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Review

HPV in oropharyngeal cancer: the basics to know in clinical practice

HPV nel carcinoma dell'orofaringe: le nozioni base da conoscere nella pratica clinica

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SUMMARY

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising in contrast to the decreasing incidence of carcinomas in other subsites of the head and neck, in spite of the reduced prevalence of smoking. Human papilloma virus (HPV) infection, and in particular type 16 (HPV-16), is now recognized as a significant player in the onset of HPV positive OPSCC, with different epidemiological, clinical, anatomical, radiological, behavioural, biological and prognostic characteristics from HPV negative OPSCC. Indeed, the only subsite in the head and neck with a demonstrated aetiological viral link is, at present, the oropharynx. These observations lead to questions regarding management choices for patients based on tumour HPV status with important consequences on treatment, and on the role of vaccines and targeted therapy over the upcoming years.

KEY WORDS: Human Papillomavirus • Head and Neck cancer • Oropharyngeal cancer • Squamous Cell Carcinoma • Prognosis • Treatment • Prevention • Vaccination • Clinical Trial

RIASSUNTO

L'incidenza del carcinoma spinocellulare dell'orofaringe (OPSCC) è in aumento in contrasto con la diminuzione dell'incidenza di carcinomi in altre sedi del distretto cervico-facciale, nonostante la ridotta prevalenza del fumo. L'infezione da Papilloma Virus Umano (HPV), in particolare di tipo 16 (HPV 16), è ora riconosciuto come un importante fattore nell'insorgenza di HPV OPSCC positivo, con diverse caratteristiche radiologiche, epidemiologiche, cliniche, anatomiche, biologiche e prognostiche rispetto all'HPV OPSCC negativo. In effetti l'unica sede del distretto cervico-facciale con un collegamento virale eziologico dimostrato è, attualmente, l'orofaringe. Queste osservazioni portano a domande riguardanti le scelte di gestione per i pazienti in base allo stato del tumore HPV con importanti conseguenze sul trattamento e sul ruolo dei vaccini e terapia mirata per i prossimi anni.

PAROLE CHIAVE: *Papilloma Virus Umano • Tumori del distretto cervico-facciale • Tumori dell'orofaringe • Carcinoma spinocellulare • Prognosi • Trattamento • Prevenzione • Vaccinazione • Studi clinici*

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Introduction

Head and neck cancer, which includes tumours that arise from the oral cavity, oropharynx, larynx, hypopharynx and sinonasal tract, represents a serious health care problem in many parts of the world, and ranks as the sixth most common cancer worldwide [1]. These tumours are linked by common characteristics including a male predominant appearance in the 5-6th decade of life, a strong aetiological link with prior tobacco, alcohol use or betel nut chewing [2], and a histopathological resemblance [3]. About 90% of head and neck cancers are squamous cell carcinomas (HNSCC).

The estimated annual burden of HNSCC is approximately 650,555 incident cases and approximately 300,000 resultant deaths [4 5]. It is considered the sixth leading cause of cancer mortality and oropharyngeal squamous cell carcinoma (OPSCC) accounts for approximately 50,000 incident cases, which is low in comparison with other head and neck squamous cell carcinoma (HNSCC) [5 6].

Multiple studies have demonstrated that the incidence of HNSCC has remained stable or even declined in the late 1980s, due to the gradual decrease in smoking and alcohol which are the primary risk factors for these cancers [2]. Despite this, the incidence of oropharyngeal squamous cell carcinoma with different characteristics, particularly

in the base of the tongue and tonsil subsites, has increased by 2-3% annually during 1973-2001, and then by 5.22% annually from 2000 to 2004 in the USA [7]. Similar trends have been noted in other countries. In particular, one study suggests that the annual number of HPV-associated oropharyngeal cancers in the United States will overtake the incidence of invasive cervical cancer cases in the United States by 2020 [8]. There is also a discrepancy in incidence of OPSCC between developed and developing countries of oropharyngeal cancer [9].

The developing world has a relatively low proportion of OPSCC (1-10% of HNSCCs), which appears to remain stable (or even to decrease) over time, while the incidence of HNSCC has steadily increased in most countries [4 10].

The developed world features a relatively high and variable proportion of OPSCCs (15-30% of HNSCC). For example, a central belt of European countries has the highest OPSCC proportions in the developed world (up to 30% of HNSCCs) with the remainder of Europe being characterised by slightly lower OPSCC proportions, while the overall HNSCCs incidence has remained stable or has even shown a declining trend over the same period [4 11 12]. These demographic data prompted researchers to search for further risk factors contributing to the incidence of OPSCC.

The impact of HPV as a risk factor for OPSCC

Most studies have demonstrated that features tobacco and alcohol consumption are major, common risk factors for HNSCC, but over the last 10-15 years HPV infection has been increasingly recognised as a major aetiological factor for a subset of HNSCCs [7-10], including mostly OPSCC. HPV infection in the aetiology of OPSCC was first shown by Gillison et al. [13]; numerous case series studies conducted in the late 1990s and 2000s evaluated the prevalence HPV infection in oropharyngeal cancer using molecular techniques such as PCR and in situ hybridisation [8 14 15]. Indeed, over the last five years it has become increasingly clear that HPV plays a pathogenic role in this subset of head and neck cancers, with distinct epidemiologic, clinical and molecular characteristics. These findings have created new opportunities for improved therapy and primary prevention for these HNSCCs [16].

At present, it should be clear that the only subsite in the head and neck with a demonstrated role for HPV infection in the aetiology of cancer is the oropharynx, as noted in the most important report by Gillison et al. [13] and confirmed by Stransky et al. in 2011 [13 17].

From a biological point of view, HPV is a DNA oncovirus and is epitheliotropic. There are over 120 different HPV subtypes, including the low-risk types such as HPV 6 and HPV 11, responsible for benign proliferation of epithelium, and the high-risk oncogenic types HPV 16 and HPV 18 which are both well-established initiators of over 90% of cervical cancers, 70% of anogenital cancers, 5% of non-oropharyngeal SCC [17] and 20-72% of OPSCC [2 4 12 17]. The oncogenic nature of high risk HPVs is due to the immortalising and transforming properties of HPV oncoproteins E6 and E7, which target the p53 and pRB tumour suppressor pathways, respectively, rendering infected cells susceptible to mutations and cancer formation [18 19]. Since the majority of HPV-HNSCCs are OPSCC, we will mainly discuss OPSCC.

Classification of oropharyngeal cancer according to HPV

According to the National Comprehensive Cancer Network (NCCN) [20] guidelines, 'HPV testing is recommended for all oropharyngeal tumours'. In addition, according to the US National Cancer Institute (NCI) [21] and Cancer Therapy Evaluation Programme (CTEP) [22], HPV status must be included as a stratification factor for trials including oropharynx cancer patients. Much evidence suggests that HPV-positive and HPV-negative OPSCCs represent distinct subgroups of OPSCC, each with unique epidemiological and biological profiles [4 5 17 21 23-27].

Differences between HPV positive and HPV negative OPSCCs

Epidemiological factors

HPV-positive patients tend to be younger with a median age of diagnosis of 54 years, less exposure to tobacco and alcohol [28-30], and higher socioeconomic status and education [31]. HPV positivity is less frequent in blacks than in Caucasians (4% of HNSCC in blacks *vs.* 34% in whites) [32], with a three fold higher incidence in males than females [28 33 34].

As in cervical cancer, oral HPV infection appears to be a sexually-acquired disease. Although the natural history of oral HPV infection is not well defined, D'Souza and colleagues recently showed in a case-control study that a high (≥ 26) number of lifetime vaginal-sex partners and 6 or more lifetime oral-sex partners were associated with an increased risk of OPSCC [odd ratio (OR) 3.1 and 3.4, respectively] [35]. An increased risk of HPV-associated OPSCC in female patients with a history of HPV-associated anogenital cancers and their male partners is also consistent with HPV transmission to the oropharyngeal cavity [36 37]. The recent increased incidence of this disease may thus reflect societal changes in sexual behaviour that have occurred over time in the developed world [38 39].

An important point to mention is that there is no clear case-control study addressing the evidence for HPV prior to development of OPSCC (i.e. temporal association), with the exception of a Scandinavian study by Mork et al.

which showed that the presence of HPV 16 L1 antibodies in pre-diagnostic serum samples was associated with a 14.4-fold increased risk of oropharyngeal cancer. Importantly, the presence of HPV 16 antibodies preceded oropharyngeal cancers by more than 10 years, underscoring a temporal association. These data confirmed that oral HPV infection increases the risk of developing OPSSC [40].
Lastly, it is possible that in addition HPV infection, other risk factors or cofactors such as genetic susceptibility or nutritional factors or tobacco and alcohol interaction have an important role in cancer onset. There is an objective need for more analytic epidemiological studies in males and females diagnosed with HPV positive oropharyngeal cancer younger than 50 years of age [40].

Anatomical sites

Several studies have noted an increased incidence of HPV-associated oropharyngeal cancers, especially tonsillar and tongue cancer. For example, in the USA they have risen by 3.9% and 2.1% among men and women, respectively, in the age group from 20 to 44 years, between 1973 and 2004 [2 41]. Similar patterns have been noted in Sweden for tonsillar cancer which rose 2.9-fold between 1970 and 2001, increasing by 2.6% per year in men and 1.1% in women [11 42].
The preference of HPV for the oropharynx is unexplained, but may be related to the unique presence of transitional mucosa in the oropharynx, predominantly found in the tonsillar tissue and which shows histological similarities to the cervical mucosa [2 11]. Another possibility lies within the genetic features of HPV 16, which accounts for more than 90-95% of all HPV associated oropharyngeal cancers, as it may facilitate survival in the tonsillar crypt epithelium [43 44]. It is also possible that the invagination of the mucosal surface of the tonsil may favour virus capture and maintenance by promoting its access to basal cells (the only dividing cells in the epithelium) [45]. If this is true, tonsillar tissue could be a reservoir for HPV in the upper aerodigestive tract. This view is partly supported by the fact that when oral samples are collected by oral rinse, the detection rate of HPV is much higher than with swabs. Finally, the persistence of HPV in tonsillar tissue might be of importance in the immune response to HPV [46].

Biological profiles

Recent global genomic screening studies searching for a biological distinction among HPV-positive and negative OPSCC have shown that HPV-induced carcinogenesis has a clear impact on the acquisition and maintenance of specific chromosomal gains and losses within tumour cells, in which OPSCCs with transcriptionally active HPV-DNA are characterised by occasional chromosomal loss/allelic imbalance [47]. Conversely, those lacking HPV-DNA are characterised by gross deletions that involve entire or large parts of chromosomal arms [32 48].
Furthermore, ploidy studies have confirmed that HPV-positive tonsillar cancers feature a lower number of chromosomal alterations compared to their HPV-negative counterparts [49 50].
The biology of HPV-positive oropharyngeal cancer is typified by p53 degradation, retinoblastoma protein (RB) down-regulation and p16 up-regulation. By contrast, tobacco-related oropharyngeal cancer is characterised by p53 mutations, down-regulation of p16 and RB up-regulation [45].
Interestingly, recent studies observed an inverse correlation between the presence of HPV and p53 mutations [17].

Clinical stage at presentation

Multiple studies have shown that HPV-positive tumours are more likely to present with early T stage (T1-T2) [51] and higher N stage (usually cystic and multilevel) [52], and have distinct histological features, such as moderate/poor tumour differentiation and non-keratinising or basaloid pathology [14 19 51]. The incidence of distant metastases was seen to be lower in patients with HPV positive tumours. Furthermore, metastases developed later and with a very different pattern from patients with HPV-negative tumours. HPV-positive oropharyngeal cancer had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence [53]. Secondary primary tumour (SPT) in patients with HPV-positive cancer is very rare, and has improved better survival rate compared to patients with HPV negative tumours [45].

Radiological imaging

Recent studies have shown radiological difference between HPV-positive and HPV-negative oropharyngeal cancer. Specifically, HPV-positive carcinomas often had small or even occult primary lesions with well-defined borders and cystic nodal metastases, whereas HPV-negative primaries more often had poorly defined borders and invasion of adjacent muscle [52 54].

Prognosis

Several studies have shown that patients with HPV-positive oropharyngeal cancer, identified through PCR, in situ hybridisation or p16 immunohistochemistry on tumour tissues, have a significantly improved overall and disease-free survival compared to patients with HPV-negative oropharyngeal cancer patients [29 53 55-61] (Table I). This holds true even after adjustment for differences in favourable prognostic factors associated with HPV positive patients (younger age, better performance status, fewer comorbidities, less smoking). Ang et al. reported that these prognostic factors explained only 10% of the observed survival differences between two subgroups [29]. However, other studies reported that survival rates improved among non-smoker HPV positive patients com-

Table I. Selected studies reporting the association of HPV infection with oropharyngeal cancer prognosis.

Study	Author, year	# of cases	HPV detection	Follow-up	OS positive vs. negative tumours
ECOG[58] 2399	Fakhry, 2008	96	HPV 16 DNA ISH	2	2-yr survival (95% *vs.* 62%)
RTOG[29] 0129	Ang, 2010	323	HPV 16 DNA ISH	4.8	3-yr survival (82.4%, *vs.* 57.1%)
TROG[59] 02.02	Rischin, 2010	185	p16 IHC	5	2-yr survival (91% *vs.* 74%)
DHANCA[60] 6,7	Lassen, 2011	794	p16 IHC	5	(62% *vs.* 47%)[c], (52% *vs.* 48%)[*]
TAX[61]) 324	Posner, 2011	111	HPV 16 DNA PCR	5	5 yr survival (82%-35%)

ISH: in situ hybridisation; IHC: immunohistochemistry; PCR: polymerase chain reaction; OS: overall survival; [*] accelerated radiotherapy; [c] conventional radiotherapy.

pared to smokers patients even in recurrent tumours, underscoring once again the benefits acquired from smoking cessation[62,63].

Why does HPV positive orophrangeal cancer have a better prognosis?

1. HPV-positive tumours may harbour fewer or different genetic alterations, which can be associated with better response to therapy[17,64].
2. HPV-positive tumours have higher radiosensitivity, probably due to intact apoptotic response to radiation[58,65].
3. The absence of field cancerisation in HPV-positive tumours[53].
4. Immunologic response may be play a role in the improved response to radio- and chemotherapy in HPV-positive tumours (due to the stimulation of immune response directed to viral specific tumour antigens[66].
5. Younger age, good performance status, fewer comorbidities of HPV-positive oropharyngeal cancer patients may also contribute to improved survival[67].

The impact of HPV on clinical management

The standard treatment for OPSCCs at present is mainly dependent on the stage of the disease and patient and clinician preferences. Single-modality treatment, in the form of surgery or radiotherapy, is usually recommended for early (T1-T2, N0) disease. For advanced stage disease, standard treatments include chemoradiotherapy with or without neck dissection, or surgical resection with reconstruction and postoperative chemoradiotherapy, as required. These current standard methods of treatment appear to apply to both HPV positive and negative subgroups[68,69].

1) Non-surgical treatment options for OPSCCs

The emergence of HPV-OPSCCs in younger patients with better prognosis and survival rates in comparison to non-HPV OPSCCs have prompted clinicians to address changes in the non-surgical management according to HPV status[2].

Multiple studies[29,58-61,68-70] tackling this issue have concluded that (Tables I, II):

1. Overall survival rates increase with HPV positive status, low EGFR and high p16[72].
2. Patients with HPV negative disease have a poorer prognosis, and therefore usually require more intensive treatment. Studies (TAX 324[61], TROG 02.02[59]) have suggested that for patients with HPV DNA-negative tumours, treatment intensification improves outcomes compared to standard treatment, but overall outcome is still poor.
3. Smoking cessation and strategies to target EGFR and Bcl-xL[70] are important adjuncts in the treatment of oropharyngeal cancer.
4. Achievement of acceptable cure rates with minimal long-term morbidity with HPV positive oropharyngeal cancer is possible.

All these data suggest that HPV status can be used in the clinical decision-making processes to select patients for less aggressive non-surgical treatment. Thus, assessing HPV presence is of utmost importance. This is especially true considering long-term outcomes of HPV-positive younger patients, since they are at risk of a lifetime compromised quality of life as a result of chronic toxicities due to chemoradiotherapy. p16 immunohistochemistry (IHC) is a current marker to detect HPV presence. However, it can be associated with a high rate of false positive/false negative responses, prompting the need for new surrogate markers for oral HPV infection. These concerns were also reported by Rietbergen et al.[71] and Bussu et al.[72]. Thus, in clinical practice it is not recommended to rely on p16 IHC alone to screen for HPV positivity.

Currently, there are on-going oncological trials that attempt to answer some questions regarding deintensification of treatment (Table III):

1. Can we use neoadjuvant chemotherapy followed by reduced radiotherapy dose in HPV positive patients?
2. What is the intensity of adjuvant therapy required in p16-positive oropharynx cancer patients?
3. Can cetuximab provide selective radiosensitisation compared with cisplatin?
4. Should the volume treated be reduced by not administering prophylactic radiotherapy to areas at risk of microscopic disease?
5. Is it possible to reduce the dose of radiation therapy when given with standard doses of chemotherapy?
6. What is the exact role of immune activation in HPV positive patients?

Table II. Retrospective analyses of HPV status and/or p16 immunohistochemical staining status as a surrogate biomarker of HPV infection and survival outcome in Phase III outcome.

Study	Treatment Regiment	Total N (n included)	Progression-Free Survival	Overall Survival	Conclusion
RTOG 0129 Ang et al. 2010 [29]	Standard-fractionated radiation + cisplatin *vs.* hyperfractionated radiation + cisplatin	743 (323)	HPV+/p16 HPV-/p16 3-yr 73.7% 3 yr 43% 3-yr 74.4% 3 yr 38%	HPV+/p16HPV-/p16 3-yr 82.4% 3 yr 57.1% 3-yr 83.6% 3-yr 51.3%	No survival differences seen between the 2 treatment arms. Secondary analysis confirmed significantly improved survival in patients with HPV-positive tumours vs. HPV-negative disease.
DAHANCA 5 Lassen et al. 2009 [70 71]	Radiation	195 (156)	5-yr p16+ (70%)	5-yr p16+ (62%)	Improved loco-regional control when nimorazole was added to radiotherapy was restricted to p16-negative patients. Improved survival in p16-positive patients treated with radiotherapy alone.
	Radiation+nimorazole	219 (175)	5-yr p16- (40%)	5-yr p16- (26%)	
DAHANCA 6&7 Lassen et al. 2011 [60]	5 Fractions w/radiation	726 (385)	5-yr p16+ (78%)	5-yr p16+ (62%)	Accelerated radiotherapy significantly improves outcome in HNSCC compared to conventional fractionation. The observed benefit was independent of tumour p16 status, and the use of a moderately accelerated radiotherapy regimen seemed advantageous for HPV/p16 positive HNSCC.
	6 Fractions w/radiation	750 (409)	5-yr p16- (64%)	5-yr p16 -(47%)	
TROG 02.02 Rischin et al. 2010 [59]	Radiation+cisplatin vs. radiation+cisplatin+tirapazamine	861 (185)	2-yr p16+ (87%)	2-yr p16+ (91%)	While there was no difference in the p16-positive group, there was a trend for improved loco-regional control with tirapazamine in p16 negative patients. The study clearly demonstrated that HPV associated oropharyngeal cancer treated with a standard regimen of concurrent cisplatin and radiation has a better outcome compared with HPV-negative OPSCC.
			2-yr p16- (72%)	2-yr p16- (74%)	

Table III. On-going clinical trials (ClinicalTrials.gov).

Study ID	NCI Trial ID	Trial Type	Total (N)	Treatment arm	Primary Endpoint
E1308	NCT01084083	Phase II	160	Sequential therapy: cisplatin/paclitaxel/cetuximab Complete response: IM RT (27 fractions) Non complete response: IM RT (33 fractions) 1cetuximab	2-yr PFS
J0988	NCT01088802	Phase I/II	60	IMRT (lower dose) + cisplatin	Toxicity/LRC
National Cancer Institute (NCI)	NCT01585428	Phase II	-	Fluderabine/cyclophosphamide/ Young TIL /Aldesleukin	Tumour response / duration
RTOG 1016	NCT01302834	Phase III	706	IMRT hyperfractionation+cisplatin *vs.* IMRT hyperfractionation +cetuximab	5-yr OS
University of Michigan Cancer Center	NCT01663259	-	-	Standard dose radiotherapy+cetuximab for stage III/IV OPSCC	Rate of recurrence
ECOG1308	NCT01084083	Phase II	83	Induction chemotherapy followed by cetuximab With low dose *vs.* standard dose IMRT	2-yr PFS
Mount Sinai School of Medicine	NCT01358097	Observational	-	Biomarkers of immune function as predictors of HNSCC in response to therapy	-

OS: overall survival, LRC: loco-regional control; DFS: disease-free survival; IMRT: intensity modulated radiation therapy; PFS: progression-free survival; TIL: tumour infiltrating lymphocytes.

2) Surgical treatment options for OPSCCs

All treatment modalities for OPSCC have similar oncological outcomes [73], but functional outcomes have significant and critical considerations when managing younger HPV positive patients with an longer expected lifetime. While nonsurgical deintensification trials are

showing great promise [29 58-61 70-72], minimally-invasive approaches, especially transoral robotic surgery (TORS), have gained more favour by achieving the satisfactory oncological outcomes without compromising functional outcome [73 74]. Indeed, three-dimensional visualisation allows the ability to manipulate [75] and perform reconstruction of the oropharynx without the need for mandibulotomy and/or pharyngotomy, thus reducing the morbidity of extensive surgery [76]. It also facilitates safer exposure and resection of the primary tumour, thereby providing complete pathologic evaluation and impacting the use of clinically-established adjuvant therapies [77]. These include use of concurrent chemotherapy [78] and effective lower doses of radiotherapy, which contribute to a decrease of swallowing dysfunction [79]. The postoperative target volume for radiation is typically smaller, and with modern techniques such as intensity modulated radiotherapy (IMRT) this procedure can significantly reduce the dose delivered to uninvolved normal structures. In patients requiring postoperative concurrent chemoradiation, this offers the potential to reduce the risk of late complications [80].

The incorporation of TORS, not only to improve oncologic results but also to decrease the long-term toxicity risks caused by non-surgical strategies, is crucial for HPV positive patients since they typically present at a younger age. To date, there are few surgical trials investigating the role of TORS in HPV positive patients. For instance, Cohen et al. [81] found no differences in oncological outcomes, overall survival or loco-regional control between HPV-positive and negative groups patients who underwent TORS surgery stratified by HPV status. Nonetheless, TORS surgery was suitable for both subgroups. The Mount Sinai group reported no differences in overall survival or loco-regional control in patients stratified by smoking status, with the assumption that patients without a smoking history are predominantly HPV positive [82].

The failure to show statistically significant differences in HPV-positive and HPV-negative tumours in TORS surgical trials for early T stage differences is unclear. It is possible that these studies were small and thus lack the statistical power to show survival differences, or that the survival advantage in HPV-positive tumours does not apply to early T-stage tumours that are surgically resected. Lastly, one may argue that HPV-negative tumours are less radio-responsive, and surgical resection provides better prognosis in the cohort being studied [83].

New multi-institutional studies are needed to confirm the exact impact of TORS on the quality of life and survival outcomes of HPV negative and positive OPSCC patients.

Future directions in HPV-positive OPSCCs

HPV-induced carcinogenesis has been extensively studied in the most widely accepted HPV-related malignancy, namely cervical cancer. HPV-associated cancers continuously express the HPV E6 and E7 viral oncogenes even during advanced stages, and repression of viral oncogene expression can prevent growth or survival of cervical cancer cells [84]. These findings raise the possibility that even late-stage HPV-associated cancers can be treated through HPV-targeted approaches with drugs that interfere with the expression or function of the viral oncoproteins or with therapeutic vaccines that elicit a cytolytic immune response in cells expressing these oncoproteins.

Vaccination

The world has greatly benefited from vaccine programmes in controlling the morbidity and mortality of infectious diseases. Hepatitis B virus (HBV) vaccine, developed for the prevention of hepatitis B virus infection, is considered the first vaccine against a major human cancer, hepatocellular carcinoma [85]. Recently, a prophylactic HPV vaccine has been included in national immunisation programmes of most developed countries with the hope of also being included in developing countries within the next few years, with the goal of preventing cervical and other non-cervical HPV related cancers [86].

Two FDA-approved HPV prophylactic vaccines are currently available [87]. The quadrivalent vaccine was initially approved in the US in 2006, and is composed of four HPV type-specific virus-like particles (VLPs) from the major capsid protein L1 of HPV types 6, 11, 16 and 18, combined with aluminium phosphate adjuvant. These are the most common HPV types found in 70% of cervical cancers and 90% of non-cervical cancers [87 88]. The bivalent HPV vaccine, approved in 2009, is composed of two HPV types, 16 and 18, which cause 70% of cervical cancers [86]. The efficacy of the quadrivalent vaccine was 100% in preventing HPV 16 and 18 related cervical intraepithelial neoplasia (CIN) grades 2/3 and vulvar and vaginal intraepithelial neoplasia (VIN) 2/3, and 98.9% in preventing HPV 6, 11, 16 and 18 related genital warts [89]. The bivalent vaccine is 98.1% efficacious in HPV 16 and 18 related CIN 2/3 prevention [90].

The Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control and Prevention (CDC) recommends [88 90 91]:

- routine vaccination of girls aged 11 or 12 years that can be started at 9 years of age;
- catch-up vaccination for females aged 13-26 years;
- routine vaccination of boys aged 11 or 12 years;
- routine vaccination recommended for both men who have sex with men (MSM) and immunocompromised individuals aged 22 through 26 years;
- men aged 13 to 21 years who were not previously vaccinated;
- men aged 22 to 26 years may also receive the vaccine;
- can be given to lactating women, patients with minor

acute illnesses and women with equivocal or abnormal Pap test.

HPV vaccine should be delivered through a series of 3 intramuscular injections over a 6-month period of time, at 0, 2 and 6 months for the quadrivalent vaccine and 0, 1 and 6 months for the bivalent one [89], inducing strong immune memory with persistent antibody up to 6.4 years (bivalent) and up to 9.5 years (HPV 16 VLP used in quadrivalent) thus entailing long-term duration of protection against infections caused by pathogenic HPVs and their disease sequelae [92].

The entrance of males into vaccination programmes is primarily due to the estimation of 7,500 cases of HPV-related cancer, primarily head and neck and anal cancer, which occur in men each year in the United States alone [93]. Furthermore, the rates of anal cancer in homosexual males are extremely high, and thus vaccination may contribute in immunisation with subsequent reduction of HPV sexual transmission.

In the future, the currently available vaccines may also show promising results on preventing HPV-associated OPSCC caused by HPV 16, and longitudinal studies comparing the incidence of disease before and after the introduction of the vaccine may clarify this issue.

Unfortunately, the prophylactic vaccine is not effective on established infections and cancer lesions, so the study of a therapeutic HPV vaccine to treat HPV-associated cancer remains an area of crucial importance [94].

Different immunotherapeutic vaccines targeting E7 and/or E6 have been developed over the last decade including peptide/protein, dendritic cell (DC), plasmid DNA and viral vector-based therapies, but with limited success in preclinical and clinical phase studies [95 96]. A recent Italian study developed a promising therapeutic vaccine based on an integrase defective lentiviral vector (IDLV) to deliver a mutated non-oncogenic form of the HPV 16 E7 protein, considered as a tumour specific antigen for immunotherapy of HPV-associated cervical cancer, fused to calreticulin (CRT), a protein that is able to activate natural killer T cells (NKTs). A single intramuscular injection prevented tumour growth in 90% of early stage tumour-bearing mice, without adjuvants and/or drug treatments. These promising results may suggest that a safe anticancer immunotherapeutic vaccine may be available in the future for human use [94].

Targeted therapies

Evaluation of epithelial growth factor receptor (EGFR)-targeted therapies in HNSCC patients have been based on the observation that EGFR is highly expressed in HNSCC, and its over-expression has been associated with reduced survival in several studies [97]. For clinical use, EGFR can be targeted either by antibodies recognising the ligand-binding domain of EGFR or by EGRF tyrosine kinase inhibitors (TKIs). Cetuximab is a humanised mouse anti-EGFR IgG1 monoclonal antibody, offering improved loco-regional control and overall survival in locally-advanced HNSCC in combination with radiotherapy [98].

Other humanised anti-EGFR antibodies such a panitumumab or zalutumumab are currently being evaluated in phase II/III clinical trials and may evolve as alternatives to cetuximab [99]. Additional prospective clinical trials are on-going to assess the value of cetuximab in management of HPV-positive OPSCCs.

Conclusions

To date, the available data corroborate some well-established concepts: oropharynx tumours have been steadily increasing over the last 20 years compared to other cancers of the head and neck worldwide, particularly in Western countries. SEER data suggest that about 18% of all head and neck carcinomas in the USA were located in the oropharynx in 1973, compared to 31% of such squamous cell tumours in 2004. Similarly, in Sweden, the proportion of oropharyngeal cancers HPV positive has steadily increased, from 23% in the 1970s to 57% in the 1990s, and as high as 93% in 2007. These data indicate that HPV is now the primary cause of tonsillar cancer in North America and Europe.

The biology of HPV-positive oropharyngeal cancer is characterised by p53 degradation, retinoblastoma RB pathway inactivation and p16 up-regulation. In contrast, tobacco-related oropharyngeal cancer is characterised by p53 mutation and down-regulation of CDKN2A (encoding p16ink4A). HPV-positive oropharyngeal cancer seems to be more responsive to chemotherapy and radiation than HPV-negative disease.

The choice of the best viral detection method in tumours is a matter of controversy, and both in-situ hybridisation and PCR are commonly used; p16 IHC is also being used to detect HPV infection, but with unreliable results [71 72]. Thus, there is clearly a need for new surrogate markers for HPV infection to give patients the best treatment strategies.

The presence of HPV 16 can also be thought of as a prognostic marker for enhanced overall and disease-free survival, but its use as a predictive marker has not yet been proven. Many questions about the natural history of oral HPV infection are still under investigation.

Regarding disease management, based on the present information, we can consider HPV-positive oropharyngeal cancer as a distinct subset of HNSCC with a more favourable outcome. Patients with HPV-positive oropharyngeal cancer are typically young and in good health. In future clinical trials, cancer centres should stratify head and neck patients by HPV status. Regardless of treatment modality, an opportunity now exists to investigate less intense treatment strategies that do not compromise survival

outcomes, but lower the risk of fatal side effects. Thus, providing a high level quality of life with the fewest treatment complications are important considerations. Potential long-term side effects of concurrent chemoradiation include dysphagia, xerostomia, feeding-tube dependency from fibrosis and scarring of the pharyngeal muscles, chronic aspiration and chronic fatigue.

However, we must always emphasise that the best cure against cancer is prevention, especially in those malignancies in which the main pathogenic agent is known. Finally, the authors wish to suggest reader to consult two very recent and excellent reviews: "New insights into human papillomavirus-associated head and neck squamous cell carcinoma" [100] and "Human papilloma virus (HPV) in head and neck region: review of literature [101].

List of Abbreviations:

CTEP: Cancer therapy evaluation programme.
DHANCA: Danish Head And Neck Cancer Group.
DNA: Deoxynucleic acid
E6: Early oncoprotein6
E7: Early oncoprotein7
ECOG: Eastern Cooperative Oncology Group
FDA: Food and Drug Administration
EGFR: Epithelia Growth Factor Receptor
HNSCC: Head and Neck Squamous Cell Carcinoma
HPV: Human Papilloma Virus
ISH: in situ hybridization
NCCN: National Comprehensive Cancer Network
PCR: Polymerase Chain Reaction
pRb: retinoblastoma tumour suppressor
OPSCC: OroPharyngeal Squamous Cell Carcinoma
RTOG: Radiation Therapy Oncology Group
TKI: Tyrosine Kinase Inhibitors
TLM: Transoral Laser Microsurgery
TROG: Trans-Tasman Radiation Oncology Group
TORS: Trans Oral Robotic Surgery
USA: United States of America
BCL-XL: B-cell lymphoma-extra large
SEER: Surveillance, Epidemiology and End Results Program

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HEAD AND NECK

Parapharyngeal space tumours: the efficiency of a transcervical approach without mandibulotomy through review of 44 cases

Tumori dello spazio parafaringeo: efficacia dell'approccio trans-cervicale senza mandibulotomia. Revisione di 44 casi

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SUMMARY

The aim of this study was to describe our experience with benign parapharyngeal space tumours resected via a transcervical route without mandibulotomy and to investigate associated postoperative sequelae and complications. The study investigated and analysed the retrospective charts of 44 patients who underwent surgery for benign parapharyngeal space tumours over a 10-year period. The diagnosis was reached in all patients with clinical and radiologic findings; preoperative fine-needle aspiration biopsy was not performed in any case. The preferred means of accessing the parapharyngeal space in all patients was a transcervical route. In 5 of these patients, transparotid extension was performed due to the position of the tumour. Tumours were classified radiologically as poststyloid in 27 cases and prestyloid in 17 cases. The final histopathologic diagnosis was vagal paraganglioma in 16 cases, pleomorphic adenoma in 13 cases, schwannoma in 10 cases and comparatively rarer tumours in the remaining 5 cases. In three patients, cranial nerve paralysis was observed during preoperative evaluation. Permanent cranial nerve paralysis occurred in 19 cases (43.2%) in the postoperative period, the majority of which were neurogenic tumours such as vagal paraganglioma (n = 16) and schwannoma (n = 2), and one case of non-neurogenic parapharyngeal tumour. The median duration of follow-up was 61 ± 33 months. There was no local recurrence in any patient during the follow-up period. A transcervical approach should be the first choice for excision of parapharyngeal space tumours, except for recurrent or malignant tumours, considering its advantages of providing direct access to the neoplasm, adequate control of neurovascular structures from the neck and optimal aesthetic outcomes due to preservation of mandibular continuity with minimal morbidity and hospitalisation time.

KEY WORDS: Parapharyngeal • Benign • Tumour • Transcervical • Mandibulotomy

RIASSUNTO

Scopo del presente studio è di descrivere la nostra esperienza riguardo i tumori benigni della regione parafaringea sottoposti a resezione chirurgica per via transcervicale senza mandibulotomia e valutarne le complicanze post-operatorie. Questo studio analizza retrospettivamente una serie di 44 pazienti sottoposti ad intervento chirurgico per tumori benigni della regione parafaringea nell'arco temporale di 10 anni. La diagnosi è stata formulata in tutti i pazienti sulla base dei dati clinici e radiologici; in nessun caso è stato utilizzato lo studio citologico su agoaspirato (FNAB). In tutti i casi l'approccio di scelta alla neoformazione è stato quello transcervicale. In 5 pazienti è stato necessario un allargamento alla regione parotidea per via della localizzazione anatomica della lesione. I tumori sono stati classificati radiologicamente in post-stiloidei in 27 casi e in prestiloidei in 17 casi. La diagnosi istopatologica definitiva è risultata in 16 casi di paraganglioma vagale, in 13 casi di adenoma pleomorfo, in 10 casi di schwannoma e di tumori relativamente rari nei rimanenti 5 casi. In tre pazienti è stata osservata paralisi di nervi cranici nel pre-operatorio. Paralisi permanente di nervi cranici è stata osservata in 19 casi (43.2%) nel post-operatorio, nella maggioranza di casi si trattava di tumori neurogenici quali paragangliomi del vago (n:16) e schwannoma (n:2) e in un caso di tumore non-neurogenico della regione parafaringea. Il periodo medio di follow up è stato di 61 mesi (SD +/- 33.10) e in questo lasso di tempo non sono state osservate recidive locali di malattia in nessun paziente. L'approccio per via transcervicale dovrebbe costituire il trattamento chirurgico di prima scelta nei tumori della regione parafaringea eccezion fatta per le forme ricorrenti o maligne. I vantaggi sono legati all'accesso diretto alla regione parafaringea, adeguata esposizione chirurgica delle strutture neurovascolari del collo, miglior risultato estetico associato al mantenimento della continuità della mandibola e ridotte morbidità ed ospedalizzazione.

PAROLE CHIAVE: *Parafaringeo • Benigno • Tumore • Transcervicale • Mandibulotomia*

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Introduction

The parapharyngeal space (PPS) is defined as the deep space that forms an inverted triangular pyramid in the neck where the posterior belly of the digastric muscle and hyoid bone forms the apex of the pyramid, and the temporal bone, its base. The fascia stretching from the styloid pro-

cess to the tensor veli palatini muscle divides the PPS into prestyloid and poststyloid compartments. The prestyloid compartment contains the deep lobe of the parotid gland, fibroadipose tissues, medial and lateral pterygoid muscles and several lymph nodes. Additionally, the internal maxillary artery and vein, lingual, inferior alveolar and auriculotemporal nerves course through the prestyloid compartment. In contrast, the poststyloid compartment contains more vital structures such as the internal carotid artery, internal jugular vein and cranial nerves (CN) IX, X and XI. The sympathetic nerve chain and numerous lymph nodes are also located in the poststyloid compartment.

Primary tumours of the PPS are very rare, comprising approximately 0.5% of all head and neck tumours [1].They often present asymptomatic growth and can stay undetected for long periods of time or may be detected as an incidental mass during screening for another reason. These tumours frequently manifest via medial displacement of the lateral wall of the oropharynx or via a growth on the upper neck, and nearly 50% of patients present with a neck mass [2]. Symptoms are generally related to the position of the tumour and may include foreign body sensation in the pharynx, difficulty in deglutition and hoarseness. Cranial nerve deficits and otologic manifestations such as hearing loss are rarely observed. A wide variety of primary tumours may be seen in this anatomical region; fortunately most are benign (70-80%) [3 4]. The most frequent benign tumour is pleomorphic adenoma followed by paraganglioma; the most common malignancies are also of salivary gland origin [3].

There are several approaches for surgery of PPS. The most preferred approaches involve a transcervical route for tumours in the prestyloid compartment and a combined transparotid-transcervical route for tumours in the poststyloid compartment or for those originating from the deep lobe of parotid gland. Transcervical approaches can also be combined with mandibulotomy for removal of malignant tumours, tumours with vascular origin and recurrent tumours [3 4]. In surgical approaches combined with mandibulotomy, damage to the inferior alveolar nerve, malocclusion and non-union-malunion defects and loss of dentition may occur. Additionally, in some types of osteotomies, lip-splitting may be required. Due to damage to the floor of the mouth during the surgery, tracheostomy and nasogastric tube feeding may be required. Fisch described an infratemporal fossa approach for extremely large PPS tumours invading the temporal bone and middle cranial fossa [5]. An alternative to this approach is the transcervical-transmastoid technique, which obtains proximal and distal control of the jugular bulb and the internal carotid artery by approaching the skull base from the neck and mastoid [4.] In the classic transoral approach to PPS described by Ehrlich in 1950, a curved incision is made along the palatopharyngeal arch and the tumour is enucleated with blunt dissection [6]. Due to its major drawbacks, Ducic et al. described a new superior parapharyngeal space approach involving transsection of the soft palate [7]. Transoral robotic surgical excision of PPS tumours is an evolving technique. Although robotic surgery is performed in the same way as the traditional transoral approach, there is less damage to the surrounding major neurovascular structures than with the transoral approach; furthermore, in cases of pleomorphic adenoma, the likelihood of capsular violation is relatively high and there is insufficient long-term data on recurrence rates [8-10]. Other disadvantages of this technique are high cost and unavailability of the robotic device.

As seen above, due to the complex anatomy of PPS, many surgical approach techniques have been utilised, and all are associated with adverse effects. Herein, we discuss the efficacy, results and complications of transcervical approaches for accessing the PPS in the presence of benign primary tumours.

Materials and methods

In this study, the records of 67 patients who underwent surgery for PPS tumours between January 2001 and December 2010 in a tertiary referral centre were retrospectively reviewed. All patients had the same surgical team. Only tumours originating from the PPS were included and metastatic lesions or tumours extending to the PPS from other parts of the head and neck were excluded. The preoperative clinical signs, symptoms, neurological evaluation of cranial nerves, operative technique, radiologic and histopathologic findings and operative complications were collected from clinical records.

In 19 cases (28.4%), mandibulotomy was performed due to high suspicion of malignancy according to radiological findings or revision surgery; therefore, all of these patients were excluded from the study. The remaining 48 patients were called for a follow-up examination to check for locoregional recurrence and cranial nerve deficits. Four patients could not be contacted and were excluded.

Diagnosis was made with the help of clinical and radiological findings. Magnetic resonance imaging (MRI) was the preferred technique, except for patients who were unsuitable for MRI and were consequently examined by contrasted computerised tomography (CT). In cases with a high suspicion of a vascular tumour, MRI angiography was additionally performed. The proximity of tumours to major blood vessels and the parotid gland were determined and their position was classified as prestyloid or poststyloid via imaging techniques. Preoperative evaluation did not involve FNAB or angiography and embolisation in any case.

During follow-up, at months 1, 2 and 6 after surgery, clinical examination was considered sufficient because all tumours had benign histopathologic diagnoses. At month 12 and yearly thereafter, a head and neck MRI was performed to detect possible recurrence of disease.

Results

Of the 44 cases, there were 15 males and 29 females with an age from 27 to 79 years (mean 44.6 years, SD ± 10.77). The most common clinical findings were neck mass (n = 24, 54.5%) and oropharyngeal mass pushing the pharyngeal structures medially (n = 16, 36.4%) (Table I). Other presenting symptoms were tinnitus, hoarseness, cough and dysphagia. In two patients (4.5%), the parapharyngeal mass was discovered incidentally during radiologic studies for other irrelevant pathologies of the head and neck.

In 3 cases a contrast CT scan was preferred due to contraindications for MRI. In the remaining 41 cases, a gadolinium contrasted MRI study was done. In the evaluation of tumours with MRI findings compatible with paraganglioma, routine use of MRI angiography was considered unnecessary, but in 5 cases with a suspicion of vascular origin, an MRI angiography was also performed following the primary radiological study. Radiologic findings compatible with benign tumour histology, which were used to assess the eligibility of the transcervical surgical approach, were defined as the following: well-circumscribed, encapsulated tumour without invasion of surrounding tissues.

The final histopathologic examination revealed vagal paraganglioma in 16 cases (36.4%), pleomorphic adenoma in 13 cases (29.5%) and schwannoma in 10 cases (22.7%) (Table II). Only one schwannoma originated from a cranial nerve, which was expectedly identified as a hypoglossal schwannoma; the remaining schwannomas were from unidentified origins. The comparatively rare tumours observed were giant cell inflammatory granulation tissue (n = 2), neurofibroma (n = 1), lipoma (n = 1) and haemangiopericytoma (n = 1). MRI findings were consistent with histopathologic findings in all cases, and tumours defined radiologically as benign were likewise histopathologically benign.

When tumours were classified radiologically according to location, 27 (61.4%) were discovered to originate from the poststyloid PPS and the remaining 17 (38.6%) originated from the prestyloid PPS. The mean tumour diameter was 5.51 cm (SD ± 1.13). The largest tumour was a pleomorphic adenoma with the longest axis of 11 cm and the smallest was a vagal paraganglioma with a diameter of 3 cm.

Table I. Clinical presentation of parapharyngeal space tumours.

Symptom	Number of patients	%
Neck mass	24	54.5
Oropharyngeal mass	16	36.4
Pulsatile tinnitus	3	6.8
Incidental	2	4.5
Hoarseness	2	4.5
Dysphagia	2	4.5
Cough	1	2.2

Table II. Final histopathologic diagnosis.

Histology	Number of patients	%
Paraganglioma	16	36.4
Pleomorphic adenoma	13	29.5
Schwannoma	10	22.7
Giant cell inflammatory granulation tissue	2	4.5
Neurofibroma	1	2.3
Lipoma	1	2.3
Haemangiopericytoma	1	2.3

In all 44 patients included in the study, transcervical approaches were preferred. In 5 of these patients, a transparotid extension was also done due to the location of the tumour. Of these 5 cases, 4 were pleomorphic adenomas originating from the deep lobe of the parotid and the remaining case was a haemangiopericytoma originating from the poststyloid PPS (Fig. 1).

Cranial nerve paralysis was observed in three patients during preoperative evaluation (Table III). The first patient underwent surgery for a PPS pleomorphic adenoma with the longest axis of 11 cm, where the preoperative cranial nerve (CN) IX, X and XII paralysis did not recover during post-operative follow-up of 18 months (Fig. 2). This was attributed to long-standing presence of the tumour in the PPS and consequent atrophy of the nerves under pressure. One patient underwent surgery for a vagal paraganglioma, with preoperative CN X paralysis, and another had surgery for a schwannoma originating from the hypoglossal nerve (Fig. 3), with preoperative CN XII paralysis. CN paralysis did not recover in any of these patients in the postoperative period because the cranial nerves had to be sacrificed for adequate tumour removal. In the remaining 41 patients (93.2%), no preoperative CN deficit was detected.

In the 41 patients without preoperative CN paralysis, no CN paralysis was observed postoperatively in 22 (50%). In addition to the three patients who showed no improvement in preoperative CN paralysis, permanent CN paralysis developed in 19 cases, the details of which are listed in Table III. No patient with vagal paralysis had obstructive respiratory problems postoperatively owing to the one-sided sacrifice of the nerve. However, all patients had problems with feeding due to aspiration, which was resolved by an Isshiki type I thyroplasty procedure performed under local anaesthesia within the first postoperative week. Patients with preoperative CN X paralysis did not require any medialisation procedure because the long-lasting paralysis was compensated spontaneously in the preoperative period. The patient with CN IX paralysis had a moderate velopharyngeal insufficiency postoperatively, which was compensated within the second postoperative week.

One patient who underwent surgery for a vagal paraganglioma experienced a right-sided diffuse cerebral infarction caused by an arterial embolism at the second post-

Table III. Complications.

Complications	Tumour histology	Details
CN Paralysis	*Patients with preoperative paralysis (n = 3, 6.8%)*	*Affected CN*
	Pleomorphic adenoma (n = 1)	IX, X, XII (permanent)
	Vagal paraganglioma (n = 1)	X (permanent)
	Hypoglossal schwannoma (n = 1)	XII (permanent)
	Patients with postoperatively developed paralysis (n = 19, 43.2%)	
	Vagal paraganglioma (n = 15)	X
	Schwannoma (n = 2)	X
	Hemangiopericytoma (n = 1)	IX
	Giant cell inflammatory granulation tissue (n = 1)	X, XII
Vascular Injury (n = 2)	Schwannoma	Laceration of the internal carotid artery
	Vagal paraganglioma	Right-sided diffuse cerebral infarction caused by arterial embolism
Tracheotomy (n = 2)	Pleomorphic adenoma	Elective tracheotomy for difficult intubation
	Vagal paraganglioma	Right-sided diffuse cerebral infarction, prolonged intubation

operative day, and a left-sided hemiplegia developed. In another patient with a hypoglossal schwannoma, the internal carotid artery was injured during surgery and was repaired primarily. However, during the postoperative 24 hours, an arterial embolism to the middle cerebral artery developed, which resolved in the second postoperative month without a permanent neurological deficit.

Tracheotomy was performed in two patients (4.5%). The first patient was the one who had a 11 cm pleomorphic adenoma. Due to the risk of difficult intubation, preoperative elective tracheotomy was performed. The second patient was monitored in the intensive care unit for a long period after having diffuse cerebral infarct caused by an arterial embolism.

The longest follow-up period was 150 months and the shortest was 30 months. The median follow-up duration was 61 months (SD ± 33.10), which was considered long enough to evaluate local recurrence and possible late complications. There was no local recurrence in any patient during follow-up; however, 4 patients died due to reasons other than the primary disease (9.1%).

Fig. 1. Haemangiopericytoma of the parapharyngeal space. Note the submandibulary gland is excised, the digastric muscle is transected and its posterior belly is resected (white arrow). A parotidectomy extension is done (white star) and following identification of the facial nerve, its marginal branch is retracted superiorly (black arrow).

Discussion

The transcervical route, first described in 1955 by Morfit [11], is most preferred surgical approach for resection of PPS tumours [2-4]. A transcervical incision is performed at the level of the hyoid bone following orotracheal intubation. The incision can be extended to the submental area to perform lip splitting if a mandibulotomy is necessitated during the operation. For larger tumours originating from the deep lobe of the parotid and for tumours with a retrostyloid location, partial parotidectomy is required. In the parotidectomy extension, following the identification of the main trunk of the facial nerve, its marginal branch is isolated and the lower half of the superficial lobe of the parotid is removed. The stylohyoid muscle, the posterior belly of the digastric muscle and the stylomandibular ligament is transected and the mandible is dislocated anteriorly. The internal and external carotid arteries, internal jugular vein, sympathetic chain and CN IX, X and XI are identified. The submandibular gland is pulled anteriorly or may be resected for exposure, and the mylohyoid muscle may be transected to reach the parapharyngeal space. Thereafter, the tumour is dissected bluntly from the surrounding tissues. The limited exposure of the parapharyngeal space is accepted as the major disadvantage of the transcervical route by some authors.[2] However, this issue remains controversial and conflicts with the results of our study.

Reviewing the literature on parapharyngeal tumours approached transcervically, two case series were found. Chang et al. reported on 51 cases with the largest tumour size of 6.8 cm, while Presutti et al. described 18 cases with the largest tumour size of 8 cm [12 13]. Our case series in-

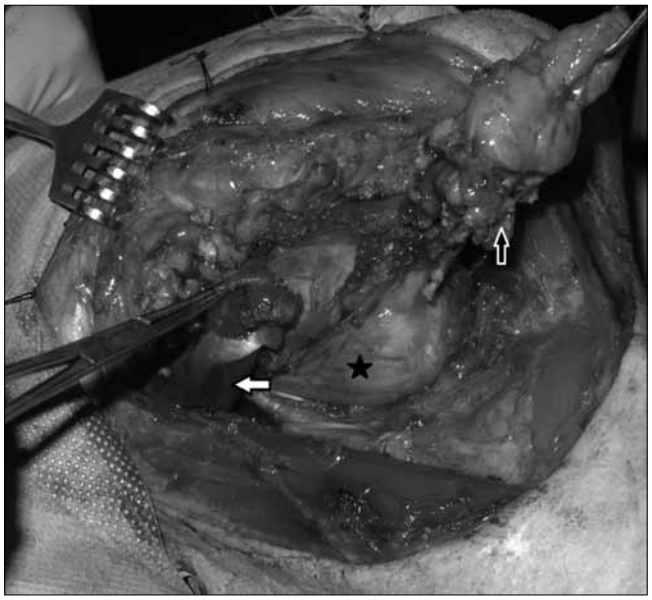

Fig. 2. Pleomorphic adenoma of the parapharyngeal space (black star). The submandibulary gland and anterior belly of the digastric muscle is pulled up anteriorly (black arrow). The posterior belly of the digastric muscle is retracted posteriorly (white arrow).

volved 44 cases and the largest tumour was a pleomorphic adenoma with a horizontal diameter of 11 cm. It should be emphasised that the vertical diameter should be evaluated rather than the horizontal diameter to determine whether the tumour is suitable for excision through a transcervical route. If the vertical extension of the tumour is suspicious for intracranial extention, a transcervical approach is dispensable. Furthermore, it should be taken into consideration, particularly in neurogenic tumours, that it might be very difficult to dissect the tumour from the surrounding tissues, especially in the vicinity of the cranial base. The

Fig. 3. A case of schwannoma originating from the hypoglossal nerve. The submandibulary gland is pulled anteriorly and the digastric muscle is retracted superiorly. The white arrow shows the hypoglossal nerve.

schwannoma that originated from the hypoglossal nerve is a good example for this situation among our patients. In this case, the tumour extended to the level of the hypoglossal canal and the internal carotid artery was gradually thinned due to pressure applied by the mass. Consequently, the internal carotid artery was lacerated during blunt dissection of the mass. For this reason, we do not recommend a transcervical approach for tumours with a long vertical dimension and radiologically suspected to invade the cranial foramens.

The indications for mandibulotomy in PPS are malignant neoplasms, recurrent neoplasms, large benign neoplasms and highly vascular neoplasms with the need for improved vascular control [14]. In our opinion, the indications for mandibulotomy should be limited only to malignant or recurrent tumours; however, size and hypervascularity of the tumour are not definite indications for mandibulotomy. As mentioned in our series, some hypervascular tumours such as haemangioperistoma and vagal paragangliomas can be safely excised via a transcervical approach. Additionally, the giant pleomorphic adenoma with a diameter of 11 cm was a good example for large PPS tumours underlining that mandibulotomy is unnecessary just owing to the size of the tumour.

In addition to transcervical and transmandibular techniques, transoral routes should be considered for well-selected cases. Nevertheless, we do not employ this technique regardless of tumour size in any parapharyngeal masses. Surgical exposure is extremely poor in this technique; the risk of tumour rupture is very high, and in the event of rupture, it is extremely difficult to clean the spilled tumour cells from the operative field successfully, so recurrence in such a vital body part is unavoidable. Furthermore, control of neurovascular structures is mostly inadequate, resulting in massive intraoperative blood loss and cranial nerve deficits.

MRI seems to be superior to CT in diagnosis and assessment of PPS tumours because it demonstrates the size of the tumour and the neighbouring tissues more clearly. The presence of dystrophic calcifications seen on CT and the well-defined, smoothly lobulated tumour contour detected on MRI are the best predictors for pleomorphic adenoma, which is the most common PPS tumour in the literature [15]. The second most common PPS tumour in the literature and the most common one in our series is vagal paraganglioma, the diagnosis of which is usually made correctly depending on MRI characteristics [16]. On MRI, the most characteristic finding of a paraganglioma is the presence of serpentine or punctate low–signal intensity regions, termed as the "salt and pepper" appearance, which results from its hypervascularity [17]. Other radiological findings of a PPS paraganglioma are the easily discernible delineation of tumour borders and the anterior displacement of the internal carotid artery. The second most common tumour type in our case series was the nerve sheet tumour, which also have characteristic radiological signs includ-

ing well defined tumour margins and homogenous overall appearance [18]. These tumours should be considered in the differential diagnosis of PPS paragangliomas and are also characterised with CN paralysis without the "salt and pepper" appearance on MRI [17]. Radiological studies can also distinguish infiltration in surrounding soft tissues and regional metastasis, which is considered as an important criterion of malignancy [19-21]. It may be difficult to distinguish malignant from benign tumours clinically, and thus the role of radiological assessment is very critical. CN palsies and pain are significant symptoms that may be related to malignancy. Nevertheless, they do not specifically point to a malignant tumour. The radiological signs of a malignancy are finding of irregular tumour margins, spread into surrounding tissues and fat planes on CT or MRI and the evidence of enlarged necrotic lymph nodes in the retropharyngeal and cervical area. In our study, none of the patients radiologically diagnosed as having a benign tumour were reported to have a malignant tumour in postoperative pathological assessment. Therefore, we conclude that preoperative radiological evaluation is sufficient to distinguish malignant from benign tumours.

PPS is an unusual target for FNAB and has some disadvantages such as difficulty in access, tumour spillage and necessity for an experienced cytologist due to the rarity of these tumours. Transcervical FNAB with or without ultrasound guidance, which is used routinely in head and neck clinical applications, may not be adequate in PPS lesions. Instead of the transcervical route, FNAB may be performed via a transoral approach in the outpatient suite or under CT guidance through a transfacial approach. However, its reliability is controversial in the literature because the diagnostic accuracy of FNAB in PPS tumours (other than pleomorphic adenomas) is dubious [22]. A diagnosis of the paraganglioma is made mostly with the help of radiology as mentioned above; moreover, FNAB of paragangliomas is not widely accepted due to its extreme vascularity and possible risks of haemorrhage inside the tumour [23]. The third common tumour type in our series was schwannoma, in which the presence of hypocellular (Antoni B) areas and the particularly cystic degeneration in larger tumours also makes FNAB ineffective [24]. Consequently, FNAB of PPS tumours is technically difficult and time consuming due to its need for a interdisciplinary team including head and neck surgeon, radiologist and cytopathologist. The distinction between benign and malignant or hypo-hypervascular tumours can be made easily with the help of radiology, so we believe that preoperative FNAB will not change preoperative treatment planning. Moreover, we do not recommend incisional biopsy in order to prevent tumour spillage and recurrence.

Due to its complex anatomic content, many types of tumours are expected to occur in the PPS. Shahab published the second largest series in the literature with 114 cases and among those, 96 patients (84%) had benign pathology, of which 34 were pleomorphic adenoma, 33 were paraganglioma (including carotid paragangliomas), 11 were schwannoma and 3 were neurofibroma [3]. Cohen published 166 cases, 145 of which were benign PPS tumours: 34 tumours of salivary gland origin, 65 paraganglioma, 16 schwannoma, and 7 neurofibroma [4]. All of our 44 cases had benign histopathologic diagnoses, which were vagal paraganglioma in 16 cases (36.4%), pleomorphic adenoma in 13 cases (29.5%) and schwannoma in 10 cases (22.7%). Although tumours with glandular origin are accepted to be the most common neoplasms in the PPS, neurogenic tumours had the greatest prevalence in our series, which is consistent with Cohen's series [4]. Our clinic is a tertiary referral centre, which may account for the high proportion of neurogenic tumours due to the difficulty of their surgical excision and the higher rate of preoperative and postoperative complications relative to glandular tumours.

There is much controversy recently as to whether these neurogenic tumours should be resected or monitored in order to observe their biological behaviour. Our principle in the treatment of such tumours is as follows: depending on the patient's preference after informed consent, we prefer surgical treatment for younger patients because of their long life expectancy. It is also clear that the sooner the tumour is excised, the fewer the resultant complications. Moreover, in the event of a complication such as nerve deficit, their tolerance is greater and rehabilitation is easier owing to better physical capacity compared with older patients. In contrast, we prefer to monitor older patients radiologically if tumours are likely to be benign neurogenic neoplasms and patients are asymptomatic. Nonsurgical treatments such as radiotherapy and stereotactic radiosurgery can be used in symptomatic cases.

The most serious complication of PPS surgery is CN paralysis involving CN VII, IX, X, XI and XII [13]. Among our patients, excluding three cases that had preoperative paralysis, permanent CN paralysis occurred in 19 cases (43.2%) in the postoperative period. However, regarding the fact that 15 of these cases were vagal paragangliomas and two were schwannomas, the high rate of paralysis is considered reasonable since CN X has to be sacrificed in the surgery of vagal paraganglioma. Neurogenic tumours like paragangliomas, particularly vagal paragangliomas are accepted to have the greatest risk of neurological sequels in comparison with other PPS tumours [4]. Informing the patient about the possible neurological complications prior to the operation will improve the patients' compliance with the rehabilitation program because speech and swallowing therapy may be necessary during postoperative rehabilitation of patients with paralysis of CN IX, X or XI. Because most of these tumours are benign and grow slowly, the morbidity that would be caused by CN sacrifice should be taken into consideration while making the decision of surgical treatment, especially in older patients. The principle of '*primum non nocere'* should be kept in mind.

There were no recurrences during the follow-up period of 61 months. This result demonstrates the efficacy of the transcervical technique, but might also be related to the fact that the majority of cases were well-capsulated neurogenic tumours.

Conclusions

The ideal surgical approach for the PPS should be one that does not damage important surrounding structures. To prevent possible perioperative vascular and postoperative neurological morbidities, all of the lower cranial nerves, internal carotid artery and internal jugular vein must be identified. The transcervical approach should be the first choice for excision of PPS tumours owing to its advantages of providing direct access to the PPS and control of neurovascular structures from the neck. With improvements in combination with video-assisted and image-guided minimally-invasive surgical techniques, the transcervical approach will be much more useful in the future [25]. Because the majority of these tumours are benign and their en-bloc excision with safe margins is sufficient for treatment, it is unnecessary to increase the postoperative morbidity by performing mandibulotomy or other highly invasive procedures.

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HEAD AND NECK

Supracricoid laryngectomies: oncological and functional results for 152 patients

Laringectomie sopracricoidee: risultati oncologici e funzionali su 152 pazienti

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SUMMARY

The purpose of this study was to evaluate the oncological and functional outcomes in patients who underwent supracricoid laryngectomies with a crico-hyoidopexy (SCL-CHP) or a crico-hyoido-epiglottopexy (SCL-CHEP) for the treatment of primary and reccurent laryngeal cancer. A retrospective study was conducted on 152 consecutive patients seen from January 1996 to December 2006. Overall survival (OS) and disease-free survival (DFS) were analysed using the Kaplan-Meier method, and were compared according to the type of surgery and clinical stage of the tumour. The mean period before decannulation, nasogastric tube (NGT) removal and recovery of a normal diet and speech were evaluated, and statistical analyses were performed regarding the association with the type of surgery and arytenoidectomy. The median follow-up period was 49.9 months (range: 10–110 months). The 3- and 5-year OS were 87.5 and 83.5%, respectively, and 3- and 5-year DFS were 78.3 and 73.7%, respectively. For patients with early stages tumours, the 5-year OS and DFS were 92.3 and 84.6% respectively, whereas for patients with locally advanced stage tumours, the OS and DFS were 74.3 and 62.2%, respectively. Significant differences in OS and DFS for patients who had early or locally advanced cancers were found ($p = 0.0004$ and $p = 0.0032$, respectively). The rate of overall local control was 92.1%, while the mean period until decannulation or NGT removal was 25.1 and 16.6 days, respectively. The mean period until NGT removal was significantly different according to the type of surgery ($p = 0.0001$) and whether arytenoidectomy was performed ($p = 0.0001$). The reliable oncological and functional results of SCL for early and locally advanced laryngeal cancers are confirmed by our series of patients.

KEY WORDS: Supracricoid laryngectomies • Functional outcome • Laryngeal cancer • Organ-preserving surgery

RIASSUNTO

Lo scopo di questo lavoro è stato valutare i risultati oncologici e funzionali in pazienti sottoposti a laringectomia parziale sopracricoidea con crico-ioido-pessia (CIP) e crico-ioido-epiglotto-pessia (CIEP) per lesioni primitive e recidive di cancro laringeo. È stato condotto uno studio retrospettivo su 152 pazienti consecutivi dal mese di gennaio 1996 a dicembre 2006. La sopravvivenza globale e la sopravvivenza libera da malattia sono state analizzate con il metodo di Kaplan-Meier e sono state confrontate secondo il tipo di intervento chirurgico e lo stadio clinico. Abbiamo valutato, inoltre, la media del tempo di decannulazione e rimozione del sondino nasogastrico, così come la ripresa della fonazione, deglutizione e respirazione. L'analisi statistica è stata eseguita in base al tipo di intervento chirurgico e alla procedura di aritenoidectomia. La mediana del follow-up è stata di 49,9 mesi (intervallo 10-110 mesi). La sopravvivenza globale e libera da malattia a 3 e 5 anni è stata del 87,5%, 83,5% e del 78,3%, 73,7% rispettivamente. I pazienti con stadio precoce hanno riportato una sopravvivenza globale e libera da malattia a 5 anni di 92,3% e 84,6%, mentre per quelli con stadio avanzato i valori sono stati di 74,3% e 62,2%. Una differenza statisticamente significativa è stata riscontrata confrontando la sopravvivenza globale e libera da malattia a 5 anni per gli stadi precoci rispetto a quelli avanzati ($p = 0,0004$ and $p = 0,0032$ rispettivamente). Il controllo locale è stato del 92,1%. La media del tempo di decannulazione è stata di 25,1 giorni; quella di rimozione del sondino nasogastrico di 16,6 giorni. Quest'ultima è risultata statisticamente significativa nel confronto sia in base all'intervento chirurgico ($p=0,0001$) che alla eventuale aritenoidectomia ($p = 0,0001$). L'attendibilità dei risultati oncologici e funzionali è stata confermata dalla nostra casistica, sia per i pazienti con stadio precoce che avanzato.

PAROLE CHIAVE: *Laringectomie sopracricoidee • Outcome funzionale • Cancro della laringe • Protocollo chirurgico di conservazione d'organo*

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Introduction

Supracricoid laryngectomy (SCL) is an organ-preserving surgery that is indicated for selected patients with T1b to T4a laryngeal cancer; SLC was first described by Mayer and Rieder in 1959 and was modified by Piquet et al. in 1974. SCLs involve the removal of the thyroid cartilage, both true and false cords, ventricles, paraglottic and pre-epiglottic spaces and the epiglottis [1 2]. The latter may or may not be resected depending on the extent of the tumour. According to the type of reconstruction, SCLs are classified as SCL-crico-hyoidopexy (SCL-CHP) or SCL-crico-

hyoido-epiglottopexy (SCL-CHEP) [3 4]. It is necessary to preserve the cricoid cartilage, hyoid bone and at least one functional cricoarytenoid unit to preserve the airways and functioning of the laryngeal sphincter to avoid permanent tracheostomy. SCLs with CHP and CHEP provide reliable oncological and functional results for selected patients with glottic and supraglottic carcinomas, as well as for patients who need salvage surgery for recurrence [5-8]. The purpose of this study was to evaluate the oncological and functional outcomes of a cohort of 152 patients at 3 and 5 years after treatment with SCL as organ-preserving surgery.

Materials and methods

A retrospective study was conducted on 152 consecutive patients who underwent SCL from January 1996 to December 2006 at the Otolaryngology Head and Neck Surgery Unit of "Azienda Ospedaliera di Rilievo Nazionale dei Colli – Ospedale Monaldi", Naples (Italy). The patients included 138 men (90.8%) and 14 (9.2%) women with a median age of 45 years (range: 24–78 years) as shown in Table I. Of the 152 patients, 29 had glottic cancer and 123 had supraglottic cancer; 16 patients were clinically categorised as N1.

SCL was the primary treatment for 144 patients (94.8%), whereas 8 (5.2%) underwent surgery for local relapse after a previous treatment: 4 (2.6 %) had been previously treated with a CO_2 transoral laser resection and 4 (2.6%) had received previous radiotherapy.

All patients had been diagnosed with squamous cell carcinoma of the larynx that was histologically confirmed by biopsy. Clinical staging of the tumour according to 2010 UICC classification system [9] was performed by instrumental analysis and functional imaging, including optical fibre videolaryngoscopy, direct microlaryngoscopy under general anaesthetic with biopsy, bronchoscopy, oesophagoscopy, blood gas analysis, spirometry, neck ultrasonography, contrast-enhanced CT and/or MRI scanning of the neck, high-resolution chest CT and, as of 2005, total body CT with positron-emission tomography (^{18}F-FDG PET/CT) for patients with locally advanced disease [10].

Table I. Characteristics of patients who underwent SCL according to age, gender and Karnofsky performance status.

Characteristic	N	%
Patients	152	
Age (years)		-
<55	32	21%
55-72	104	68.4%
>72	16	10.6%
Median (years)	45	-
Range (years)	24–78	-
Gender		
Male	138	90.8%
Female	14	9.2%
Karnofsky performance status		
100	37	24.3%
90	69	45.3%
80	46	30.4%

The type of SCL chosen was based on the localisation and extension of the tumour.

The indications for CHEP were: (1) glottic tumours classified as T1b as limited to the vocal cords, with both vocal cords having normal mobility; (2) glottic tumours classified as T2, with tumour extension to the ventricle, false vocal cord, petiole of the epiglottis, and/or an impaired true vocal cord; (3) selected glottic tumours classified as T3 due to paraglottic spread without fixation of the arytenoid cartilage; or (4) selected tumours classified as T4a due to limited anterior invasion through the thyroid cartilage. The indications for CHP were: (1) supraglottic tumours classified as T2 due to invasion of the vocal cords and anterior commissure, with or without impaired mobility of the true vocal cords; (2) selected supraglottic-glottic tumours classified as T3 due to fixation of the true vocal cords and/or invasion of the pre-epiglottic space, but without fixation of arytenoid cartilage; and (3) selected tumours classified as T4a due to limited anterior invasion through the thyroid cartilage.

The local contraindications for SCL were: (1) invasion of the posterior commissure; (2) massive invasion of the posterior paraglottic space, with potential diffusion to the submucosa of the pyriform sinus or involvement of the retrocricoid area or trachea; (3) cancer involving both arytenoids; (4) true arytenoid fixation; (5) invasion of the cricoid cartilage, front or posterolateral subglottic invasion of > 5 mm; (6) extralaryngeal spread of tumour; and (7) cN of ≥ 2. For our team, the general contraindications for SCL were uncontrolled diabetes mellitus, severe chronic obstructive pulmonary disease (FEV1 of <30%), severe heart failure, age over 75 years (except in very specific exceptions), psychiatric syndromes, personal motivations and a Karnofsky index less than 80% [11].

The resection of one arytenoid was indicated in the surgical register by the symbol "+A", followed by the side from which the arytenoid was removed. In all cases, laryngeal reconstruction was performed if the intraoperative examination of resection margins using frozen sections was reported as negative; later, the margins were checked again using definitive pathology.

Surgical treatment

Thirty-one (20.4%) patients underwent SCL-CHEP +A, 27 (17.7%) underwent SCL-CHEP, 64 (42.1%) underwent SCL-CHP +A, and 30 (19.8 %) underwent SCL-CHP. Neck dissection (ND) was performed in 138/152 (90.8%) of patients: ND was bilateral in 92 (60.5%) cases

and unilateral in 46 (30.3%) cases. Elective ND was performed in 122 cN0 patients (80.3%) and curative ND was performed in 16 cN+ (10.5%) patients. Fourteen patients affected by cT1bN0 glottic cancer (9.2%) did not undergo ND (10 were between 70–75 years old and 4 had previously been treated by carotid endarterectomy).
Unilateral selective ND (SND II-IV) was performed in 46 patients staged cT2N0; bilateral SND was performed in 76 patients (50%), 14 of whom were staged cT1bN0 and 63 of whom were staged cT3N0. Modified radical ND (MRND) Type III ipsilateral to the lesion and contralateral SND were performed in 14 patients (9.2%) with clinical evidence of neck metastasis. Finally, ipsilateral MRND Type III and contralateral SND extended to level VI and thyroidectomy was performed in 2 patients affected with cT4aN1 cancer.
The diseases were reclassified according to the 2010 UICC classification system [9] as follows: pathological examination of the specimen showed that 27 patients had glottic cancer: 23 pT1b and 4 pT4a. Among the 125 patients who were affected by supraglottic cancer, 55 were pT2 and 70 pT3. A total of 106 patients (76.8%) were pN0, whereas 32 patients (23.2%) had at least one positive lymph node (reported as pN+): 6 of these patients were pN1, 10 patients were N2a, 13 patients were N2b and 3 patients were N2c (Table II). Early (local or systemic) and later complications were assessed in all patients.

Postoperative treatment

Adjuvant radiotherapy was recommended for patients with histopathologically positive N stage tumours, positive surgical margins, or extracapsular tumour spread. In our series, 32 (21%) pN+ patients were treated with adjuvant radiotherapy according to the guidelines of the National Comprehensive Cancer Network (NCCN) [12]. The dose range was 44 to 60 Gy (2.0–1.6 Gy per fraction) since pathological examination did not reveal extracapsular spread or tumour-positive margins.

Table II. Pathological staging in the cohort (UICC 2010).

pTNM	Glottic		Supraglottic		Total
	N	%	N	%	N
pT1b	23	15.1	0	0	23
pT2	0	0	55	36.2	55
pT3	0	0	70	46.1	70
pT4a	4	2.6	0	0	4
					152
pN0	9	6.5	97	70.3	106
pN1	2	1.5	4	3	6
pN2	0	0	26	18.7	26
pN2a	0	0	10	7.2	10
pN2b	0	0	13	9.4	13
pN2c	0	0	3	2.2	3
					138

The same rehabilitation protocol was applied to all patients, except for those who developed severe early complications. Our protocol entailed the following: A) from the second postoperative day, placement of a non-cuffed fenestrated tracheostomy tube for phonation exercises; B) from the sixth postoperative day onward, intermittent occlusion of the tracheostomy tube during the day and breathing exercises; and C) starting from the eighth postoperative day, rehabilitative exercises for swallowing.

Oncological outcomes

The primary oncological endpoints included overall survival (OS) and disease-free survival (DFS) calculated from the date of surgery. The endpoint for OS was the date of death, regardless of cause, whereas the endpoint for DFS was date of recurrence. In both cases, censored data were calculated based on the date of last follow-up. Three- and five-year data were reported. We calculated the above-cited endpoints according to T stage (early T1b-T2 vs. locally advanced T3-T4a) for both surgical procedures (CHP vs. CHEP). Survival curves were calculated using the Kaplan-Meier method.

Functional outcomes

For evaluation of the short-term postoperative recovery, the primary endpoints included the mean time until decannulation and nasogastric tube (NGT) removal, calculated from the date of surgery. The NGT was removed under the supervision of a speech therapist after the patient was able to swallow liquids without aspiration; the tracheostomy tube was removed if the patient tolerated the procedure well without dyspnoea. We evaluated the above-cited endpoints according to the surgical procedure (CHP vs. CHEP) and removal of one cricoarytenoid unit (SCL vs. SCL +A).
For evaluation of long-term postoperative recovery, we utilized the Performance Status Scale for Head and Neck Cancer Patients edited by List [13] one year after the surgical procedure. This scale includes three major outcomes, each one corresponding to a subscale: normalcy of diet, intelligibility of speech and eating in public.
The normalcy of diet subscale assessed the degree to which a patient is able to eat a normal diet; it involves a ranking of 10 food categories that are arranged from easy-to-eat at the low end to hard-to-eat at the high end. The rating is based on the highest-ranking food that the patient is able to eat.
The intelligibility of speech subscale is a 5-item scale with descriptors ranging from "never understandable" to "always understandable." The rating is based on the degree to which the interviewer is able to understand the patient's speech.
The latter subscale assesses the degree to which the patient eats in the presence of others. It consists of five levels ranging from "always eats alone" at the low end to "no restriction of place, food, or companion" at the high end.

Statistical analysis

For comparison of survival curves, we used the Log-rank and Wilcoxon tests. For comparison of mean values, we used a univariate ANOVA. For all tests, the α level was fixed at 0.05. Statistical analyses were performed using JMP®, Version 10.0.0. SAS Institute Inc., Cary, NC, 1989-2007.

Results

The median follow-up period was 49.9 months (range: 10–110 months); 17 patients were lost to follow-up.

Oncological results

Thirteen patients died of laryngeal carcinoma, 9 due to locoregional recurrence and 4 for distant metastasis, while 12 patients died from causes other than laryngeal carcinoma.

For the entire cohort of patients, the OS was 87.5% after 3 years and 83.5% after 5 years, whereas the DFS after 3 and 5 years was 78.3% and 73.7%, respectively, as shown in Figure 1.

The SCL-CHP subgroup had a 5-year OS of 76.6% and a 5-year DFS of 67.1%, whereas the SCL-CHEP subgroup had a 5-year OS of 83.7% and a 5-year DFS of 81% (Fig. 2-A and Fig. 3-A).

For patients with early stage tumours, 5-year OS was 92.3% and 5-year DFS was 84.6%. For patients with locally advanced tumours, 5-year OS was 74.3%, whereas the 5-year DFS was 62.2% (Fig. 2-B and Fig. 3-B).

The difference between the OS for patients with early or locally advanced tumours was significant (Log-rank (df = 1) = 10.323, p = 0.0013; Wilcoxon (df = 1) = 12.534, p = 0.0004), whereas the difference between OS for the SCL-CHP and SCL-CHEP subgroups was not significant (Log-rank (df = 1) = 1.2003, p = 0.2733; Wilcoxon (df = 1) = 1.3436, p = 0.2464).

The difference between DFS of patients with early or locally advanced tumours was significant (Log-rank (df = 1) = 9.425, p = 0.0021; Wilcoxon (df = 1) = 8.679, p = 0.0032), whereas the difference between DFS of the SCL-CHP and SCL-CHEP subgroups was not significant (Log-rank (df = 1) = 2.919, p = 0.0875; Wilcoxon (df = 1) = 2.790, p = 0.0948). Oncologic results are reported in Table III.

In the subgroup of patients who had been previously treated, 5-year OS and DFS was 100% (4/4) and 75% (3/4) respectively, for patients treated with CO_2 transoral laser surgery, while 5-year OS and DFS was 50% (2/4) and 50% (2/4) respectively for patients treated with radiation therapy.

Local control and recurrence

The overall recurrence rate was 26.3% (40/152), while the locoregional recurrence rate was 13.2% (20/152). There were 12 local recurrences, for which the following salvage treatments were given: total laryngectomy (TL) alone in 3 cases, TL and adjuvant radiotherapy in 6 cases, TL and neck dissection limited to the sixth level in 2 cases and TL and adjuvant chemoradiotherapy in one case. Three patients died after salvage surgery, whereas at the last follow-up, 9 patients were alive and disease-free. The overall local control rate was 92.1%.

Recurrence in the neck was observed in 8 patients, 3 of whom who were previously classified as cN0 and 5 as cN1. Five patients were treated with MRND and adjuvant chemotherapy, whereas 3 patients underwent chemotherapy alone. Two patients died from regional recurrence and 6 patients were alive and disease free at the last follow-up; overall, after neck salvage therapy, the regional control rate was 94.7%.

Sixteen patients developed distant metastases, including 13 cases of lung metastases, 2 cases of bone metastases and one case of liver metastases. Four patients died, whereas 12 were still alive at the last follow-up; the rate

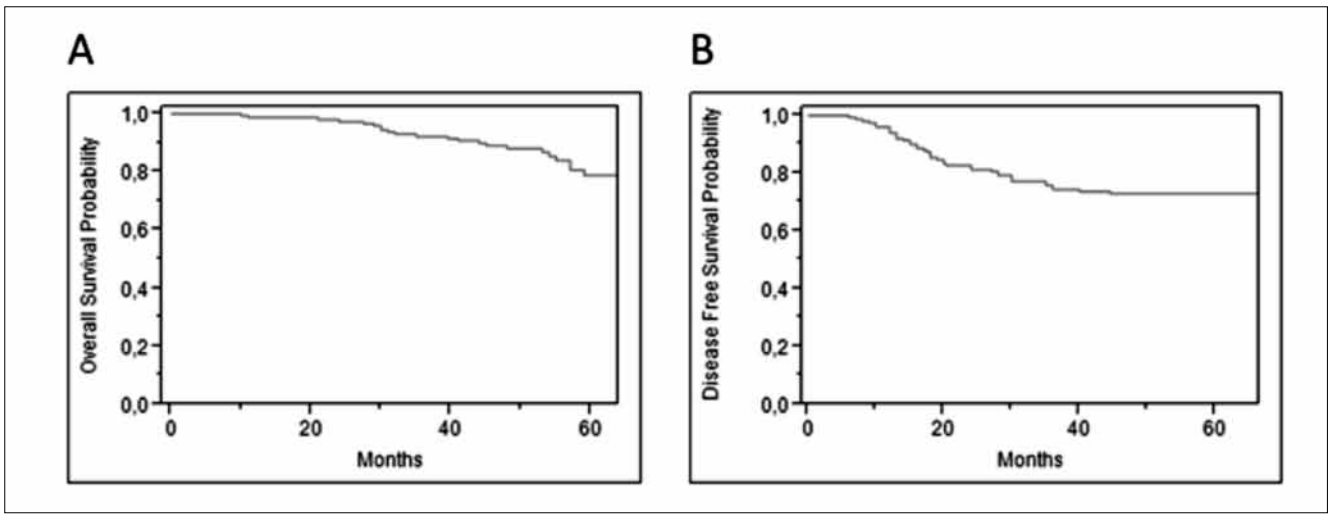

Fig. 1. Probability of overall survival (A) and disease-free survival (B) for the entire cohort.

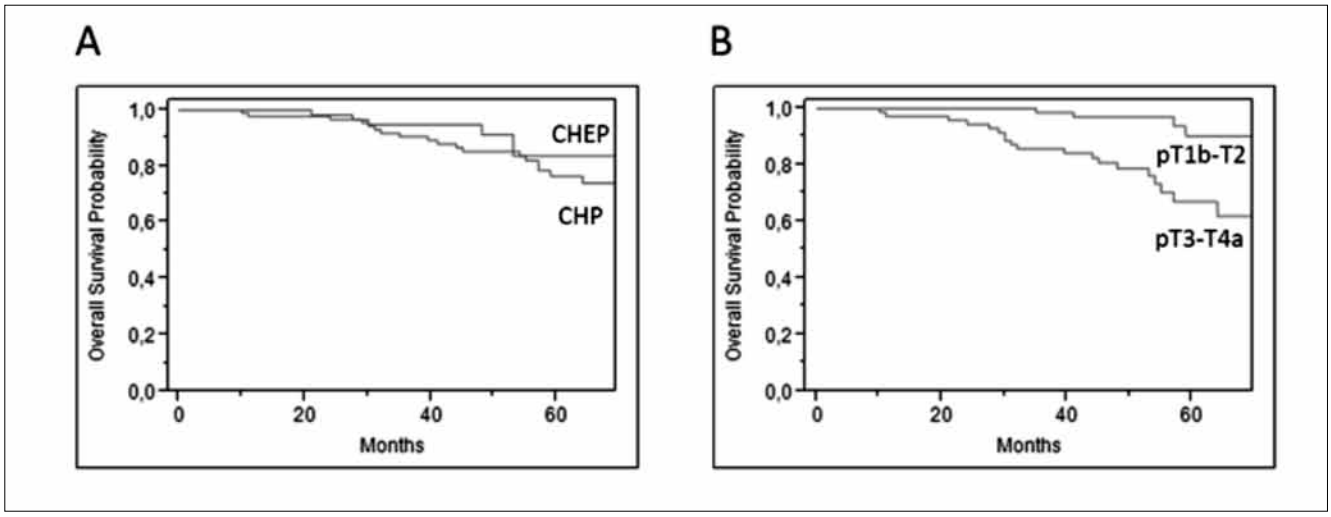

Fig. 2. Probability of overall survival according to the type of surgery (A) and pathological stage (B). CHEP: crico-hyoido-epiglottopexy; CHP: crico-hyoidopexy. Pathological staging was conducted according to the 2010 UICC classification system.

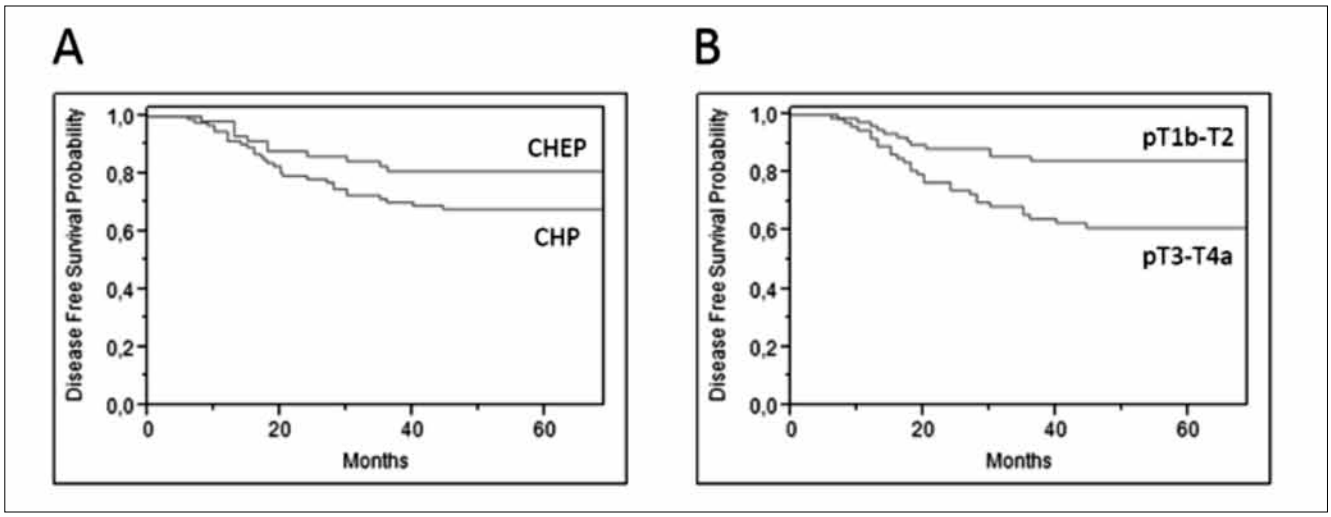

Fig. 3. Probability of disease-free survival according to the type of surgery (A) and pathological stage (B). CHEP: crico-hyoido-epiglottopexy; CHP: crico-hyoidopexy. Pathological staging was conducted according to the 2010 UICC classification system.

of distant metastases was 10.5% (16/152). Finally, the frequency of second primary tumours was 2.6%, with 4 cases of second primary cancers of the colon.

Functional results

1. Comparison of short-term postoperative recovery

Respiratory function of all patients was restored by natural means, with decannulation after an average of 25.1 days (median: 25, range: 22–30). One patient who had been treated with SCL-CHP +A was not able to swallow without aspiration and it was necessary to use percutaneous gastrostomy until the subsequent functional recovery of swallowing occurred 3 months later. The mean time until NGT removal was 16.6 days (median: 16, range: 12–63). The mean time until NGT removal was 13.6 days after SCL-CHEP and 18.4 days after SCL-CHP: these values were significantly different (p = 0.0001). In contrast, the mean time until decannulation was 25.2 days after SCL-CHEP and 25 days after SCL-CHP, with no significant difference (p = 0.502).

Table III. Analysis of oncological results according to type of surgery and clinical stage.

	Global	Early	Locally advanced	p value	CHP	CHEP	p value
5-year OS	83.5%	92.3%	74.3%	0.0004	76.6%	83.7%	0.2464
5-year DFS	73.7%	84.6%	62.2%	0.0032	67.1%	81%	0.0948

OS, overall survival; DFS, disease-free survival; CHP, cricohyoidopexy; CHEP, cricohyoidoepiglottopexy

The mean time until NGT removal was 12.9 days when both of the arytenoids were spared and 18.8 days when one cricoarytenoid unit (+A) was removed. The difference between these subgroups was significant (p = 0.0001). In contrast, the mean time until decannulation was 25.2 days when both of the arytenoids were spared and 25 days when one cricoarytenoid unit (+A) was removed; these values were not significantly different (p = 0.493).

Considering only SCL-CHEP patients according to whether an arytenoidectomy performed, the difference between the mean times until NGT removal was significant (p = 0.0001), whereas the difference between the mean times until decannulation was not significant (p = 0.443).

Considering only SCL-CHP patients according to whether an arytenoidectomy performed, the mean times until NGT removal were significantly different (p = 0.0001), whereas the difference between the mean times until decannulation was not significantly different (p = 0.703).

The short-term functional results are reported in Table IV.

2. Comparison of long-term postoperative recovery

The mean score for intelligibility of speech was 94.6. The difference between the SCL-CHEP (mean 96.5) and SCL-CHP (93.3) groups was not significant (p = 0.126). Likewise, there was no significant difference (p = 0.143) between the group that received one arytenoidectomy (+A) (mean 93.4) and the group that in which both arytenoids were spared (mean 96.5).

The average score for eating in public was 92.7 for the entire cohort. The difference between the SCL-CHEP (mean 93.1) and SCL-CHP (92.5) groups was not significant (p = 0.818). Likewise, there was no significant difference (p = 0.884) between the group that received one arytenoidectomy (+A) (mean 92.9) and the group that in which both arytenoids were spared (mean 92.5).

The mean score for the normalcy of the diet was 95.7. There was no significant difference (p = 0.717) between the SCL-CHEP (mean 96.0) and SCL-CHP (95.5) groups. Likewise, there was no significant difference (p = 0.631) between the group that received one arytenoidectomy (+A) (mean 95.5) and the group in which both arytenoids were spared (mean 96.1).

Complications

Early complications occurred in 7 (4.5%) of patients, whereas late sequelae were observed in 6 (4%) cases (Table V). All complications were treated successfully with medical or surgical treatment. It was necessary to reduce the mucosal flap using CO_2 laser surgery in 3 patients (2 CHP and 1 CHEP) because of narrowing of the airway space at the level of the neoglottis.

In terms of the type of surgery provided, we observed 4 complications in the CHEP patients (2 early and 2 late) and 9 in CHP patients (5 early and 4 late). No patient died of complications.

Discussion

The management of laryngeal cancer is focused on improving survival while preserving function; total laryngectomy is undoubtedly an effective oncological surgery, but substantially impairs the quality of life, mainly due to the permanent tracheostoma and loss of voice [14].

Various types of surgical and non-surgical approaches to avoid total laryngectomy have been used. Currently, radiation therapy alone, concurrent chemoradiotherapy, transoral laser surgery and supracricoid laryngectomy are generally utilised of treatment for early and selected locally-advanced laryngeal cancers that have the advantage of preserving laryngeal function, although the optimal primary treatment is still debated [15-20].

Nevertheless, attention to functional preservation and conservative approaches that are gradually replacing total laryngectomy as primary treatment are most likely some of the reasons for the failure in improving survival rates of patients with laryngeal cancer in the last 30 years [21-23].

Since the reports by Mayer and Rieder and Piquet et al. describing SCL with CHEP or CHP for the treatment of selected glottic and supraglottic carcinomas, numerous reports have demonstrated the reliable oncological and acceptable functional results of this procedure [12].

When the indications and contraindications are carefully assessed and surgery is performed with precise attention to the technical details of the procedure, goods result can be achieved using SCL [24].

In the case of any of the oncological contraindications for SCL that were described in the Materials and Methods section, organ preservation can be achieved only by

Table IV. Analysis of the functional results according to the type of surgery and arytenoidectomy.

	Global	CHP	CHEP	p value	SCL	SCL + A	p value
Decannulation, days	25.1	25	25.2	0.502	25.2	25	0.493
NGT removal, days	16.6	18.4	13.6	0.0001	12.9	18.8	0.0001
	Global	**CHEP**	**CHEP + A**	**p value**	**CHP**	**CHP + A**	**p value**
Decannulation, days	25.1	25.4	25	0.443	25	25.1	0.703
NGT removal, days	16.6	11.5	15.4	0.0001	14.1	20.4	0.0001

CHP, cricohyoidopexy; CHEP, cricohyoidoepiglottopexy; SCL, supracricoid laryngectomy; A, arytenoidectomy.

Table V. Early and late postoperative complications.

Complication	N	%
Early		
Acute cervical bleeding	2	1.3
Aspiration pneumonia	3	2
Wound infection	2	1.3
Late		
Frequent aspiration	2	1.3
Laryngeal soft tissue stenosis	4	2.6
Laryngeal fibrosis	0	0

chemoradiotherapy, even if total laryngectomy is often the most appropriate option [25-31].

The literature includes reports of 3-year survival rates of 71.4–95.7% and 5-year survival rates of 79–88% for patient with laryngeal cancer [26-29]. In our series, the 3- and 5-year OS rates were 87.5% and 83.5%, respectively, with 3- and 5-year DFS rates of 78.3% and 73.7%, respectively. Our series of laryngeal cancer patients is one of largest described to date, and the results are in agreement with those of previous papers.

Our data demonstrated a significant correlation ($p = 0.0013$ and $p = 0.0004$ for OS; $p = 0.0021$ and $p = 0.0032$ for DFS) between pathological stage (pT) and overall/disease-free survival rates; as expected, survival was inversely correlated with pT score.

In contrast, there was no correlation ($p = 0.2733$ and $p = 0.2464$ for OS; $p = 0.0875$ and $p = 0.0948$ for DFS) between the type of surgery performed and survival rates, indicating that both CHEP and CHP are effective techniques for management of laryngeal cancers.

Recurrence and metastasis of laryngeal cancer have also been discussed in the literature. Pinar et al. [8] reported a 92.5% local control rate (LC) in SCL patients; in the series reported by Topaloglu [24], the local control rate was 97.8 % following CHP. Dufour et al. [25] reported a 5-year local control rate of 91.4%; similarly, Chevalier [31] reported a rate of 92% in patients treated with CHEP. Of our 152 patients, 7.9% developed local recurrence, 5.3% developed regional metastasis, 10.5% developed distant metastasis and 2.6% developed a second primary tumour, for a local control rate of 92.1%.

In the subgroup of patients for whom previous treatment had failed to control the same type of laryngeal cancer, SCL performed as a salvage procedure provided a good oncological outcome (patients previously treated with CO2 trans-oral laser had OS and DFS of 100% and 75% respectively, whereas patients treated with radiation therapy had OS and DFS of 50% and 50% respectively). These results are consistent with those of recent reports and demonstrate that SCL is a reliable salvage procedure; in addition, the outcome of SLCs compare favourably with the mainstay of salvage and oncological laryngeal surgery in general, namely total laryngectomy [7 20 22].

Although the neoglottic mechanism for swallowing and generating voice after SCL resembles that of the normal larynx, laryngeal function is not normal and there is evidence that these patients have chronic problems with swallowing and aspiration and have a perceptibly abnormal voice with a breathy, strained and rough quality [33-36].

The mean time until decannulation and NGT removal, which indicate proper functioning of the neoglottis, are are commonly used to evaluate short-term functional outcome of SCLs.

The time of decannulation is the most important event for functional success in terms of respiration, and its delay may be associated with laryngeal stenosis, granulations and impaired laryngeal elevation, resulting in dysphagia. The times reported in the literature vary from 7 to 38 days [37-39]. Our rate of decannulation was 100% with a mean time until decannulation of 25.1 days.

The time of NGT removal is used to evaluate functional success in terms of swallowing. The rate of NGT removal reported in the literature varies from 92% to 100% and the mean time until NGT removal after SCLs that has been reported is between 15 and 70 days [37-39]. In our study, the rate of NGT removal was 99.3% and the mean time until NGT removal was 16.6 days. Therefore, the results obtained in the current series are in agreement with previous reports.

The SCL techniques for the removal (CHP) or preservation (CHEP) of the suprahyoid epiglottis differ; therefore, the consequences of these surgeries on the dynamics of swallowing and aspiration are different, which was also the case for patients with locally advanced tumours who received unilateral arytenoid resection. Our series is one of the largest in which functional outcome was related to the type of surgery and arytenoidectomy.

Pinar et al. [8] recently reported that the mean time until decannulation and NGT removal was significantly longer in CHP patients than in CHEP patients; Yuce et al. [40] reported a significant difference for both functional endpoints between patients treated with CHP or with CHP +A. In the paper by Park et al. [41], there was significant difference between both mean values for patients who were treated with CHEP or CHEP +A, but not for the subgroups treated with CHP or CHP +A, most likely owing to the small number of such patients. According to Bron et al. [5], the type of SCL and arytenoidectomy did not have a significant effect on swallowing. Our results showed a significant difference in the time until NGT removal according to the type of surgery ($p = 0.0001$) and whether unilateral arytenoidectomy was performed ($p = 0.0001$), whereas there was no significant difference in the time until decannulation of these groups ($p = 0.502$ and $p = 0.493$, respectively).

In the present series, complications related to aspiration (5/152) occurred more frequently in CHP patients (4/5)

than in CHEP patients (1/5), whereas laryngeal stenosis (4/152) occurred with similar rates in these two subgroups, and was related to arytenoid oedema, posterior prolapse of the epiglottis or a mucosal flap of the neolarynx. None of the patients required a revision of the pexy or conversion to total laryngectomy.

The present results confirm that the preserved suprahyoid portion of the epiglottis may help protect the airway during swallowing; the resection of one arytenoid in addition to the SCL has a negative effect on this function. The compensatory overactivity of the remaining arytenoid and a mass effect due to hypertrophy of the mucosa covering the arytenoidectomy site lead to complete glottic closure [41]. In any case, it is clear that SCL patients require extensive rehabilitation after surgery to achieve good functional outcomes [36].

The long-term functional outcomes involve recovery of 3 main functions of the larynx: speech, breathing and swallowing. Some authors [42] have stressed that speech in SCL patients is obviously worse than that of normal subjects. Nevertheless, most authors have reported acceptable functional results for SCL [8 33].

Luna-Ortiz et al. [43] evaluated patients who underwent SCLs, mostly with preservation of both arytenoids, using the Performance Status Scale for Head and Neck Cancer Patients, whereas Bron et al. [7] used the same scale for patients treated with SCL, mostly associated with a unilateral arytenoidectomy. In spite of the differences in these series, the results obtained were similar.

Our results demonstrated no significant differences in the scores for the 3 sections of the Performance Status Scale for Head and Neck Cancer Patients according to the type of surgery and arytenoidectomy (intelligibility of speech: $p = 0.126$ and $p = 0.143$; eating in public: $p = 0.818$ and $p = 0.884$; normalcy of diet: $p = 0.717$ and $p = 0.631$, respectively) in agreement with the results of previous reports.

Currently, the oncological results of treating early laryngeal carcinomas with laryngeal transoral laser surgery (TLS) and radiotherapy are comparable to those of SCL, reaching 80% to 95% control of local disease [15 16]; the former options are valid, less invasive and provide good functional results and fewer problems in functional recovery. Furthermore, TLS appears to be a cost-effective alternative to surgical procedures and radiotherapy [44].

However, local control by TLS may be inadequate when the cancer has invaded the anterior commissure [45 46]; in this case and/or in the case of difficulties in exposition, SCL may be indicated.

The impossibility of addressing laryngeal areas that are out of direct sight, hidden, or placed "around the corner" during TLS, along with the reduced local control for patients affected by anterior commissural cancer who are undergoing TLS [45 46], may be remedied by using transoral robotic surgery (TORS) [47]. Given its intrinsic features, such as angled 3D visualisation of the surgical field, instrumentation with multiple degrees of rotation and increased surgical accuracy and precision, it should be considered complementary and not as an alternative to TLS. Whenever the indications for TLS or TORS are not fulfilled, SCL is desirable.

Currently, the non-surgical options for locally advanced cancer are radiotherapy alone or chemoradiotherapy, according to the protocols of Department of Veteran Affairs Laryngeal Cancer Study Group (VA) and the RTOG91-11 trials [18 19]; these organ-sparing treatments have a higher rate of acute and late toxicities [48] and appear to be associated with lower rates of survival and organ-preservation than SCL [28].

Therefore, in our opinion, when patients with contraindications are carefully excluded, SCL should be the preferred option for treatment of locally advanced laryngeal squamous cell carcinomas, considering its results in terms of disease control and functional preservation [49].

Conclusions

Reliable oncological results in terms of the overall and disease-free survival rates and local control for patients undergoing SCL have been reported in the literature and were confirmed in our analysis of patients with early and locally advanced laryngeal cancer. SCL-CHEP and SCL-CHP provided similar short-term functional results considering the time to NGT removal and closure of the tracheostomy. The long-term functional results, as assessed by recovery of normal diet and speech were also comparable. We strongly believe that the fundamental requirements to obtain good oncological and functional results are proper patient selection, adherence to surgical indications and early, intensive rehabilitation after surgery.

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HEAD AND NECK

Contemporary role of pectoralis major regional flaps in head and neck surgery

Attuale ruolo dei lembi di grande pettorale nella chirurgia della testa e del collo

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SUMMARY

Countless disadvantages of the "old" pectoralis major have been listed while the amazing versatility of the free flap armamentarium gives the opportunity to suit the defect deriving from virtually every ablative head and neck surgery with a tailored reconstruction. Nevertheless, pectoralis major is still the "workhorse" for head and neck reconstruction in developing countries thanks to its ease of harvest, and minimal requirements in term of instrumentation. Furthermore, even in facilities with a high volume of reconstructions by free flaps, a certain number of pectoralis major flaps is still raised every year. The history, present role and current indications of the most widely head and neck reconstructive procedure ever has been reviewed.

KEY WORDS: Pectoralis major • Head and neck reconstruction • Regional flaps • Myocutaneous flaps • Fasciocutaneous flaps

RIASSUNTO

Mediante i lembi liberi microlascolari è ad oggi possibile una ricostruzione "su misura" virtualmente di ogni difetto nel distretto testa e collo. I vantaggi delle innumerevoli possibilità ricostruttive offerte dai lembi liberi rispetto al "vecchio" lembo peduncolato di grande pettorale sono ben noti. Tuttavia il lembo di grande pettorale è tuttoggi il workhorse per la ricostruzione della regione testa e collo nei paesi in via di sviluppo, grazie alla relativa semplicità dal punto di vista tecnico, ed al minimo strumentario chirurgico richiesto. Inoltre, anche nelle strutture con un alto volume di procedure ricostruttive mediante lembi liberi, viene sempre indicata in una quota di casi una ricostruzione con lembo di grande pettorale. Nel presente lavoro vengono prese in esame la storia, il ruolo e le attuali indicazioni della procedura ricostruttiva più utilizzata nel testa e collo.

PAROLE CHIAVE: *Grande pettorale • Ricostruzione testa e collo • Lembi regionali • Lembi mio cutanei • Lembi fasciocutanei*

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History of the pectoralis major

Evolution of the technique

Pectoralis major myocutaneous (PMMC) flap, based on the thoracoacromial artery, whose first description is commonly attributed to Ariyan in 1979 who exhaustively described the technique and its anatomical basis [1], was however reported in 1977 by at least two authors [2,3]. It has been considered for decades the workhorse for head and neck reconstruction, and is still often mentioned as a reliable and easy-to-raise flap [4]. Since then, an impressive number of modifications to the original technique have been proposed over the years, with different goals:

- to reconstruct different types of defects;
- to increase mobility of the flap itself;
- to reduce donor site morbidity.

All these modifications and technical refinements have been ultimately aimed at widening the indications for pectoralis major reconstruction.

Since 1984, a variant of the flap called pectoralis major myofascial (PMMF) flap, without the skin paddle overlying the muscle, and intended to reduce the thickness and bulkiness of the original flap, has been described and increasingly used mainly for the reconstruction of hypo/oropharyngeal defects [5-9]. Obviously, while PMMC is more suitable for reconstruction involving skin defects, the PMMF variant better complies with mucosal defects as it is covered early by a substantially normal mucosal layer [10].

Between the 1980s and the 1990s other major variants of the PM flap that incorporated a bony component, potentially very useful for combined mandibular reconstructions, have been described, including a vascularised section of the fifth rib [11,12] or a non-vascularised section of

the iliac crest [13 14]. A third variant of the osteomyocutaneous flap that included a segment of the outer table of the sternum, sterno-costal joint and rib was reported by Jones and Sommerland who used it for the reconstruction of the zygoma, temporo-mandibular joint and hemi-mandible [15]. Maruyama et al. described the transfer of the flap through a midline section of the clavicle [3], a technique that has since been more extensively studied and refined in cadaver models by Freeman et al. who reported a lengthening of the pedicle within the range of 0.5 to 6.5 cm [16]. The section of the clavicle is the only way to guarantee greater length and a wider range of movement to the flap: in 2001, Kerawala et al. showed that the subclavicular route was both feasible and safe [17], although later other authors exposed some reservations about the effective advantages offered by this solution [18]. Shortly after the report of their first experience with the PMMC, Maruyama et al. proposed a dynamic variant in which the transfer of the flap was combined with selective neuro-anastomoses to provide dynamic muscle action [19]. Aesthetical concerns about PMMC in women led to describe "female-friendly" variants with modifications in the harvesting site (as the inframammary paddle described by Ariyan [20]) or in the shape of the skin paddle (as the crescentic skin paddle raised medially to the nipple described by Crosher [21]).

Since 1980, some authors have reported double paddle variants of the flap for reconstruction of defects involving two separate areas [22-24], which required the preservation of both the thoracoacromial artery and the lateral thoracic arteries, and allowed preservation of the nipple area complex [25 26]. With the same aim, many authors have described combinations of the pectoralis major myofascial flap with latissimus dorsi [27], deltopectoral flap both in combination [28] or assembled in a bilobed flap version [29 30], and with free flaps such as radial forearm flap, fibula flap and anterolateral thigh flap [31-33]. In 1981, Sharzer et al. reported a parasternal paddle that crossed the midline reaching the contralateral internal mammary perforators [34], and during the same year Dennis and Kashima described a "Janus flap" variant used to repair defects that required two skin surfaces (i.e. cervical oesophagus and pharynx) [35]. Later, in the same year, Strawberry et al. described reconstruction with a bilateral PMMC [36]. A tubed version of the flap was described by Neifeld et al. in 1983, representing a great advance in oesophageal reconstruction [37]. With an eye towards function sparing, in 1985 Morain et al. proposed a medially based segmental transfer of a single intercostal portion of the pectoralis major muscle supplied by a single perforating branch of the internal thoracic artery [38]. The same year Lawson described a PMMF flap covered with amnion to prevent partial necrosis in diabetic and elderly patients [39]. Katsantonis tried to solve the problem related to function in total glossectomy reconstruction by describing an animal model of neurotisation of PMMC by the hypoglossal nerve [40]. In 1988, in an effort to find new ways to reduce thickness, even liposuction of the flap was proposed [41], although this technique, like many others, was most likely never actually employed.

Wei et al., in 1984, described a technique to harvest a muscle-free, longer, and much more movable pedicle by transecting the pectoralis major muscle along its horizontal fibres above the emergence of the thoracoacromial artery [42]. Further modifications of this variant have been recently described [43 44], as it remains the most widely used trick, with less risk for the pedicle and patient, to increase the mobility of the flap and reduce undesired bulk in the neck.

It was 1993 when a pectoralis major free flap made its first appearance in the literature, and described by Gateley et al. in a case report that showed a composite variant based on the thoracoacromial artery [45]. Chaturvedi et al. have proposed both a sub-mammary approach for women and a flap harvested exclusively through the skin paddle incision [46 47]. An endoscopic assisted technique to harvest the pedicle was proposed by Turkmen and Perks in 2005 [48]. Other innovations involved vascularisation of the flap, which was originally based only on the thoracoacromial artery. In 2006, a technique that preserved the lateral thoracic artery was published [49] and three years later Rikimaru et al. described another way to improve vascularisation and avoid possible complications related to circulation by including the third intercostal perforating branch of the internal thoracic artery [50]. The most widely used technique for closure of the donor site is undoubtedly primary closure. Nevertheless, it may be difficult or impossible to achieve when particularly wide skin pads are harvested to accomplish a proper reconstruction, and several authors have described alternative closure techniques for these cases [51-54].

Evolution of indications

In its long history, the pectoralis major flap has seen alternating indications. Since the beginning of the 1980s, until the end of the 1990s, the indications for pectoralis major flaps have progressively broadened, made possible by the unprecedented reconstructive possibilities they offered, which were further increased by the above cited technical refinements. Therefore, many head and neck surgeons worldwide have been trained in these techniques, which became the most widely used reconstructive procedure in the head and neck region to date, the so-called "workhorse of head and neck reconstruction". This reconstructive potential also contributed to enlarging the indications for ablative surgery itself, in cases in which the limitation was related to the possibility to close the defect (i.e. extensive pharyngeal or skin involvement), making many more head and neck malignancies operable.

The preponderance of pectoralis major flaps as a reconstructive option in the head and neck was progressively called into question in the beginning of the XXI century,

and pectoralis major is no longer the first option, at least in developed countries, and is often replaced by a wide choice of free flaps that can suit virtually every defect in the head and neck region. Accordingly, reconstruction is no longer an issue for ablative surgery in the head and neck. Nevertheless, many pectoralis major flaps are still harvested, and while its indications have changed and are less extensive, it still remains a very useful tool in several clinical situations.

In 1979, before the development of the techniques that would have pushed this flap to its theoretical limits, Ariyan described his experience with the reconstruction after exenteratio orbitae [55] and temporal bone resection [56]. Primary reconstruction of oropharyngeal, hypopharyngeal (including the base of the tongue), pharyngolaryngeal and oral cavity defects (including full thickness cheek defects, hemi- and total glossectomy) after highly invasive oncological surgery [3 5-9 35 57-59]; carotid artery protection after radical neck dissection or repair of an orocutaneous, tracheoesophageal and pharyngocutaneous fistula [28 60-62]; stomal recurrence after laryngectomy [63]; management of osteoradionecrosis of the mandible [64]; and salvage of necrotic wounds of the pharynx and neck [65] were among the first indications to be proposed.

The original technique, compared with late variants, allowed only limited mobility of the skin paddle. With the introduction of variants with longer pedicles [16 44 66], tubed [37], split and combined with other flaps [22 23], greater mobility and the possibility to reconstruct larger defects have been achieved, allowing broadening of the indications for reconstruction of nasopharyngeal defects, the anterior skull base [67] and the cervical oesophagus, as well as all skin defects located as far as the forehead [68] and extremely wide as midfacial reconstructions [69]. In the 1980s, variants of the flap were also proposed for treatment of facial palsy [70], septic and necrotic wounds [71] and reconstruction of mediastinal trachea [72].

During 1990s, while free flaps were strongly gaining momentum and direct comparisons between free and pedicled flaps were starting to appear in the literature [73-75], the main indications for pectoralis major flaps partially changed in favour of salvage operations. Reconstruction after free flap failure is still one of the major indications for pectoralis major flaps due to the high failure rate of second free tissue transfers [76-79]. During the last 10 years, many authors have reported on their experience with this flap, which underlined a shift in the type of subsite reconstructed, with less reconstruction of oral cavity defects over the years, and more hypopharyngeal and oropharyngeal reconstructions [80-82]. While the superiority of free flaps over pedicled flaps for tongue and mandibular reconstructions due to functional and esthetical advantages was clearly demonstrated [83-87], due to a higher total failure rate of free flaps other authors tended to still consider the pectoralis major an option when a bone reconstruction is not needed [88], especially in patients with poor overall conditions or in case of unsuccessful microsurgical flaps [89]. Other applications that are still valid include management of carotid artery exposure [90], cervical skin defects, dead space filler, infections [78], vessel depleted necks [91], mandible reconstruction when a free flap is not advisable, by rolling the PMMF on a metal plate [88 92 93], pharyngocutaneous fistula [94], closure after total laryngectomies to prevent fistula [95] and reconstruction of full thickness defects of the cheek [96].

The above described evolutions in the indications for pedicled pectoralis reconstruction refers mainly to developed countries, and to settings where patients have access to free flap reconstruction, even though it is noted that the majority of the world population is not in the same condition. In developing densely populated countries, such as India, pectoralis major flaps remain the workhorse for head and neck reconstruction with all of their original indications [97].

Currently adopted techniques

Among the main considerations for currently recommending a pectoralis major reconstruction in a free flap facility in developed countries are shorter operating time, ease of harvest and favourable early and late morbidity profile. For these reasons, the above described complex variants, with multiple paddles, with bone, with a higher rate of failure and/or of donor site complications, or simply with longer operative time, are only seldom raised.

In general, we believe that two main variants: PMMF and PMMC, are by far the most employed techniques. Even if every surgeon has his own way and little tricks for raising a pectoralis major flap, at present most surgeons, to increase the flap mobility while reducing at the same time the bulk in the neck and over the clavicle, prefer the "island" technique described by Wei [42], with successive modifications [43 44], rather than more complex and invasive steps such as cutting the clavicle or passing the flap below the clavicle itself [98] since this increases operative time, morbidity, complications and even causes vascular/pedicle issues for the flap itself. In the same way and for similar reasons, most surgeons in the current literature transfer the flap to the head and neck region through a supraclavicular subplatysmal tunnel, without any incision of the skin overlying the clavicle (which would compromise the vascular supply of a deltopectoral flap (or of its propeller variant internal mammary perforator flap). The only technical differences between the two variants are that the PMMF is harvested without skin, with consequent changes in skin incision and aesthetic outcomes of the donor site, and in operative time (which is even shorter).

Relative advantages and indications

The two variants, even if very similar in terms of the har-

vesting technique, show many relevant differences for reconstructive potential, postoperative rearrangements and results with clear relative advantages and disadvantages that have an impact on their indications. The PMMC flap was described first and is probably still the most employed variant worldwide. Its advantages lay mostly in the short operative time, ease of harvest, potentially large amount of well-vascularised tissue, relatively low morbidity on the donor site and, most of all, great versatility, as it can close virtually every defect in the head and neck region. The disadvantages and limits should be assessed in comparison with the other reconstructive options available, mainly free flaps, but also the PMMF variant.

Comparison with free flaps, which offer on the whole a huge spectrum of reconstructive options, and are in most situations the gold standard for long-term functional and aesthetic results, which is probably the key issue when evaluating the present role of pectoralis major flaps and will be discussed in detail below.

The skin of the PMMC is not 100% reliable, especially if it is not over the muscle and/or if the skin island is too small. In fact, the vascular supply to the skin comes from musculocutaneous perforators from the pectoralis branches of the thoracoacromial artery, and partial skin losses are relatively frequent (from 5 to 30%) in all series as the perforating vessels are usually not looked for. At any rate, in general, when a skin defect is created, the PMMC variant is always preferable (Figs. 1, 2). The PMMC can be used for mucosal resurfacing with good results as well (Fig. 3).

PMMF, in comparison with PMMC, is characterised by an even faster harvest, a wider and more pliable myofascial surface (potentially the entire surface of the pectoralis major muscle) for the closure of the defect. It is thinner, is not covered by hair and is usually resurfaced by the mucosa which normally covers the resected area, whose borders with native mucosa are not usually recognisable in few weeks after insetting (Fig. 4). The shape of the area closed by muscle fascia can be arbitrarily chosen in this case by the surgeon by applying a stitch along the desired suture line.

The reduced thickness and the coverage with normal, not

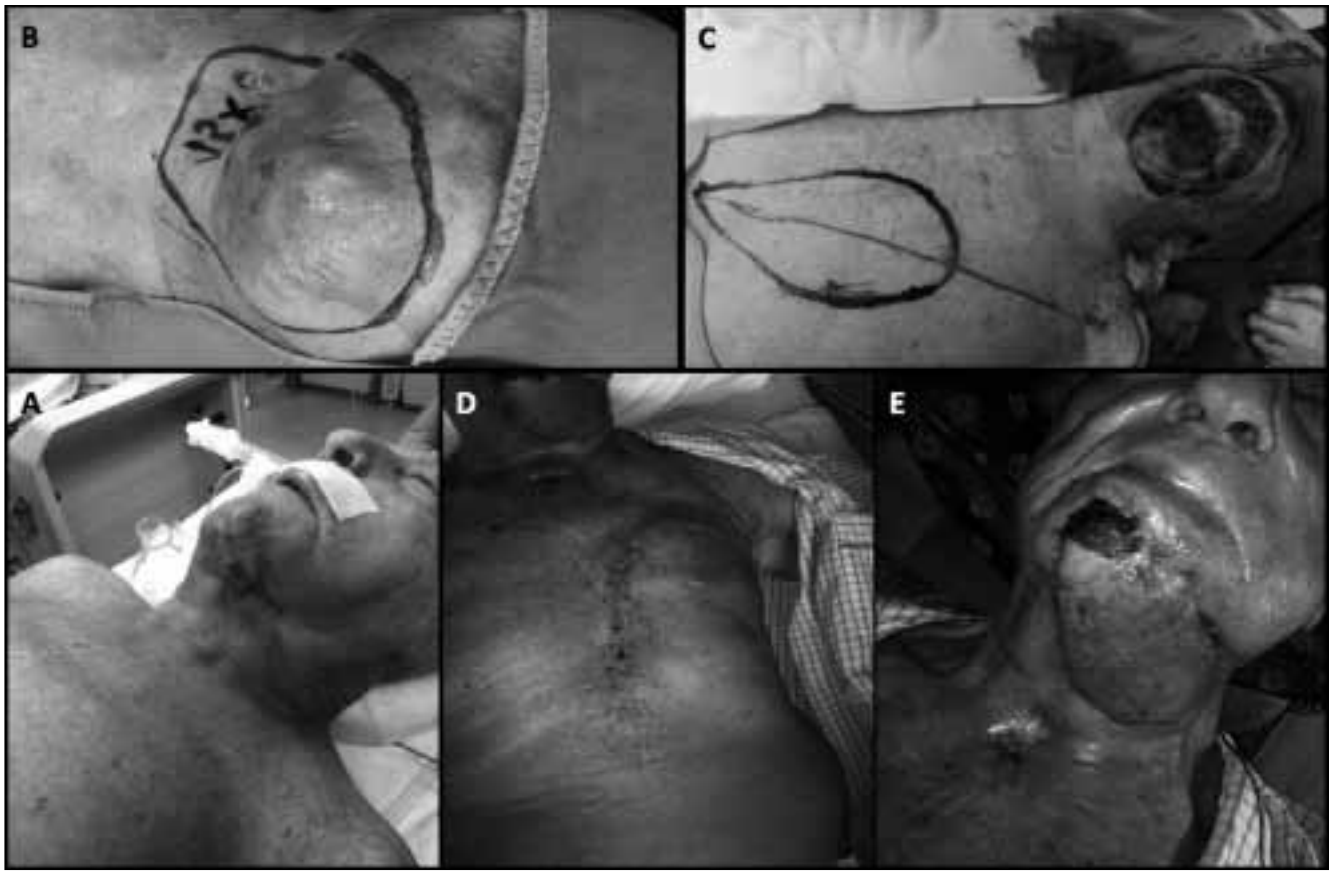

Fig. 1. A second neck submandibular recurrence with skin invasion (A, B) of a cutaneous SCC in a 92-year-old patient, was treated with a revision of the neck dissection and a wide skin excision (C). The large defect (B, C) was closed with a PMMC flap with a large (15 cm major axis) skin paddle (C, E), partially lying beyond the inferior limit of the pectoralis major muscle (C). For this reason a small distal part of the skin paddle (C), not vascularised enough by muscolocutaneous perforators, has undergone partial necrosis (E). Despite the large dimensions of the skin paddle, a primary closure of the donor site was successfully performed without any complication (D).

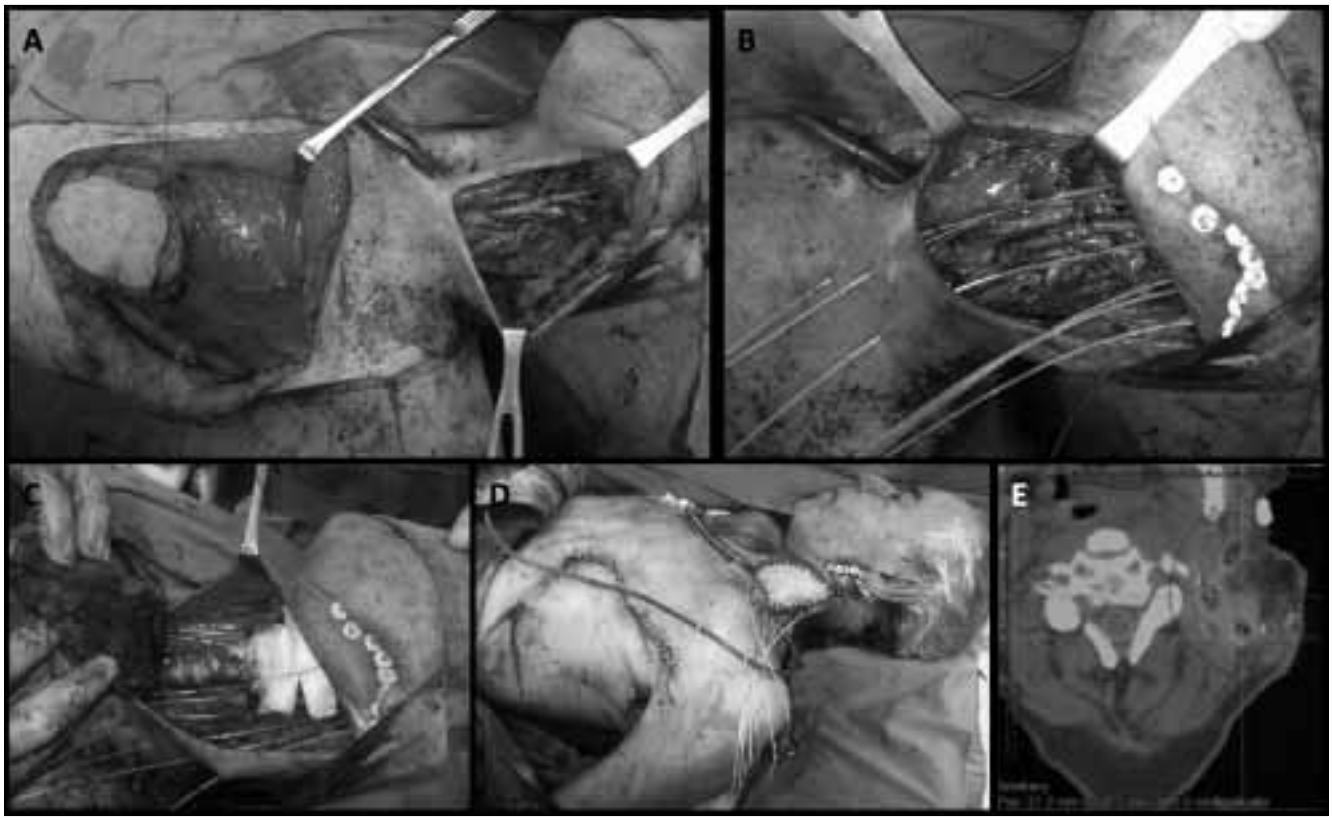

Fig. 2. A neck recurrence in a patient previously treated with salvage total laryngectomy and neck dissection for a persistent laryngeal cancer after radiochemotherapy, and salvaged again by radical neck dissection (A, B). A pectoralis major myocutaneous flap was raised (A, C, D) to fill the dead space, protect the carotid axis and allow a safe re-irradiation by HDR brachytherapy through the plastic tubes placed during the operation (B, C, D). With this precaution, most of the adjuvant dose is given to the previously non-irradiated pectoralis muscle as shown in the axial image of the treatment plan (E).

Fig. 3. (A,B) 75 ys old patient with gum scc invading bone and skin. (C)Wide demolition including skin and mandible was performed. The patient was not suitable for microsurgical recostruction. (D) A titanium plate was inserted in order to reconstruct the mandibular profile. (E,F)Pedicled pectoralis flap was harvested and wrapped on the plate. (H, I, L, M)The coutaneous portion of the flap was used to reconstruct the gum and the skin defect was reconstructed with rotation local flap.

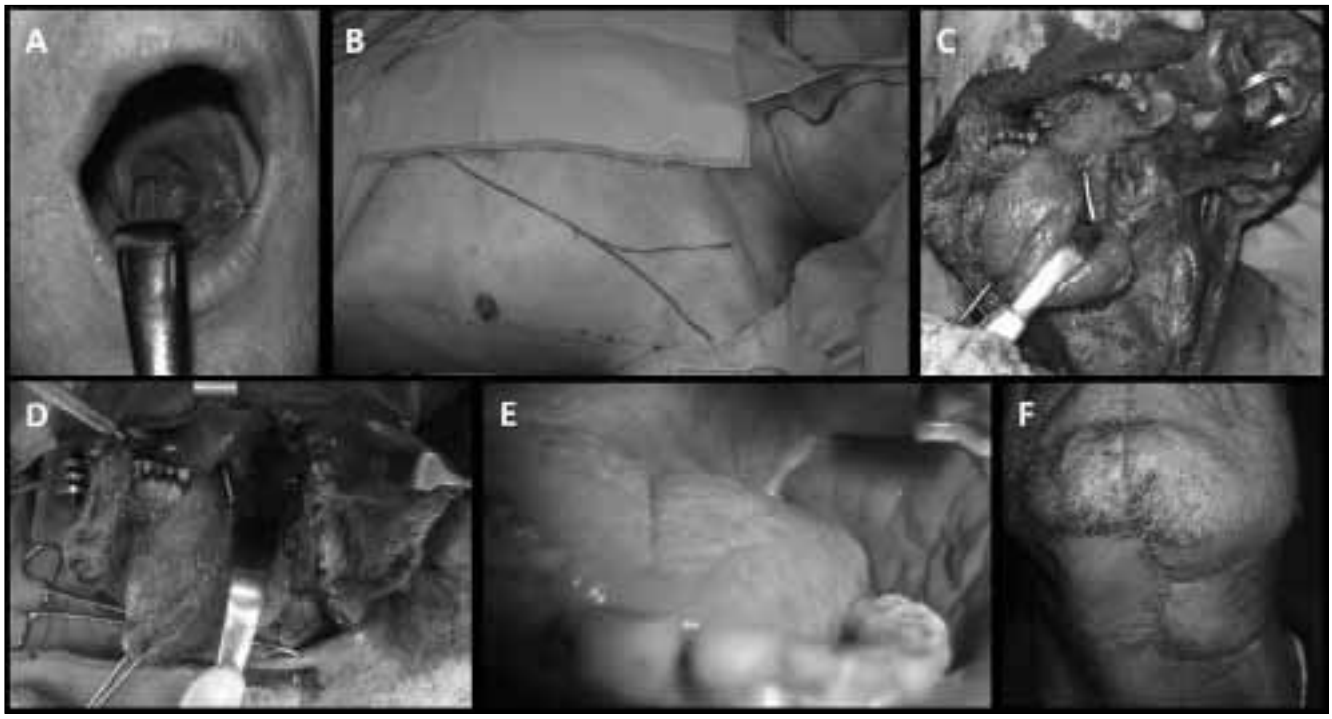

Fig. 4. The local recurrence after radiochemotherapy of a SCC of the left posterior faucial pillar (A,C) was salvaged by a partial pharyngectomy through a transmandibular approach (C, D). The defect was restored through a PMMF flap (B, D), with complete re-epithelialisation and acceptable aesthetic results (E, F). The patient was able to feed with a normal diet at 3 weeks after the salvage surgery and did not report dysphagia.

hairy, mucosa are undoubtedly a relevant argument supporting the use of PMMF in reconstructions of the oro- and hypopharynx (Figs. 4, 5), as the bulk and the hair of the PMMC variant (and also most free flaps) can cause a functional impairment and complaints from patients. On the other hand, one of the main issues considering the functional results of pectoralis major reconstructions, also deriving in pedicled flaps from muscle denervation, is muscle fibrosis and consequent retraction. This is much more evident in the PMMF variant in which it involves the surface of the defect: in pharyngeal defects involving a wide angle of the circumference in the axial plane, it is associated with a high rate of long-term dysphagia, stricture and dependence on PEG [99 100] even in our personal experience (Fig. 5).

On the other hand, the wide pliable myofascial surface can be very useful to be rolled around a reconstruction plate in case of a segmental mandibular defect (Fig. 3). Even in these cases, if no skin area is resected, PMMF may be an alternative to PMMC [93 97 101 102]. Considering that most free bony tissue transfers, characterised by relevant donor site morbidity, surgical complexity and duration and complications, are not followed by restoration of dentition through osteointegrated implants, they remain a undeniably valuable option for reconstruction of mandibular defects, especially if lateral, with less aesthetic and functional issues [102].

Salvage total laryngectomies after irradiation are characterised by a high rate of fistulas [103]; in these cases, pectoralis major flaps may work as dead space fillers, bring well-vascularised tissue in the irradiated field, reinforce the pharyngeal suture and have been demonstrated to markedly reduce the risk of this complication. For this reason, in post- radiation laryngectomies several authors propose to electively reinforce the suture line and the pharyngeal wall with a pectoralis major [95 104 105]. If a skin island is not needed for a skin defect, better results have been shown with a thin, well vascularised PMMF [95]. For the same reason, many authors use the pectoralis major to protect the carotid axis after a salvage radical neck dissection following radiotherapy failure [8 78 106]. At the same time, the well vascularised muscular tissue fills the dead space, and the vascular supply reduces post-irradiation neck fibrosis. If a PMMC is raised, its well vascularised skin reduces the tension and retraction of the suture line and later of the scar (Fig. 2). The inset of the PMMC flap in vessel depleted necks after salvage neck dissection has allowed us in some cases to place plastic tubes to administer further adjuvant perioperative brachytherapy (Fig. 2).

The protective and trophic effect of pectoralis muscle on neck vessels and tissues is an advantage in all cases after radiotherapy and neck dissection, even if the reconstructed defect is in the pharynx, oral cavity, or

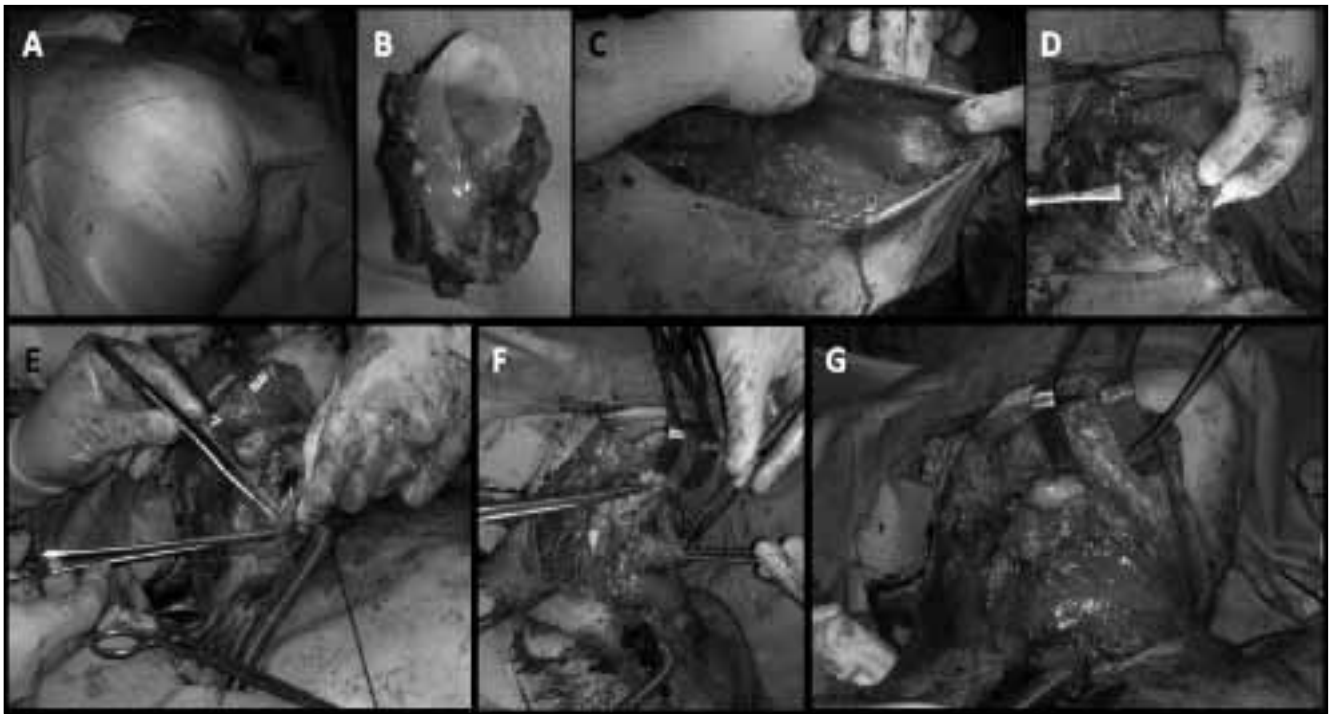

Fig. 5. Local recurrence after radiochemotherapy of a hypopharyngeal postcricoid SCC was salvaged by total laryngectomy and subtotal pharyngectomy (B). The pharyngeal tube was restored suturing the superficial fascia of a PMMF flap (A, C) to the residual posterior hypopharyngeal mucosa (D, E, F, G). The portion of the hypopharyngeal circumference restored with the procedure was more than 50% (D) and the patient, after the recovery of a normal swallowing without complications, showed progressive dysphagia after 4 months. A recurrent hypopharyngeal stricture was diagnosed, and after two endoscopic dilatations a gastrostomy tube was placed endoscopically (PEG).

other head and neck sites: in fact, the humeral end of the raised muscle always tends to remain in the neck (Figs. 1-5). Many free flap surgeons use both the variants of the pectoralis flap in combination with free tissue transfer, based upon these considerations and with similar indications, also for coverage and protection of microanastomosis [83 115].

Complications and morbidity

PMMC and PMMF are both related to some complications that have partially changed both in type and frequency, thanks to evolution of the technique. The very first report of complications in 42 cases of reconstruction with PMMC [57] did not show any major necrosis, while minor necrosis was present in three cases (7%). appeared later report documented a wider range of complications including those involving the donor site, such as chest wall haematoma and infections, the reconstructed areas, including fistula and neck abscess, or the flap itself with partial and total necrosis [108].

Later, in 1983, two interesting and larger reports provided deeper insight into the actual complication rates. Mehrhof et al. [109], describing their experience on 67 patients treated with 73 PMMC, reported a complication rate of 54%. Major complications were total flap necrosis (4%) and partial flap necrosis (12%). The vast majority were minor complications that did not require second procedures for correction: orocutaneous fistulas (16.5%), suture line dehiscence (12%), neck wound complications (11%), donor site complication (1.3%) and sequelae related to mandibular replacement (not a complication of the flap itself but related to a metal device used by the authors to restore mandibular continuity in 10 patients included in this series) (11%). In the same year, Ossoff et al. [110], while reporting an overall complication rate similar to those previously reported, warned other authors about the insidious possibility of a delayed detection of recurrence hidden by the flap itself, which occurred three times in their experience (86 patients, 95 PMMC). In 1984, Donegan et al. reported another rare complication, namely osteomyelitis of the rib in the donor area of the PMMF [111]. Even if unusual, this complication gave rise to a number of publications discussing its treatment, with the use of a vertical rectus abdominis myocutaneous flap proposed by Nagarjuna et al. being the latest [112]. Other reported complications include exposure of the plate covered by the flap in reconstructions of the mandible [91] and cervical contracture leading to severe functional impairment [113]. Cervical contracture has been specifically addressed by some authors by secondary myectomy and subclavicular route [17 114], but a certain amount of contracture is unavoidable, deriving from the

fibrotic retraction of the denervated muscle, even in the "island" technique.

In 1990, an interesting report on 168 cases of PMMC and PMMF performed at MD Anderson Cancer Center in Texas by Kroll et al. was published [115] in which the rate of overall complications was 63%, but with a flap loss rate of only 2.4%, with a relatively higher complication rate in smokers and patients with larger tumours. Later, in the same year, Shah reported his experience [116] which consisted of 211 patients treated with PMMC. Similar to that seen at MD Anderson, he reported an overall complication rate of 63%. On the other hand, despite the apparently high complication rate, he reported only 2 cases in which a second flap was required (1%), and 33 cases in which reoperation was required to resolve complications. Such a low rate of major complications was substantially confirmed in the 1990s by other authors [117]. A correlation between complications and some variables was also shown, namely: age over 70 years, female sex, overweight, albumin less than 4 g/dl, oral cavity reconstruction after total glossectomy and systemic disease. Some of these correlations had been previously reported by Kroll et al. and later by other authors with the adjunct of prior chemotherapy and secondary reconstructions [117-119]. The higher rate of flap necrosis seen in women by those authors was attributed to the interposition of breast tissue between muscle and the skin paddle. In fact, the authors noted that only PMMC were involved by this phenomena, while in their series PMMF had the same complication rates between men and women [115]. Both Shah and later Keidan et al. outlined the absence of a significant correlation between prior radiation therapy and complication rates [120].

Starting from 2000, reports in literature from both wealthy and poor-developing countries, substantially confirm a slight drop in complications, with very few to no total flap losses recorded and an overall complication rate around 20–50% as seen in many papers published during this period [7 91 113 119 121 122]. At present such complications rates are probably even lower, at least in developed countries. A rare complication of PMMC with very few reports in literature published in the last 15 years is metastasis at the flap donor site, for which some possible mechanisms have been proposed based on anatomical and physiological considerations [123].

Comparison with free flaps

Since the development of reconstructive techniques involving free flaps [124], we participated in a lively debate on the advantages and disadvantages of both pedicled and free flap techniques applied to head and neck sites. In an attempt to summarise the data from the literature, it should be kept in mind that pectoralis major is often confronted to different types of free flaps and in different types of reconstructions, thus making it impossible to make any general statements. Each type of reconstruction would ideally require a separate discussion to come to definitive conclusions. During the last 30 years, the three main topics of discussion have been functional results, morbidity and costs of the two techniques. In all these areas, when comparing free flap with pectoralis major patients, several biases can be seen, the most important being in our opinion that in the free flap era many patients were recommended pedicled flaps when they are in poor general conditions, with the preference for an option with short operative time, technical ease and low morbidity. As a result, radically different groups, at least in terms of comorbidities, are often compared. For this reasons, we believe that comorbidity, or at least age, should be considered and matched in every attempt at comparison.

Functional results

Each subsite would ideally deserve a separate discussion, even if not all the papers in the literature analytically evaluate the functional differences according site and size of the defect. Paradoxically, despite the amount of publications evaluating reconstructive techniques in the head and neck, there is still a lack of evidence-based data about the functional differences between free and pedicled flaps, and no definitive conclusions can be made at present. Actually, the concept of function in head and neck cancer patients is controversial and consensus about the objective evaluation of functional results is lacking. The most used tools are questionnaires, which are not specific and sensitive in evaluating the functional aspects addressed by the different reconstructive techniques. Nonetheless, a few investigations give some clues with which to initiate definite functional comparison site by site.

An impressive series was presented by Hsing et al. in 2011 [125]. They reported their experience with 491 patients treated for oral cavity cancer, 100 of which completed a quality of life questionnaire. They found no significant difference in overall quality of life between patients treated with PMMC versus free flaps, nor did they find differences in the domains regarding pain, appearance, activity, recreation, swallowing, chewing, taste, saliva, or anxiety. Nevertheless, they reported significant differences between the free flap and PMMC flap groups in speech, shoulder mobility and mood domains with better outcomes for the free flap group.

Xiao et al., also focusing specifically on oral cavity cancer and analysing two groups, one characterised by reconstruction performed with an anterolateral tight (ALT) flap and the other by PMMC, found no significant differences between groups for pain, activity, recreation, swallowing, chewing, speech, taste, saliva, or mood and anxiety domains. However, significant differences were seen between the PMMC and ALT groups for the shoulder and

appearance domains, and a higher emotional impact left by the scar and the aesthetic appearance left by PMMC [126]. A similar study with similar results was presented in 2014 by Zhang et al., with the only difference being slightly worse speech outcome for patients treated by ALT [127].
O'Neill et al., in 2010, published an interesting comparison between radial forearm free flaps and PMMC in reconstruction of oral and oropharyngeal defects [128]. In their report, they outlined that while no differences in deformity, diet, or socialisation were found, only 22.2% of patients reconstructed with PMMC were satisfied with their speech compared with 53.1% of patients reconstructed with RFFF. Deganello et al. noted a difference in diet with all PMMC in their series able to feed only by soft or liquid diet postoperatively [99 129].
As free flaps show a predisposition to better performance in functional outcomes [86], many authors have tried to close the gap by developing variants of the PMMC/PMMF meant to improve functional results, such as the dynamic variant [19] and attempts of neurotisation of the flap with the hypoglossal nerve [40]. These complex techniques, however, are associated with loss of the renowned advantages of pectoralis flaps in terms of ease and speed.

Morbidity

Pectoralis major has a rate of complications that is not to be underestimated, and the rate of overall complications raised some concerns in the past. An interesting comparison of complications rate between the free tissue transfer option and the PMMC were made by Mallet et al. in 2009 [130] who analysed the results of 70 consecutive patients treated alternatively with both techniques (25 FTT and 45 PMMC). They outlined a similar rate of postoperative complications and the same duration of use of tracheostomy tube and feeding tube. Similar results, prone to a substantially similar morbidity of free flaps and PMMF/PMMC, have been reported by other groups [125 131], some of which also highlighted a similar failure rate [78]. O'Neill, reporting on a series of 114 patients treated alternatively with PMMC or radial forearm free flap (RFFF) reported that the only significant differences in complications were suture dehiscence, which were more frequent in PMMC, and atelectasis, which was more frequent in RFFF; major flap complications, leading to another surgery, were more frequent in the RFFF group [128].
In a similar study, de Bree et al. reported a higher rate of medical complications, flap failures and admissions to intensive care units in the radial forearm group, but more overall surgical complications (partial flap necrosis, dehiscence, wound abscesses and fistula) with PMMC [132], as seen in other studies [73 133], thus leading to a longer postoperative hospitalisation for treatment of complications.

Costs

In the last years, in light of spending reviews and rationalisations of resources, especially in Italy, the costs of reconstructive procedures must be taken into account. The main factors contributing to the increase in costs, in our experience, are the time spent in the hospital postoperatively (heavily influenced by the complication rate), time spent in the operating room and number of surgeons required. PMMC is often recognised as a faster technique considering operating time [125 126 129-132 134-136], and most reports outline that free flap surgery requires more surgeons at the same time [129 130 137]. In many departments, FFT in the head and neck are performed by two teams at the same time, thus reducing the operative time, but not the overall costs. Data regarding discharge time after surgery seems to be uniform in the literature with most authors outlining a similar if not shorter time needed after a procedure involving free flaps [128-132]. Nevertheless, when it comes to costs estimated in single experiences, data are rather conflicting. Some authors reported higher costs with free flaps [91 129 134 136 138], while others have documented that overall costs for PMMC are either higher [115 132] or not significantly different [131 139]. In particular, Funk et al. hypothesised that although surgical costs were higher for free flaps, postoperative hospitalisation due to treatment of complications, which is higher in PMMC, balanced the costs and abolished any economic advantages [139].
While a generally acceptable, definitive statement about respective costs is probably not possible at present, according to the literature we can at least definitely accept that, even with highly significant differences between various reports, the time spent in the operating room for reconstruction with a pedicled flap is undeniably shorter. Importantly, as outlined by de Bree et al. [132], most studies on costs have selection biases, and do not consider differences in age and comorbidity, thus probably complicating any possible evaluation on discharge time and complication rates.
Notably, in settings where resource constraints are a matter of fact, along with the lack of available technologies and expertise, such as in developing countries, extensive use of pectoralis major at the expense of free flaps remains a reality [91 97 138].

Our experience

Our 20-year clinical experience in pectoralis major reconstructions at the main big facilities in Italy performing a high volume of free flap procedures is shown in Table I. Virtually every defect in the head and neck region has been addressed, with a very low rate of complications (less than 5% of patients experienced any kind of procedure-related sequelae). Such complication rate is lower than what reported in most paper in the literature, nevertheless in our opinion it reflects the state of the art as for pectoralis major reconstruction and appears the main general argument supporting the use of pectoralis major regional flaps in most cases. The 274 cases (Table I) have

Table I. Descriptive statistics of the main variables concerning patients, primary sites and defects.

Characteristic	N = 274
Age at diagnosis	
Median	70
Range	29-92
Sex [N (%)]	
Male	199 (72.6%)
Female	75 (27.4%)
Variant (PMMC vs. PMMF) [N (%)]	
PMMC	237 (86.5%)
PMMF	37 (13.5%)
Primary site [N (%)]	
Larynx and Hypopharynx	21 (7.7%)
Mandible	19 (7%)
Oropharynx	85 (31%)
Skin	5 (1.8%)
Occult primary	1 (0.3%)
Oral cavity	143 (52.2%)
Retromolar	56 (20.4%)
Tongue	87 (31.8%)
Hystotype	**N (%)**
SCC	255 (93%)
Salivary histotypes	17 (6.2%)
Malignant ameloblastoma	1 (0.4%)
Osteosarcoma	1 (0.4%)
Type of defect	
Mucosa	141 (51.5%)
Mucosa+bone	112 (40.9%)
Mucosa+skin	11 (4%)
Skin	10 (3.6%)
Previous treatments for HNSCC	
None	209 (76.3%)
Radio±chemotherapy	48 (17.5%)
Surgery	3 (1.1%)
Surgery+ radio±chemotherapy	14 (5.1%)
Adjuvant /perioperative treatments	
None	154 (56.2%)
Radiotherapy	102 (37.2%)
Brachytherapy	4 (1.5%)
Radio±chemotherapy	14 (5.1%)
Timing	
Immediate	265 (96.7%)
Delayed (management of radiotherapy sequelae)	9 (3.3%)
Early and late complications of the procedure	
Partial skin necrosis	8 (2.9%)
Total necrosis	2 (0.7%)
Donor site dehiscence	2 (0.7%)
Late hypopharyngeal stricture/ gastrostomy	1 (0.4%)
Death	1 (0.4%)
None	261 (95.3%)

been operated along 20 years, in this long period several changes in the use and indications for pectoralis major reconstructions have been occurred, mostly reflecting the above cited literature evidences. In fact the number of pectoralis major flaps raised per year has on the whole decreased, and in particular it is now only seldom used for tongue and skin defect. The median age of the patient has increased together with their comorbidities. Interestingly, in recent years pectoralis major inset has been also useful for allow safe further irradiation by brachytherapy in a few cases, by protecting neck vessels and bringing non-previously irradiated tissue (Fig. 2).

Conclusions

We are definitely in the era of free flap surgery. In developed countries, in excellence centres, and in patients with good general conditions, the amazing versatility of the free flap armamentarium gives the opportunity to suit the defect deriving from virtually every ablative head and neck surgery with a tailored reconstruction. Such possibilities, even in the absence of definitive evidence-based data on better functional outcomes compared with pectoralis major flaps, make free tissue transfer the standard for head and neck reconstruction. Countless disadvantages of the "old" pectoralis major have been listed, such as flap thickness, functional and cosmetic defects, excessive bulk in obese or muscular patients, poor reliability of the skin in PMMC, difficulty in obtaining reliable bone tissue and long-term fibrotic muscle retraction.

Nevertheless, even in facilities with a high volume of reconstructions by free flaps, a certain number of pectoralis major flaps is still raised every year in the head and neck. The easier indication is reconstruction after a free flap failure due to the high failure rate of second free tissue transfers [76 77]. Other indications, which are much more common, are probably controversial, and therefore more interesting to discuss. They can be driven by the setting in which patients are cured, by clinical status and comorbidities of patients and perhaps, in very selected cases, by the type of the defect.

The healthcare system and the facilities in which patients are cured are also key considerations in determining epidemiology and death rates for cancer worldwide. Raising a pectoralis major just requires a knife, forceps and retractors as surgical instrumentation, few hours of operative time, shorter training time and less surgical skills. Mainly for these reasons in developing countries such as India the pectoralis major remains the workhorse for head and neck reconstruction [97]. Nevertheless, in forthcoming years, the public discussion about health system resources and spending reviews may bring these arguments to many Western countries in recession. As previously outlined, another reason why pectoralis major can still be indicated is related to patient conditions, which may require ease of

harvest and shorter operative times (and therefore, especially in the elderly, a lower perioperative complication rate).

Finally, there are some situations in which pectoralis major still appears as a valuable option even in facilities performing free flaps and for patients in good general conditions [78]. One such situation is prevention of pharyngocutaneous fistula in case of salvage total laryngectomies after irradiation. In these cases, several authors have proposed to electively reinforce the suture line and pharyngeal wall with a PMMF [95 104 105]. In the same way, PMMF/PMMC can be used to protect the carotid axis after salvage radical neck dissection following radiotherapy failure [8 78 106], and in these cases a further adjuvant perioperative brachytherapy can be safely administered (Fig. 2). Lastly, recent reports stress [7 80 99 100 140] the utility of pectoralis major flaps for reconstruction of pharyngeal defects. In case of circumferential defects, long-term stricture due to muscle fibrotic retraction is probably frequent (Fig. 5), but in lateral defects (less than 50% of pharyngeal circumference) the reduced thickness and coverage with normal, not hairy, mucosa are relevant advantages supporting the use of PMMF (Fig. 4). In case of a segmental lateral mandibular defect, if restoration of dentition is not planned, a PMMC or PMMF rolled around a reconstruction plate may be a valid option characterised by low morbidity [93 97 101 102].

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HEAD AND NECK

Technical refinements in mandibular reconstruction with free fibula flaps: outcome-oriented retrospective review of 99 cases

Accorgimenti tecnici nelle ricostruzioni mandibolari con lembi liberi di fibula: analisi retrospettiva dei risultati su 99 casi

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SUMMARY

Congenital disease, major trauma, tumour resection and biphosphonate-related osteonecrosis can lead to partial, subtotal, or total loss of the mandibular bone. Minor defects can be easily reconstructed using bone grafts, whereas microvascular free tissue transfer may be unavoidable in the case of major bone loss or poor quality of soft tissue. Simple bone or composite osteocutaneous fibula free flaps have proven invaluable and remain the workhorse for microvascular mandibular reconstruction in daily practice. Our experience with 99 consecutive fibular free flaps confirms the available data in terms of high success rate. In these cases, 90% had total success, while 7 had complete flap failures. Three of our patients showed skin paddle necrosis with bony conservation. This report focuses on the technical refinements used by the authors that can prove valuable in obtaining predictable and precise results: in particular, we discuss surgical techniques that avoid vascular pedicle ossification by removing the fibular periosteum from the vascular pedicle itself and reduce donor site morbidity and aid in management of the position in the new condylar fossa. Finally, new technologies such as intraoperative CT and custom premodelled fixation plates may also increase the predictability of morpho-functional results.

KEY WORDS: Mandibular reconstructions • Fibula free flap

RIASSUNTO

Patologie congenite, traumi, osteonecrosi da bifosfonati, osteoradionecrosi o resezioni mandibolari conseguenti a patologie neoplastiche spesso comportano deficit ossei mandibolari parziali, subtotali o totali. In presenza di piccoli difetti, si ricorre generalmente all'impiego di innesti ossei; diverso il caso di grandi deficit che richiedono ricostruzioni complesse che si servono di lembi liberi microvascolari. In questo articolo gli autori presentano la loro esperienza con 99 lembi liberi microvascolari di fibula impiegati nelle ricostruzioni mandibolari, confermando l'elevato tasso di successo già riportato in letteratura: questo lavoro infatti riporta un successo totale nel 90% dei casi, con 7 perdite complete del lembo e 3 perdite parziali, vale a dire limitate alla padella cutanea del lembo. Gli autori hanno posto l'attenzione su accorgimenti tecnici che contribuiscono a garantire eccellenti risultati, in particolar modo per quel che concerne l'ossificazione del peduncolo vascolare del lembo ricostruttivo, la morbidità a carico del sito di prelievo e il posizionamento della nuova testa condilare nella fossa articolare. Infine vengono prese in considerazione le nuove tecnologie proposte recentemente in letteratura, quali l'impiego della TC intraoperatoria e di mezzi di sintesi customizzati premodellati, che garantiscono una maggiore predicibilità dei risultati.

PAROLE CHIAVE: *Ricostruzioni mandibolari • Lembo libero microvascolare di fibula*

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Introduction

Mandibular integrity can be affected by a variety of causes, including infection, benign and malignant neoplasms, osteoradionecrosis and trauma. Restoration of mandibular integrity after such insults is pivotal in restoring form and function. Furthermore, adequate bone height must be provided if dental fixture positioning is requested by the patient [1].

In case of minor resections with total or nearly-total conservation of the mandibular margin, a bone graft usually provides more than adequate bone height for reconstruction and subsequent implant positioning [2].

Larger defects and/or defective recipient soft tissues, as in the case of osteonecrosis or radiation therapy, pose a completely different surgical challenge. Such defects may only be addressed through free tissue transfer of osseous flaps with or without skin paddles [1 3 4].

Different flaps have already been proposed including the iliac crest microvascular free flap [5], radial forearm flap with partial radius inclusion [6] and scapula osteocutaneous flap [7]. Nevertheless, the fibula flap, introduced by Taylor and colleagues [8] and rendered popular in oral reconstructions by Hidalgo [9], has become the gold standard in mandibular reconstruction due to its favourable characteristics (co-harvesting with multiple skin paddles [10], harvesting as a neurosensory flap [11], optimal form restoration and acceptable functional results [1]), high rate of success and low rate of complications in both recipient and donor sites.

While ancillary techniques such as virtual surgical planning using computer-assisted modelling [12 13] and distraction osteogenesis [14] are undoubtedly changing the rules of fibula flap mandibular reconstructions, there are nevertheless some basic, somewhat minor, aspects of fibula free flap harvesting and defect reconstructions that must not be forgotten in order to ensure the highest rates of success.

The authors retrospectively review all their fibula flap mandibular reconstructions performed between 2002 and 2010, providing information on patients, procedures and results, with the aim of describing the technical refinements used during planning and execution which have proven valuable in obtaining precise and predictable results.

Materials and methods

We performed a retrospective review to identify all patients who underwent free flap mandibular reconstructions between 2002 and 2010. A total of 109 free flap mandibular reconstructions were performed. Ten patients who underwent mandibular reconstruction using free flaps other than fibula were excluded from this study. The remaining 99 patients underwent free fibula flap reconstruction and were included in the study. Mean age was 56.98 ± 14.78 years (minimum age 14 years, maximum age 76 years). Patient demographics, specific information on presentation at diagnosis, type of resection and type of reconstruction are detailed in Table I. Mean follow-up time was 8.62 ± 2.42 years (minimum 4.48 years, maximum 12.76 years).

All procedures were carried out under general anaesthesia following the widely used technique originally proposed by Hidalgo [9]. Antithrombotic agents were routinely used during the postoperative period. All patients underwent preoperative CT angiography to investigate the presence of peripheral vascular disease and tibio-peroneal arterial anatomic variants, such as peroneal arteria magna [15] and peroneal artery absence [16].

Results

The incidence of complete flap loss was 7% (7 flaps); partial flap losses (fibular skin paddle necrosis) were encountered in 3 cases (3%). Overall, the total success rate was 90% with fibular free flaps for mandibular reconstruction; the partial success rate was 93%.

Other common complications included the ossification of the vascular pedicle of the fibula around the periostium (4%) and partial or total necrosis affecting the skin graft used to reconstruct the donor site (18%). One patient presented extensive muscle and skin necrosis of the leg surrounding the site of harvest and required major microvascular reconstruction of these soft tissues; this procedure was performed elsewhere. Two of our most representative

Table I. Demographic and clinical data on sex, reason for mandibular resection, extent of mandibular resection and type of free fibula flap employed in reconstruction.

	Number of patients	% of patients
Sex		
male	71	72%
female	28	28%
Reason for mandibular resection		
resection of malignant tumour	85	86%
resection of benign tumour	9	9%
trauma	3	3%
osteonecrosis	2	2%
Extent of mandibular resection		
partial mandibulectomy	13	13%
hemimandibulectomy	34	34%
total mandibulectomy	52	53%
Type of flap used		
osteofascial flap	81	82%
osteofasciocutaneous flap	18	18%

microvascular reconstructions are presented in Figures 1 and 2 and 3-5, respectively.

Discussion

Most authors report a success rate with the fibula free flap of 90-100% with almost no donor site morbidity [17 18]. Such optimal characteristics make the fibula flap an excellent choice for mandibular reconstructions, independent of the cause of bone loss [1 19 20].

Data in the present case series are strongly coherent with literature reports. Flap failure (both complete or limited to the skin paddle) is well below 10% and reports of morbidity in the donor site are around 1% for major complications and 20% for minor complications such as necrosis of local skin graft. It is of utmost importance, no matter how trivial it may seem, that a high rate of success can be achieved only through an extremely careful procedure, as suggested in the literature [21-23].

It is obviously beyond the scope of this paper to provide a step-by-step description of the procedures required to maximise the success rate. However, we would like to briefly point out some minor aspects that are often overlooked, which appear pivotal in our experience. Such features involve both pre-surgical planning, the surgical procedure itself, and during and after flap harvesting and preparation.

Concerning pre-surgical planning, vascular imaging plays a major role in the donor site. If we observed no nervous or vascular complications in the donor site, this is mostly due to the use of routine lower limb vascular CT scan. In fact, vascular CT scans can highlight blood flow anomalies in the popliteal trifurcation, motivating the switch to different flaps, such as the free iliac crest. Vascular CT scans, as well as Doppler echography and, most notably, vascular MRI are nowadays considered an invaluable tool during surgical planning that are able to identify pre-existing conditions and potentially dangerous anatomical anomalies [25 26].

Focusing on flap harvesting, first of all we believe that a delicate and respectful attitude is mandatory in managing peroneal vessels, and that the same treatment should be given to the recipient vessel. As Khoukri stated [23], it is probably during this phase that reducing the pace and increasing the delicateness and attention is most critical and typical of the experienced microvascular surgeon. A careful harvesting phase not only increases the chance of successful reconstruction, but also dramatically reduces donor site morbidity, such as muscle and skin necrosis, thrombosis, chronic pain and abnormal gait [24 27].

After carefully harvested the flap, modelling should also be performed with the utmost attention in order to grant the best results. Most notably, the chance of ossification of the periosteum of the fibula must be taken into account if this is elevated with the vascular pedicle as pointed out by Autelitano et al. [22 28]. Therefore, instead of raising the vascular pedicle from the bone subperiosteally, it is wise to carefully separate the pedicle from the periosteum and then discard the excess bone with the attached periosteum secondarily. Since we introduced this technical innovation, we have not experienced an increase in flap failure. Therefore, we consider pedicle separation to be a safe procedure.

Another useful and safe "tip" we adopted is exploiting any periosteal excess in the flap to grant a better blood supply, mostly in the case of planned post-surgical radiotherapy, as suggested by Trignano et al [29]. Obviously, reconstruction of the surgical defect is the most delicate part of the process, and the surgeons' attention should be addressed to several relevant issues. When using a reconstructive plate, pre-plating is associated with good results, both in the literature and in our experience [30]. Nevertheless, pre-

Fig. 1. Case 1. (A) Preoperative 3D-CT scan with window for bone and soft tissues. A bulky tumour involves the whole right mandible and half of the left mandible. (B) 3D-CT scan showing the simulated position of the fibula free flap for reconstruction of the right mandibular body and ramus. (C) Post-operative 3D-CT scan showing mandibular reconstruction with fibula free flap.

Fig. 2. Case 1. (A) Intra-operative view of the mandibulectomy specimen including the right condylar process (arrow). Intra-operative image showing the fibula free flap placed to reconstruct the mandible (small blue arrows) and stabilised with a reconstructive plate and screws (yellow arrow). Note the microvascular anastomosis (blue and red arrows).

plating is not feasible whenever the tumour has involved the surrounding soft tissues and or has deformed the original shape of the mandible. In these cases, a custom premodelled plate, CT custom osteotomy guides, or surgery simulators can offer the best reconstructive chances [31 32]. However, the high cost of these instruments is an issue that still must be addressed, and we have been unable to implement them at our institution.

If the resection involves the condylar process, it is imperative to correctly place the newly created condyle in the articular fossa. If this is not achieved, then a postoperative loss of occlusion is very likely to occur. We usually adhere to the following "condyle position check" protocol: after resection, if the glenoid fossa is near and visible, a blind tentative positioning can be performed. Having positioned the neocondyle, the plates used for rigid fixation are secured and mandibular movements are checked. This procedure, however, can be tricky and even in the most experienced hands it is prone to failure. Intraoperative CT can be useful to verify the condyle position in difficult cases. If intraoperative CT scan is not available, the glenoid fossa must be accessed surgically to validate the position of the condyle. Even if more sparing accesses to the condylar fossa are available [34 35], we believe that the most appropriate access to the glenoid fossa in major mandibular reconstructions is the preauricular access with or without endaural modification. Once the glenoid fossa is reached a resorbable suture can be passed through the newly created condyle and the bony glenoid fossa by inserting a hole in both bony stumps. The suture can finally be tightened to hold the new condyle in place.

One last important consideration should be given to intermaxillary fixation. We routinely use intermaxillary fixation in order to maximise the precision of the reconstruction. There are, however, many new techniques that may be employed to achieve intermaxillary fixation. While intermaxillary fixation screws are one of the most popular techniques, despite their routine use in mandibular trauma, we do not rely on them in major mandibular reconstructions since conventional arch bars are more precise where teeth contacts are less immediate and where more stability is needed.

After having harvested and modelled the flap, most of the surgeons' attention is devoted to reconstructing the surgical defect, and donor site health if often jeopardised. For example, one patient in our series suffered from extensive necrosis of the skin and muscles around the donor site. This complication can be related to two major causes: primary closure of the donor site with excess tension and local administration of anaesthetics at the donor site that may have masked the signs of compartmental syndrome. Aggressive debridement followed by free flap reconstruction of the donor site skin defect can circumvent this the complication. We therefore strongly advise against administration of long-acting anaesthetics for control of post-operative pain.

Lastly, another interesting method that may be performed at the end of the procedure should be mentioned, namely bone banking. If a major part of the fibula is to be discarded, it is possible to bank the remaining bone at the harvesting site. In one of our patients, who required a second surgical procedure for pre-prosthetic purposes, we harvested the banked bone which had survived with minimal resorption. This issue needs further investigation, but it might prove useful, or prudent at least, to perform in any patient where a major bone discard is required. It is important to not mistake bone banking with flap prefabrication prosed by Nazerani et al. [33], the use of which we strongly discourage.

In our experience, if all of the above steps are followed, a more predictable and precise outcome can be expected in mandibular reconstructions with free fibular flaps.

Fig. 3. Case 2. (A) Frontal pre-operative picture showing severe facial asymmetry characterised by bulging in the right ramus and condylar region. (B) Frontal view of the patient 2 years after surgery showing the excellent symmetry of the face.

Fig. 4. Case 2. (A) Pre-operative CT scan showing the neoplasm, which extends through the whole right mandibular ramus and the posterior part of the body. (B) Post-operative 3D-CT scan showing microvascular mandibular reconstruction using a fibula free flap.

Conclusion

While many reconstructive surgeons consider the fibula as the workhorse for mandibular reconstructions, we believe that many small details are often underlooked. However, greater attention to a few crucial aspects can help the surgeon to obtain a predictable result [36]. Many new techniques, such as intraoperative CT scan and custom premodelled reconstructive plates, are powerful tools that can be of considerable value during the reconstructive phase.

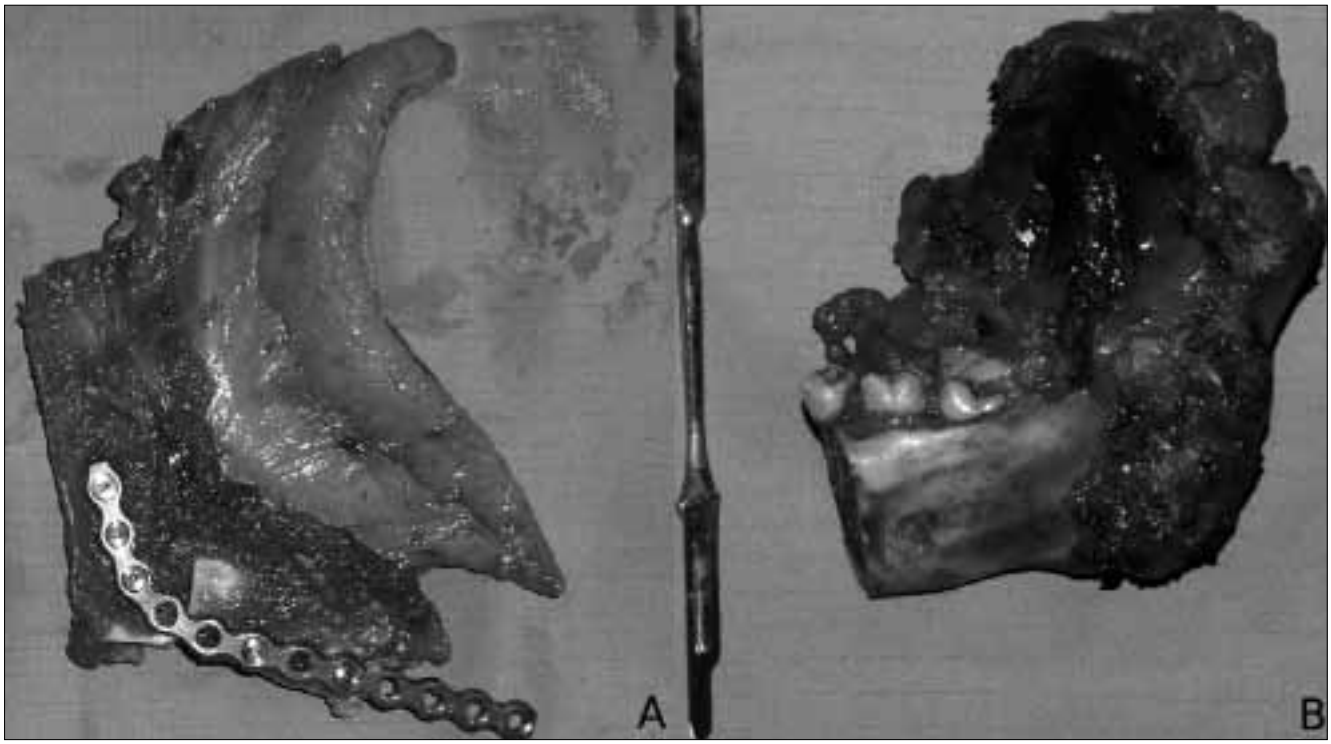

Fig. 5. Case 2. (A) Intra-operative view of the right hemimandibulectomy specimen and (B) fibula flap before its position in the surgical site.

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VESTIBOLOGY

Association of cinnarizine and betahistine in prophylactic therapy for Ménière's disease with and without migraine

L'associazione di betaistina e cinnarizina nella profilassi degli episodi vertiginosi nella Sindrome di Ménière con e senza comorbidità emicranica

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SUMMARY

Prophylactic therapy of Ménière's disease (MD) includes betahistine and calcium-blockers (the latter also useful for migraine prevention). The aim of our work was to assess the efficacy of combined therapy with cinnarizine and betahistine in MD subjects both with and without migraine and poorly responsive to betahistine alone. Fifty-two MD subjects were included who were poorly responsive to betahistine during 6 months of follow-up; 29 were migraineurs. Combined therapy was administered with betahistine 48 mg/day and cinnarizine 20 mg BID for 1 month, 20 mg/day for 2 weeks and 20 mg every 2 days for 2 more weeks, and then repeated. Results were collected over 6 months of follow-up. MD subjects with and without migraine demonstrated a decrease in both vertigo spells and migrainous attacks during combined therapy (from 9.4 to 3.8 and from 6.8 to 5.9 in 6 months, respectively, for vertigo spells, while migraine decreased from 3.8 to 1 in 6 months, respectively). A correlation was seen between decrease of vertigo spells and headaches in the sample of MD subjects with migraine. Our data support a proactive role for cinnarizine in preventing vertigo spells, especially in MD patients with migraine.

KEY WORDS: Ménière's Disease • Migraine • Therapy • Betahistine • Calcium-Blockers • Cinnarizine

RIASSUNTO

La betaistina e i calcio-antagonisti si sono dimostrati efficaci nella profilassi della Sindrome di Ménière; i calcio-antagonisti sono utilizzati anche nella prevenzione degli episodi di cefalea emicranica. Scopo del nostro lavoro è stato quello di stabilire l'efficacia della terapia combinata con cinnarizina e betaistina nella prevenzione delle crisi vertiginose in un gruppo di pazienti affetti da Sindrome di Ménière senza e con comorbidità per emicrania. Cinquantadue pazienti affetti da Sindrome di Ménière, poco responsivi alla sola terapia con betaistina in un periodo di 6 mesi, sono stati inclusi nello studio, 29 dei quali emicranici. Nei 6 mesi successivi è stata effettuata terapia combinata con betaistina (48 mg al giorno) e cinnarizina 20 mg due volte al giorno per 1 mese, 20 mg al giorno per 2 settimane e 20 mg a giorni alterni per 2 ulteriori settimane; lo schema terapeutico è stato indi ripetuto. I dati relativi alla frequenza delle crisi vertiginose sono stati collezionati nei 6 mesi successivi. In entrambi i gruppi è stato dimostrato un decremento delle crisi vertiginose (da 9.4 a 3.8 in 6 mesi e da 6.8 a 5.9 in 6 mesi rispettivamente nel gruppo con e senza comorbidità per emicrania; le crisi di cefalea si sono inoltre ridotte da 3.8 a 1 in 6 mesi). È stata evidenziata una correlazione tra la diminuzione degli attacchi di vertigine ed emicrania. I nostri dati sottolineano un ruolo terapeutico della cinnarizina nella prevenzione degli attacchi di vertigine soprattutto nei soggetti con comorbidità emicranica.

PAROLE CHIAVE: *Sindrome di Ménière • Emicrania • Terapia • Calcio-antagonisti • Cinnarizina • Betaistina*

Acta Otorhinolaryngol Ital 2014;34:349-353

Introduction

Ménière's disease is an inner ear disorder characterised by recurrent episodes of vertigo, hearing loss, fullness and tinnitus. Increased endolymphatic pressure is commonly accepted as the pathogenetic mechanism [1], although according to some authors hydrops may be the consequence of a primitive damage of the inner ear [2].

Criteria for the diagnosis of definite MD, established in 1995 by the AAO-HNS, are mainly based on phenotype of episodic vertigo, consisting in the presence of at least two episodes of vertigo of at least 20 min, audiometrically confirmed sensorineural hearing loss on at least one occasion, tinnitus or aural fullness during episodes and exclusion of other possible causes of vertigo [3]. Demonstrated

hearing loss in the vertigo-free period is not required for the diagnosis of definite MD.

Migraine is a neurological disorder characterised by episodic headaches of pulsatile quality, often associated with phono- and photophobia, with a prevalence of 15-17% in women and 5-8% in men [4].

Epidemiological studies have shown an association between MD and migraine, variously reported between 43% and 56% [5 6] and described by Prosper Ménière himself [7]. The high frequency of migraine in MD population may underline a pathophysiological link between the two disorders [8]. Recent papers have focused on increasing evidence that migraine per se may provoke episodic vertigo, and clinical entity is defined as vestibular migraine (VM) [9].

Among other symptoms, diagnosis of MD relies more on audiometric findings, even though fluctuation of hearing level has also been reported in patients with VM [10]. In some cases, at the initial stages of episodic vertigo, differential diagnosis between MD and VM may be a puzzling dilemma [11].

Betahistine has been demonstrated to be useful in prevention of episodic vertigo in MD [12 13], while calcium-blockers are among the most widely used drugs in prophylactic therapy of migraine [14]. Cinnarizine has also been studied as monotherapy for MD, but demonstrated a lower efficacy compared to betahistine in preventing vertigo spells in a sample of 36 MD subjects [15]. A recent report focused on the possibility that nimodipine may increase efficacy of betahistine in prevention of vertigo spells in MD patients [16].

The aim of our investigation was to confirm the efficacy of combined prophylactic therapy with calcium-blocker and betahistine in MD subjects with and without comorbidity for migraine, and to establish a possible correlation between reduction of both headache and vertigo spells in MD subjects with migraine.

Materials and methods

In our study we included 29 patients affected by definite Ménière's Disease according to AAO-NHS criteria also presenting a diagnosis of migraine according to IHS criteria and 23 patients with MD but without migraine. They were recruited among outpatients who attended the Centre for vestibular disorders at San Raffaele hospital in Milan and Policlinico San Matteo in Pavia between January 2010 and July 2011.

They were consecutively recruited if they completed 6 months' follow-up among patients poorly responsive to monotherapy with betahistine 48 mg/day during the first 6 months. During the next 6 months, they underwent combined therapy with betahistine 24 mg BID and cinnarizine 20 mg BID for 1 month, then 20 mg/day for 2 weeks and 20 mg every 2 days for 2 further weeks; successively, they restarted cinnarizine 40 mg/day.

Exclusion criteria were current exposition to noise, a middle ear disorder or previous intratympanic therapies with gentamycin or steroids. During the 12 months of the study, no further therapies for MD or migraine (e.g. diuretics, steroids, antiepileptics) or drugs active on the central nervous system (benzodiazepines and selective serotonin reuptake inhibitors) were given. However, dietary measures were suggested in all patients, especially increased fluids and reduced salt intake.

Clinical history included the presence of a familial history of vertigo and an autoantibody screening (anti-nucleum, smooth muscle, thyroids, cardiolipin, lupus-like anticoagulant and β2-glycoprotein). In our sample, 4 patients referred a familial history of vertigo. In the group of patients with migraine, 11 of 29 (38%) presented positivity for at least one of the autoantibodies (in 7 anti-thyroids), including 5 of 23 among those without migraine (22.7%).

Mean age at inclusion of the sample of migraineurs was 48.8 ± 9.6 years and 22 were females, while non-migraineurs presented with a mean age of 49.2 ± 7.6. No statistical difference was detected between the two groups.

The first attack of vertigo was noted at 36.9 ± 7.8 years of age in the sample of migraineurs and 40.9 ± 10.4 among non-migraineurs, with the first headache at the age of 28.9 ± 5.5 years. Headache preceded the occurrence of vertigo in all subjects except one, in which they occurred in the same year. Ten patients referred that a vertiginous attack was followed by headache in at least two cases.

Audiometric values were saved at the beginning of combined therapy and the 12 month control, and the mean value of pure tone audiometry (PTA) at 500, 1000, 2000 and 3000 Hz at the beginning and at the end of combined therapy was calculated.

Main outcome was considered the number of spells during the 6 months before combined therapy and the following 6 months. According to AAO-HNS guidelines, efficacy was evaluated with the formula (x/y) x 100, where x is the average number of vertigo spells per month in the 6 months of combined therapy, and y the average number of spells per month in the 6 months of previous monotherapy. The same formula was used to assess efficacy of therapy in controlling headaches. The lower the number, the more beneficial the therapy.

Statistical analyses

The significance of any difference in continuously distributed variables between the two groups was examined by t-test for independent samples. Significance of non-normal distributed values was assessed with a Mann-Whitney test. The chi-square test was used to assess differences for nominal values. Correlations were assessed with a Spearman test.

Results

Results and statistics of MD patients with migraine are

Table I. Number of vertigo spells, headaches and PTA average (db HL) in 6 months of monotherapy and 6 months of combined therapy in the sample of MD patients with migraine (n = 29).

	Betahistine	Betahistine + cinnarizine	P value
Vertigo spells	9.4 ± 4.3	3.8 ± 3.4	p = 0.0001
Headaches	3 ± 1.9	1 ± 0.6	p = 0.0001
PTA mean value	45.7 ± 8	53.4 ± 7.8	p = 0.001

Table II. Number of vertigo spells, headaches and PTA average (db HL) in 6 months of monotherapy and 6 months of combined therapy in the sample of MD patients without migraine (n = 23).

	Betahistine	Betahistine + cinnarizine	P value
Vertigo spells	6.8 ± 3.5	5.9 ± 3.9	p = 0.01
PTA mean value	50.5 ± 7.5	55.8 ± 9.2	p = 0.002

summarised in Table I, while Table II shows the results in the sample of subjects with MD without migraine.

Among migraineurs, the value of the formula (x/y) x 100 for vertigo spells was lower than 50% in 13 cases, in the range between 50-75% in 3 more cases, while in 13 cases therapy demonstrated no efficacy. In this sample, seven of 11 subjects with positivity for autoantibodies, and 6 of 18 without positivity, presented a value lower than 50 (p = 0.1).

The value of the formula (x/y) x 100 for headache attacks was below 50% in 17 cases, in the range between 50-75% in 2 cases and over 75% in 10 cases. Nine of eleven subjects with positive autoantibodies and 8 of 18 remaining subjects presented a value lower than 50% (p = 0.05).

Among non-migraineurs, the value of the formula (x/y) x 100 for vertigo spells was lower than 50% in only 1 subject, in the range between 50-75% in 3 cases, while non-responders was 19. A chi square test on the number of responders to the therapy demonstrated significant difference between the 2 groups (p = 0.001). A Mann-Whitney test demonstrated a significant decrease of vertigo spells in migraineurs than in non-migraineurs after combined therapy (p = 0.003). Finally, in the sample of MD subjects with migraine, a correlation was seen between decrease of vertigo spells and headaches (p = 0.03).

Discussion

As previously reported, migraine and MD often present with a comorbidity [17]. Moreover, around 51% of migraineurs suffer from vertigo or dizziness [18 19]. In some cases, differential diagnosis between MD and VM is complicated [11], and relies mostly on audiometric exam [20]. However, a fluctuating low-frequency hearing loss has also been described in vestibular migraine [10].

Calcium-channel blockers have been demonstrated to be useful in migraine prophylaxis [21], and there is evidence of efficacy of antimigrainous drugs (including Ca^{2+}-blockers) in preventing vertigo spells [22]. Above all, cinnarizine has been reported to ameliorate vestibular vertigo [23], and both cochlear and vestibular symptoms have been reported to improve in MD sufferers [23 24]. Cinnarizine has long been believed to act through a direct block of voltage-gated Ca^{2+} currents [25]. A recent work, however, suggests that its main action is an inhibition of K^+ currents, which may be activated in case of endolymphatic hydrops [26]. Flunarizine has also been shown to be effective in peripheral vertigo due to its calcium entry blocking properties provoking an increase in inner ear perfusion [27]. A recent retrospective study reported that MD patients undergoing prophylactic therapy with an association of nimodipine and betahistine presented a decreased number of vertigo spells compared to patients receving betahistine alone [16].

Our study confirms the efficacy of the association of betahistine and a Ca^{2+}blocker in both MD patients with and without migraine, although significantly better results were obtained in migraineurs. Nonetheless, hearing loss progressed without beneficial effects in either group.

Two possibilities should be considered to explain our findings. It has been suggested that the association of the two diseases could depend on a vascular alteration. Vasospasm has long been considered a characteristic of some migraine-associated features (such as visual auras) [28]. Some authors propose that migraine vasospasm causes ischaemic damage of small arteries of the inner ear, and endolymphatic hydrops develops on the previously damaged ear [29]. MD, therefore, would complicate migraine [30]. On the other hand, migraine may have an impact on frequency of MD attacks. MD patients refer increased spells in the catamenial period, similarly to when migraineurs experience headache more frequently [31]. The occasional low-frequency hearing loss in young women suffering from migraine has also been described mainly during the menstrual period [31]. In both pathogenic theories, Ca^{2+}-blockers should be useful in preventing MD spells.

A common underlying susceptibility to the two diseases may be explained by the importance of calcium and other ions in both disorders. Ion channels in the inner ear are

essential for the high potassium-concentration needed for endolymph maintenance. Both elevated and reduced concentrations of Ca^{2+} have been shown to suppress transduction currents [32 33]. It has been reported that mice lacking Ca^{2+} channels suffer from delayed-onset hearing loss [34]. Moreover, experimentally induced endolymphatic hydrops in guinea pigs was accompanied by increased Ca^{2+} level in the vestibular end-organ [35].

This study, although performed on a small sample, underlines the different effects of cinnarizine in MD patients with and without migraine; it also infers a different action of cinnarizine on vestibular and cochlear symptoms in MD. Further studies are needed to define the origin of this disparity.

Conclusions

Our data confirm the efficacy of association of betahistine and cinnarizine in prophylaxis of MD, especially with comorbidity with migraine; further studies should confirm if prevention of migraine in these subjects may play a role in reduction of vertigo spells.

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PEDIATRIC OTORHINOLARYNGOLOGY

Long-term surgical and functional outcomes of the intact canal wall technique for middle ear cholesteatoma in the paediatric population

Risultati funzionali e chirurgici nel lungo periodo nelle timpanoplastiche chiuse nella popolazione pediatrica affetta da colesteatoma dell'orecchio medio

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SUMMARY

In this paper, we report the postoperative outcomes in canal wall up procedures with second stage surgery in 40 children undergoing intervention for cholesteatoma of the middle ear. The residuals, recurrences and the hearing results were analysed. All 40 patients had a follow-up of at least five years. Of the 39 patients who underwent two staged surgery, 18 (46.1%) had a residual lesion that was identified and excised during the second surgery. Over a five year follow-up period, there were five (12.5%) patients with recurrences, all belonging to the group in whom a residual cholesteatoma was identified during the second staged surgery. The rate of residual cholesteatoma tends to decrease as age increases. The type of cholesteatoma, acquired or congenital middle ear, were not statistically related to the incidence of residual cholesteatoma. Hearing analysis showed that hearing recovery was excellent with canal wall up procedures and remained stable over five years.

KEY WORDS: Cholesteatoma • Paediatric • Canal Wall Up (CWU) • Second stage surgery • Ossiculoplasty • Recurrence • Residual • Hearing results • Follow up

RIASSUNTO

In questo lavoro, abbiamo riportato i risultati nel post-operatorio di 40 bambini operati per colesteatoma dell'orecchio medio e sottoposti a timpanoplastica chiusa in 2 tempi. Colesteatoma residuo, ricorrente e risultati audiologici sono stati analizzati. Tutti e 40 i pazienti hanno avuto un follow-up di almeno 5 anni. In 39 pazienti sottoposti ad un secondo tempo, 18 (46,1%) hanno avuto un colesteatoma residuo che è stato identificato e rimosso durante il secondo tempo chirurgico. Nei 5 anni di follow-up, ci sono stati 5 (12,5%) pazienti con colesteatoma ricorrente, tutti e cinque rientranti nel gruppo nel quale un colesteatoma residuo era stato individuato durante il secondo tempo chirurgico. Il tasso di colesteatoma residuo tende a ridursi con il progredire dell'età. Il tipo di colesteatoma, acquisito o congenito, non è statisticamente correlato all'incidenza di colesteatoma ricorrente. I risultati audiologici mostrano che il recupero uditivo è stato ottimo nelle timpanoplastiche chiuse e si è mantenuto stabile nei cinque anni.

PAROLE CHIAVE: *Colesteatoma • Pediatrico • Timpanoplastica chiusa • Secondo tempo chirurgico • Ossiculoplastica • Ricorrente • Residuo • Risultati audiologici • Follow-up*

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Introduction

The debate between intact canal wall or canal wall up (CWU) and canal wall down (CWD) mastoidectomy both in children and adults is on-going since the 1970s. This issue is pertinent because, in children, the effects of deafness can have social, educational and behavioural consequences, thereby necessitating the need for hearing preservation. Though CWU mastoidectomy achieves the important objective of hearing preservation, two of its main drawbacks are recurrence of cholesteatoma due to limited intraoperative exposure and occurrence of postoperative retraction pockets due to a dysfunctional Eustachian tube (ET). This led some surgeons to focus on disease elimination by CWD mastoidectomy at the cost of hearing. However, the drawbacks of CWU, namely recurrence and retraction, were addressed respectively by the addition of a second look surgery and positioning of cartilage in the attic region to prevent retraction. This technique has gained favour among most surgeons for cholesteatoma in the paediatric population. Despite this, the CWU technique is not always a suitable option. It is not advisable to perform CWU in certain situations like extensive disease, disease in a well pneumatised mastoid, low lying dura, anterior placed sigmoid or a cleft palate, where CWD surgery is the surgery of choice [1].

It has been shown in various studies [1-4] that recurrences of cholesteatoma in CWU surgery normally take several years to manifest. Silvola et al. [2], reported that 92% of all their recurrences occurred within 5 years. Similar observations have been made by other authors who advocate a minimum of a 5-year follow up [1-4]. However, there have been very few studies in the past with a long-term follow-up. It is in this context that our series assumes importance as we present the results of 5 year follow-up in homogenous study conditions.

Materials and methods

A retrospective chart review of patients operated for cholesteatoma at the ENT Department of the University of Parma, Italy from 2001 to 2005 was carried out. Of a total of 273 patients treated for COM with cholesteatomas, 54 patients in the age group of two years to 16 years who underwent surgery for acquired or congenital middle ear cholesteatomas were identified. 14 patients with simple retraction pockets and patients with revision surgeries resulting from operations performed elsewhere were excluded from the study. Two additional patients who underwent CWD procedures were excluded, resulting in a total of 40 patients operated by the CWU technique in the study population. Otomicroscopy findings, preoperative pure tone air conduction (AC), bone conduction (BC), speech reception audiometry and tympanometry were noted. HRCT was done in all cases. Otomicroscopy and pure tone audiometry findings in the 1st, 3rd, 6th 12th, 24th months and at the 5th year were recorded. Pre- and postoperative pure tone averages (PTA) were calculated using thresholds at 500, 1000, 2000 and 3000 Hz. Residual cholesteatoma at second stage surgery and recurrences during the follow-up period were recorded. Residual disease was defined as persistence of disease due to incomplete removal revealed during second stage surgery. Recurrent cholesteatoma was defined as a newly formed disease process secondary to a retraction pocket after second stage surgery.

Surgical technique

A postauricular approach was used in all patients. Mastoidectomy was performed preserving the posterior canal wall. A posterior tympanotomy was done and the facial recess was opened. The cholesteatoma sac was identified and excised using a combined approach. A silastic sheet was placed in the middle ear and antrum followed by reconstruction of the tympanic membrane by temporalis fascia. Bone patè in case of small defects or homologous rib cartilage[5] for large defects was used to reconstruct the scutum. A second surgery was planned after 6-12 months to discover any residual or recurrent cholesteatoma. The silastic sheet was removed and ossicular reconstruction was done using autologous incus. When the incus was absent, a homologous rib cartilage was used.

Reconstruction

When the stapes was present and mobile, a partial ossicular cartilage prosthesis (PORP) was sculpted. At the end of the shaft, an indentation (1 mm wide and 0.5-1 mm in depth) was created with a diamond burr in order to accommodate the capitulum of the stapes. The head of the prosthesis was placed in contact with the tympanic membrane or the graft used for its repair. When the malleus was present, the prosthesis was placed parallel to it and a groove was created to accommodate the handle. When the stapes superstructure was absent, a total ossicular cartilage prosthesis (TORP) was used. In this case, the shaft was longer than in a PORP but the head of the T shaped prosthesis was identical. The end of the shaft was placed in contact with the footplate and the head was placed in contact with the tympanic membrane or the graft used for its repair.[5]

Statistical analysis

Data was analysed with a statistical software programme (SPSS Statistics for Windows version 20, Chicago, IL). Continuous data was summarised as mean ± interval of confidence at 95% (CI). Categorical data was presented as frequencies and percentages. Factors related to the rate of recidivism were estimated with univariate analysis. Preoperative and postoperative hearing results were evaluated for the entire sample and the acquired and congenital middle ear cholesteatoma groups. P values below 0.05 were considered statistically significant.

Results

40 patients fitted into this study criteria of CWU procedures for paediatric cholesteatomas. 31 (77.5%) patients had acquired cholesteatoma and 9 (22.5%) had congenital middle ear cholesteatoma. 24 (60%) were males and 16 (40%) were females, with an average age of 10.10 years (95% CI 8.83-11.37; range 2-16 years) at the time of surgery. The age distribution is shown in Figure 1.

Clinical findings

The most common symptoms were otorrhoea seen in 34 (85%) of patients, followed by hearing loss in 19 (47.5%) patients. Otorrhoea and hearing loss coexisted in 15 (37.5%) patients. According to Zini & Sanna's classification, the cholesteatoma was localised in the mesotympanum (type A) in 20 (50%) patients, in the epitympanum (type B) in 10 (25%) patients, in the mesoepitympanum (type AB) in one (2.5%) patient and retrotympanum (congenital middle ear) in nine (22.5%) patients (Fig. 2). In two (5%) patients a polyp was found in the external auditory canal. Otomicroscopy in the contralateral ear showed

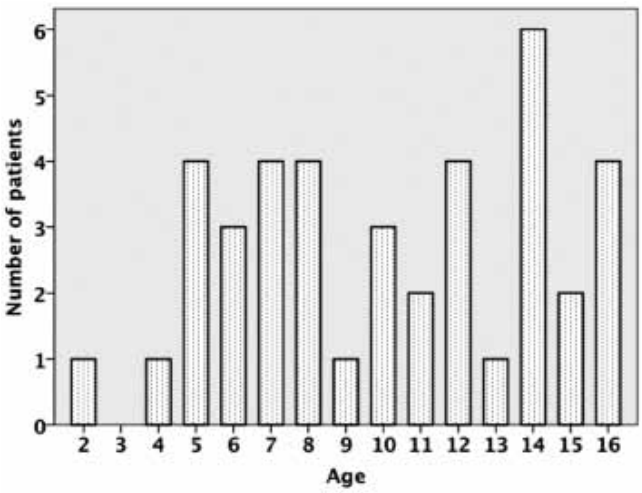

Fig. 1. Age distribution of paediatric patients with cholesteatomas.

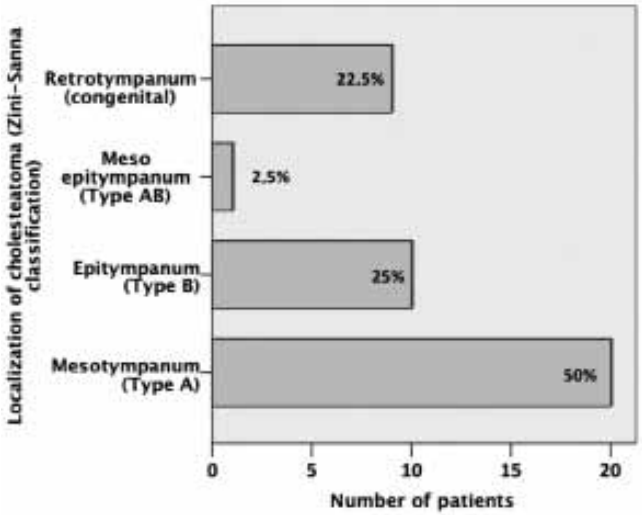

Fig. 2. Localisation of cholesteatomas according to the Zini-Sanna classification.

a retraction pocket in the tympanic membrane in 13 (32.5%) patients, middle ear effusion in 2 (5%), atelectasis of the middle ear in 3 (7.5%), a large tympanosclerosis in one (2.5%) and a tympanic membrane perforation in one (2.5%) patient.

Surgical procedure

All 40 patients underwent CWU surgery. No labyrinthine fistulae were detected intraoperatively in any patient. The cholesteatoma was found to be diffuse in 30 (75%) and encapsulated in 10 (25%) cases. In all but one patient, CWU mastoidectomies were performed in two stages. In the remaining case, CWU was performed in a single stage owing to the small size of the cholesteatoma and preservation of the ossicular chain. In 22 (55%) patients, the scutum was found to be eroded and was reconstructed with bone patè or homologous rib cartilage. Ossicles were found to be eroded in 39 (97.5%) patients and were reconstructed in all. Homologous rib cartilage was used in 21 (53.8%) patients, autologous malleus in 4 (10.3%) and incus in 14 (35.9%).

Recidivism in the second stage surgery

Of the 39 patients who underwent a second stage surgery, 18 (46.1%) had a residual lesion. In eight (44.4%) patients the cholesteatoma appeared as a single pear shaped lesion, in seven (38.9%) as multiple pear shaped lesions and in three (16.7%) as a diffuse lesion. In three of the 18 (16.7%) patients, ossicular reconstruction was postponed to a third stage after another 6-12 months due to infiltrative disease. Of nine patients with congenital middle ear cholesteatomas, four (44.4%) had a residual cholesteatoma found during second staged surgery. The clinical type of cholesteatoma (acquired vs. congenital middle ear) and histological type (encapsulated vs. diffuse) were not statistically related to the incidence of residual cholesteatoma ($p = 0.85$ and 0.24 respectively, chi-square test). The average age in the group of patients that had a residual lesion was 8.72 years (95% CI 6.80-10.70), and 11 years (95% CI 9.30-12.79) ($p = 0.06$, U Mann-Whitney test) in the group that did not have a residual lesion. This difference, although not statistically significant, is worthy of mention as this was the only factor closest to achieving significance among all factors analysed in relation to the incidence of residual lesion. Moreover, when patients were categorized by age into three groups (≤5 years old, 6 and 10 years and ≥ 11 years), the rate of residual cholesteatoma was 66.7%, 46.7% and 38.9%, respectively ($p>0.05$ Fisher's exact test).

Follow-up

All patients were followed-up for at least five years. The mean follow-up was 84 months (range 60-120 months). Eight (20%) patients had a 10 year follow-up, 24 (60%) between six and nine years and eight (20%) patients for five years. In the follow-up period, there were five (12.5%) patients with recurrences, all belonging to the group in whom a residual cholesteatoma was identified and removed during the second staged surgery. Of these, one was converted into a CWD mastoidectomy, while in another case, due to extensive pathology and erratic follow up, a radical mastoidectomy was done. The cavity was obliterated with fat and a cul-de-sac closure of EAC was performed. In the only patient who underwent a single stage CWU mastoidectomy, a suspicious residual cholesteatoma was detected after 2 years and the patient underwent a second stage surgery. The cholesteatoma was confirmed to be near the stapes, which was removed. The average duration of onset of recurrence was 2.5 years after surgery (range 1-4 years). There were no recurrences in the group of patients who were disease-free during the

second staged surgery. Three patients developed a retraction pocket, one developed an atelectasis and three patients developed a glue-ear. There were no cases of perforations of the tympanic membrane.

Hearing outcomes

Preoperatively, pure tone audiometry could not be conducted in two patients because one suffered from Down's syndrome and the other was too young (two years) at the time of surgery. Pre- and postoperatively pure tone audiograms of 38 patients with CWU mastoidectomies with a follow-up of five years were available and analysed. Of the 38 patients, six were excluded from further study because one suffered from Down's syndrome and five had recurrent cholesteatoma after the second stage surgery. In addition, the audiogram of one patient was incomplete and therefore excluded. Consequently, pre- and postoperative audiograms of 31 patients were compared. No patients developed a dead ear postoperatively.

Hearing results in the whole sample

The mean air conduction (AC), bone conduction (BC) and air bone gap (ABG) noted preoperatively, six months and five years postoperatively are shown in Table I and Figure 3. Postoperatively, AC improved significantly from 36.21 dB to 28.06 dB (p = 0.02, Wilcoxon test). This result remained significant at five years of follow-up (p=0.006). There was also a significant improvement between preoperative ABG (23.53 dB) and postoperative ABG at 6 months (17.24 dB) (p = 0.01). This improvement consolidated at five years of follow-up and remained significant (p = 0.001). Mean preoperative BC was 12.47 dB and remained unchanged postoperatively at six months (p = 0.75) and five years (p = 0.43) after surgery.

Preoperatively, the average ABG was < 10 dB in four (10.5%) patients, between 11 and 20 dB in nine (26.3%) patients, between 21 and 30 dB in 10 (28.9%) patients and > 30 dB in 11 (34.2%) patients. Postoperatively at six months follow-up, ABG was < 10 dB in 12 (34.3%) patients, between 11 and 20 dB in 10 (28.6%) patients, between 21 and 30 dB in seven (20%) patients and > 30 dB in six (17.1%) patients. At five years of follow-up, the ABG was < 10 dB in 10 (32.3%) patients, between 11 and 20 dB in nine (29%) patients, between 21 and 30 dB in 8 (25.8%) patients and > 30 dB in four (12.9%) patients (Fig. 4).

Hearing results in acquired cholesteatoma

The mean AC, BC and ABG preoperatively, and postoperatively at six months and five years in patients with acquired cholesteatoma are shown in Table II. The mean AC improved from 34 dB before surgery to 28 dB at 6 months and at 5 years (p = 0.07, U Mann-Whitney test). The reduction in ABG was statistically significant from a mean ABG of 22 dB before surgery to 17 dB at 6 months and 5 years (p = 0.007). Mean preoperative BC, which was 12 dB, remained unchanged postoperatively at six months (p = 0.13) and five years (p = 0.22).

Hearing results in congenital middle ear cholesteatoma

The mean AC, BC and ABG preoperatively and postoperatively at six months and five years for patients with congenital middle ear cholesteatoma are shown in Table III. Among the nine patients with congenital middle ear cholesteatomas, one patient suffering from Down's syndrome was non-compliant. In the remaining patients, there was significant improvement between preoperative AC (mean PTA of 42.50) and postoperative AC (mean PTA of 25.63 dB) at six months (p = 0.042, Wilcoxon test). The reduction in ABG from 27.96 dB preoperatively to 17 dB postoperatively at six months was statistically significant (p = 0.006). Both results were statistically significant at

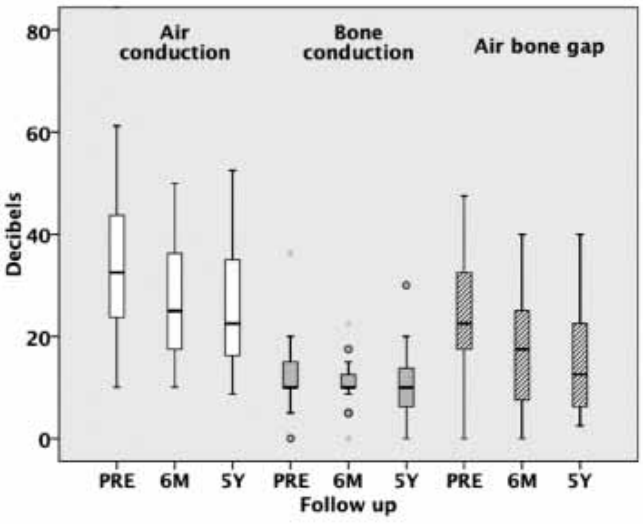

Fig. 3. Box-plot showing median AC, BC and ABG according to follow-up. Preoperatively (PRE), 6 months after surgery (6M) and at 5 years follow-up (5Y).

Table I. Hearing outcomes in middle ear cholesteatomas after CWU surgery preoperatively, 6 months and 5 years of follow-up.

Mean PTA (95% CI)	Preoperative	Postoperative	
		Follow-up at 6 months	Follow-up at 5 years
Air conduction	36.21 (26.96-42.45)	28.06 (23.23-32.89)	26.46 (21.66-31.26)
Bone conduction	12.47 (9.41-15.54)	10.80 (9.06-12.54)	10.43 (8.21-12.64)
Air bone gap	23.53 (18.99-28.08)	17.24 (12.69-21.80)	16.12 (11.91-20.32)

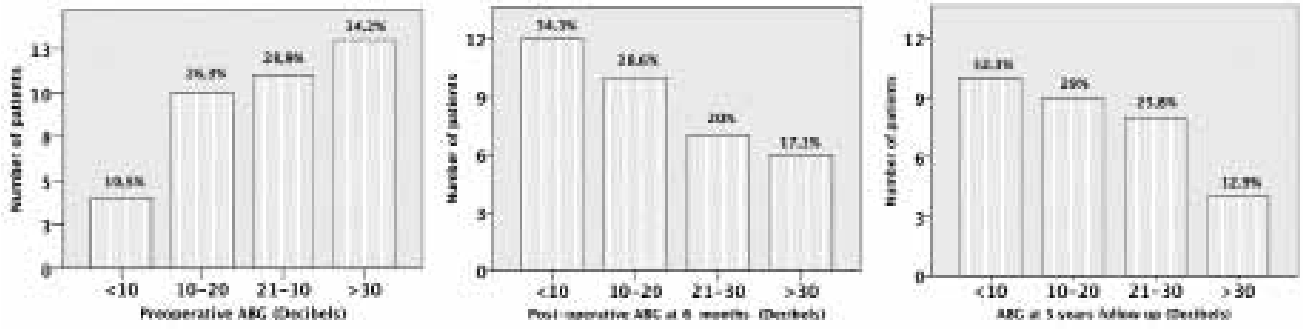

Fig. 4. Bar diagrams showing the number of patients in each ABG group before surgery, at 6 months follow-up, and at 5 years follow-up.

five years follow up (p = 0.028 and p = 0.028 respectively). Mean preoperative BC, which was 13 dB, remained unchanged postoperatively at six months (p = 0.86) and five years (p = 0.22).

There were no statistically significant differences in the preoperative AC, BC and ABG between acquired and congenital middle ear cholesteatoma groups (p > 0.05, U Mann-Whitney test). However, in the congenital group, the improvement in AC (20.20 dB, 95% CI 28-12) and ABG (-14.20 dB 95% CI, -21 -[-7.5]) at five years was better than the AC (7 dB, 95% CI 15-[-1]) and ABG (-5.6 dB 95% CI, -11 -[-0.33]), in the acquired group p=0.017 and p=0.029, respectively (U Mann-Whitney test).

Discussion

The incidence of cholesteatoma in childhood is estimated to be 3-6 per 100,000 individuals [6]. Various arguments dictate the surgical choice in paediatric cholesteatoma. While some authors [7-10] consider that cholesteatoma is a more aggressive in children with a higher percentage of recidivism than in adults and hence warrants more radical surgery, others [11 12] are of the opinion that the behaviour of the cholesteatoma is the same in children as in adults. The second disagreement is that of CWU versus CWD surgery in dealing with paediatric cholesteatomas. While it is important to preserve hearing in the child, which plays a major role in social and educational integration after surgery, it is even more important to eradicate the disease without complications. The introduction of the staged procedure in CWU, use of cartilage for reconstructing the attic to prevent postoperative retractions and advances in ossicular reconstruction have helped surgeons to tackle cholesteatomas in the paediatric population with a CWU technique, thereby preserving hearing and eliminating the risk of recurrence. Furthermore, studies using DW-non-EPI and DWI propeller sequences show promising results in improved diagnostic sensitivity and specificity for even small (< 5 mm) cholesteatomas, thus allowing avoidance of second-look surgery in the future [13-16].

Principles behind surgery

We prefer a CWU mastoidectomy with a planned second stage surgery as the primary option. A CWD is used in patients with extensive cholesteatoma, difficult anatomy, cleft palate and unsure follow up. The second stage sur-

Table II. Hearing outcomes in acquired cholesteatoma.

PTA results	Preoperative	Postoperative	
		Follow-up 6 months	Follow-up 5 years
PTA AC	34 (27-41)	29 (23-34)	28 (22-33)
PTA BC	12 (9-16)	12 (10-13)	11 (8- 13)
ABG	22 (17-28)	17 (12-22)	17 (12-22)

Table III. Hearing outcomes in congenital middle ear cholesteatoma.

PTA results	Preoperative	Postoperative	
		Follow-up 6 months	Follow-up 5 years
PTA AC	42.50 (31.97-53.03)	25.63 (11.02-40.23)	22.29 (12.70-31.87)
PTA BC	13.00 (7.65-18.35)	7.42 (1.29-13.54)	8.33 (2.91-13.75)
ABG	27.96 (20.10-35.82)	17.01 (11.80-22.22)	13.75 (4.32-23.17)

gery is planned 6-12 months after the 1st surgery. This is because the healing process of a middle ear with active infection, granulation tissue, and/or areas of absent mucosa will be variable. Formation of adhesions between the medial wall of the mesotympanum and the tympanic membrane or the ossicular implant can promote tympanic membrane retraction and/or implant displacement [17]. To avoid this, we place a silastic sheet in the middle ear which remains until the time of the second stage surgery, when it is removed and ossicular reconstruction is performed. If residual cholesteatoma is present and is a small pearl, we remove it and continue with ossicular reconstruction in the same session. If it is found to be extensive, or in the presence of infection, the cholesteatoma is removed and the ossiculoplasty is postponed to another session. We do not hesitate to convert the CWU into a CWD as and when necessary.

In assessing outcomes in our series, we agree with previous authors that the total percentage of cholesteatoma recidivism should be the basis for evaluation of the outcome of surgery [2]. We defined residual disease as persistence of disease after incomplete removal as revealed during second stage surgery. Recurrent cholesteatoma was defined as a newly formed disease process secondary to a retraction pocket after second stage surgery. It is unlikely that a good surgeon will leave behind (residual) cholesteatoma after two surgeries. This differentiation is crucial in reporting data. We compared our study to those of other authors, and the results are summarised in Table IV. In our series, as in most others, the residual cholesteatoma was identified during the second stage procedure mostly in the form of a white pearl that could be removed easily. The recurrent cholesteatoma presented to us between a minimum of one year and a maximum of five years, possibly due to poor Eustachian tube function. The age difference between patients who had a residual lesion (average 8.72 years), and those who did not (average 11 years) was close to significance ($p = 0.06$). It is also important to note that the rate of residual cholesteatomas decreases as the age progresses [(66.7% (≤ 5 years), 46.7% (6-10 years) and 38.9% (≥ 11)], respectively ($p > 0.05$ Fisher's exact test). This may point to the fact that younger patients may indeed have a more aggressive disease. The reported rate of residual cholesteatoma in closed procedures is between 19-63.5% and that of recurrent cholesteatoma is between 7.5-22% [17-26]. While none of our patients who did not have a residual cholesteatoma identified at the second stage went on to develop a recurrence, Schraff et al. [27] reported a 1% recurrence rate in such a category. A period of five years of follow-up is essential for all children undergoing CWU surgery.

Hearing outcomes

Our analysis of the hearing outcomes validates the fact that CWU procedures bring about a significant improvement in AC that is statistically significant. Moreover, this improvement is consolidated at five years and remains statistically significant. Likewise, the improvement in ABG is also maintained at five years. Patients with congenital middle ear cholesteatoma tend to have similar preoperative AC, BC and ABG than with acquired cholesteatoma. However, at 5 years, the postoperative improvement in hearing was superior in congenital middle ear cholesteatoma patients compared to those with acquired cholesteatoma.

Studies indicate that the status of the ossicles, their reconstruction and the type of surgical technique are important factors for postoperative hearing restoration in cholesteatoma surgery. Incus transposition is most frequently used for reconstructing an ossicular discontinuity. However, cholesteatoma usually causes significant destruction of ossicles, especially the incus, so that other materials must be considered [28]. In the absence of the incus, we routinely use rib cartilage for the reconstruction of the attic and the

Table IV. Comparison of residual and recurrence cholesteatoma in our series with other authors.

Authors	# patients	Residual %		Recurrent %		Mean follow-up (years)
		closed	open	closed	open	
Dodson et al. [17]	66	19	12	22	0	9.2
Mutlu et al. [18]	83	38	11	11	0	4
Sanna et al. [19]	151	40	50	11	25	1.5
Schimd et al. [20]	57	24	7.5	12	7.5	7
Magnan et al. [21]	210	26	0	19.5	0	NA
Triglia et al. [22]	80	41	35	16	8	4
Desaulty et al. [23]	80	63.5	0	7.5	0	2.5
Roger et al. [24]	199	54	72	19	0	2.5
Lerosey et al. [25]	57	26	28	12	12.5	7
Charachon et al. [26]	160	31	38	20	0	NA
Our series	43	45	0	12	0	8

NA=Not available

ossicles. Because of their flexibility and elasticity, cartilage prostheses rarely damage the stapes or the footplate during the surgical maneuver [5].

As stated by Dodson et al. [26], serviceable hearing depends primarily on middle ear parameters such as mucosal status (stenosis and granulation), condition of the TM (thickness, contour), depth of the middle ear cleft and presence or absence of stapes suprastructure erosion. Mutlu et al. [18] demonstrated a ≤ 25 dB hearing loss in 85% of those with an intact stapes supra structure. Historically, worse hearing results have often been cited as a criticism of CWD but several studies dispute this notion [29-31]. Schraff et al. [27] showed that those undergoing CWD have worse hearing pre-operatively and less improvement post-operatively compared with children using the ICW approach. This may be a result of more aggressive disease rather than failure in technique. Nevertheless, CWU surgeries provide a distinct advantage due to the fact that children do not need to worry about mastoid cavities, can swim and may benefit from a good fitting of a hearing aid when necessary.

Conclusions

A two-staged CWU mastoidectomy is the surgery of choice for paediatric cholesteatomas. Placing a silastic sheet to promote regeneration of mucosa with ossiculoplasty in the second stage and reconstruction of the scutum to avoid retraction have made CWU procedures an effective option in dealing with paediatric cholesteatomas. Hearing analysis showed that hearing recovery was excellent with canal wall up procedures and remained stable over five years. There is a higher incidence of recurrence during long-term follow-up in patients in whom residual cholesteatoma was detected during second stage surgery. The rate of residual cholesteatoma tends to decrease as the age increases. Follow-up for a minimum of five years is recommended in all patients with paediatric cholesteatoma.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Hyoid myotomy without suspension: a surgical approach to obstructive sleep apnoea syndrome

Miotomia del muscolo ioideo senza sospensione: un approccio chirurgico per la sindrome delle apnee ostruttive nel sonno

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SUMMARY

The aim of this study was to verify if hyoid myotomy without hyoid suspension is effective in surgical treatment of obstructive sleep apnoea syndrome (OSAS). We recruited six patients with OSAS, aged between 34 to 60 years, with retropalatal and retrolingual upper airway obstruction, non-obese (BMI < 27) and non-compliant to continuous positive airway pressure therapy. Pre-surgical clinical and instrumental evaluations included clinical examination, cephalometry, polysomnography (PSG) and sleep endoscopy. Surgical treatment included nasal surgery, uvulopalatopharyngoplasty, tonsillectomy and hyoid myotomy without hyoid suspension. Follow-up evaluations were performed with serial PSGs, performed early (one week after surgery), and at 1, 6 and 18 months after surgery. We observed that surgery was followed by immediate normalisation of breathing parameters evaluated by PSG that persisted after 18 months. Thus, hyoid myotomy without suspension combined with nasal and palatal surgery may be considered a valid treatment of non-obese OSAS patients with retrolingual and retropalatal collapse. Furthermore, we suggest that hyoid bone suspension, binding it to mandibular or to thyroid cartilage, might be unnecessary in selected cases.

KEY WORDS: Obstructive sleep apnoea syndrome • Hyoid myotomy • Uvulopalatopharyngoplasty • Sub-hyoid muscles

RIASSUNTO

Obiettivo di questo studio è stato verificare se la miotomia ioidea senza sospensione è efficace nel trattamento chirurgico della sindrome delle apnee ostruttive del sonno (OSAS) nell'ambito del primo step della chirurgia multilivello. Abbiamo reclutato sei pazienti affetti da OSAS, di età compresa tra i 34 e i 60 anni, con un'ostruzione delle alte vie aeree a livello retropalatale e retrolinguale, non obesi (BMI <27) e che mostravano scarsa tolleranza nei confronti della terapia con ventilazione meccanica a pressione positiva continua delle alte vie aeree. Durante la valutazione clinica pre-intervento i pazienti sono stati sottoposti a esame clinico otorinolaringoiatrico, cefalometria, polisonnografia (PSG) e sleep-endoscopy. Tutti i pazienti sono stati sottoposti nella stessa seduta a chirurgia nasale, uvulopalatofaringoplastica, tonsillectomia e miotomia ioidea senza sospensione. Nel corso del follow-up i pazienti sono stati sottoposti a PSG seriali, all'inizio (una settimana dopo l'intervento chirurgico), ed a 1, 6 e 18 mesi dopo l'intervento chirurgico. I dati polisonnografici hanno messo in evidenza un significativo miglioramento dei parametri respiratori nell'immediato post operatorio che si è mantenuto stabile per almeno 18 mesi. Alla luce della nostra analisi preliminare l'intervento di miotomia ioidea senza sospensione in combinazione con la chirurgia nasale e palatale può essere considerato un valido trattamento per i pazienti affetti da OSAS, non obesi, con collasso delle alte vie aeree a livello retrolinguale e retropalatale. Per tale motivo la sospensione ioidea, con ancoraggio alla mandibola o alla cartilagine tiroidea, in alcuni casi selezionati, potrebbe non essere necessaria.

PAROLE CHIAVE: *Sindrome delle apnee ostruttive del sonno • Miotomia ioidea • Uvulopalatofaringoplastica • Muscoli sottoioidei*

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a multifactorial pathology consequent to upper airway obstruction and often associated with cardiovascular and metabolic comorbidities [1 2]. Treatment of OSAS must be based on the exact determination of the site of upper airway collapse obtained through careful clinical evaluation including endoscopy of the upper airway during awake status and during drug-induced sleep endoscopy [3-6].

Several surgical and non-surgical procedures have been proposed as an alternative to continuous positive airway pressure (CPAP) for treatment of patients with OSAS. Among the non-surgical techniques, good results have been obtained with the use of oral devices, especially when there is evidence of improvement of the breathing space after mandibular advancement manoeuvres during sleep endoscopy [7]. Surgical approaches have been described to treat OSAS patients and include na-

sal surgery, pharyngeal surgery, tongue surgery, hyoid bone surgery [8-11] and maxillary surgery with several variations and personalisations [12-15] with the aim of achieving good and safe results [16]. Riley et al. [8 9] proposed a multilevel surgical approach consisting of two phases. The first includes nasal surgery, uvulopalatopharyngoplasty (UPPP), genioglossus advancement and hyoid bone suspension; the second phase (applied to patients not responding to the first phase of treatment) includes bi-maxillary advancement and tongue base surgery.

In the present report, we describe a multilevel surgical approach to the treatment of adult, non-obese patients with severe OSAS and both retropalatal and retrolingual collapse in agreement with the protocol of Riley et al. [8 9] combining nasal surgery, UPPP and hyoid myotomy. In contrast to other surgical procedures, we do not perform hyoid suspension. The hyoid bone is freed from its lower connections (by cutting the sub-hyoid muscles), but it is not suspended to nearby anatomical structures. Herein, we present our surgical technique and the results achieved.

Clinical techniques and technology

We enrolled 6 patients (5 males/1 female; mean age 44.3 ± 8.8) with a body mass index < 27 kg/m^2, cephalometric parameters consistent with retropalatal and retrolingual obstruction confirmed by sleep endoscopy, absence of major cranio-facial abnormalities, apnoea-hypopnoea index (AHI) > 20 events per hour of sleep documented by full-night laboratory-based polysomnography. The study conformed with the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave written informed consent for surgical treatment.

According to standard protocols [17], pre-surgery evaluation included clinical otorhinolaryngoiatric examination, cephalometric evaluation [in particular the posterior airway space (PAS) measured as the minimal distance between the base of the tongue and the posterior pharyngeal wall, and the mandibular planus–hyoid bone distance (MP-H)], nasal and oro-pharyngeal endoscopy in awake status and during drug-induced sleep.

Four full-night laboratory nocturnal polysomnographies (PSGs) were performed: the first before surgical treatment (PSG#1), the second at one week after surgery (PSG#2), the third after 6 months follow-up (PSG#3) and the fourth at 18 months after treatment (PSG#4). PSGs were recorded with a Micromed System '98 digital polygraph with electroencephalographic electrodes, electro-oculographic electrodes, electromyography of submental and intercostal muscles, airflow measured by oronasal thermocouple, thoracic and abdominal effort, EKG (V2 modified derivation) and peripheral haemoglobin saturation. Sleep registration lasted from 11:00 pm to 7:00 am. A trained technician was present during data acquisition. Sleep stages were visually classified according to the criteria of Rechtschaffen and Kales [18]. The scoring and classification of sleep-related respiratory events was made visually. Apnoeas were defined as a decrease of the airflow signal up to >= 90% from the baseline for more than 10 sec. Hypopnoea events were defined by a decrease of amplitude of the airflow signal by 30% or more and the event lasts at least 10 sec and the blood oxygenation drops by 4% or more or the event is associated with an EEG arousal (3 sec or more of fast, desynchronised activity). AHI was the ratio of apnoeas plus hypopnoea per hour of sleep (excluding central events). PSG features of patients are summarised in Table I.

All patients, after diagnostic assessment, were prescribed a nocturnal ventilator treatment (nasal CPAP or BiLevel) and underwent a titration night. None of the 6 patients were compliant to ventilator therapy and voluntarily chose to undergo upper airway surgery.

Turbinate ablation with radiofrequency and septoplasty was performed in all patients. Palatoplasty and tonsillectomy were also performed in all patients according to the technique described by Riley et al. [8 9] Successively, sub-hyoid myotomy was performed via a 3 cm transversal cut, including total sectioning of the sub-hyoid muscles. In contrast to the other techniques proposed, the hyoid bone was not anchored to either thyroid cartilage or the mandibular bone. Surgery was well tolerated by all patients, and all patients were able to swallow normally at 7 to 10 days after surgery.

The results of PSG studies are detailed in Table I (for sleep-related breathing abnormalities). Before surgery, baseline PSG results were consistent with severe OSAS. The AHI ranged from 27.0 to 54.6 with a mean of 35.4 ± 13.7. Immediately after surgery, all PSG parameters showed improvement relative to sleep breathing abnormalities: in particular, the AHI decreased from 35.4 ± 13.7 events/hour before surgery to 7.9 ± 4.1 events/hour after surgery (Student's t-test p = 0.0054). After 18 months of follow-up, the AHI was 7.4 ± 3.2.

At cephalometry before surgery, the posterior airways space (PAS) ranged from 3 mm to 9 mm (mean 6.0 ± 2.4 mm). After surgery, a dramatic increase in PAS was seen, ranging from 12 mm to 16 mm (mean 14.8 ± 1.5 mm). This increase was statistically significant (Student's t-test p = 0.00079). The Mandibular Planus – Hyoid bone distance (MP-H) before surgery ranged from 10 mm to 16 mm (mean 12.8 ± 1.9 mm). After surgery the MP-H ranged from 6.8 mm to 13 mm (mean 9.0 ± 2.1 mm) thus showing a significant reduction (Student's t-test p = 0.00026). The values were unchanged after 18 months of follow-up.

Discussion

Hyoid bone suspension can be achieved by several surgical procedures [4-10]. All of these interventions aim to displace the hyoid complex forward and upward, and to

Table I. PSG features of patients before and after surgery.

Before surgery								
Breathing abnormalities	1	2	3	4	5	6	Mean	SD
All Apnoeas	82	69	23	29	44	117	60.67	35.77
All Hypopnoeas	62	319	178	89	55	420	187.17	151.29
Central Apnoeas	6	1	3	0	0	0	1.67	2.42
Central Hypopnoeas	3	6	2	9	6	54	13.33	20.08
Mixed Apnoeas	2	3	1	0	0	0	1.00	1.26
Mixed Hypopnoeas	7	70	36	23	29	29	32.33	20.90
Obstructive Apnoeas	16	65	19	29	44	117	48.33	38.19
Obstructive Hypopnoeas	52	243	140	57	20	337	141.50	125.25
Apnea + Hypopnea Index	24.0	54.6	28.5	24.0	25.1	66.3	37.09	18.56
Desaturations								
Total number	63	296	139	103	130	425	192.67	214.28
Desaturation index	26.3	46.3	17.8	25.1	19.2	50.1	30.80	13.92
Baseline SaO_2	98	97	98	98	98	97	97.33	0.82
Minimum SaO_2	80	71	82	76	82	64	75.83	7.17
Time with $SaO_2 < 90\%$	14	38	32	18	29	47	29.67	12.31

6 months after surgery								
Breathing abnormalities	1	2	3	4	5	6	Mean	SD
All Apnoeas	33	53	24	28	43	61	40.33	14.61
All Hypopnoeas	22	19	8	22	30	30	21.83	8.16
Central Apnoeas	2	5	0	0	5	3	2.50	2.26
Central Hypopnoeas	3	0	0	0	5	6	2.33	2.73
Mixed Apnoeas	0	1	0	9	0	0	1.67	3.61
Mixed Hypopnoeas	0	6	0	3	5	0	2.33	2.73
Obstructive Apnoeas	31	47	24	19	38	58	36.17	14.61
Obstructive Hypopnoeas	19	13	8	19	20	24	17.17	5.71
Apnea + Hypopnea Index	5.9	9.9	3.5	3.8	8.6	11.9	7.27	3.41
Desaturations								
Total number	47	59	21	39	65	78	51.50	20.24
Desaturation index	3.6	10.5	4.6	3.9	9.6	9.9	7.02	3.30
Baseline SaO_2	98	99	98	98	98	98	98.17	0.41
Minimum SaO_2	83	74	91	83	92	85	84.67	6.53
Time with $SaO_2 < 90\%$	3	3	1	1	5	7	3.33	2.34

fix it to a nearby anatomical structure, either the mandible or thyroid cartilage. This movement increases the PAS, both in its posterior and, mainly, in its lateral portions [4].

The choice to leave the hyoid bone free was suggested by the hypothesis that, by fixing the hyoid to another anatomical structure as in classical surgery, this could induce passive lengthening of the supra-hyoid muscles (upper airway dilators). Therefore, this might impair the physiological action of these muscles in keeping the upper airways open during sleep. In this view, hyoid suspension might abolish one of the physiological mechanisms aimed at preventing upper airways collapse during sleep. Moreover, when the hyoid bone is fixed to thyroid cartilage, supra-hyoid muscle is subject to chronic stretching induced by inspiration; such stretching could possibly worsen OSAS [19]. Hyoid myotomy without suspension could theoretically prevent such mechanical stress.

The most relevant finding in our study was that the employed surgical approach was effective in non-obese patients with severe OSAS. Furthermore, these positive results persisted after 18 months. The improvement was not associated with significant variation in the BMI. The omohyoid, the sternohyoid and thyrohyoid muscles were sectioned. All these muscles act by lowering the hyoid bone and opposing the upward movement of the larynx. Hyoid myotomy induces a spontaneous movement upward and forward of the hyoid bone. We did not perform

1 week after surgery								
1	2	3	4	5	6	Mean	SD	
25	70	24	19	56	77	45.17	25.64	n°
17	29	8	20	26	32	22.00	8.83	n°
0	3	3	0	4	4	2.33	1.86	n°
2	1	2	0	1	5	1.83	1.72	
1	4	1	5	2	8	3.50	2.74	n°
0	10	1	5	2	4	3.68	3.61	n°
24	63	20	14	50	65	39.33	22.73	n°
15	18	5	15	23	23	16.50	6.69	n°
5.1	12.3	3.2	4.8	9.3	12.8	7.92	4.12	Per hour
33	74	17	28	71	79	50.33	27.27	
4.1	9.6	2	3.4	8.5	10.1	6.28	3.52	Per hour
97	98	98	98	98	97	97.67	0.52	
85	76	90	86	91	83	85.17	5.42	
3	4	1	2	4	8	3.67	2.42	% of SPT

12 months after surgery								
1	2	3	4	5	6	Mean	SD	
40	51	27	27	35	54	39.00	11.61	n°
29	27	18	17	14	36	23.50	8.50	n°
4	4	6	8	2	4	4.67	2.07	n°
6	5	2	1	3	4	3.50	1.87	n°
2	6	2	3	3	4	3.33	1.51	n°
2	5	4	1	0	4	2.67	1.97	n°
34	41	19	16	30	46	31.00	11.87	n°
21	17	12	15	11	28	17.33	6.35	n°
4.6	12.1	5.2	4.3	7.8	10.4	7.40	3.27	Per hour
40	65	32	35	48	77	49.50	17.92	
4.1	9.6	5.0	3.8	7.0	9.3	6.52	2.64	Per hour
98	98	98	97	98	98	97.83	0.41	
81	80	89	82	91	95	84.67	4.50	
2	2	1	1	4	2	2.00	1.10	% of SPT

hyoid suspension following hyoid myotomy: in this view, the proposed technique differs from the most widely applied techniques [4 8-11]. Although commonly employed in literature, hyoid bone suspension and fixation was not necessary for clinical improvement in our sample of OSAS patients. In our opinion, several factors can explain this result:

a) After the described intervention, the respiratory mechanics of upper airway muscle appear to be modified: during inspiration, the decrease of thoracic pressure cannot be transmitted to the hyoid bone and tongue base, thus preventing the downward stretching of hypopharyngeal structures. In this way, the supra-hyoid (involved in digestive functions) and sub-hyoid muscular systems (involved in respiration) act "in parallel" rather than "serially".
b) Following sectioning of sub-hyoid muscles, the hyoid is pulled forward and upward (Fig. 1). Accordingly, the supra-hyoid muscles (pharyngeal dilators) are consequently stretched upwards [4 10 19]. It is well known that the force generated by muscle contraction largely depends on muscle length at rest [20]. Thus, it can be hypothesised that, by fixing the hyoid to another anatomical structure, classical surgery induces passive stretching of the supra-hyoid muscles (upper airway dilators). Such stretching modifies the operating length of supra-hyoid muscles, and it might therefore interfere with the ability of these muscles to keep

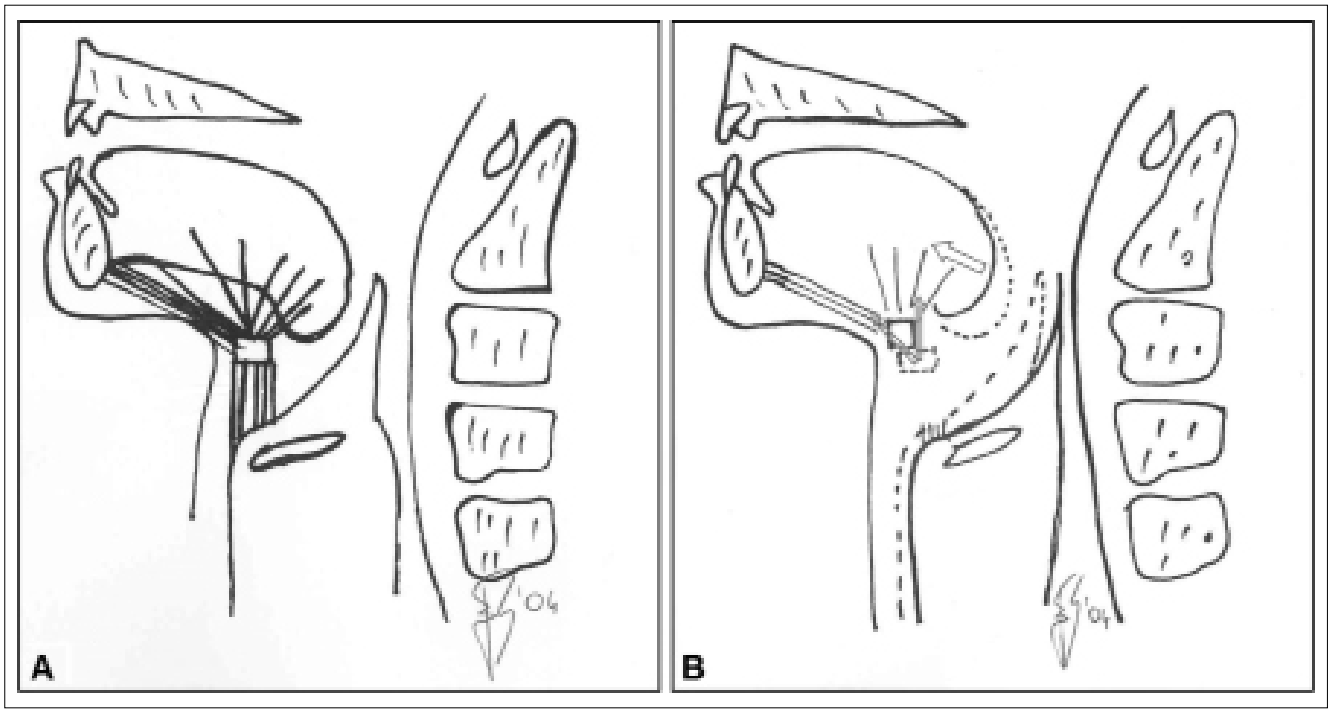

Fig. 1. (A) Hyoid muscles before surgery. (B) Hyoid bone and tongue displacement after surgery. Arrows indicate strength vectors. Following the sectioning of the sub-hyoid muscles, the hyoid is pulled forward and upward, and the supra-hyoid muscles (pharyngeal dilators) are consequently stretched upwards. The tongue base moves forward, inducing an increase in the posterior airway space.

the upper airways open during sleep [20], and by abolishing one of the physiological mechanisms aimed at preventing upper airway collapse in sleep.

Nonetheless, it must be stressed that all our patients were affected by not extremely severe OSAS. Moreover, all were young, and with relatively short clinical history of snoring and sleep apnoea. In fact, it has been reported that the natural history of non-treated OSAS induces morphological, physiological, biochemical and histochemical modifications in the upper airway muscles. It is conceivable that, in our group of patients, early diagnosis allowed surgical treatment before the appearance of such modifications. Therefore, the integrity of the upper airway dilator (supra-hyoid) muscles did not require fixation to the hyoid bone.

In conclusion, the present data, although collected from a small sample, suggests that hyoid myotomy is an effective, minimally-invasive and well-tolerated surgical technique that may be associated with nasal and palatal surgery in a multilevel approach for patients with OSAS and retrolingual and retropalatal collapse. For these reasons, we suggest that hyoid bone suspension to mandibular or thyroid cartilage might be unnecessary in selected cases. Future studies with a larger number of patients are necessary to confirm our preliminary observations.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Arterial microanastomoses on the reverse flow of the internal carotid artery reverse flow: an extreme solution in free-flap revascularisation. How we do it

Microanastomosi arteriosa su flusso retrogrado dell'arteria carotide interna: una soluzione estrema nella rivascolarizzazione dei lembi liberi

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SUMMARY

Microvascular free tissue transfer in head and neck reconstruction requires suitable recipient vessels, which are frequently compromised by prior surgery, radiotherapy, or size of the tumour. A surgical description of an arterial free flap pedicle anastomosis on the reverse internal carotid arterial flow in a vessel-depleted neck is presented. A 66-year-old male with a relapse of hypopharyngeal squamous cell carcinoma previously treated with both surgical and radiation therapy for carcinoma of the tongue and the larynx was successfully reconstructed using a free forearm flap with reverse internal carotid arterial flow. The involvement of the carotid glomus and prior surgery excluded the other vessels as recipients. The forearm free flap survived without any complications. This procedure can be considered an alternative rescue technique for salvage reconstruction in a vessel-depleted neck.

KEY WORDS: Head and neck cancer • Free-flap • Microanastomoses • Carotid artery • Reverse flow

RIASSUNTO

La ricostruzione con lembi liberi richiede la presenza di vasi riceventi che spesso possono essere compromessi da precedenti interventi chirurgici, radioterapia o dalle dimensioni del tumore. In questo articolo abbiamo riportato la tecnica chirurgica da noi utilizzata per la realizzazione di una microanastomosi effettuata sul segmento distale dell'arteria carotide interna sfruttando il suo flusso retrogrado effettuata in un collo privo di altri vasi utilizzabili. Un paziente di 66 anni con recidiva di carcinoma squamocellulare dell'ipofaringe, precedentemente trattato con chirurgia e radioterapia per un carcinoma squamocellulare della lingua e della laringe, è stato ricostruito con successo con un lembo libero di avambraccio rivascolarizzato con il flusso retrogrado dell'a. carotide interna. Il coinvolgimento del glomo carotideo ed il precedente trattamento chirurgico avevano impedito l'utilizzo di altri vasi del collo. Il lembo di avambraccio non ha riportato complicanze nel post-operatorio. Questa procedura può essere considerata un'alternativa estrema per consentire la ricostruzione nei casi in cui i vasi del collo risultino inadeguati e/o assenti.

PAROLE CHIAVE: *Tumori testa e collo • Lembo libero • Microanastomosi • Arteria carotide • Flusso retrogrado*

Acta Otorhinolaryngol Ital 2014;34:368-371

Introduction

To date, microvascular free-tissue transfer represents a reliable technique for reconstruction of defects following surgical treatment of head and neck cancer. Free tissue transfers have a high overall success rate, ranging between 91% and 99% of cases [1], and are generally performed with good functional and aesthetic outcomes, even considering donor-site morbidity [2 3]. However, the procedure requires specific surgical skills, especially for management of the vascular pedicle. In particular, identification and preparation of recipient vessels and microsurgical vascular anastomoses are crucial steps in the field of reconstructive surgery [4 5]. Meticulous attention to these points should be paid to avoid dangerous and life-threatening complications, and improve the overall success rate.

In fact, the management of vascular pedicles can be a troublesome aspect, especially in pre-irradiated graft beds, on the basis of vascular fibrosis and endothelial thickening. In addition to this, surgeons faced with free-flap reconstruction have to be trained, to modify *in itiner* during a radial forearm flap set up for reconstruction following resection of a relapsing hypopharyngeal tumor in an irradiated patient.

Clinical techniques and technology

A microvascular transfer of the radial forearm was planned to reconstruct the digestive tract in a 66-year-old man with a relapsing hypopharyngeal squamous cell carcinoma (SCC). The patient's relevant history began 14 years before when he underwent a partial glossectomy with bilateral functional neck dissection for an undifferentiated SCC, followed by post-operative radiotherapy. In July 2010, a total laryngectomy was performed for the development of an undifferentiated SCC in the left pyriform sinus, extending to the homolateral larynx.

The patient was also affected by arterial hypertension and chronic obstructive pulmonary disease.

For the tumour recurrence in the residual hypopharyngeal lateral left wall (Fig. 1), also considering his previous irradiation history, surgery was therefore planned. An en bloc tumour resection englobing the proximal portion of the involved common carotid artery at the level of the carotid artery bifurcation (previously undetected to the pre-operatory radiologic assessment) was performed, and a right fascio-cutaneous radial forearm flap was set up and tubulised for reconstructive purposes (Figs. 1, 2).

Due to the lack of appropriate arterial flow on the arteries tributary to both the ipsilateral and contralateral external carotid artery, the reversed flow in the distal portion of the left internal carotid artery was used for arterial microanastomoses. Venous microanastomosis was performed between the right tyreo-linguo-facial venous trunk and the cephalic donor vein.

A left pectoral muscle flap was then transposed to protect the residual carotid artery, and a cutaneous Tiersch graft taken from the anterolateral left thigh was used to cover the residual donor site defect.

Discussion

To date, microsurgical reconstruction of the head and neck after oncological surgery based on free flaps is, in experienced hands, an effective and successful technique [6]. The most common used recipient vessels for arterial microanastomoses are the branches of the external carotid artery, such as the facial, superior thyroid, and lingual arteries. However, it is generally accepted that each artery having, once resected, any pulsatile and adequate flow at its distal end can be used as a recipient vessel [7].

However, in managing head and neck reconstruction, surgeons must be ready to modify *in itinere* their reconstructive strategy on the basis of unexpected anatomic extension of the disease (e.g. vascular involvement) or impairment of vascular structures suitable for microanastomoses due to unsuspected flow obstruction or reduced vascular flow (e.g. related to atheromatous disease, post-attinic atherosclerosis, or, less frequently, to intimal injury after the positioning of intra-arterial infusion catheter). In addition to these, some technical difficulties may arise, in-

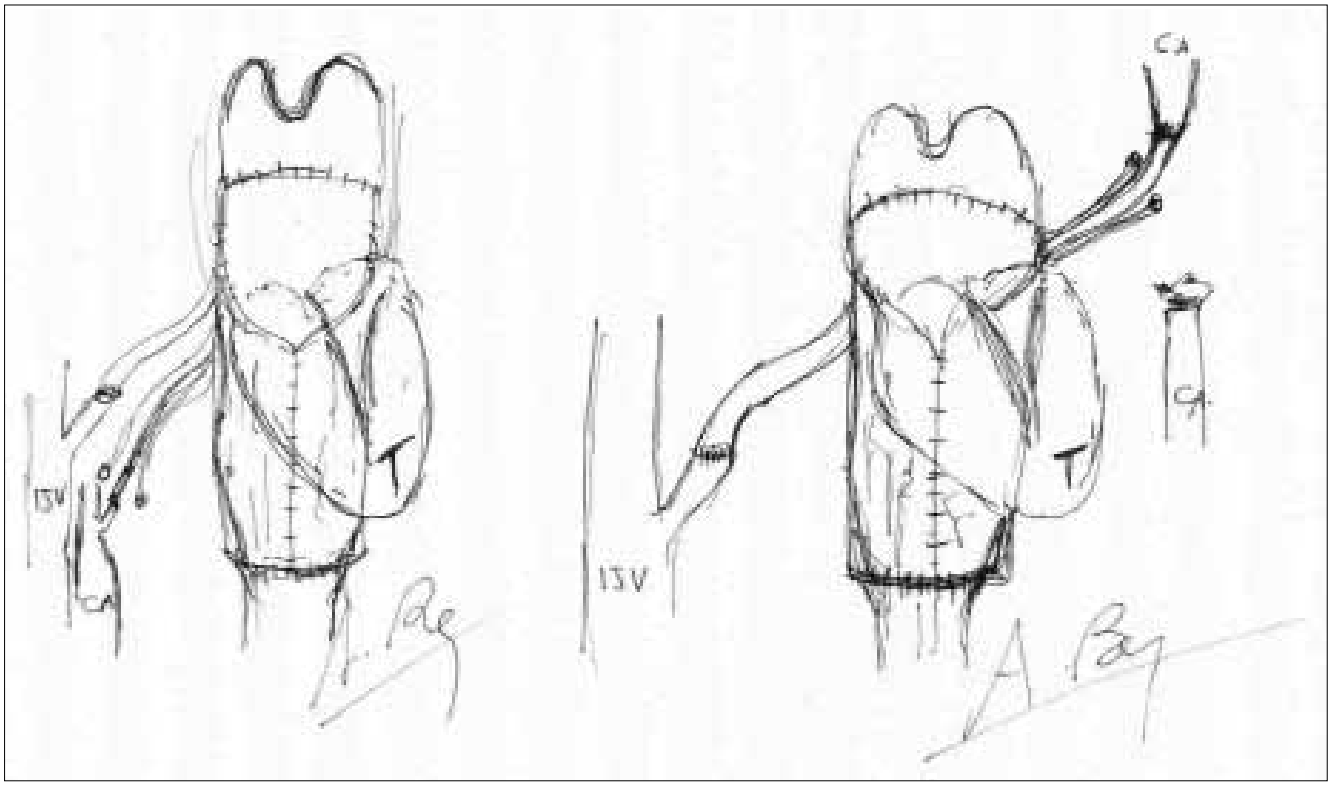

Fig. 1. Ablation.

Fig. 2. Reconstruction.
T: tongue; IJV: internal jugular vein, C: carotid artery.

cluding troublesome pedicle management due to limited pedicle length, reduced vessel caliber or kinking of the pedicle [8 9]. In order to overcome these pitfalls, some authors [10] have suggested that interposition of venous grafts can be used to reach an adequate pedicle length. However, it must be pointed out that surgical strategies using fragile and thin-walled vessels such as graft veins may predispose to intravascular thrombosis.

Therefore, under unexpected and unfavourable conditions, aside from other less effective reconstructive techniques such as delayed locoregional flaps [11], the use of reverse arterial flow can be considered as an extreme surgical choice. In fact, Neligan and co-workers described 28 cases of superior thyroid and facial artery reverse flow used for free flap revascularisation with good clinical outcomes [8]. These positive results may be related to adequate arterial flow, corresponding to 57-76% of systemic arterial pressure as documented by clinical and physiopathologic studies [9]. In addition to this, Batchelor [7] stated that the distal flow of an extracranial reverse flow vessel would be enhanced by recruitment of its peripheral capillary branches resulting in overflow leading to an adequate flap blood supply. At any rate, it may be speculated that the above mentioned conditions related to extracranial reverse flow recipients would be valid in case of intracranial vessels, thus leading to a successful outcome such in this case. However, to our knowledge, no previous descriptions of arterial microanastomoses performed on the reverse flow of the internal carotid artery have been reported.

With regards to the donor site, forearm free flaps should be considered as the preferred choice compared to perforator flaps in such difficult situations, on the basis of

their long and well-caliber pedicles [12 13]. Indeed, in our patient, the forearm flap allowed us to reach the distal portion of the inner carotid artery and use its reverse flow for revascularisation. Moreover, the large size of the radial artery used achieved a good matching with the most of the secondary arterial neck branches and even with the internal carotid artery. In addition to this, a long pedicle is useful when contralateral arterial supply management is required, as in our report, due to impaired patency of the ipsilateral arterial.

In conclusion, microvascular surgery in vessel-depleted necks is a challenge and somewhat troublesome aspect. The case presented herein suggests the feasibility of internal carotid artery reflow for free flap revascularisation when no other safer or easier technical options are possible.

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Calendar of events – Italian and International Meetings and Courses

Acta Otorhinolaryngol Ital 2014;34:372-374

Information, following the style of the present list, should be submitted to the Editorial Secretariat of Acta Otorhinolaryngologica Italica (actaitalicaorl@rm.unicatt.it).
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NOVEMBER-DECEMBER 2014

ORL ENDO 2014 • *Modena – Italy*
Chirurgia endoscopica dei seni paranasali (Endoscopic sinus surgery) • *November 11-12, 2014*

Course Director: Livio Presutti. Scientific Secretariat: Angelo Ghidini, Daniele Marchioni. Tel. +39 059 4222402 - 4223022 – E-mail: Ghidini.angelo@policlinico.mo.it, Marchioni.daniele@policlinico.mo.it - Website: www.meetandwork.it/orl-endo2014

THE MODERN SINONASAL SURGERY • *Varese – Italy*
Advanced Course: November 17-19, 2014

Director: Paolo Castelnuovo. Website: www.ospedalivarese.net/corsinformazione/con-iscrizione

INTERDISCIPLINARY TEACHING COURSE ON HEAD AND NECK BRACHYTHERAPY
November 20-28, 2014 • Rome – Italy

Course Directors: G. Kovacs, G. Paludetti, V. Valentini. Website: www.brachiterapiaitalia.it/entcourse
Antonella Sales: Phone + 390630156054 – Email: segprim.rt@rm.unicatt.it

ISIAN-IRS-PARS 2014. RHINOLOGY UNITES • *November 21, 2014 • Dubai – UAE*

President: Reda Kamel. Website: www.isian-irs-pars2014.org

IV CONGRESSO NAZIONALE AIOCC • *November 21, 2014 • Genova – Italy*

Info: segreteria@stilema-to.it. Website: www.aiocc.it

60° RADUNO "DOPO LA TRACHEOTOMIA" • *November 29, 2014 • Piacenza – Italy*

Direttore: Domenico Cuda. Website: www.piacenzaorl.it

X EDITION: HANDS-ON MICROSURGERY COURSE IN FLAPS RECONSTRUCTION
December 3-5, 2014 • Pavia – Italy

Course Director: Marco Benazzo. Email: g.bertino@smatteo.pv.it – giulia.bertino@tin.it

WORKSHOP 2014 - CHIRURGIA ENDOSCOPICA FUNZIONALE NASO-SINUSALE
December 4-5, 2014 • Budrio (BO) – Italy

Direttore del Corso: Ernesto Pasquini (Bologna). Informazioni: segreteria@symposiaeventi.it

RHINOFORUM 2014 • *December 5-6, 2014 • Warszawa – Poland*

President: Antoni Krzeski. Website: www.rhinoforum.pl

1° CORSO DI RINORADIOLOGIA E CHIRURGIA IN DIRETTA
December 10-11, 2014 • Rovereto (TN) – Italy

Website: www.entcourses.eu

3° MEETING ITALO-BULGARO DI RINOLOGIA "IL RUOLO DELLA DIAGNOSTICA PER IMMAGINI IN RINOLOGIA" • ***December 11-13, 2014 • Rovereto (TN) – Italy***

Website: www.entcourses.eu

JANUARY-DECEMBER 2015

CORSO DI DISSEZIONE OTOLOGICA OTONEUROLOGICA e IMPLANTOLOGIA UDITIVA
January 6-8, 2015 • Paris – France

Direttori: Olivier Sterkers e Daniele Bernardeschi. Istituto di anatomia, Università Saint Pères, 45 rue de Saint Pères, Paris. E-mail: daniele.bernardeschi@psl.aphp.fr

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

Ospedale Pediatrico Bambino Gesù – IRCCS. Palidoro, Rome (Italy).
Direttori del Corso: Sergio Bottero, Angelo Ghidini. Email: marilena.trozzi@opbg.net. Website: www.ospedalebambinogesu.it

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

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

8° CORSO INTERNAZIONALE "BIENNALE MILANO MASTERCLASS"
A. CHIRURGIA ENDOSCOPICA RINOSINUSALE, ORBITA E BASE CRANICA
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Course Directors: P. Castelnuovo, P. Nicolai, M. Tschabitscher. Organizing Secretariat: informazioni@attingo-edu.it. E-mail: www.attingo-edu.it

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

Website: http://www.rhinology2015.com/Scientific-program.htm

102° CONGRESSO NAZIONALE SIO (Società italiana e Otorinolaringologia e Chirurgia Cervico-Facciale)
May 27-30, 2015 • Rome – Italy

Presidente: Giuseppe Spriano. Segreteria Organizzativa NordEst Congressi. Tel. +39 06 68807925 – Fax +39 06 68212211 – Website: www.sio2015.com

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

Website: Congress secretariat: GUARANT International Na Pankraci 17, 14021 Prague4, Czech Republic. Website: www.CEorl-hnsprague2015.com

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

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

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

Website: www.iced2015.com

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

Website: www.wclc2015.org

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

Website: meniere2015.eu

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

Information: congresors2015@gmail.com