC is not helpful. Due to its rarity and benign nature, there is debate in the literature on the need for surgical removal. Wait-and-see is a valid option, but may give problems in secondary surgery. Stripping or near-total removal can be useful in cases of limited involvement of the nerve. Neuroorrhaphy can provide good functional results when facial sacrifice is needed.

KEY WORDS: Schwannoma • Neurilemmoma • Parotid neoplasm • Facial nerve

### RIASSUNTO

*Gli schwannomi sono tumori benigni rari che prendono origine dalle cellule di Schwann. Tali cellule formano la guaina mielinica dei nervi periferici permettendo la trasmissione saltatoria, attraverso i nodi di Ranvier, del segnale neurale. Certamente quello più conosciuto e studiato è lo schwannoma vestibolare che ha origine generalmente dalla branca inferiore del nervo vestibolare. Più frequentemente, però, gli schwannomi originano dai nervi sensitivi periferici e fra i nervi cranici il vago è quello più frequentemente interessato. Nel distretto testa-collo la localizzazione parafaringea è la più comune. Lo schwannoma del nervo facciale intraparotideo è un'evenienza molto rara che rende conto del 10% circa di tutti gli schwannomi che interessano il volto e fino a circa l'1,5% di tutti i tumori parotidei. Al momento in letteratura se ne contano meno di 100 casi. In questo studio abbiamo revisionato la casistica operatoria di due centri ospedalieri italiani riportando due casi di schwannoma del nervo facciale insieme ad una review della letteratura. Nel primo caso abbiamo eseguito una parotidectomia superficiale con dissezione smussa del tumore dalle fibre assonali realizzando una procedura molto simile alla demielinizzazione su base infiammatoria (es. sindromi demielinizzanti acute). Nel secondo caso invece, sempre dopo aver eseguito la parotidectomia, non è stato possibile salvare il nervo facciale per cui, dopo resezione, è stata praticata una neurorrafia con il nervo ipoglossale. Nell'immediato post-operatorio entrambi i pazienti hanno sviluppato una paresi facciale di grado V secondo House-Brackmann. Dopo terapia medica e riabilitativa il primo caso ha residuo un paresi di II-III grado (follow-up di 24 mesi) mentre il secondo una paresi di III (follow-up di 30 mesi). La diagnosi preoperatoria di questa neoplasia è alquanto difficoltosa, in particolare perché non esistono segni radiologici distintivi (di frequente anzi gli schwannomi sono confusi con i molto più comuni adenomi pleomorfi) e spesso anche la FNAC non consente una diagnosi. Fra le opzioni di trattamento, data la rarità e benignità, il wait-and-see può essere ritenuta una scelta valida, sebbene questa possa inficiare il risultato di un'eventuale chirurgia successiva. Al contrario la rimozione subtotale o la dissezione dalle fibre assonali possono essere utili anche se con precise limitazioni. Infine nei casi in cui la sezione del nervo è necessaria, la neurorrafia può consentire risultati soddisfacenti.*

PAROLE CHIAVE: Schwannoma • Neurilemmoma • Neoplasia parotidea • Nervo facciale

## Introduction

Schwannomas are very rare benign tumours that arise from the Schwann cells which form the sheath of peripheral nerves.

Schwannomas have no sex preference, in the literature there are studies with both female<sup>1</sup> and male prevalence<sup>2</sup>. Although the most studied and known schwannoma is intra-cranial vestibular, it is not the most frequently involved nerve. More often schwannomas arise from sensitive peripheral nerves, and the vagous is most involved among the cranial nerves. The parapharyngeal space is the most common head and neck site of occurrence<sup>2-4</sup>.

A facial nerve schwannoma is very rare and normally grows from the intratemporal portion of the nerve. Intraparotid facial schwannoma account for just 10% of all cases of facial involvement, and so it is an extremely rare localisation. To our knowledge, less than 100 cases of intraparotid facial nerve schwannomas have been reported in the scientific literature.

Herein, we present two cases of intraparotid schwannoma, one in a 39-year-old woman and the other in a 45-year-old man, extracted from the clinical records of two otorhinolaryngology departments (San Giovanni Addolorata Hospital in Rome and Garibaldi Hospital in Palermo). We also review the literature on preoperative signs, surgical management and outcomes.

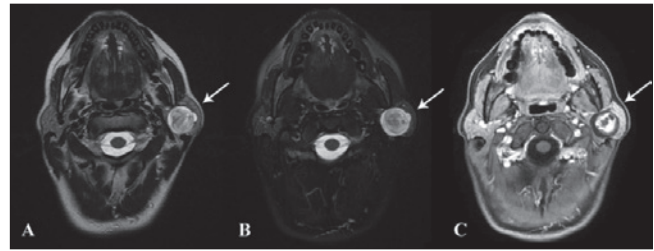
## Case reports

### 1<sup>st</sup> case

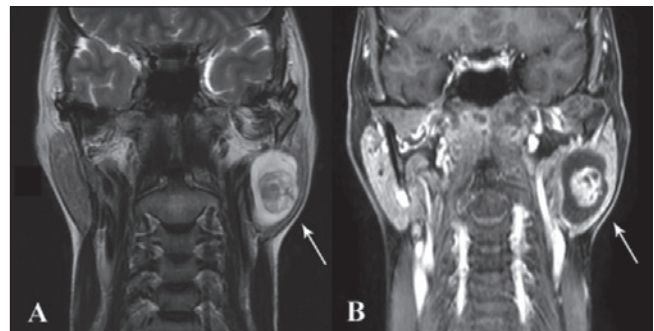
A 39-year-old woman came to our ENT clinic with an asymptomatic parotid mass that appeared 2 years before and grew slowly. In the last 2 months, she started to feel a dull facial pain, but no signs of facial palsy. She had two FNAC (both undiagnosed), ultrasound and an MRI (mass rising from the deep portion of parotid, isointense in T1 image and hyperintense in T2-weighted without clear diagnostic indications) (Figs. 1, 2).

At parotidectomy, we found a tumour involving the facial nerve trunk near its division into the two main branches with an atypical aspect of multilobular soft and encapsulated mass, similar to a lipoma. We dissected the tumour from the facial nerve, helped by loupe magnification (3.5x), attempting to preserve as many fibres as possible and performed surgical excision as a neural unsheathing (Figs. 3, 4).

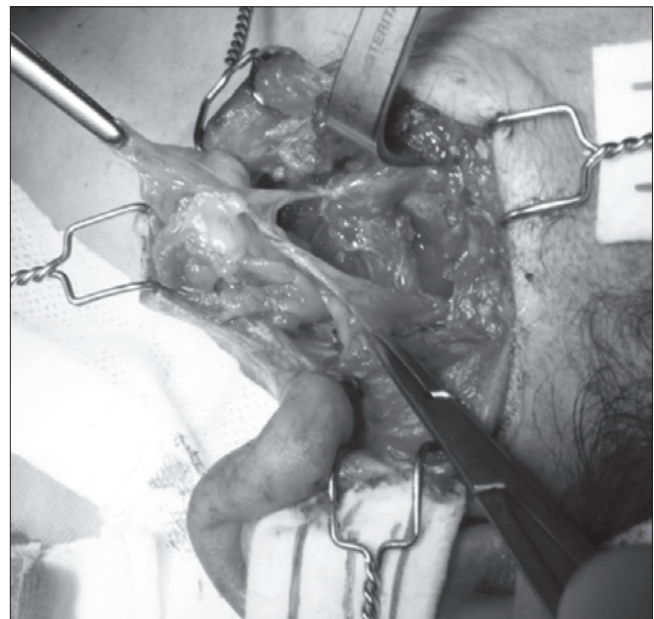
At the end of the surgical procedure, we verified neural functions by a needle neurostimulator using 1.2 µs of electrical tension with complete but weaker facial contraction (demonstrating an integrity of the facial nerve even if its structure was not completely preserved).



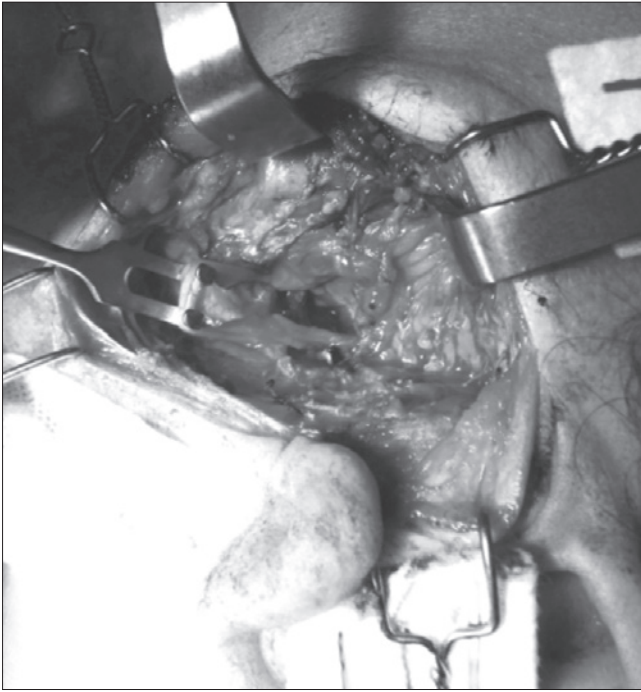
**Fig. 1.** Axial MRI scan: A) T2 FrFSE (Fast Relaxation Fast Spin Echo), B) FrFSE FAT SAT (Fast Relaxation Fast Spin Echo Fat Saturation) and C) T1 with contrast medium. In all scans the arrows show a mass with more cellular central portion (with a good enhancement after contrast medium) opposite to a more mixoid peripheral component.



**Fig. 2.** Coronal MRI scans: A) T2 FrFSE (Fast Relaxation Fast Spin Echo) and B) T1 with contrast medium. In both scans the arrows show, as in previous figure, a more cellular central portion opposite to a more mixoid peripheral portion. In this scan, we also observe the relatively proximity of the mass to the stylomastoid foramen even if there isn't invasion of the Fallopiian canal.



**Fig. 3.** The facial nerve at its main trunk with yellowish and soft mass partially dissected from the nerve, but still adhering to it.



**Fig. 4.** The facial nerve at its main trunk after radical dissection. The integrity of the nerve is achieved by unsheathed dissection.

Post-operative histology found an “ancient schwannoma” with cystic and haemorrhagic areas and perivascular hyalinisation; immunophenotype: vimentin+, S100+, CD34- and actin-.

At post-operative Day 1, the patient had a House-Brackmann grade IV palsy and after rehabilitation and medical therapy at 24 months follow-up she had grade II-III HB.

*2<sup>nd</sup> case*

A 45-years-old man in good health came to our clinic with a left parotid mass that had appeared 3 years prior and slowly increased in volume. The mass was soft and elastic at palpation, not fixed on the skin or deep plane and not painful. No facial deficit was found.

The patient had a FNAC positive for fibromixoid tissue and a contrast medium CT (bulky mass arising from the deep portion of left parotid without enhancement after contrast medium) (Figs. 5, 6).

At parotidectomy, we found a multilobular and encapsulated mass involving the facial nerve at its exit from the stylo-mastoid foramen until the division into the main branches. Unfortunately, we could not dissect the tumour without the sacrifice of the facial nerve so we performed hypoglossal-facial neuroorrhaphy.

Post-operative histology founded a neuroma (immunophenotype: vimentin+, S100+, CD34- and actin-).

On post-operative Day 1, the patient had House-Brackmann grade V palsy, whereas at 30-month-follow-up, after rehabilitation and medical therapy, this was HB grade III.

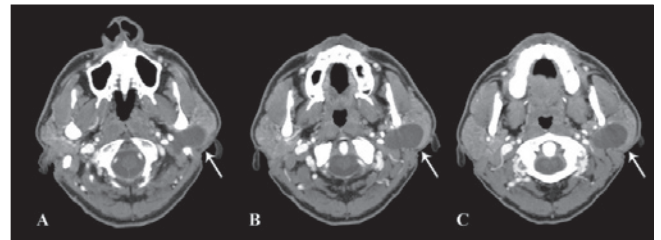
**Discussion**

An intraparotid facial schwannoma is extremely rare tumour. In a retrospective study (2004), Caughey et al<sup>5</sup> reviewed 3722 patients in a tertiary referral centre (Shady-side Facial Paralysis Center in Pittsburgh) finding only 29 (18 women and 11 men; 0.78%) patients with facial schwannomas. Among these only 8 cases (27.5% of facial schwannomas and 0.21% of the entire cohort) had an intraparotid localisation.

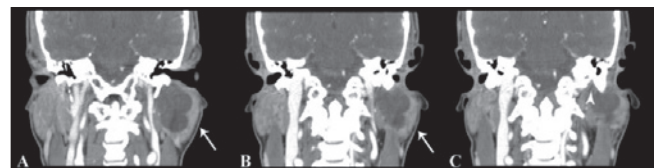
In another study focused on extracranial schwannomas, Kang et al.<sup>3</sup> found only 4 cases of intraparotid localisation in 22 patients with cranial nerve schwannomas over a 10 year personal review.

Similarly, in a series of 113 nerve sheath tumours of the head and neck, Tabriz et al. found only 7 (6%) cases of intraparotid schwannoma<sup>6</sup>.

Normally, the intraparotid facial nerve schwannoma is characterised by an intraglandular longstanding mass without specific symptoms and a low growth rate<sup>5,7</sup>. At physical examination, it appears as a painless mass with increased but soft consistency and well-defined margins. A functional deficit of the facial nerve is rarely observed. In cases in which it is, it would be more often over a longtime and with a large mass<sup>5,8,9</sup>. Facial pain is observed on occasion.



**Fig. 5.** Axial CT scan with contrast medium. The arrows show the schwannoma growth in deep gland portion that goes upward under the mastoid tip (A scan).



**Fig. 6.** Coronal CT scan with contrast medium. The arrows in the A and B scan show the mass growth toward the stylo-mastoid foramen, which is more evident in last scan (arrow head in C scan).

Preoperative diagnosis of facial nerve schwannoma is a major challenge. However, it is extremely important since post-operative palsy is common and often of higher grade (IV or higher in House-Brackmann scale).

Unfortunately, schwannomas have similar radiologic signs to more common parotid tumours, among which pleomorphic adenoma is the most common. At MRI, they usually show an isointensity to muscle in T1-weighted and hyperintensity in T2-weighted image with well defined margins. In contrast enhanced scans they show heterogeneous enhancement due to more cellular Antoni A parts mixed with the more mixoid Antoni B. Moreover, in “ancient schwannoma” type (as in our case), the tumour can present with degenerative changes typified by perivascular hyalinisation, calcification, cystic necrosis, relative loss of Antoni type A tissue and degenerative nuclei that may be misinterpreted as sarcomatous pleomorphisms<sup>10-13</sup>.

In a retrospective analysis of 5 cases of extratemporal facial nerve schwannomas, Shimizu et al. reported, as radiological signs of suspicion, tumour growth toward the facial canal and the presence of a “target sign” (peripheral hyperintensity with central hypointensity), corresponding to more cellular Antoni A type in central regions and more myxoid Antoni B peripherally<sup>10</sup>.

In another study, Banks analysed the target sign, reporting its validity to identify the PNSTs (peripheral nerve sheath tumours), but were not able to distinguish a benign from malignant one<sup>14</sup>.

In the same way, FNAC is of little help. In most cases, cytology is non-specific and non-diagnostic; or worse it can give a misleading diagnosis of more common pleomorphic adenoma or suspected a malignant tumour<sup>3 12 14-18</sup>.

All these make treatment of this tumour very challenging because diagnosis is often intra-operative. Moreover, there is still debate on the relevance of surgical removal since radical surgery leads to facial nerve deficit.

The same group of authors suggest a decision-making algorithm<sup>19</sup> based on a previous proposed classification<sup>9</sup> of facial nerve schwannomas. They recognise four kinds of schwannoma presentations: type A and B (the tumour grows on the neural edge or involves a peripheral nerve branch), type C (the tumour grows around the nerve involving it completely at the main branch or trunk) and D (the tumour grows around the nerve involving both main branch and trunk). If the patient has a type A or B tumour or pre-operative House-Brackmann grade IV or worst, the authors propose radical resection with nerve reconstruction. Otherwise, with a type C or D tumour or preserved nerve function (HB III or less grade), they avoid resection and suggest only biopsy to rule out malignancy<sup>19</sup>.

Other authors have also proposed intra-operative biopsy to obtain diagnosis and then manage it conservatively<sup>20</sup>. This could be a good algorithm, but one point needs deeper discussion: frozen sections of a malignant peripheral sheath nerve tumour may not be diagnosed due to inexperience of the pathologist or to inappropriateness of the intra-operative biopsy. Moreover, frozen section can lead to misinterpreting a schwannoma as a sarcoma, leading to an unnecessary radical surgery<sup>8</sup>.

Thus, the assumption on what the surgical choice should be based on can be, in some cases, unreliable.

Moreover, it is more difficult to perform a conservative approach to the facial nerve after first surgery with a mass biopsy, due to post-surgical fibrosis as in relapses of a pleomorphic adenoma.

Other authors suggest a “stripping microscopic surgery” or a “subtotal surgery” to remove the mass of schwannoma from the facial nerve while preserving the neural continuity without functional deficit (Lee et al. in their series had preservation of facial nerve function in all their 6 cases)<sup>21 22</sup>.

In a more recent paper Rigante et al.<sup>23</sup>, propose intracapsular enucleation under microscopic vision. They made a longitudinal epineurium incision on the schwannoma body and gently blunt dissected the neural fascicles from the tumour under microscopic magnification. They report a post-operative facial nerve deficit of IV on the HB scale, which improved after three months of medical and physical rehabilitation (reaching II-III).

We agree with these authors. In fact, as schwannomas arise from Schwann cells (the peripheral sheath of the nerve), theoretically radical dissection can be obtained by removing the nerve sheath along with the mass, in a process similar to “acute demyelination”. Probably this can explain our observation of more weak contraction of facial muscles at stimulation after tumour removal and the need for higher electrical tension to stimulate the nerve (1.2  $\mu\text{s}$  isn't normally used on nude nerves).

This could achieve a radical resection with nerve function recovery by new myelination of axons. This procedure would require, however, careful dissection of the mass from the nerve without lesion to the axons; moreover, the re-myelination may not be complete a remaining a partial facial deficit. Thus, we would suggest such a procedure only in limited involvement of nerve branches or the main trunk (as in our case), so the rate of an axonal lesion is very low and the portion of unsheathed nerve is small.

In this way, radical dissection of the mass can be performed, even in type C schwannoma (by Marchioni classification) in cases with a limited extension of nerve involvement (we suggest 1 cm or less).

In all other cases, we would suggest subtotal surgery (con-

sidering the exceptionality of malignant transformation of solitary schwannomas)<sup>3</sup> or MRI annual follow-up avoiding surgery in agreement with Alicandri-Ciufelli et al.<sup>19</sup>.

## Conclusions

Intraparotid schwannomas are a rare entity. Pre-operative diagnosis is difficult despite FNAC and radiological investigation, and most often diagnosis is intra-operative.

The gold standard management is radical surgery with preservation of acceptable neural function, which can be obtained in almost 50% of cases. In other cases, a reasonable approach is wait-and-see, with strict clinical and radiological follow-up. However, an alternative approach has also a place in management, i.e. microscopic or loupes magnification surgery (for limited involvement of nerve) or subtotal surgery (due to the extremely rare malignant transformation) which can achieve good functional results.

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## In Memoriam of Prof. Giovanni Motta

Professor Giovanni Motta was born in Catania in 1930 and earned his degree in Medicine and Surgery in 1952. His thesis was entitled “The blind flight of bats and the ari-epiglottic folds as the organ that produces ultrasound” was published in the *Acts of the Accademia dei Lincei* in 1954.

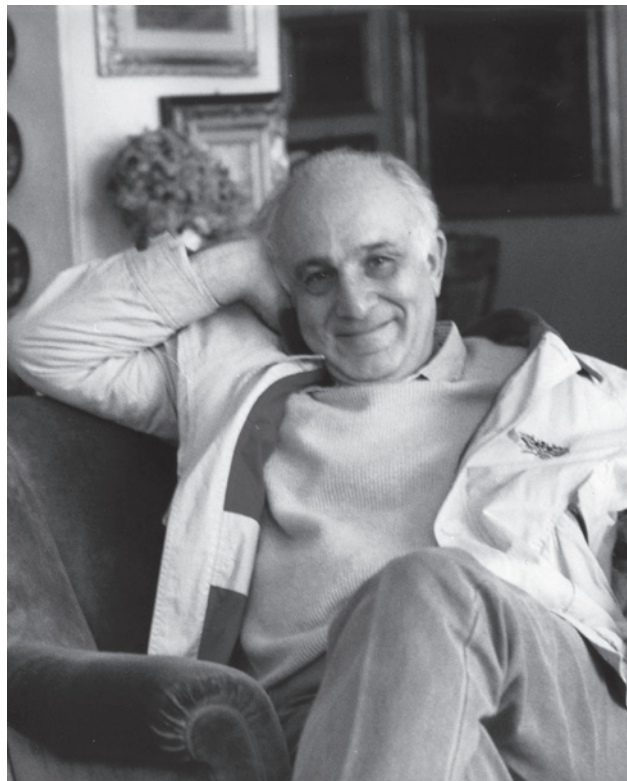
He served in the Otorhinolaryngological Clinic in 1958 and in Audiology in 1964. He directed the Otorhinolaryngology Clinic of the University of Bologna (1966-69), the University of Cagliari (1970-74), the Second Faculty of Naples (1975-76) and finally “Federico II” University of Naples (1977-2002). He chaired the Italian Society of Phoniatics and Speech Therapy (SIFEL) during 1983-1985, Associazione Universitaria Otorinolaringoiatri (AUORL) during 1989-1991, the Società Italiana di Otorinolaringoiatria Pediatrica (SIOP) during 1988-1991 and the Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale (SIO) during 1994-1996.

In 1992, he was the President of the 2<sup>nd</sup> European Congress of Otorhinolaryngology and Head and Neck Surgery. In the same year, he was awarded the gold medal by the Ministry of Health. His scientific production includes more than 300 publications in national and international journals that cover all fields of Otorhinolaryngology.

During his long academic career, he was a speaker or co-author of Official Relations at National Congresses and Official Manifestations of the various societies of otorhinolaryngology, always highlighting his personal experiences. In this regard, we remember the following: “The peripheral and central factors of dysgeusias” (SIO, 1958), “Psychosomatic Medicine in Otorhinolaryngology” (SOOI, 1963), “The alterations of hearing in cranial traumatised with labyrinthine lesions” (SIO, 1964), “Medical-legal evaluation of deafness” (SIAF, 1974), “Surgical treatment of maxillary sinus tumours” (SIO, 1974), “Reconstructive surgery in carcinomas of the cervico-facial area” (SIO, 1978), “Anesthetic problems in paediatric otorhinolaryngology” (SIOP, 1983), “Benign neofomations of the larynx: rehabilitative and surgical treatment” (SIFEL, 1983), “Tinnitus” (SIO, 1983), “The legal responsibility of the otolaryngologist” (SIO, 1987), “The prosthetic rehabilitation of adult neurosensory deafness” (AUORL, 1991) and “The CO2 laser in endoscopic laryngeal surgery” (SIO, 2001).

He also directed two SIFEL Courses: “Recent acquisitions on the equipment to be used in phoniatic diagnosis and logopaedic rehabilitative therapy” (1985), “The singing voice: current possibilities of phoniatic investigations for clinical classification and therapeutic treatment” (1989).

At the end of the 1990s, he directed the “World Laboratory” project to promote technological and cultural updates in China, Egypt and Malta. In the field of CO2 laser surgery, Professor Motta was one of the staunchest advocates, especially with regards to its use in laryngeal surgery; he was the first to classify CO2 laser surgical techniques in the field of oncology. After organising two International Meetings on laser surgery in 1982 and 1996, in subsequent years he presented his results at numerous conferences in Italy and abroad, based on the case studies at his department, which are among the most numerous on an international level.



Maurizio Jengo