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Surgical treatment of hypopharyngeal cancer: a review of the literature and proposal for a decisional flow-chart

Introduction

Squamous cell carcinoma of the hypopharynx accounts for about 5% of all head and neck cancers and includes primary hypopharyngeal tumours and advanced tumours from other sites, most notably the larynx. The most frequently affected site is the pyriform sinus representing 70% of cases, followed by the retrocricoid region (15-20%) and the posterior wall (10-15%).

Carcinomas in this region are generally more common in males, aged around 55 years, the exception being tumours in the retrocricoid region, seen in about 30% of British women and unrelated to alcohol consumption or smoking, which are the two main risk factors for hypopharyngeal cancer.

Given the late presentation of symptoms and considerable submucosal spreading of the tumour, squamous cell carcinoma of the hypopharynx is usually detected in advanced stage (III and IV), often with locoregional and/or distant metastases and, consequently, has a poor prognosis.

Treatment options include radiotherapy, chemotherapy and surgery, alone or combined. Early cancers of the hypopharynx can be treated with radiotherapy alone. In terms of locoregional control and survival rates, results are comparable to those of partial surgery.

However, radiotherapy alone does not appear to provide a satisfactory outcome in advanced tumours compared to radical surgery and eventual adjuvant radiotherapy, in terms of locoregional control and survival. In fact, mean five-year survival in patients treated with radiotherapy alone is estimated to be between 12.7 and 13.9%. Survival rates among patients undergoing radical surgery followed by post-operative radiotherapy range from 25-
60% 6. Moreover, salvage surgery performed after high dose radiotherapy gives poor results and has high morbidity rates, especially considering the formation of salivary fistulas 7-12. Neoadjuvant chemotherapy for head and neck tumours has been studied to establish whether it improves the outcome of surgery and radiotherapy albeit with poor results, or as a palliative treatment 11 12. Several authors claim that chemotherapy, alone or combined with radiotherapy, appears to ensure control over locoregional recurrence and disease-free survival, with results comparable to those achieved by surgical procedures, preserving speech and swallowing, for a better outcome 9.

Another therapeutic approach involves concurrent chemoradiation, which appears to guarantee good results in terms of five-year survival (30.7%) 9. However, the highly toxic effects of this concurrent treatment should be taken into account. In the long term, patients often complain of persisting severe dysphagia that sometimes requires percutaneous endoscopic gastrostomy; a further possible complication is pharyngeal-oesophageal stenosis needing multiple dilation procedures. Some patients, instead, continue to rely on tracheal cannula 13.

Surgical resection, more or less radical, continues to be the standard therapeutic choice, whether or not combined with postoperative radiotherapy, even in advanced-stage patients or in those who are unfit to tolerate the other forms of treatment mentioned above. Surgical resection, followed by radiation therapy if necessary, has a higher disease-free survival rate compared to protocols aimed at organ preservation (chemo-radiotherapy) (five-year survival 52 vs. 42%), particularly in the event of large tumours and the presence of neck metastases 9. In addition, primary surgery ensures greater tumour extirpation resulting in better disease control.

Preoperative management

The most suitable therapeutic approach for the management of hypopharyngeal carcinomas must be decided after a thorough preoperative assessment of the patient. Precise data regarding the patient’s medical history is the first crucial diagnostic tool. Dysphonia and dysphagia are the first symptoms reported by patients; associated symptoms may also include reflex otalgia and dysphoena if the tumour is large. Collection of data regarding medical history must be followed preferably by high definition endoscopic examination with narrow band imaging (NBI) and/or autofluorescence (AF). Although they use different principles, these methods allow a much clearer definition of the areas affected by the tumour compared to standard white light endoscopy, thus ensuring better clinical staging of the disease 14 15.

Some subsites, such as the pyriform sinus and the retrocricoid area, are difficult to explore with a fiberscope. However, evidence of indirect signs like oedema and hyperaemia of the mucosa and/or the presence of impaired salivary drainage should point to the need for further diagnostic investigation 7 16.

In these cases a direct microlaryngoscopy with rigid angled optics is mandatory, eventually associated with NBI and/or AF. This allows the surgeon not only to carry out a systematic evaluation of the upper aerodigestive tract and oesophagus (searching for signs of any synchronous tumours), but also to perform targeted biopsies of the lesions visualized 7 11 12.

Tumour staging should then be completed with computed tomopgraphy (CT)-scan, MRI or positron emission tomography (PET)-CT imaging. CT determines both the locoregional extent and depth of invasion of the tumour as well as lymph node involvement. If the tumour extends laterally, the thyroid cartilage, the first barrier to cancer spread, may present signs of sclerosis in the event of initial invasion, or be completely interrupted. Sagittal sections are able to determine whether the tumour has invaded the paraglottic and pre-epiglottic space, (if tumour volume extends inward and forward) 11.

Compared to CT, MRI offers a better resolution of soft tissue and a higher sensitivity in evaluating cartilage infiltration (albeit CT has better specificity); however, it is much more sensitive to the slightest movement of patients and therefore, is not routinely used in the clinical staging of hypopharyngeal tumours 11. Compared to other imaging techniques, PET is less frequently used to clinically stage tumours in the hypopharynx region. Despite its high sensitivity in identifying tumour presence, it has a much lower specificity due to false positive results caused, for instance, by inflammatory processes or foci of infection, which is not uncommon in this region 12.

Integrated PET-CT has been introduced to improve spatial specificity and resolution. Some studies report that PET-CT seems to have a sensitivity equal to PET alone, but a considerably higher specificity compared to CT alone, both in initial staging (90.5 vs. 62.2%, p < 0.01) and during follow-up (97.2 vs. 74.4%, p < 0.01) 17. Furthermore, combined PET-CT appears to be very useful in the search for an unknown primary tumour presenting with laterocervical metastases 15. PET and/or PET-CT are therefore particularly indicated for a more thorough assessment of synchronous tumours, distant metastases and retropalatine lymph node involvement, which are decisive factors in the choice of treatment 19 20 as well as during follow-up. Thanks to their sensitivity in detecting the slightest disease persistence or recurrence, salvage treatment can be initiated earlier 21 22.

Ultrasound scanning of the neck is rapid, non-invasive and inexpensive, and can assess the status of laterocervical lymph nodes and provide a diagnosis through fine needle aspiration cytology. However, it achieves a high sensitivity and specificity only if performed by experts with a long-standing experience in this diagnostic field 23.
Surgical treatment of hypopharyngeal cancer

Decisional flow charts

The surgical management of the hypopharyngeal cancer depends on the lesion’s extension and the subsites involved, and often requires some form of reconstruction. Reconstructive strategies for patients with defects of the upper aero-digestive tract are extremely versatile and depend on whether the larynx, or part of it, has been preserved. If the larynx is totally resected, in fact, a separate conduit for breathing and swallowing are established and restoration of the principal functions to this region are markedly different. Urken et al., in 1997, proposed a classification system based on the anatomic and functional regions of the laryngopharynx; in this scheme, the division of the hypopharynx into the lateral and posterior walls is useful to reflect if a defect needs to be resurfaced after partial or radical surgery.

In 2003, Disa et al. proposed a classification based on the types of defect of the pharyngo-oesophageal segment after total laryngectomy so as to choose the most suitable reconstruction method. The following resection methods were described:

Type 0: minimal defects of the pharyngo-oesophageal segment that are amenable to primary closure
Type I: partial lesions affecting less than 50% of the pharyngo-oesophageal segment but are not amenable to primary closure
Type II: partial lesions affecting more than 50% of the pharyngo-oesophageal segment
Type III: extended longitudinal lesions involving other anatomical regions (nasopharynx, oropharynx, floor of the mouth or jaw)

Type IV: pharyngo-oesophageal defect with extension to cervical oesophagus.

These Authors claimed that type 0 lesions can be closed primarily. For a type I or II defect, the use of a pharyngeal strip of native mucosa is recommended to prevent a circumferential scar forming at the proximal or distal end of the repair; if the native tissues have been exposed to radiation and/or chemotherapy, the risk of development of a fistula or a stricture is high.

To prevent this complication, Urken et al. proposed a new classification scheme:

Type 0: minimal defects of the pharyngo-oesophageal segment that are amenable to primary closure
Type I: non-circumferential defect with a presence of a viable strip of mucosa, measuring a minimum of 2 cm in width
Type II: circumferential defect extended no further cephalad than the level of the vallecula
Type III: circumferential or non-circumferential defect extended cephalad to the level of the vallecula
Type IV: any resection that extends caudal to the level of the clivices.

Moreover, they include a superscript “i” to indicate the wound healing is impaired because of prior therapy and likely to be problematic and the superscript “s” to indicate the necessity of a flap of skin for wound closure.

We believe that the decisional flow-chart of the reconstructive methods after surgery of the hypopharynx should be based not only on the extent of resection, but also on the subsites involved.

Partial resections

Figure 1 shows our proposal of decisional flow-chart in case of partial resections of the hypopharynx, i.e. in T1, T2 and some T3 tumours involving only one of the subsites of the hypopharynx (lateral wall, pyriform sinus, posterior wall). Above all, the choice of surgical procedure depends on the close proximity of hypopharyngeal mucosa to the larynx: in fact, in most cases, this usually involves having to carry out partial or total resection of the larynx itself.

The resection defect of tumours affecting the lateral wall of the pyriform sinus can be closed directly if the extent of the lesion is less than 50%; otherwise, reconstruction is needed, preferably with a thin, pliable flap.

Reconstructive techniques may involve the choice of a pedicled myocutaneous platysma flap, a radial forearm free flap (RFFF) or anterolateral thigh flap (ALT). If the tumour has invaded the entire pyriform sinus, conservative surgery for advanced lateral pharyngo-laryngeal tumours is feasible only in selected cases:

- pharyngo-laryngeal tumours limited to one wall with or without extension into the pyriform sinus apex;
- the tumour must not cross the midline of the retrocricoid region;
- the tumour must not extend cranially infiltrating the inter-arytenoid mucous membrane (putting contralateral arytenoid cartilage at risk);
- the integrity and movement of the healthy vocal cord should be preserved to re-establish functional speech;
- tumour extension into the posterior hypopharyngeal wall need not be an absolute contraindication to surgery as long as the lateral wall of the contralateral pyriform sinus is not affected.

![Fig. 1. Principles of reconstruction after partial resection of the hypopharynx.](image)
One surgical approach that can be used in these cases is that put forward by Urken. This procedure involves vertical hemilaryngectomy and removal of half of the hyoid bone, the epiglottis, thyroid cartilage and the cricoid, if the tumour involves the pyriform sinus apex. The following step is the reconstruction of the anatomical defect with a RFFF, together with the harvesting of a segment of rib cartilage so as to recreate the glottic plane. Hagen suggested modifying this technique, eliminating the use of cartilage to widen the remaining breathing space in the larynx.

Instead, when the tumour affects the posterior wall of the hypopharynx without extension below the arytenoid plane and into the cervical oesophagus, the choice of reconstruction method has to consider functional outcome in terms of swallowing. In the past, this tumour site required total laryngectomy due to the lack of reconstructive techniques. Nowadays, however, the larynx can be preserved as a result of the introduction of free flaps.

Reconstruction of the posterior wall can be carried out using a platysma flap, particularly if less than 50% of the mucosa has to be resected. This pedicled flap has the advantage of being thin and pliable with a reduced operating time compared to free flaps. However, traction on the vascular pedicle involves a high risk of flap necrosis. For this reason, reconstruction should use a RFFF or ALT if the clinical patient’s condition is good. Some Authors consider the RFFF an excellent reconstructive choice in these kinds of patients; however, they do report a high risk of chronic aspiration with the resulting need for long-term enteral feeding.

In accordance with this, Lydiatt et al. retain that partial laryngectomy and subsequent reconstruction with a RFFF-FA is feasible with acceptable morbidity in patients with no underlying diseases (ASA 1 and 2); this procedure is unadvisable in patients for whom anaesthesia poses a higher risk (ASA ≥ 3). In our case-series of 165 hypopharyngeal reconstructions performed between November 1995 and April 2012, 41 patients (25%) underwent reconstruction following partial pharyngectomy with partial or total resection of the larynx. Hemipharyngo-total laryngectomy was performed in 15% of patients; partial pharyngectomy in 2% of cases and 8% of patients underwent vertical hemipharyngolaryngectomy according to Urken’s technique.

Table I summarizes the type of ablative surgery and reconstruction performed. A pedicle flap was used in 46% of these cases (group A); while a free flap was conducted in the other 54% (group B).

Table II reports the analysis of complications in the different types of partial pharyngectomies. Minor complications, i.e. those requiring only medical treatment, occurred in 27% of the cases; major complications, i.e. those requiring re-intervention, occurred in 12% of the cases; while flap necrosis occurred in 2 cases of Urken’s technique.

Circular resections

Figure 2 shows the decisional flow chart to be used in case of circumferential resection of the hypopharynx. The surgical treatment of advanced stage tumours (T3-T4) necessitates a different reconstruction method depending on whether or not the tumour extends into nearby structures (cervical oesophagus, neck, oropharynx). In particular, if the tumour extends downward in the upper mediastinum, or in case of a synchronous tumour of the thoracic oesophagus, circumferential pharyngolaryngectomy needs to be associated with total oesophageal resection.

A study published by Dudhat et al. analyzed the incidence of complications that may occur after gastric pull-up. These are divided into intraoperative complications (rupture of the trachea and pleura), post-operative complications (detachment from the anastomosis, hypocal-

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urken PM</td>
<td>-</td>
<td>-</td>
<td>13 (32%)</td>
</tr>
<tr>
<td>Hemipharyngo-TL</td>
<td>16 (40%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Partial pharyngectomy</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (46%)</td>
<td>22 (54%)</td>
<td>41 (100%)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Urken</th>
<th>Hemipharyngo-TL</th>
<th>Partial pharyngectomy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>2 (15%)</td>
<td>7 (28%)</td>
<td>2 (66%)</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Major</td>
<td>3 (23%)</td>
<td>2 (8%)</td>
<td>-</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Flap necrosis</td>
<td>2 (15%)</td>
<td>-</td>
<td>-</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>7/13 (53%)</td>
<td>9/25 (36%)</td>
<td>2/3 (66%)</td>
<td>18/41 (44%)</td>
</tr>
</tbody>
</table>

TL: total laryngectomy.
caemia, secondary haemorrhage and abdominal wound dehiscence), and long-term complications, such as tracheal stoma stricture and gastric reflux. The authors conclude that gastric pull up involves minimal mortality, acceptable morbidity and short hospital stay.

If hypopharyngeal tumour extension is limited to the neck above sternum, the aim of reconstruction must bear in mind the two main functions of the hypopharynx, such as swallowing and speech. In the former case, contraction of the hypopharyngeal walls moves the food bolus into the oesophagus, while in the latter distension and vibration of the pharyngeal walls is responsible for phonation. Thus, reconstruction does not simply consist in replacing the oro- or nasopharynx better than other flaps, and improves the quality of the patient’s remaining life span.

Reconstruction of the hypopharynx using a jejunal flap requires two surgical teams. Disadvantages include a high risk of necrosis, fistulas and bowel complications.

Another problem is the discrepancy between the lumen of the flap and the pharyngeal defect when the resection extends to the oro- or nasopharynx.

Two reconstructions to overcome this problem have been proposed in our previous study. One solution is the creation of an end-to-side anastomosis of the cranial end, easy and rather quick to perform, but with risk of kinking, stenosis, or creation of a blind loop; the second possibility is the creation of a jejunal reservoir. This technique is more difficult, longer, with a high risk of salivary fistulas, even though the recovery of the swallowing function is much more effective.

Other authors have reported the possibility to use other free flaps, such as RFFF and ALT, which are equally thin and pliable. In fact, these flaps have been shown to involve a much lower percentage of complications, such as fistulas and stenoses caused by scar tissue, compared to the jejunal flap, as well as offering comparable if not better speech production outcomes.

The lower rate of complications at the donor site, the opportunity to close the donor site primarily and that of using a myocutaneous flap are advantages that lead some authors to prefer the ALT rather than the RFFF to reconstruct this anatomical site.

If a RFFF or ALT are chosen, these should be tunnelled and sutured to the prevertebral fascia instead of being tubed, to reduce the incidence of strictures and fistulas. A salivary stent has to be used during tunnel reconstruction to avoid salivary fistulas and to reduce retraction of scar tissue.

In case of poor clinical conditions or poor prognosis, it is better to adopt a quick and easy reconstruction. In this case, the first choice is represented by the pectoralis major flap (PM).

This pedicled flap has an excellent blood supply which allows for single-stage reconstruction of the defect with minimal donor site morbidity; furthermore, its thickness can be used to fill large defects and helps to protect the carotid artery. However, the flap is often too bulky to allow tailoring into a tube for the reconstruction of circumferential defects of the pharyngo-oesophageal segment without the risk of stricture of the neopharyngeal lumen.

To avoid this complication, several surgeons have adapted a surgical technique put forward by Fabian in 1984 consisting of tunnelling the pectoralis major flap to reconstruct the lateral and anterior walls of the hypopharynx and covering the prevertebral fascia with a skin graft. In this way, the bulkiness caused by the flap itself is reduced, re-establishing a sufficiently wide lumen which is kept open thanks to the positioning of a salivary stent (which is removed after 4-6 weeks). The modification suggested by Spriano avoids using a skin graft and involves suturing the posterior walls of the oropharynx and cervical oesophagus directly to the prevertebral fascia, which will form the posterior wall of the neopharynx.

This technique has been supported by Soussez et al., who also did not consider it necessary to place a salivary stent.

Several authors believe that pedicled flaps should be preferred over free flaps due to the relative ease of their placement, reduced operating times and shorter hospital stay. Moreover, compared to jejunal flaps, they do not give rise to complications that may be linked to abdominal surgery.

There is no doubt that pedicled flaps must represent the standard choice for salvage surgery after primary chemoradiation protocols, due to the patient’s poor general condition, advanced stage of the disease and low life expectancy.

Moreover, other authors state that the functional outcome is not linked to the intrinsic characteristics of the flap, but to the surgical expertise used during reconstruction. In our experience, 121 (73%) of the 165 patients underwent reconstruction following total laryngectomy and cir-
cumferential resection of the pharynx for squamous cell carcinoma of the hypopharynx. Thirty-five percent of the patients were reconstructed with a pedicle flap (group A); while in the remaining 65% of cases reconstruction was performed with a free flap (group B) (Table III). Flap necrosis occurred in 7% of patients of the group A and in 13% of patients of the group B. Major and minor complications were similar in the two groups (Table IV). The results in terms of recovery of swallowing after reconstruction with PM flap are controversial. Some authors found no significant differences in terms of recovery of free diet in patients undergoing reconstruction with a PM flap compared with patients reconstructed with free flaps. Others have observed longer periods of NG-tube feeding and more dietary restrictions in reconstructions with pedicled flaps. Our experience has shown a higher possibility of restoration of normal feeding with free flaps instead of PM flap.

If the recovery of swallowing function after circumferential resection is obviously required, the recovery of vocal function is, wrongly, regarded as secondary, probably because of the low life expectancy of these patients. We have already demonstrated that oesophageal voice rehabilitation is often impossible for both free and pedicled flaps. Pedicled flaps are usually too thick and stiff to vibrate during the passage of air from the stomach to the mouth, the jejunum flap does not allow the passage of air for its intrinsic peristalsis and the RFFF or ALT flaps, although thin and pliable, require a high air pressure to vibrate. The shunt between the trachea and the flap, thanks to the high expiratory pressure provided by the lungs, allows the vibration of the walls of free flaps, but it is insufficient to overcome the resistance offered by the walls of the pedicled flap. A voice-prosthesis represents the only opportunity to restore the capacity of communication in these kind of patients.

Conclusions

Poor diagnosis generally affects the severity of hypopharyngeal carcinomas. This occurs because they are asymptomatic for a long time and have thus reached an advanced stage by the time they are diagnosed. Cervical metastases are often the first signs of disease. Organ-preservation protocols have low survival rates and can, however, give rise to serious complications. Surgery often involves extensive resection, but reconstructive techniques using free flaps can minimize functional complications using tissues that are able to re-establish contractions and vibration of the walls of the pharynx.

If free flap reconstruction is not possible, the surgical approach must resort to using pedicled flaps. Even in this event, however, a thorough surgical procedure can guarantee acceptable functional outcomes. The oncological surgeon should be aware of and able to perform all the radical and reconstructive procedures so as to guarantee the patient not only adequate disease management, but also the best possible quality of residual life.

Table III. Type of reconstruction for circumferential resection.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPL PM</td>
<td>40 (33%)</td>
<td>10 (8%)</td>
<td>50 (41%)</td>
</tr>
<tr>
<td>CPL LD</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>CJenun RFFF</td>
<td>64 (53%)</td>
<td>5 (4%)</td>
<td>74 (61%)</td>
</tr>
<tr>
<td>CJenun ALT</td>
<td>50 (41%)</td>
<td>13 (16%)</td>
<td>64 (53%)</td>
</tr>
<tr>
<td>Total</td>
<td>79 (65%)</td>
<td>16 (13%)</td>
<td>95 (77%)</td>
</tr>
</tbody>
</table>

Table IV. Type of complications vs. type of partial pharyngectomy.

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>17 (40%)</td>
<td>14 (18%)</td>
<td>31 (26%)</td>
</tr>
<tr>
<td>Major</td>
<td>4 (10%)</td>
<td>23 (29%)</td>
<td>27 (22%)</td>
</tr>
<tr>
<td>Flap necrosis</td>
<td>3 (7%)</td>
<td>13 (16%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>24/42 (57%)</td>
<td>50/79 (63%)</td>
<td>74/121 (61%)</td>
</tr>
</tbody>
</table>

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Surgical treatment of hypopharyngeal cancer


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Head and neck

Vascular pedicle ossification of free fibular flap: is it a rare phenomenon? Is it possible to avoid this risk?

Ossificazione del peduncolo vascolare del lembo libero di fibula: si tratta di un fenomeno realmente raro? È possibile evitarlo?

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SUMMARY
Free fibula flap is the most common free tissue transfer for maxillary and mandibular reconstructions. The distal part of the harvested bone is transferred, while the proximal part is removed by sub-periosteum dissection. The vascularized periosteum attached to the vascular pedicle has osteogenic potential. 61 patients reconstructed with free fibula flaps were divided in 2 groups: 41 flaps performed with a standard technique and 20 flaps performed by dissecting the periosteum from the pedicle. Patients were followed up with orthopantomography and CT scan at 6, 12, 18 and 24 months after surgery. The minimum follow-up time was 18 months. With retrospective analysis of the first group we diagnosed 7 pedicle ossifications on 41 reconstructions (17%). In the second group, no pedicle ossification was observed (p < 0.05). The dissection of periosteum from the vascular pedicle of free fibula flaps avoids the risk of ossification.

KEY WORDS: Free fibula flap • Vascular pedicle ossification • Mandibular reconstruction • Maxillary reconstruction • Microsurgery

INTRODUCTION
Free flaps, by combining a high success rate with low donor site morbidity, are considered the gold standard for the reconstruction of tissues lost during oncologic surgery. Free fibula flap is routinely used for large jaw reconstructions. This can be considered a safe surgical procedure even in elderly head and neck cancer patients. The harvested flap transfers almost the full length of bone, while preserving the integrity of the knee and ankle joints. The harvested fibula is contoured to match the shape of the surgical defect by removing the proximal part of the bone, which permits the pedicle to be lengthened to join the neck vessels. For contouring the flap, osteotomies preserve the interconnections between the periosteum and pedicle, while retaining the surrounding muscle to preserve the blood supply to the bone. The osteogenic potential of vascularized periosteum is well described in the literature, and many factors have been associated with an increased osteogenic activity in periosteal tissue.

The vascularized periosteum attached to the vascular fibula pedicle has osteogenic potential, and some reports of this uncommon phenomenon have been cited in the
recent literature, with a maximum reported incidence of 9.3%. This study aimed to investigate bony free flap pedicle ossification through a 7-year retrospective study to calculate the frequency of the condition. We also discuss its management and propose a surgical technique, applied prospectively in our cohort of patients, to avoid this phenomenon.

Materials and methods

We performed a retrospective-prospective study on 61 patients who underwent maxillofacial reconstructions with free fibula flaps after oral cancer ablation at “S. Orsola Malpighi” Hospital in Bologna (Maxillo-Facial and Plastic Surgery Units) during 2004 to 2011.

Patients were divided in two groups: in the first we enrolled 41 flaps performed using a surgical standard technique during 2004 to 2007, and assessed retrospectively. Due to the high percentage of pedicle ossifications in the first group, from January 2008 all flaps were harvested in our Unit according to the surgical periosteum dissection technique. In this second group, we enrolled 20 flaps performed by dissecting the periosteum from the vascular pedicle from 2008 to 2011. This second group was evaluated prospectively.

Follow-up included clinical examination and radiographic evaluation. All patients were followed up systematically with orthopantomography and CT scan at 6 and 12, 18 and 24 months after surgery, according to the standard oncological follow-up procedure. The minimum follow-up time was 12 months.

We evaluated the descriptive statistics of bony free flaps in the two groups, and the percentage of pedicle ossification was assessed. Demographic characteristics were evaluated and univariate analysis was performed. A p < 0.05 was considered statistically significant.

Surgical technique of periosteum dissection

The technique of fibula harvesting is well known and standardized. During the harvest of the fibula free flap, approximately 20 cm of bone is harvested. The proximal aspect of this bone is seldom necessary for reconstruction, but is removed with the flap to facilitate vascular pedicle dissection. Subsequently, during flap contouring, the unnecessary proximal fibula is discarded.

A subperiosteal dissection is performed along the area of bone to be discarded to avoid damage to the vascular pedicle. This results in up to 10 to 15 cm of well-vascularized periosteum along the peroneal vascular pedicle. This tissue can usually be draped along native bone at the side of the reconstruction or placed over the vessels in the neck to protect the anastomoses.

To avoid the risk of pedicle ossification we performed, in our second study group of patients, a periosteum dissection technique by removing the periosteum exceeded from the proximal peroneal vascular pedicle. This was performed before vascular anastomoses, and can be done using optical loop magnification. It takes about 10-15 min more than the standard surgical procedure.

Results

The flap survival rate was 100% in both groups. Microsurgery was performed on the superior thyroidian artery in 79% of cases, and on the lingual artery in 21% of cases. In all patients the recipient vein was the thyrolinguofacial trunk. In the first group of patients, 7 pedicle ossifications were diagnosed (17%); 3 were in men and 4 in women. In 6 cases (85%), the fibula was used for mandible reconstruction; in 1 case (15%), the flap was performed for maxillary reconstruction.

Clinical signs were reported in 2 patients (28%). One patient had hard swelling of submandibular region; one patient had pain in cervical region associated with trismus. Onset of vascular pedicle ossification occurred between 115 and 370 days (median 196 days). Diagnosis was made using orthopantomography (Fig. 1) and CT scan (Fig. 2). In 1 patient, the ossification was diagnosed at the 6 month post-operative follow-up, and in 6 patients at 12 months follow-up.

Only the 2 symptomatic patients were surgically treated. Surgical resection of ossified pedicle was performed through submandibular access (Fig. 3). It did not influence the vitality of the flap.

Asymptomatic patients were also followed up. In the second group of 20 patients, we performed dissection of the periosteum from the vascular pedicle. In this group, to date, no pedicle ossification has been observed. Univariate analysis showed a statistically significant difference (p < 0.05) between the two study groups. No significant increase in operative time was noted, and additional complications were not observed.

Fig. 1. Orthopantomography showing free fibula pedicle ossification of a young patient treated for oral squamous cell carcinoma.
Vascular pedicle ossification of free fibular flap

Discussion

Only four articles in the literature report ossification of the vascular pedicle in free fibula flaps. Few of the reported cases were symptomatic, presenting trismus, hard swelling, severe pain during mastication and during twisting of the ipsilateral neck.

In one case report ossification was an incidental finding during re-intervention for recurrence. The reported symptomatic cases were studied using orthopantomography, CT scan and in one case biopsy for the suspect of recurrence. The maximum incidence reported in literature is of 9.3%. The incidence of ossification diagnosis seen in the present study was higher (17%) probably in relation to the systematic radiological follow-up performed in this series.

In our study, 5 of 7 patients were asymptomatic, and most of the time there were no clinical expressions of the calcified pedicle. This is the reason why ossified pedicles are underestimated. Undiagnosed ossified pedicles may potentially lead to complication as pain, trismus and swelling.

Clinically, trismus may be the result of the involvement of masticatory or buccal spaces, subsequent to the disposition of the vascular pedicle in the cheek during the reconstruction of maxillary defects. Swelling of the submandibular region is the typical sign of ossification of pedicle in the reconstruction of mandibular defects. Usually, this sign can be interpreted as a local relapse.

Gonzalez Garcia reported a histological study showing that the bone seems to be mature along the entire pedicle with no gradation, and that bone formation is invasive towards the vascular pedicle.

The factors influencing the osteogenic potential of vascularized periosteum have been described: contact with vascularized bone, mechanical stimuli, growth factors, systemic steroids and hormones. In all cases presenting vascular pedicle ossification, the contact and continuity between the reconstructed bone and periosteum was preserved, which is fundamental for osteogenesis. In a periosteal free flap in which no contact with bone occurs, the level of ossification is inferior. This contact may play a role because progenitor cells and bone morphogenetic proteins (BMPs), factors participating in osteoprogenitor recruitment, proliferation, and differentiation into chondrocytes and osteoblasts have been detected in the site of bone fracture. During free flap surgery, osteotomy can be considered a fracture.

Local mechanical tension is another critical factor in bone healing. A recent study suggests that mechanical stress supports BMPs signalling. Mechanical forces applied to the stabilized free flap and micromotion, associated with speech or chewing, may enhance bone healing and callus formation. In addition, in our series, for maxillary reconstruction, the pedicle passed through a subcutaneous tunnel in the cheek. This is a potential risk of periosteum stretching. Instead, in mandibular reconstruction, the vascular pedicle, when short, may be stressed by movements of the head. It was postulated that this mechanical stimulus resulted in bone formation by the periosteum.

Smith and Funk reported a 12-year-old girl with periosteal ossification and suspected that hormonal factors can also have effect on osteogenesis. Tenenbaum and Heersche demonstrated in an in vitro chick model that brief exposure to dexamethasone promoted periosteal osteogenesis. Oestrogen deficiency is also known to lead to osteoporosis, but the exact role of oestrogen in bone metabolism is difficult to quantify. In our cases, the female-to-male ratio was 4:3. All females were in an active hormonal status, and one was in the immediate post-partum period.
Finally, inflammation could be a potential factor play an active role in osteogenesis. The mechanism is not well defined, but is possible that the increase of blood flow during inflammation allows osteoprogenitor recruitment. In our series, correlation with inflammation can be noticed, as in 6 of the 7 ossifications an inflammatory complication occurred. Indeed, all these patients had postoperative infection and inflammation at the reconstructed site. In our experience we did not notice any correlation with gender, as postulated by Autelitano. We agree with all prior reports that recommend surgery for the removal of the ossified pedicle only in symptomatic patients. Autelitano proposed to modify the technique and dissect the periosteum from the vascular pedicle to avoid the risk of ossification. Gonzalez Garcia is instead reluctant to perform “extra” dissection of the periosteum that would increase the time and risk of vessel damage.

In our experience, pedicle ossification is not a rare phenomenon, being radiologically present at 12 months in the 17% of free fibula reconstructions performed with the classical technique. Moreover, the dissection of the periosteum from the pedicle avoids the risk of ossification without increasing the rate of complications in this series.

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Is there a role for postoperative radiotherapy following open partial laryngectomy when prognostic factors on the pathological specimen are unfavourable? A survey of head and neck surgical/radiation oncologists

Ha un ruolo la radioterapia postoperatoria dopo laringectomia parziale quando i fattori prognostici istopatologici sono sfavorevoli? Survey di ORL e radiooncologi


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SUMMARY

Our aim was to survey the opinions of Italian radiation and ENT oncologists regarding the role of postoperative radiotherapy (PRT) and the appropriate dose to be given to patients with remnant larynx (RL) after open partial laryngectomy (OPL). The radio-oncologists (ROs) of the Italian Radiation-Oncologist Association (AIRO) and the ENts of the Head-Neck Oncology Society (AIOC-IIIHNS) were contacted through a SurveyMonkey online interface questionnaire. There were 148 usable responses. The majority of ROs recommended PRT in the case of positive/close margins (R+ or Rclosed) or in the case of initial involvement of thyroid cartilage (pT3tci). In the same cases, ENts prefer a “watch and wait” policy (w&w). Both disciplines recommended w&w in the case of negative margins (R-). Finally, the majority of ROs recommended irradiating RL with 62-66 Gy in R+, with 56-66 Gy (61.4%) in Rclosed and with 56-60 Gy (34%) in pT3tci. In conclusion, OPL raises new considerations about PRT.

KEY WORDS: Larynx • Postoperative radiotherapy • Conservative laryngectomy • Partial laryngectomy • Head and neck cancer

RIASSUNTO

L’introduzione nella pratica clinica della Chirurgia conservativa nei carcinomi laringei e della Radioterapia ad intensità modulata (IMRT) conformabile ai volumi non problematiche alla comunità scientifica relativamente alle dosi e volumi da radiottrattare ed alle tolleranze non note del residuo laringeo. Il principale scopo di questa “Survey” è di raccogliere le opinioni di ORL e radiooncologi italiani relativamente al ruolo della radioterapia postoperatoria (PRT) e l’entità di dose da erogare al residuo laringeo (RL) dopo chirurgia conservativa open-neck (OPL). Un questionario online (attraverso l’interfaccia SurveyMonkey) è stato inviato ai radiooncologi della Associazione Italiana di Radiooncologia (AIRO) ed agli ORL della Associazione Italiana di Oncologia cervicocefalica (AIOC-IIIHNS). Le risposte utilizzabili sono state 148. La maggioranza dei Radiooncologi ha raccomandato la PRT nei casi di margini positivi o close (R+ o Rclosed) o nel caso di coinvolgimento iniziale della cartilagine tiroide (pT3tci). Negli stessi casi gli ORL preferivano un atteggiamento di vigilare attesa (“watch and wait”) (w&w). Entrambi gli specialisti raccomandavano w&w nel caso di margini negativi (R-). Infine la maggioranza dei Radiooncologi raccomandava l’irradiazione del residuo laringeo a dosi di 62-66Gy nel caso di R+; a dosi di 56-66 Gy (61,4%) nel caso di Rclosed e di 56-60 Gy (34%) nei pT3tci. In conclusione l’introduzione nella pratica clinica della laringectomia conservativa open-neck solleva nuove riflessioni relativamente al ruolo della Radioterapia postoperatoria per quanto riguarda le indicazioni, le dosi da utilizzare sul residuo laringeo (se giudicato a rischi di recidiva) ed i volumi da radiottrattare.

PAROLE CHIAVE: Laringe • Radioterapia postoperatoria • Laringectomia conservativa • Laringectomia parziale • Tumori testa-collo
Introduction

The optimal treatment strategy for squamous cell carcinoma (SCC) of the larynx is still a matter of debate. Radiotherapy (RT), with or without chemotherapy (CT), open partial laryngectomy (OPL) and endoscopic resection are established options for functional preservation treatment. Various factors influence the choice of the treatment strategy: primary tumour site, stage and expected results, as well as the expertise of the multidisciplinary team, availability of the service and rehabilitation facilities, along with the patient’s decision.

The early clinical stages of supraglottic and glottic cancer that do not require total laryngectomy (most T1-2 N0 cases) are usually considered for either conservative surgery (endoscopic resection, OPL with/without neck dissection) or RT. Single-modality treatment with surgery or RT is generally recommended for early-stage disease (stage I or stage II) in order to preserve the other choice in case of recurrence.

Resectable, advanced-stage glottic and supraglottic primaries are usually managed with a combined modality approach. If treated with primary surgery, total laryngectomy is typically required. However, some authors recommend an OPL approach even in selected advanced cancers with or without postoperative radiotherapy (PRT). These selected cases often need to resort to PRT, which could add additional risk of late laryngeal toxicity, jeopardizing the expected functional outcome.

Furthermore, early-stage laryngeal cancers (T1-2 N0) can be clinically under-staged (16.3%) and postoperative adverse pathologic findings might place these cases into a pathologically advanced stage (i.e. early invasion into the thyroid cartilage, metastatic adenopathies (pN+) with or without extra-capsular extension (ECE) or positive residual margins (R(+))

In these situations, the optimal treatment option, whether to transform a conservative approach into immediate total laryngectomy (ITL), or to preserve the organ function by adopting PRT – CT or a close “watch and wait” policy, is unclear. At present, the most common Head and Neck Cancer (HNC) guideline leaves wide freedom of choice among possible therapeutic options (re-excision, RT, RT-CT), and the recommendations regarding the choice of clinical volumes to be targeted and the respective radiation dose to be released are vague.

The aim of this study was to evaluate the opinion of Italian Radiation Oncologists (ROs) and ENTs on PRT ± CT when clinical early-intermediate stage (cT1-T2) or limited T3 conservatively operable with cN0) glottic and supraglottic cancer are pathologically upgraded in consequence of their unfavourable histopathologic prognostic factors (e.g. pT3n0, or R(+)).

In particular, the following were investigated:

- suggestions of HNC specialist regarding the treatment of RL in the presence of the following unfavourable histopathologic prognostic factors: R(+), (margins < 1 mm) or R(close) (margins 1-5 mm) or pT3tci,
- when neck volumes without metastatic adenopathies need to be targeted in circumstances in which the RL needs to be irradiated;
- the dose of radiation that ROs recommend for the RL, considering the risk of sequelae are not fully known.

Materials and methods

A multidisciplinary review board (ROs and ENTs:) approved the online questionnaire that was sent to RO members of the Italian Association of Radiation Oncology AIRO head and neck workgroup (161 ROs), and the ENT members of the Italian Head and Neck Oncologic Society (AIOPC-CHNS) (101 ENTs). The questionnaire focused on the behaviour of different disciplinary specialists facing glottic and supraglottic clinically early-intermediate staged head and neck cancer (T1-T2-and conservatively operable T3 with cN0) after OPLs, when the histological prognostic factors placed these cases into more advanced stages.

The survey was prepared on the SurveyMonkey online interface (www.SurveyMonkey.com). Personalized e-mail invitations with direct links to the survey were sent on 9 January 2012. No compensation was offered to respondents. Responses were collected over a 2-month period (until 9 March 2012).

Survey questions

The survey contained demographic information and 12 multiple-choice questions. The first five questions (Table I) regarded respondents’ clinical setting and experience. Questions 6-9 (Figs. 1-4) focused on the therapeutic approach to RL after OPLs in the case of unfavourable prognostic factors regarding T-site (N-site prognostic factors were not considered in these questions). Questions 10-11 (Fig. 5) focused on radiation target volumes (RL ± lymph-nodal areas) in those cases in which the N-site prognostic factors are considered uncertain in the hypotheses in which the RL needed to be irradiated. The last question (Fig. 6, Table II) was reserved for ROs in order to know the radiation dose level recommended for RL in the case of R(+), or R(close) or R(tci) or pT3tci.

Analytical overview

Dataset analysis was clusterized into ENTs and ROs for direct comparison.

Statistical analysis

Descriptive statistics, Fisher’s exact tests (Fisher’s P(2-tailed)) or chi-square tests (P(chi-square) were performed using Winpepi software, where appropriate. When a significant chi-square association was found, adjusted residuals were calculated to indentify those cells that contributed most
to the chi-square. Using the contingency table of Fisher’s exact tests, the examined specific endpoint (e.g. PRT) was tested against the sum of remaining endpoints (i.e. ITL and w&w policy), considered together with the alternative hypothesis (see Figs. 1-4). Frequencies were automatically calculated by Survey-Monkey.

### Results

A total of 154 of 262 questionnaires sent (161 to ROs and 101 to ENTs) were filled in (58.8% response rate). Of the 154 respondents, 6 were excluded because they answered only the first three questions, which were concerned only with institutional demographics. Consequently, 148 usable responses (56.4%) were included in the final analysis: 109/161 ROs (respondent RO \( \% = 67.7 \% \)) and 39/101 ENTs (respondent ENT \( \% = 38.6 \% \)).

**Respondents’ clinical setting and experience (Table I)**

Respondents represented a variety of working settings: primarily exploiting activity in non-academic hospitals (58%), academic hospitals (25%), and private institutions (17.0%). Most respondents (87.2%) had a HNC-board (HNCB) in their institution. Particularly, 65.1% of respondents evaluated all patients before any specific treatment within their HNCB, while 34.9% evaluated only selected patients (inoperable patients selected by ENTs or patients who did not meet institutional guidelines).

Among those who answered the questionnaire, 31/39 ENTs (79.5%) vs. 56/109 ROs (51.4%) had more than 10 years’ experience working with HNC patients (Fisher’s \( P(\text{two tailed}) = 0.002 \)) (see details in Table I, Question 1). Conversely, more ROs than ENTs worked in institutions with less than 50 HNCPs per year (see details in Table I; Question 1).

#### Table I. Respondents’ clinical setting and experience.

| 1. How many years have you been working with Head and Neck Cancer Patients (HNCPs)? | RO N (%) | ENT N (%) | Ratio RO%/ENT% | \( p^* \)  \\
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>a) Less than 5 years</td>
<td>18 (16.5%)</td>
<td>1 (2.5%)</td>
<td>6.44</td>
<td>0.025&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>b) 6-10 years</td>
<td>35 (32.1%)</td>
<td>7 (17.9%)</td>
<td>1.78</td>
<td>0.09&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>c) 11-20 years</td>
<td>36 (33.0%)</td>
<td>12 (30.8%)</td>
<td>1.073</td>
<td>0.79&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>d) More than 20 years</td>
<td>20 (18.3%)</td>
<td>19 (48.7%)</td>
<td>0.37</td>
<td>0.000&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

| 2. How many HNCPs are taken care of per year in your institution? | RO N (%) | ENT N (%) | Ratio RO%/ENT% | \( p^* \)  \\
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Less than 50</td>
<td>39 (35.8%)</td>
<td>5 (13.6%)</td>
<td>2.7</td>
<td>0.09&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>b) From 51-100</td>
<td>37 (33.9%)</td>
<td>17 (44.7%)</td>
<td>0.76</td>
<td>0.235&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>c) From 101-150</td>
<td>19 (17.4%)</td>
<td>7 (18.4%)</td>
<td>0.95</td>
<td>0.890&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>d) More than 150</td>
<td>14 (12.8%)</td>
<td>9 (23.7%)</td>
<td>0.54</td>
<td>0.113&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

| 3. How many HNCPs submitted to conservative laryngectomy do you see per year? | RO N (%) | ENT N (%) | Ratio RO%/ENT% | \( p^* \)  \\
|---|---|---|---|---|
| a) Less than 5 | 25 (22.9\%) | 4 (10.2\%) | 2.236 |  \\
| b) 5-10 | 39 (35.8\%) | 13 (33.3\%) | 1.073 |  \\
| c) 11-20 | 26 (23.8\%) | 11 (28.2\%) | 0.846 |  \\
| d) More than 20 | 19 (17.4\%) | 11 (28.1\%) | 0.618 |  \\

| 4. Do you have a head and neck cancer board (HNCB) in your institution? | RO N (%) | ENT N (%) | Ratio RO%/ENT% | \( p^* \)  \\
|---|---|---|---|---|
| a) Yes | 93 (85.3\%) | 36 (92.3\%) |  \\
| b) No | 16 (14.7\%) | 3 (7.7\%) |  \\

| 5. Does your HNCB evaluate: | RO N (%) | ENT N (%) | Ratio RO%/ENT% | \( p^* \)  \\
|---|---|---|---|---|
| a) Selected patients (inoperable patients selected by ENT)? | 27 (29.03\%) | 6 (16.67\%) | 1.742 |  \\
| b) All patients before any specific treatment? | 58 (62.37\%) | 26 (72.22\%) | 0.864 |  \\
| c) Other? (please specify) | 8 (8.6\%) | 4 (11.11\%) | 0.774 |  \\

<sup>*Chi-square tests; † Adjusted residuals (cell-by-cell analyses).</sup>
Finally, considering the numbers of HNCPs submitted to OPL per year seen for each specialist (Table I, Question 3) there was no statistically difference ($P_{\text{Chi-square}} = 0.22$) between the two specialist groups.

When does the remnant larynx need further treatment? (Figs. 1-4)

The clinical scenario of T-site prognostic factors (with no consideration of lymph-nodal prognostic factors) is shown in Figs. 1-4. In the case of $R_+(+)$ after OPL (Fig. 1, Question 6), the majority of specialists recommended RT, with no significant statistically difference between the two specialist groups ($p = 0.60$). However, ROs more frequently would add CT to RT ($RO(\%)_{\text{ENT(%)}} = 3.27$). In the case of $R_{\text{close}}$ (Fig. 2, Question 7), the opinions between the two specialist groups were statistically different ($p = 0.000047$) since more ROs recommended RT ± CT, while a higher ENT(%) recommended a w&w policy ($p = 0.000029$). In the case of $R_-(+)$ disease (Fig. 3, Question 8), the majority of both specialist groups would recommend a w&w policy. Finally, in the case of $pT_3tci$ (Fig. 4, Question 9) a higher RO (%) advised RT ± CT ($p = 1.3 \times 10^{-7}$), while a higher ENT(%) advised a w&w approach ($p = 0.000028$).

When do neck volumes need to be targeted? (Fig. 5)

Two scenarios in which the RL needed to be irradiated (considering T-site unfavourable prognostic factors) were provided for: first in which the neck was not dissected with clinical negative metastatic lymph-nodes (cNo) and second in which elective neck dissections did not reveal metastatic lymph nodes (pNo). In the former scenario, 64.7% of ROs recommended irradiating both cNo areas and RL, while in the latter the majority of RO recommended irradiating only the RL. The attitude of ENts was not statistically different for the two scenarios ($p = 0.132$) (Fig. 5).
Which doses are more frequently recommended on remnant larynx? (Fig. 6, Table II)

Fig. 6 shows the dosage recommended by 103/109 RO respondents.

Discussion

This study attempted to compare the points of view of ROs and ENTs concerning a relatively new question on the postoperative approach to OPL. To our knowledge, this is the first nationwide survey on this topic. Data from literature are only retrospective and come from mono- or bi-institutional studies. The most reported late toxicities are severe oedema condritis (7%) and radionecrosis (5.5%), aspiration and pneumonia (29.4%) and toxic death (4%) (Table III).

Indeed, the modern approach of OPL has reached prominence in the clinical field only in recent years, and different conservative laryngectomy procedures have been adopted for different extensions of tumour. Recently, a systematic review of retrospective mono-institutional studies in the English language literature has given more credence to the oncologic efficacy and reliable function preservation of these procedures considering the high local control (90%) reported in over 5000 patients and the high larynx preservation rate (91%) in over 3000 patients. However,

Table II. Which radiation dose do you recommend to the laryngeal remnant when radiotherapy is advisable or when the patient refuses immediate total laryngectomy? (Question 12) (see also Fig. 6).

<table>
<thead>
<tr>
<th>Answer Options</th>
<th>Not recommended</th>
<th>&lt; 56 Gy</th>
<th>56-60 Gy</th>
<th>62-66 Gy</th>
<th>&gt; 66 Gy</th>
<th>Response Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>- R+ (margins &lt; 1 mm)</td>
<td>4</td>
<td>1</td>
<td>15</td>
<td>54</td>
<td>29</td>
<td>103</td>
</tr>
<tr>
<td>- R-close (margins 1-5 mm)</td>
<td>17</td>
<td>11</td>
<td>30</td>
<td>32</td>
<td>11</td>
<td>101</td>
</tr>
<tr>
<td>- Ro (margins &gt; 5 mm)</td>
<td>70</td>
<td>6</td>
<td>19</td>
<td>5</td>
<td>1</td>
<td>101</td>
</tr>
<tr>
<td>- Ro (in patients with cartilage invasion- pT3)</td>
<td>27</td>
<td>15</td>
<td>34</td>
<td>20</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>answered question</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>skipped question</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>
Table III. Tissue tolerance in the case of open neck conservative laryngectomy plus postoperative radiotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts (irradiated)</th>
<th>Surgery</th>
<th>RT technique</th>
<th>Remnant larynx average dose</th>
<th>Neck dose</th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robbins 1988</td>
<td>25</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>Not reported</td>
<td>Not reported</td>
<td>8/25 (32%)</td>
</tr>
<tr>
<td>Spaulding CA</td>
<td>23</td>
<td>Standard supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>50-61 Gy</td>
<td>50-61 Gy</td>
<td></td>
</tr>
<tr>
<td>Lee 1990</td>
<td>50 (+10 not irradiated)</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D-RT</td>
<td>55 Gy</td>
<td>63 Gy</td>
<td>NA (mixed to non irradiated patients)</td>
</tr>
<tr>
<td>Steiniger 1997</td>
<td>17 (vs. 12 without postoperative radiotherapy)</td>
<td>Horizontal supraglottic laryngectomy 1 extended to the tongue base HSGL</td>
<td>2D-RT, 4-6 MV LINAC 60Co beam</td>
<td>59.30 Gy (50.4-68 Gy)</td>
<td>45.10 Gy (40-50 Gy)</td>
<td></td>
</tr>
<tr>
<td>Laccourreye 2000</td>
<td>90</td>
<td>Standard supraglottic laryngectomy Supracricoid partial laryngectomy</td>
<td>2D RT 60Co beam</td>
<td>51.2 Gy (25-71)</td>
<td>50.6 Gy (22-70)</td>
<td>15/90 (16.6%)</td>
</tr>
<tr>
<td>Spriano 2000</td>
<td>56</td>
<td>Standard supraglottic laryngectomy</td>
<td>2D RT-60Co beam 2D RT- 6MV LINAC</td>
<td>50 Gy</td>
<td>46 Gy</td>
<td>30/56 (54%)</td>
</tr>
<tr>
<td>Oksuz 2008</td>
<td>79</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D RT-60Cobalt beam</td>
<td>50 Gy (48-70 Gy)</td>
<td>50 Gy</td>
<td>22/79 (27.8%)</td>
</tr>
<tr>
<td>Garibaldi 2009</td>
<td>36</td>
<td>Horizontal supraglottic laryngectomy</td>
<td>2D RT- 6MV LINAC 3DCRT</td>
<td>59.5 Gy (45-70.2)</td>
<td>50.4 Gy (39.6-55.8)</td>
<td>21/32 (65.6%)</td>
</tr>
</tbody>
</table>

Thomas reported that approximately 22% of the patients (1151 of 5196) did not have a T-stage available. Thus, blurred stage selections, surgical technique and postoperative care represent challenges that nowadays limit OPL to specific expertise to ensure reproducible results. Specifically, this new scenario generated some concerns among ROs because of the limited amount of data on this subject (Table III), and in particular concerning the radiation tolerance of RL after OPL. Nevertheless, information concerning the risk of toxicity is lacking in tissues (e.g. resected larynx) from high radiation dosages. This opportunity is raising interest for PRT.

At the same time, the possibility to reserve a rescue total (or sometimes partial) laryngectomy without survival detriment can drive physicians’ opinion towards a w&w policy when unpredicted, unfavourable prognostic factors are found in the pathological specimen. Indeed, in our survey a higher ENT, advised a w&w policy in case of R chronic or pT3a (Figs. 2, 4).

In addition, the recent introduction in radiation oncology practice of modern intensity modulated radiotherapy (IMRT), allowing for conformal RT adaptation to irregular neck shape helps to spare organ function and critical tissues (e.g. resected larynx) from high radiation dosages. This opportunity is raising interest for PRT.

This expectation could explain the higher percentage of ROs’ responses (67.8%) vs. ENTs (38.6%) (RO%/ENT(%) = 1.76), tending to testify a higher concern among ROs.

With regards to the Italian-HNC specialists’ attitude towards the T-site prognostic factors, the results describe substantial agreement both in not using PRT in R close patients and in using it in R close. Their opinions diverge in the case of R chronic and pT3a (Figs. 2, 4). Indeed, in these cases ROs advise RT more frequently. In contrast, ENTs more frequently suggest a w&w policy in R chronic and pT3a cases. However, in the case of R chronic, the majority of ROs recommended adding CT to RT, while the majority of ENTs did not recommend it (Fig. 1, Question 6). The discussion of
this item brought about an interesting question among the Authors of the present study: does the positive margin of an early-stage tumour in a conservative scenario have the same negative prognostic significance of the positive margin in an advanced-stage tumour in a non-conservative scenario? It is possible that the majority of ENTs did not add CT to RT because they attributed a less negative prognostic meaning to early-stage positive margins. Regarding radiation volumes (Questions 10 and 11), comments were gathered from both specialist groups’ questionnaires (ROs = 9; ENTs = 7) concerning the fact that the questions did not specify the T-stage and/or the T-site (glottis or supraglottis) contexts. With these limits in mind, the evaluation of responses to two questions permitted us to conclude that in the case of cNo both specialist groups would recommend RT both on the undissected neck and the RL whenever the latter needed to be irradiated. This trend is reversed in the case of cNo where only RL irradiation is more often recommended (Fig. 5, Questions 10-11).

Finally, the questionnaire asked ROs to specify the advised radiation dose on the RL. As shown in Fig. 1, a 62-66 Gy dosage was more frequently recommended in R(+) patients, and 56-60 Gy in the case of pT3ct. The recommendations were substantially equally split between 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of R(-) patients, and 56-60 Gy in the case of pT3ct. The recommendations were substantially equally split between 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of R(-) patients, and 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of pT3ct. The recommendations were substantially equally split between 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of R(-) patients, and 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of pT3ct. The recommendations were substantially equally split between 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of R(-) patients, and 56-60 Gy (29.7%) and 62-66 Gy (31.7%) in the case of pT3ct.
radiation-induced complications (Table II): their estimation ranges from 50 Gy to 60 Gy. However, the substantial pitfalls of these studies are that they are retrospective, mono/double-institutional and heterogeneous in evaluation methodology.

Our study has some limitations since it is an opinion-based survey with mainly motivated respondents, and thus it might not reflect actual clinical practice in Italy. In addition, the need to keep the questionnaire short in order to encourage respondents to fill it in limited the clarity of some questions. As mentioned above, it would have been useful to specify: the primary site (glottic or supraglottic), to define margins to be considered disease-free based on the relative anatomical site (either glottis or supraglottic), and to better define the clinical stage in each scenario. Furthermore, the survey was limited to OPL and did not consider trans-oral approaches. Nevertheless, to our knowledge, this study is the first to gather the opinions of ROs and ENTs from two national scientific societies (AIRO and AIOCC-IHNS) concerning RT indications after OPL. Taking into account the modern concepts of function-sparing laryngectomy and latest radiation technology, this topic will probably be increasingly important in institutional HNCB multidisciplinary debates.

Conclusions

This Italian survey of 109 ROs and 39 ENTs shows that:

- both specialist groups would recommend PRT in the case of R(+) disease, but most ROs would add chemotherapy. Most ROs (52.4%) recommend 62-66 Gy;
- in the case of R(+) disease, but most ROs would add chemotherapy. Most ROs (52.4%) recommend 62-66 Gy;
- in the case of R(s) or pT3(c), while ENTs prefer a w&w policy, the majority of ROs prefer RT with a dose of 56-60 Gy (29.7%) – 62-66 Gy (31.7%); in the case of R(c) or pT3(c),
- neither specialist groups would recommend PRT in the case of R(c) disease, but both would recommend RT for undissected cN0 neck when RT is indicated for the RL.

The issues dealt with in this survey call for renewed attention and prospective studies, considering the introduction of the unique combination of function-sparing laryngectomy concepts in clinical practice and the latest IMRT-techniques allowing for selective target volume irradiation.

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References


Received: November 26, 2012 - Accepted: March, 7, 2013
The rs39335 polymorphism of the RELN gene is not associated with otosclerosis in a southern Italian population

Il polimorfismo rs39335 del gene RELN non è associato con l’otosclerosi in una popolazione del Sud Italia

Otology

SUMMARY

Otosclerosis, the single most common cause of hearing impairment in white adults, is characterised by bone dystrophy localized to the otic capsule and isolated endochondral bone sclerosis with alternating phases of bone resorption and formation. Conductive hearing loss develops when otosclerotic foci invade the stapedio-vestibular joint (oval window) and interfere with free motion of the stapes, but affected subjects frequently develop profound sensorineural hearing loss. The aetiology of otosclerosis is unknown. In the last years, several association studies have been performed and have suggested that single nucleotide polymorphisms in some genes may be implicated in development of otosclerosis. The strongest association has been demonstrated for the relalin gene, located on chromosome 7q22.1, which encodes an extracellular matrix protein. The involvement of relalin in the pathogenesis of otosclerosis is controversial; it was identified in European and North African populations, but was excluded in an Indian population. To analyze the role of relalin in otosclerosis, it has been studied in a case-control analysis for the polymorphism rs39335 in a southern Italy population. In this population, the pathogenic link between the rs39335 variant and otosclerosis was excluded.

KEY WORDS: RELN gene • Otosclerosis • Single nucleotide polymorphism • rs39335

Introduction

Otosclerosis (OTSC) is the single most common cause of hearing impairment among white adults with a prevalence of 0.3-0.4% in the European population. Otosclerosis is characterized by bone dystrophy localised to the otic capsule and isolated endochondral bone sclerosis with alternating phases of bone resorption and formation: mature lamellar bone is removed by osteoclasts and replaced by osteoblasts with a thicker, more vascular bone. Conductive hearing loss develops when otosclerotic foci invade the stapedio-vestibular joint (oval window) and interfere with free motion of the stapes, but about 10% of
affected subjects develop profound neurosensory hearing loss across all frequencies. Mean age of onset is between the third decade, and 90% of affected individuals are under 50 years of age at the time of diagnosis. The aetiology of otosclerosis is unknown, although several theories have been postulated. For the familiar forms, which present a dominant form of transmission with reduced penetrance eight loci have been identified: OTSC1 (15q25-26) (OMIM 166800), OTSC2 (7q34-36) (OMIM 605727), OTSC3 (6p21.2-22.3) (OMIM 608244), OTSC4 (16q21-23.2) (OMIM 611571), OTSC5 (3q22-24) (OMIM 608787), OTSC6 (6q13-16.1) (OMIM 611572), OTSC8 (9p13.1-9q21.11) (OMIM 612096) and OTSC10 (1q41-44), but no causative gene has been yet identified. Moreover, in the last years several association studies have been performed and have suggested the implication of single nucleotide polymorphisms (SNPs) in several genes in otosclerosis aetiology. For some genes the results are controversial. In particular, an interesting and controversial case is represented by the reelin (RELN) gene which was associated in some populations, but not in others. The RELN gene, located on chromosome 7q22.1 and encoding the extracellular matrix protein reelin, is expressed by neural tissues. The results regarding reelin expression in the inner ear and in human stapes footplates are also controversial, making the aetiologic role of RELN in the pathogenesis of otosclerosis unclear. In previous studies, among the identified single nucleotide polymorphisms (SNPs) in RELN gene, the rs39335 variant was one of the most promising. In order to add information about a possible role of RELN in the aetiology of otosclerosis, we performed a case-control association study in a southern Italian population for the SNP rs39335.

Materials and methods

Patient selection

A total of 92 otosclerotic subjects were recruited by clinical centres present in Naples (Otolaryngology Units of University of Naples “Federico II”; Oto-rhinolaryngology Unit of “C. Ascalesi” Hospital, Naples, Italy). Subjects (65 females and 27 males) were all unrelated: age range 30-50 years. For 51 patients, clinical diagnosis was based on surgical findings during stapes surgery, while for the 41 remaining patients was based on audiological data. The control group was composed of 92 healthy individuals. Affected and control subjects are all originated from the Campania region. Written informed consent was obtained from all participants for DNA analysis according to the principles of the Helsinki Declaration.

SNP analysis and genotyping

Genomic DNA was extracted by conventional salt precipitation protocols from peripheral blood samples obtained in EDTA-containing tubes. For genotyping the rs39335 SNP in RELN the following primers were used (RELN1F 5’-GT-CAATGTATGGAATGTTAATGTATA and RELN1R 5’-GAGAGAGACTAGCCAGGATC-3’): the RELN1F primer introduces a recognition site for the restriction enzyme Bstz17I. The primer pairs were designed using the PIRA PCR programme at http://cedar.genetics.soton.ac.uk/public_html/primer2.html. To amplify the region of interest in RELN, a polymerase chain reaction (PCR) was performed using 50 ng of purified genomic DNA in a PCR mix containing 10X Buffer II, 25 mM MgCl2, 5 U/µl Ampli Taq Gold; (Applied Biosystems) in the presence of 2.5 mM deoxynucleotide triphosphate (dNTP) and 25 mM primers. For the RELN gene PCR was carried out with an initial denaturation cycle of 95°C for 10 min, 38 cycles with denaturation at 95°C for 1 min, annealing at 54°C for 1 min, elongation at 72°C for 1 min, and finally elongation at 72°C for 10 min. PCR products were digested overnight at 37°C according to the manufacturer’s instructions.

Statistical analysis

The association of the rs39335 SNP with otosclerosis was analyzed by an exact chi-square test, comparing SNP frequencies using the software FINETTI (http://ihg2.helmholtz-muenchen.de.). Hardy-Weinberg equilibrium (HWE) of tested groups and Amirtag’s trend test (ATT) as well as allele and genotype frequencies and odds ratios were also calculated using the FINETTI software.

Significant differences were considered to be when p < 0.05. Genotype and allele frequencies were compared between the two groups (otosclerotic subjects and healthy controls).

Results

Case-control analysis for the SNP rs39335

To add information about a potential pathogenic link between a rs39335 SNP and otosclerosis, a case-control study in 92 patients and 92 controls was performed using a restriction enzyme assay for the presence of the polymorphism rs39335, which was one of the more strongly associated SNPs in previous studies, with the G allele frequency higher in otosclerotic subjects than in controls. Table I shows the distribution of G allele frequencies in OTSC patients and healthy controls. In the examined population, it was less frequent in otosclerotic subjects than in controls. Table II shows the frequencies of the different genotypes (AA, AG, GG) in otosclerotic and control subjects. The AG and GG phenotypes were more frequent in control subjects, while the AA genotype was more frequent in otosclerotic subjects.

The frequency of the G allele was 16% (29/184 alleles) in otosclerotic individuals compared to controls in which the frequency was 23% (42/184 alleles) (Table I). The difference in genotype distribution for the rs39335 SNP did
not reach statistical significance (p = 0.0813; OR = 0.626; 95% CI: 0.37-1.07).

**Discussion**

Otosclerosis is a complex disease; although several studies have been carried out, the aetiology of otosclerosis remains poorly understood. In the last years, several association studies suggesting that nucleotide variations in some genes may predispose to otosclerosis have been carried out 1-15. One of the genes analyzed was RELN for which a strong association in French, Belgian-Dutch German, Swiss, Romanian and northern Italian populations was demonstrated 14 16 17. This association was, however, not confirmed in an Indian population 18. Moreover, other data supporting the exclusion of the RELN gene as causative for otosclerosis are reported in a recent paper 19 where it was shown that this gene does not show active expression in adult stapes footplates. Confirmatory studies in genotype-phenotype association are important for establishing the credibility of results. In fact, frequently, initial results cannot be confirmed. In this case-control study, both allele (Table I) and genotype (Table II) distributions of one of the most associated variants in previous works 16 17, the SNP rs39335, show no statistically significant association, suggesting that the rs39335 SNP is not a risk factor for otosclerosis.

**Conclusions**

The results obtained in this study show that, in the Campania population, there is no association between the rs39335 SNP and otosclerosis. Other variants, however, may still play a role in the disease. Further studies analyzing other variants and additional populations of different ethnic origin would be useful to verify the exact role of RELN in development of otosclerosis.

**Acknowledgements**

We thank all subjects who participated in the present project.

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**Table I.** Frequencies of the G allele between otosclerotic patients and control subjects.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Position</th>
<th>Sequence change</th>
<th>Frequency in control subjects</th>
<th>Frequency in otosclerotic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs39335</td>
<td>28637145</td>
<td>A &gt; G</td>
<td>42/184 (23%)</td>
<td>29/184 (16%)</td>
</tr>
</tbody>
</table>

**Table II.** Genotype distribution of the RELN rs39335 SNP in otosclerotic patients and control subjects.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>54 (69%)</td>
</tr>
<tr>
<td>OTSC</td>
<td>65 (71%)</td>
</tr>
</tbody>
</table>

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RELN polymorphism and otosclerosis

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Rhinology

Posterior lacrimal sac approach technique without stenting in endoscopic dacryocystorhinostomy

Dacriocistorinostomia endoscopica con approccio posteriore al sacco lacrimale senza utilizzo di stent

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SUMMARY

The purpose of this study is to evaluate the effectiveness of endoscopic dacryocystorhinostomy by the posterior lacrimal sac approach without use of lacrimal stents or harvest of mucosal flaps as a valid surgical procedure for the treatment of an obstruction of the lacrimal pathways. A retrospective evaluation was conducted in a cohort of 75 patients between 2007 and 2011. A total of 78 endoscopic dacryocystorhinostomies were analyzed in 75 patients. After a mean follow-up of 25.7 months (minimum 12 months), 93.3% had a complete relief of symptoms after surgery. Our experience appears to confirm that the endoscopic posterior lacrimal sac approach with no stent insertion or mucosal flaps creation is a good alternative to other known endoscopic procedures.

KEY WORDS: Dacryocystorhinostomy • DCR • Epiphora • Endoscopy • Lacrimal sac • Posterior approach • Stent • Mucosal flap • Endoscopic surgery

Introduction

Dacryocystorhinostomy (DCR) is a surgical procedure aimed, most commonly, at the relief of chronic epiphora, frequently observed in cases of chronic dacryocystitis and in patients with lacrimal sac or nasolacrimal duct (NLD) obstruction. Historically, ophthalmologists used an external approach (ex-DCR) for the relief of symptoms, with good results. This procedure, however, required some facial skin incisions and was not free of complications, such as disruption of the canthal ligaments with a consequent lacrimal pump dysfunction. The initial descriptions of an intranasal approach started to appear about a century ago. The first to describe this latter technique theoretically were Caldwell, West and Mosher. More recently, the first modern endoscopic endonasal procedure was described by McDonogh and Miering in 1989. In recent years, with the development of new surgical instruments, treatment has evolved, and nowadays an endonasal endoscopic technique is the approach of choice in most cases.
An effective approach for endoscopic dacryocystorhinostomy

Materials and methods

Patients
After approval by the Ethics Committee, a retrospective data review was performed on a group of patients that underwent endoscopic DCRs for acquired nasolacrimal duct obstruction between January 2007 and August 2011 (minimum follow-up: 1 year) in the ORL University Clinics of Pavia and Padua (Italy). This work updates the results of an oral presentation presented at the ERS & ISIAN Congress in Geneva in June 2010. Both centres applied a uniform policy for the management of nasolacrimal obstruction. The preoperative studies included: an accurate ophthalmological study, including probing of the lacrimal pathway and a lacrimal irrigation examination (through Jones I and II tests), an endoscopic endonasal evaluation and a computed tomography (CT) scan of the paranasal sinuses. Dacryocystography was usually not obtained, since nearly all patients had a previous examination by an expert ophthalmologist of our team to confirm the diagnosis. Patients with canalicular or common canalicular obstruction (pre-saccal stenosis) were excluded.

Operative technique
In all patients, surgery was performed after informed consent under general anesthesia in a slightly reversed Trendelenburg position (30°). Upon intubation we performed a decongestion of the nasal mucosa with pledgets soaked in xylometazoline hydrochloride 0.1% + oxybuprocaine chlorhydrate 0.01% solution and injection of 1% lidocaine with 1:100,000 epinephrine at the level of the head of the middle turbinate and the lateral nasal wall. When septal or middle turbinate anatomical variants blocking access to the lacrimal sac were present, such as deviations/spurs or concha bullosa, they underwent correction as the initial step; standard endoscopic sinus surgery was performed in cases of concomitant chronic rhinosinusitis or nasal polyposis. The projection of the lacrimal sac on the lateral nasal wall corresponds to the region of axilla of the middle turbinate. In cases of a prominent agger nasi cell covering the lacrimal sac (Fig. 1), the former was opened with cutting instruments (Fig. 2). Another important anatomical detail is the insertion of the uncinate process on the lateral nasal wall as detected on the CT scan; in particular, we observed two main cases: an anterior insertion along the frontal process of the maxillary bone/lacrimal bone, and a posterior one along the dorsal part of the lacrimal bone. In the first case, an uncinctomy should precede the approach to the lacrimal fossa and sac; in the second case, the sac may be opened without an associated uncinctomy. Intraoperative localization of the lacrimal sac was enhanced by transillumination of the latter from a 20-gauge light pipe inserted (Karl Storz, Tuttingen, Germany) through the inferior canaliculus and endoscopically detected on the lateral nasal wall. After successful exposure of the lacrimal bone, we proceeded with its removal using a diamond burr. Drilling was performed directly on the postero-medial wall of the lacrimal bone, in a medial to lateral direction, as the bony shell at

![Fig. 1. Coronal CT scans (sequence) showing the relation between agger nasi (white triangle), lacrimal sac (white star) and nasolacrimal duct (white circle).](image1)

![Fig. 2. Intraoperative pictures of a right-side agger nasi cell.](image2)
this point is thinner than its anterior part (Fig. 3). The lacrimal bone should be drilled until complete and adequate exposition of the lacrimal sac is obtained. Upon exposition, the sac was identified and its medial wall was put in tension by a probe inserted through the inferior canaliculus; the latter wall was then incised with a beaver, a sickle knife or the angled cutting forceps recently proposed by P. Castelnuovo (Karl Storz, Tuttlingen, Germany). Subsequently, under both 0° and 45° scopes, a calibration of the dacryo-cysto-rhino-stomy was performed using microdebriders or cutting forceps, thus creating an ample dacryo-cysto-rhino-stoma (Fig. 4A). As a final step, the patency of the lacrimal pathways was checked with several saline irrigations. Nasal packing was performed only in cases of associated sinus surgery or septrhinoplasty.

Postoperative care
Patients were usually discharged the day after treatment, and in cases of concomitant sinus surgery or septrhinoplasty after two or three days postoperatively. All patients received broad-spectrum antibiotic therapy for one week after surgery. Topical nasal steroids were initiated some days after surgery and were prescribed for one month. Saline irrigations were recommended until the nasal mucosa was completely healed. The first endoscopic consultation was performed one week postoperatively, along with lacrimal irrigation. Subsequent endoscopic medications were performed at one, three, and six months and one year after surgery (Fig. 4B). Postoperative ophthalmologic evaluation performed at six months and one year included lacrimal irrigation, fluorescein dye disappearance test and Jones test I.

Results
The group consisted of 75 patients, 53 females (70.7%) and 22 males (29.7%) with a mean age of 58.2 years (range 25-84 years). Most patients reported epiphora as a result of chronic dacryocystitis, but we also observed cases of recurrent dacryocystitis and dacryocystocele. All patients included in this study had post-saccal or saccal stenosis of the lacrimal pathways. In three patients (4%), surgery was performed bilaterally; thus we performed a total of 78 DCRs. Within the cohort, 11 patients (14.7%) presented a positive medical history for previous surgery or facial trauma. To obtain correct access to the lacrimal fossa, we performed two septrhinoplasties (2.7%) and 12 middle turbinate reductions (16%). Eight patients required additional endoscopic surgery to treat chronic rhinosinusitis or nasal polyposis (10.7%). No major intra- or post-surgical complications were observed. Follow-up ranged between 12 and 56 months (mean 25.7 months). Four patients (5.3%) developed a clinically asymptomatic synchia between the middle turbinate and the lateral nasal wall. We observed five cases of DCR-failure due to rhino-stomal scarring stenosis (6.7%), confirmed by ophthalmologic evaluation (positive fluorescein disappearance test and negative Jones I test). These patients successfully underwent revision endoscopic surgery (minimum follow-up 12 months). Finally, our success rate was 93.3% after endoscopic DCR.

Discussion
Historically, dacryocystorhinostomy is surgical procedure aimed at the restoration of patency of the lacrimal pathways through an external approach, as proposed by Toti and also described by Dupuy and Dutemps and Bourget 1-12. It is usually aimed at the relief of epiphora, the main symptom in most cases of chronic dacryocystitis, and on occasion with obstruction of the lacrimal sac or duct. In 1893, Caldwell was the first to suggest an intranasal approach to re-
store patency of the lacrimal pathways, followed by West
and Mosher, who described a possible intranasal procedure
to address lacrimal obstruction. Subsequently, the first
clinical study on an endoscopic DCR technique appeared
in 1989 by McDonogh and Meiring. In recent years, and
along with the success of endoscopic sinus surgery, endo-
scope DCR has proven to be a valid alternative to exter-
nal approaches, as shown by many authors. Disadvan-
tages of external dacryocystorhinostomy include scarring
of facial skin, risk of copious haemorrhage, and disruption
of medial canthal anatomy. On the other hand, the main
advantages of endoscopic techniques are the enhanced
visualization through straight and angled scopes and the
avoidance of unnecessary skin incisions, thus avoiding any
functional damage to the orbicularis muscle.

Adequate selection of patients is a key point to obtain a good
outcome rate: accurate ophthalmologic examination should
be performed to distinguish between saccal, pre-saccal and
post-saccal stenosis of the lacrimal pathways. CT scan is
mandatory to show the anatomy and the variations of key
structures such as the agger nasi and the uncinate process
(Figs 1, 3). The success rate of the endonasal endoscopic
approach, as reported in recent studies, is between 58% and
97%, which are lower than rates with external DCR (75-
99%). The most common cause of surgical failure
in the former approach is a rhino-stomal stenosis. In our
personal experience, the success rate of endoscopic DCR
(93.3%) falls within the range reported in the literature.

Within the endoscopic DCR group, there is much discussion
in the literature today about technical details that may influence the functional results, incidence of com-
lications and, finally, the rate of surgical failures. Among
the most discussed are: surgical instrumentation, silicon
tube stenting, use of mucosal flaps and peri-stomal injec-
tion of antimetabolites, such as mitomycin C. The ulti-
mate objective of these technical variations is the patency
of the new lacrimal drainage pathway and prevention of
an eventual restenosis, and thus recurrence of symptoms.

In a recent study, Naraghi et al. evidenced that the simple
“punch technique”, with the use of punch forceps for per-
forming rhinostomy, preserves the advantages of endoscopic
DCR while diminishing the expenses of powered or laser in-
strumentation with comparable results: they reported a 95%
success rate on 100 cases of endoscopic DCRs. Despite
the popularity of silicon stents, few studies have addressed
this issue and described how it correlates with the surgical
outcome. Allen, in 1989, highlighted that the use of silicon
stents may increase the risk of surgical failure by stimulation
of a peri-stomal granulomatous reaction. More recently,
other authors have agreed with Allen about stent utiliza-
tion; however, some included a mucosal flap creation in
their technique. The rationale of the mucosal flap is to boost
primary intention healing and create a well-designed epithe-
lialized surgical fistula. Recently, Khalifa et al. conducted
the first prospective randomized controlled trial to compare the
safety and efficacy of endoscopic DCR with double poste-
riorly based nasal and lacrimal flaps to conventional endo-
sic DCR in adult patients; they concluded that the flap
technique has a comparable success rate, operative time and
safety profile, with a possibly better healing profile in terms
of mucosal recovery, wound healing and less need for de-
bridement. Moreover, there is insufficient evidence for the
efficacy of mitomycin C or other antimetabolites in endo-
sic DCR. In fact, the results reported in the literature
are controversial: some authors consider the application of
mitomycin C safe and successful for surgical outcome; on
the other hand, according to other reports, it has no proven
beneficial effect on the success rate of the surgery.

We propose a variation of the procedure initially pro-
posed by Metson and recently reported by other authors
through the creation of a stoma along the posterior por-
tion of the lacrimal sac; the theoretical basis of this
proposal depends on the thickness of this bony portion,
which is much thinner than its anterior counterpart. Our
variation, unlike Metson’s technique, is based on the
lack of lacrimal stenting. Based on the results of our
experience, we propose posterior endoscopic DCR with
no stent application as an alternative to other successful
endoscopic approaches and with a comparable rate of
complications and failures.

Conclusions

The posterior lacrimal sac approach technique without
application of lacrimal stents for endoscopic DCR has been
demonstrated to be a valid alternative to other endoscopic
procedures. We observed an elevated high success rate
in selected patients that is directly comparable to other
endoscopic techniques, even without the use of mucosal
flap, lacrimal stent or topical postoperative administration
of mitomycin C. The keys to a successful surgical outcome
are adequate selection of pa-
tients, meticulous study of
 sinonasal anatomy and good
experience in endoscopic si-

Table I. Demographic data and clinical features of patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>75 pts (53 females; 22 males)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>25-84 years (mean 58.2 years)</td>
</tr>
<tr>
<td>Positive medical history for previous surgery or facial trauma</td>
<td>11 pts (14.7%)</td>
</tr>
<tr>
<td>Septoplasties</td>
<td>2 pts (2.7%)</td>
</tr>
<tr>
<td>Middle turbinate reduction</td>
<td>12 pts (16%)</td>
</tr>
<tr>
<td>Endoscopic sinus surgery for CRS or NP</td>
<td>8 pts (10.7%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>12-56 months (mean 25.7 months)</td>
</tr>
<tr>
<td>Success rate of surgery</td>
<td>93.3%</td>
</tr>
</tbody>
</table>
References


Received: September 24, 2012 - Accepted: March 6, 2013
Evaluation of hearing aid benefit through a new questionnaire: CISQ (Complete Intelligibility Spatiality Quality)

La valutazione del beneficio protesico mediante un nuovo questionario: CISQ (Complete Intelligibility Spatiality Quality)

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SUMMARY
The purpose of this work was to create a rapid and simple instrument to evaluate the benefits of a hearing aid, that was at the same time reliable and complete. We created a new questionnaire by integration of other well consolidated psychometric tests to better investigate all the aspects that contribute in determining the hearing aid benefit, also considering as important some areas that are not usually considered (spatiality and quality of sound). We started from a 36-item questionnaire divided in six subscales (spatiality and quality of signal, intelligibility in silence, background noise intelligibility, averseness and reverberation), and submitted it to patients before hearing aid application and at 2-3 months after that. A statistically significant difference between results before and after hearing aid application was found. To obtain the final 30-item questionnaire, we analyzed the reliability of each subscale using Cronbach’s alpha coefficient, and eliminated the item whose internal consistency was lower for every subscale. For these reasons, the CISQ questionnaire is a rapid and simple test that can be considered a reliable and complete instrument to evaluate the benefits of a hearing aid.

KEY WORDS: Hearing aid benefit • Psychometric test • Hearing aid

Introduction
Hearing aid satisfaction or hearing aid surrender is the general advantage that a patient with a hearing aid has that derives from his handicap reduction. Hearing aid satisfaction is influenced by numerous factors such as the type and the severity of the deafness, cognitive ability of the patient, expectancy about the hearing aid, motivation and, furthermore, his character and overall quality of life. Hearing aid satisfaction is something that is difficult to predict and evaluate. Hearing aid satisfaction can be
defined as the sum of hearing aid gain with hearing aid benefit. Hearing aid gain refers to the difference between the unaided and the aided auditory threshold, and can be measured with subjective and objective tests. Subjective tests are the tonal auditory test and vocal auditory test with and without the auditory aid. Objective tests are the real ear unaided response (REUR), the real ear occluded response (REOR), the real ear aided response (REAR) and the real ear insertion response (REIR).

The REAR is also called the in situ gain and is the prosthetic amplification measured in situ. The insertion gain derives instead from the difference between the REAR and the REUR. These in situ measures are used to have an objective evaluation of hearing aid gain, but are not able to investigate the aided benefit.

Hearing aid benefit can be evaluated using a questionnaire that checks the acoustic universe and the psychological sphere of the patient. Measures of aided benefit include the client oriented scale of improvement and the profile of hearing aid benefit. Shorter measures of benefit include the abbreviated profile of hearing aid benefit (APHAB) and the international outcome inventory for hearing aids.

Certainly the most used questionnaire nowadays is the APHAB. It derives from the PHAB inventory whose value is limited in clinical applications because the time required to complete the 66 items (about 30 min) is not always available. However, the time needed to complete the APHAB questionnaire is about 10 min or less and produces scores for unaided and aided performance as well as hearing benefit. The APHAB does not consider however some situations that need to be investigated.

In our practice, a rapid, reliable and complete instrument is needed to evaluate the aided benefit. For this reason, we created a new questionnaire, the CISQ (Complete Intelligibility Spatiality Quality) questionnaire, to better investigate some areas that are not usually considered such as spatiality and quality of sound.

Materials and methods

Subjects

A total of 40 subjects (21 males and 19 females) were recruited in our Audiology Department and participated in the study; the mean age was 69.8 years and the age range was 25 to 86 years.

All patients were evaluated with the tonal auditory test and vocal auditory test. The mean value of the neurosensorial hearing deficit on 0.5/1/2/3/4 kHz frequencies was 58.75 dB.

The hearing aid fittings were binaural in 36 cases (90%) and monaural in four (10%). The hearing aids used were conventional and digital instruments in 39 cases. They were behind-the-ear in 37 cases (92.5% of total), and in-the-ear in two cases (5%). One patient used a bone conduction hearing aid.

Study design

We submitted the 36-item questionnaire to patients before the hearing aid application and 2-3 months after that, at the end of the period of hearing aid adaptation. We analyzed the distribution of answers in the two conditions (before and after hearing aid application), looking at the absolute and percentage frequency of the answers, and evaluating the difference between the mean values in the two conditions. After that we conducted statistical analysis to obtain a 30-item questionnaire, whose consistency and reliability were considered optimal.

CISQ questionnaire

We created the questionnaire by integration with other well established and consolidated tests. These tests are called psychometric tests and use subjective measures to evaluate motivation, expectancy, abilities and personality traits of patients.

We considered the Denver Scale and the hearing handicap inventory of elderly (HHIE), which investigates communicational abilities in different situations, the COSI, usually used to best understand a patient’s expectation from the hearing aid, and the APHAB, currently the best instrument to evaluate hearing aid benefit that consists of 24 statements, four subscales (ease of communication, background noise, reverberation, averseness) and has a 7-point rating scale.

To create our test we started from a 36-item questionnaire developed in six subscales: spatiality of signal, quality of signal, reverberation, background noise intelligibility, averseness and intelligibility in silence.

The subscale “spatiality of signal” examines the subject’s ability to discriminate from which direction the sound source arrives. The subscale “quality of signal” examines the third property of the sound: the tone. More in general this subscale investigates about the clarity of sounds. The third subscale evaluates the subject’s ability to hear in a large, empty place, where sounds are altered by reverberation. The subscale “background noise intelligibility” investigates the verbal communication capacity of the subject in noisy places. The subscale “averseness” investigates about loud sounds, and the latter about the verbal communication capacity of the subjects in silence. The questions were divided in six groups, so that in every group there was an item for each subscale.

The answers were represented by an 11-point rating scale (0-10), in which the minimum and the maximum were labelled with descriptive words (never and always; Fig. 1). We used this format to obtain a quantifiable result so that the questionnaire had good measurability. The measur-
ability of the instrument is a primary element of its practicability and concreteness, and is something that a questionnaire with a more qualitative approach, as many others in literature, may not always have.

At the end of the questionnaire we inserted a graphic that the physician (or the audiometrist) has to fill in to provide the patient with an immediate perception of the handicap (before the hearing aid application) and benefit (after the hearing aid application; Fig. 2). For every subscale, the patient can clearly see the average of his/her answers, and easily compare it with the average of the answers in the other condition.

Results

As mentioned earlier, we submitted the 36-item questionnaire to patient before the hearing aid application and 2-3 months after that, at the end of the period of hearing aid adaptation. The distribution of answers had a larger frequency among the numbers from 0 to 5 before the hearing aid application, and a larger frequency among the numbers from 5 to 10 after the hearing aid application. We calculated the average of answers in each condition (before and after hearing aid application) and found a significant difference in 35 of the 36 items. In all cases, in fact, the mean value was higher after hearing aid application than before; this difference was statistically significant with a student’s t-test. Item 32 was non-significant with a similar distribution of the answers in the two examined conditions.

Comparing the averages of the answers of each subscale, we again found a difference between the two situations (before and after hearing aid application) that was statistically significant (Table I). We observed a small difference in the subscale “quality of signal”, in which there was question 32, whose difference between the mean of the answers in the two situations was not significant.

To obtain the final questionnaire composed of 30 items, five for each subscale, we analyzed the reliability of each subscale using Cronbach’s alpha coefficient, which is commonly used as a measure of the internal consistency or reliability of a psychometric test score. Cronbach’s alpha describes the coherence of a group of items; a high alpha value indicates that the examined subjects show a coherent behaviour on each item of every subscale. Cronbach’s alpha will generally increase as the intercorrelation among test items increases, and is thus known as an internal consistency estimate of reliability of the test score. To be considered appropriate, with an acceptable level of internal consistency, a psychometric test should have an alpha value of at least 0.6.

We decided to eliminate one item for every subscale to obtain the 30-item questionnaire, whose internal consistency was optimal. We calculated the Chronbach’s alpha of each subscale alternately removing each item, and decided to definitely eliminate from the questionnaire the item whose removal lead to a higher alpha value. For example, in the subscale “quality of signal” the removal of the question 8 lead to an alpha value of 0.79, which estimated a very good level of internal consistency. Removing question 32, this level jumped to an alpha level of 0.95. For this reason, on this subscale we eliminated question 32 (Table II). We made the same analysis for each subscale and obtained a 30-item questionnaire, in which every subscale could be characterized by an optimal level of reliability (because of an alpha value of at least 0.92; Table II).
Table II. Reliability analysis. A) Difference in mean, variance and Cronbach’s alpha values after the removal of each item of the subscale “quality of sound”. B) Alpha values of every subscale after the removal of the question with the lower scale correlation.

<table>
<thead>
<tr>
<th>A Subscale</th>
<th>Scale Mean if Item Deleted</th>
<th>Corrected Variance if Item Deleted</th>
<th>Item–Total Correlation</th>
<th>B Alpha if Item Deleted</th>
<th>B Subscale</th>
<th>B Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2</td>
<td>23.35</td>
<td>55.41</td>
<td>0.70</td>
<td>0.63</td>
<td>sp</td>
<td>0.95</td>
</tr>
<tr>
<td>Q8</td>
<td>22.27</td>
<td>47.74</td>
<td>0.84</td>
<td>0.75</td>
<td>qu</td>
<td>0.92</td>
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<tr>
<td>Q14</td>
<td>22.63</td>
<td>49.06</td>
<td>0.81</td>
<td>0.70</td>
<td>re</td>
<td>0.94</td>
</tr>
<tr>
<td>Q20</td>
<td>23.93</td>
<td>54.33</td>
<td>0.72</td>
<td>0.55</td>
<td>bni</td>
<td>0.95</td>
</tr>
<tr>
<td>Q26</td>
<td>23.55</td>
<td>51.23</td>
<td>0.79</td>
<td>0.73</td>
<td>av</td>
<td>0.94</td>
</tr>
<tr>
<td>Q32</td>
<td>24.40</td>
<td>67.94</td>
<td>0.12</td>
<td>0.11</td>
<td>is</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Discussion

The purpose of this work was to create a rapid and simple instrument to evaluate the benefits of a hearing aid that was reliable and complete. The time needed to complete the 30 questions of the CISQ questionnaire is about 10 minutes and it can be used in any Audiology Department without excessive waste of time for operators or patients. The questions are formulated in a simple way, so that all patients can easily understand them. For each subscale there are five different items that investigate different situations, so that all types of patients can identify themselves in a situation that is close to their daily life (patient working in an office, patient who stays all day at home…). The CISQ questionnaire is a complete test to evaluate hearing aid benefit because it investigates important areas that are not always considered (e.g. subscales about spatiality and quality of sound).

Moreover, each subscale can be considered to be characterized by an optimal level of reliability thanks to the Cronbach’s alpha analysis. Eliminating the item whose scale correlation was lower from every subscale, we obtained the 30-item questionnaire, with optimal internal consistency. The removal of the six items whose scale correlation was lower also changed the statistics of every scale. Analyzing the mean values of the answers before and after hearing aid application, and calculating the difference, we found a different odds compared to the values found before the removal of the items (Table III). Before the removal of the question 32 of the quality subscale, for example, we found a subscale mean value-before of 4.67, a mean value-after of 7.37, with a difference between the two values of only 2.7. After its removal, the mean of the answers for this scale before the hearing aid application was 4.88, after the hearing aid application of 8.07, with a difference between the two conditions of 3.19 (Table IV). This can be explained by the fact that in the subscale of quality, the question with the lower scale correlation, was also a question with a low difference of distribution of the answers in the two conditions. This means that the questionnaire resulting from the removal of each item with the lower scale correlation, consisting of 30 questions divided in six subscales whose internal consistency is high (α > 0.92 for every scale), is composed of questions that lead to a net difference in the answers in the two conditions (if the patient has a benefit from the hearing aid, of course).

As mentioned before, there is another important factor to evaluate in hearing aid benefit, namely the psychological aspects. This text was conceived to investigate the effect of the hearing aid on the quality of life of the patient, focusing on all those situations in which the patient may have problems with an auditory impairment. It is clear that if we want to investigate the impact that the disability resulting from a bad hearing aid gives to the psychological sphere of the person, then further psychometric tests are needed. There are many psychometric texts in the literature that are commonly used to evaluate the correlation between a disability and its impact on the psychological aspect of the patient [14, 15].

In conclusion, we believe that the CISQ questionnaire can be considered a good instruments to evaluate hearing aid benefit, not only at its first application, but also to follow any changes over time. In case of worsening of the auditory impairment, in fact, the auditory aid can become insufficient, and this could be rapidly verified by repeating the test, leading to a faster correction of the hearing aid.

Table III. Descriptive statistics and difference between mean values after the removal of the item with the lowest scale correlation for each subscale.

<table>
<thead>
<tr>
<th>subs.</th>
<th>Before</th>
<th>After</th>
<th>Diff.</th>
<th>T-Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sp</td>
<td>4.38</td>
<td>1.90</td>
<td>2.48</td>
<td>3.18</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>qu</td>
<td>4.88</td>
<td>1.65</td>
<td>3.23</td>
<td>3.53</td>
<td>0.01</td>
</tr>
<tr>
<td>re</td>
<td>3.83</td>
<td>1.46</td>
<td>2.37</td>
<td>3.53</td>
<td>0.01</td>
</tr>
<tr>
<td>bni</td>
<td>4.24</td>
<td>1.49</td>
<td>2.75</td>
<td>3.53</td>
<td>0.01</td>
</tr>
<tr>
<td>av</td>
<td>4.08</td>
<td>1.93</td>
<td>2.15</td>
<td>3.53</td>
<td>0.01</td>
</tr>
<tr>
<td>is</td>
<td>5.13</td>
<td>1.55</td>
<td>3.58</td>
<td>3.53</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table IV. Descriptive statistics and differences between mean values in the subscale “quality of sound” with and without question 32.

<table>
<thead>
<tr>
<th>Quality</th>
<th>Before</th>
<th>After</th>
<th>Diff.</th>
<th>T-Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>With 32</td>
<td>4.67</td>
<td>1.45</td>
<td>3.22</td>
<td>2.7</td>
<td>13.11 &lt; 0.01</td>
</tr>
<tr>
<td>Without 32</td>
<td>4.88</td>
<td>1.65</td>
<td>3.23</td>
<td>2.7</td>
<td>13.11 &lt; 0.01</td>
</tr>
</tbody>
</table>
References

5. Dillon H, James A, Ginis J. Client Oriented Scale of Improvement (COSI) and its relationship to several other measures of benefit and satisfaction provided by hearing aids. J Am Acad Audiol 1997;8:27-43.

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Appendix 1. CISQ Questionnaire (ENG)

1. Do people’s voices seem clear and natural? [quality]
2. You are listening to a conference: are you able to understand most of the words? [reverberation]
3. You are in a crowded supermarket: are you able to understand what the shop assistant is telling you? [background noise intelligibility]
4. An unexpected noise (like an alarm) is for you tolerable? [averseness]
5. Are you able to follow a conversation with your relatives when you are at home? [intelligibility in silence]
6. You are at your friend’s home, in silence. A door slams: are you able to understand from which direction the noise is coming? [sp]
7. Does your voice seem natural? [qu]
8. Are you able to well understand the dialogues in a film or at the theatre? [re]
9. You are in your car talking with your friends: are you able to understand the news on the radio? [bni]
10. Is the noise of traffic tolerable for you? [av]
11. Are you able to follow a conversation in a small office? [is]
12. You are outdoors, a dog barks: are you able to understand from which direction does the noise is coming? [sp]
13. Are you able to recognize a friend of yours from his/her voice? [qu]
14. Are you able to talk with a person who’s at the other side of a large, empty room? [re]
15. You are at a dinner, sitting at a table with other persons. Are you able to follow the conversation with one of them? [bni]
16. Are the noises of an airport or a train station tolerable for you? [av]
17. You are talking with a person in a calm, silent living room: are you able to well understand what he’s saying? [is]
18. You are on a street: are you able to understand from which direction does the bus come without looking? [sp]
19. While you are listening to music are you able to understand which instrument is playing? [qu]
20. You are in a silent place: are you able to follow a conversation while more than one person is talking at the same time? [bni]
21. Is the noise in a crowded restaurant tolerable for you? [av]
22. Are you able to follow the conversation with your physician while you are in his office? [is]
23. Are you able to understand how far away a car is without looking? [sp]
24. Do the common sounds of your everyday life seem to you clear? [qu]
25. Are you able to well understand who’s talking in an election conference? [re]
26. Are you able to understand in which direction a car is running without looking? [sp]
27. You are in a church: are you able to understand the words of the sermon? [re]
28. Are you able to understand who’s talking to you if there’s an air conditioner on? [bni]
29. Is the noise of screeching tires tolerable for you? [av]
30. You are talking with a friend in a silent room: can you avoid asking him to repeat things? [is]
Appendix 2. CISQ Questionnaire (ITA)

1. Le voci degli altri ti sembrano chiare e naturali? [qualità]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

2. Quando ascolti una conferenza, sei in grado di comprendere gran parte dell’argomento trattato? [riverbero]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

3. Quando sei in un supermercato affollato e parli con la cassiera, riesci a seguire agevolmente la conversazione? [intelligibilità nel rumore]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

4. Riesci a sopportare un forte rumore inaspettato, come un allarme? [percezione dei rumori forti]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

5. Riesci a seguire agevolmente una conversazione quando sei a casa con i familiari? [intelligibilità nel silenzio]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

7. La tua stessa voce ti sembra naturale? [qu]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

8. Riesci a capire i dialoghi in un film o in uno spettacolo teatrale? [sr]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

9. Se ascolti il notiziario in macchina col motore acceso, in compagnia dei familiari che parlano, riesci a seguire le notizie? [ir]
   0 1 2 3 4 5 6 7 8 9 10
   Mai sempre

10. Sono sopportabili i rumori del traffico? [f]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre

11. Riesci a seguire una conversazione con una persona in un piccolo ufficio? [i]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre

12. Sei all’aperto e senti un cane abbaia forte. Riesci a capire dove si trova il cane senza guardare? [sp]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre

13. Ti riesce facile fra persone che conosci individuare ognuno dalla sua voce? [qu]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre

14. Se parli con qualcuno che si trova all’altro capo di una grande stanza vuota, riesci a capire le parole che pronunci? [sr]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre

15. Sei a tavola con altre persone e cerchi di conversare con una di loro, riesci a seguire agevolmente il discorso? [ir]
    0 1 2 3 4 5 6 7 8 9 10
    Mai sempre
16. Sono sopportabili i rumori di un aeroporto o di una stazione ferroviaria? [f]
   ![](image)

17. Stai parlando con una persona in un salottino tranquillo e silenzioso. Riesci a seguire ciò che dice questa persona? [i]
   ![](image)

18. Sei sul marciapiede di una strada molto trafficata. Riesci a capire la direzione di provenienza di un autobus prima che tu riesca a vederlo? [sp]
   ![](image)

19. Quando ascolti la musica riesci a capire quale strumento sta suonando? [qu]
   ![](image)

20. In un ambiente silenzioso riesci a seguire la conversazione anche quando parlano contemporaneamente diverse persone? [ir]
   ![](image)

21. Sono sopportabili i rumori prodotti da una pizzeria affollata? [f]
   ![](image)

22. Quando parli tranquillamente con il tuo medico nel suo studio, riesci a seguire la conversazione? [i]
   ![](image)

23. Riesci a capire dal rumore quanto è lontano un autobus o un camion? [sp]
   ![](image)

24. I suoni comuni della vita di tutti i giorni ti sembrano chiari (non “sfocati”)? [qu]
   ![](image)

25. Riesci a capire ciò che viene detto durante un comizio? [sr]
   ![](image)

26. Riesci a capire la direzione di marcia di un camion o di un autobus senza guardare (esempio: da sinistra a destra o da destra a sinistra)? [sp]
   ![](image)

27. Riesci a capire le parole di una predica quando assisti ad una funzione religiosa? [sr]
   ![](image)

28. Riesci a capire chi ti parla quando è in funzione un condizionatore o un ventilatore?[ir]
   ![](image)

29. È sopportabile lo stridio di pneumatici sull’asfalto? [f]
   ![](image)

30. Conversando con qualcuno a quattr’occhi in una stanza tranquilla, riesci a non chiedergli di ripetere? [i]
   ![](image)
The impact of a multidisciplinary approach on response rate of mandibular advancing device therapy in patients with obstructive sleep apnoea syndrome

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SUMMARY

The aim of the present study was to evaluate the importance of a multidisciplinary approach on increasing the response ratio expectation to mandibular advancing device (MAD) therapy in patients with obstructive sleep apnoea syndrome, especially in severe cases. Forty-two mild-to-severe OSAS patients were selected, after comprehensive evaluation by neurologists, otorhinolaryngologists and orthodontists, and treated with a Somnodent® device. Six months later, a polysomnographic exam with the MAD in situ was performed. The paired t-test evaluated the effectiveness of therapy and the results were compared with data from systematic reviews. The average treatment response was statistically significant for the apnoea/hypopnea index (AHI) and oxygen desaturation index and was higher than the outcomes presented in literature. An optimum therapy response (AHI < 5) was observed in 53% of patients (40% in severe OSAS) and a good response (AHI < 10) in 73% of patients (50% in severe OSAS). The Somnodent® device was effective and the multidisciplinary patient selection improved the response ratio compared to that reported by previous systematic reviews.

KEY WORDS: Multidisciplinary approach • Sleep apnoea • Mandibular advancing device • Response rate • Efficacy

RIASSUNTO

Lo scopo dello studio è quello di valutare l’impatto dell’approccio multidisciplinare nel determinare la percentuale di risposta alla terapia con dispositivi ad avanzamento mandibolare nei pazienti affetti da OSAS, anche di severa entità. Dopo una valutazione che ha compreso una visita neurologica, otorinolaringoiatrica ed ortodontica, 42 pazienti sono stati selezionati e sono stati trattati con un dispositivo ad avanzamento mandibolare (MAD) a tipo Somnodent®. A 6 mesi dalla consegna del MAD, i pazienti sono stati sottoposti ad un esame polisomnografico con il dispositivo in situ. Un paired t-test è stato utilizzato per valutare l’efficacia della terapia e le percentuali di risposta ottima (AHI < 5) e buona (AHI < 10) ottenute sono state confrontate con quelle riportate dalle revisioni sistematiche presenti in letteratura. Sono state raggiunte una risposta ottima nel 53% dei pazienti (40% nei pazienti gravi) e una risposta buona nel 73% dei pazienti (50% nei pazienti gravi). I risultati ottenuti confermano l’efficacia del Somnodent® e dimostrano come la selezione multidisciplinare del paziente possa determinare un’incremento della percentuale di risposta alla terapia odontoiatrica, rispetto a quella riferita dalla revisione sistematica della letteratura.

PAROLE CHIAVE: Approccio multidisciplinare • Apnea, dispositivo ad avanzamento mandibolare • Percentuale di risposta • Efficacia

Obstructive sleep apnoea syndrome (OSAS) is a common sleep breathing disorder characterized by snoring and repetitive complete (apnoea) or partial (hypopnoea) cessations of airflow during sleep, resulting in oxygen desaturation and sleep fragmentation. It affects approximately 2 to 4% of the middle-aged population, and is considered a serious public health problem that can lead to an impaired quality of life for its signs and symptoms (excessive daytime sleepiness and impaired cognitive ability). It is also associated with an increased morbidity and mortality because of its potential pathophysiological consequences (increased risk of cardiovascular,
cerebrovascular, metabolic diseases and motor vehicle accidents) 1-5. While continuous positive airway pressure (CPAP) is considered the gold standard treatment for this disorder, mandibular advancing devices (MADs) are recommended as an effective alternative therapy for patients affected by mild to moderate OSAS 3-6, and also represent a treatment option in severe OSAS patients, who cannot tolerate or refuse CPAP or are poor candidates for surgery 3-9. Randomized trials have documented significant decreases in the apnoea/hypopnoea index (AHI) and in excessive daytime sleepiness with MAD therapy, confirming their effectiveness in inducing anatomical changes in the oropharynx and in stabilizing upper airway caliber 10 11. Low nasal resistances, shorter soft palatal length, supine-dependent OSAS, increased retropalatal airway space and a prevailing retrolingual collapse are all associated with good response to MAD treatment 12-15. The objective of the present study was to evaluate the importance of a multidisciplinary approach in the diagnosis and in patient selection to increase the response ratio expectation to MAD therapy, especially in severe cases of OSAS.

Materials and methods

Study design

Forty-two adult patients (38 males and 4 females) with a mean age of 53.2 ± 11.1 years, recruited by neurologists and otolaryngologists of the Neurology and Ear, Nose and Throat (ENT) Departments of “S. Orsola-Malpighi” University Hospital of Bologna (Italy) and by a private practitioner orthodontist between March 2011 and May 2012, were selected for the study. The inclusion criteria were mild to moderate OSAS (patients who presented a number of apnoeas and/or hypopnoeas per hour of sleep less than or equal to 30) or severe OSAS (patients who presented a number of apnoeas and/or hypopnoeas per hour of sleep greater than 30), when CPAP or surgical procedures were refused and in case of CPAP intolerance 3 8, retrolingual collapse ≥ 50% and retropalatal collapse ≤ 50% during Müller manoeuvre, tonsillar grade < 3 16, low nasal resistance (no important nocturnal nasal obstruction complained by the patient, no important inferior turbinate hypertrophy or septal deviation) 13 17, sufficient tooth anchorage (at least 6 teeth in the lower arch), no substantial tooth mobility or untreated periodontal disease, no temporomandibular joint (TMJ) pain and ability to protrude the mandible > 6 mm 18. Inclusion criteria are shown in Table I. At baseline (T0), all patients underwent comprehensive medical history collection, body mass index (BMI) recording, night-time polysomnography (PSG) recording pulse oximetry, thoracic respiratory movements, nasal and oral airflow measurements and body position and an otorhinolaryngologic assessment including fibre-optic nasopharyngoscopy with the Müller manoeuvre. The dentist carried out an objective exam (dental, periodontal and functional examination), radiological (lateral teleradiography and relative cephalometric tracing, panoramic radiography) and a dental cast analysis. The examinations performed at T0 are summarized in Table II. Nine patients underwent oral pretreatment for the presence of caries and/or periodontal disease before inclusion in the study. All patients received an oral device and were instructed about its management. One week, one month and three months after delivery, patients and their bed partners were interviewed on subjective improvement in OSAS symptoms and quality of sleep, and the short-term side effects were evaluated. Six months later (T1), a PSG exam with the same conditions of the exam at T0 was performed with the MAD in situ and all patients were interviewed on improvements, adherence and adverse effects. The BMI of all patients at T1 was recorded to exclude the hypothesis that weight variations influenced PSG values.

Table I. Inclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate OSAS or severe OSAS when CPAP or surgical procedures were refused and in case of CPAP intolerance</td>
</tr>
<tr>
<td>Retrolingual collapse ≥ 50% and retropalatal collapse ≤ 50% during Müller Manoeuvre</td>
</tr>
<tr>
<td>Tonsillar grade &lt; 3</td>
</tr>
<tr>
<td>Low nasal resistance</td>
</tr>
<tr>
<td>At least 6 teeth in the lower arch</td>
</tr>
<tr>
<td>No substantial tooth mobility or untreated periodontal disease</td>
</tr>
<tr>
<td>No temporomandibular joint (TMJ) pain</td>
</tr>
<tr>
<td>Ability to protrude the mandible more of 6 mm</td>
</tr>
</tbody>
</table>

Table II. Multidisciplinary examination performed at T0.

<table>
<thead>
<tr>
<th>Neurologist</th>
<th>ENT</th>
<th>Orthodontist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history collection</td>
<td>Anatomical upper airway evaluation</td>
<td>Clinical extraoral examination</td>
</tr>
<tr>
<td>Sleep evaluation</td>
<td>Mallampati scoring</td>
<td>Clinical dental and periodontal examination</td>
</tr>
<tr>
<td>PSG evaluation</td>
<td>Tonsillar grading</td>
<td>TMJ examination</td>
</tr>
<tr>
<td>BMI recording</td>
<td>Nasal resistance evaluation</td>
<td>Orthopantomography evaluation</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngoscopy with Müller manoeuvre</td>
<td>Lateral teleradiography evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cephalometric tracing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dental cast examination</td>
</tr>
</tbody>
</table>
Oral device

Patients were treated with a Somnodent® mandibular advancement splints (MAS) appliance (Somnomed® Ltd, Australia), a custom-made two-piece device with vertical extensions to induce mandibular protrusion with an adjustable screw mechanism on the upper splint to achieve a gradual advancement (Figs 1, 2). Its design allows a high degree of freedom for lateral and vertical movements, and its construction material (Bflex) also allows obtaining adequate anchorage if the patient is completely edentulous in the upper arch, provided that six teeth are present in the lower arch. The initial therapeutic position was individuated with a George Gauge bite fork with a 5 mm vertical interincisal opening; this amount of anterior bite opening was not altered during the study (Fig. 3). An advancement of the 50-60% of maximal protrusive range was performed, depending on patient tolerance and OSAS severity. The protrusion was gradually increased after four weeks of adaptation, in patients who reported no sufficient improvement of symptoms. All appliances were delivered with the instruction to use vertical elastics to prevent mandibular collapse.

Statistical analysis

Data are presented as mean ± standard deviation. A paired t-test was used to evaluate the effectiveness of MAD therapy. The analyzed variables with and without the appliance were: BMI; AHI (calculated as the average number of respiratory events per hour of sleep); AHI in supine (AHIsup) and in non-supine position (AHInsup); oxygen desaturation index (ODI) (calculated as the average number of > 4% drop in oxygen saturation per hour of sleep); minimum arterial oxygen saturation level (MinO₂Sat); the p values < 0.05 were considered statistically significant (Table II). The percentage of patients who obtained an optimum response (AHI at T1 < 5 events per hour) and a good response (AHI at T1 < 10 events per hour) with MAD treatment were compared with systematic reviews available in the literature.

<table>
<thead>
<tr>
<th>Table III. Effect of Somnodent MAS on BMI and polysomnographic parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>AHI</td>
</tr>
<tr>
<td>AHIsup</td>
</tr>
<tr>
<td>AHInsup</td>
</tr>
<tr>
<td>ODI</td>
</tr>
<tr>
<td>CT &lt; 90%</td>
</tr>
</tbody>
</table>

T student paired t-test; [SD Standard Deviation; * p < 0.05; † p < 0.01; NS: not significant; BMI: body mass index; AHI: apnoea/hypopnoea index; AHIsup: apnoea/hypopnoea index in supine position; AHInsup: not in supine position; ODI: Oxygen Desaturation Index]
Results

All patients (100%) and their bed partners were satisfied by the treatment and in the reduction in snoring. Some patients experienced side effects only during the first months of treatment: TMJ discomfort occurred in 15 patients, difficulty chewing in the morning in 7 patients and tooth discomfort in only 1 patient. These side effects did not preclude, in any case, the use of the device. No patient discontinued treatment after six months because of short-term side effects. No significant differences in BMI values from T0 to T1 were noted, and therefore variation in patient weight did not influence the results of this study. The average response to treatment was statistically significant for both AHI and ODI (p < 0.01) (Table III). In this study, a significant mean AHI at T1 reduction of 19.2 events per hour was obtained, with a significant mean reduction of AHIsup of 26.1 events per hour, a significant mean reduction of AHInsup of 9.1 events per hour, a significant average ODI reduction of 16.6 events per hour and significant mean increase of MinO2Sat of 3.9%. An optimum response was seen in 53% of patients, compared to 35-38% in randomized, crossover, placebo-controlled studies included in the Hoffstein systematic review11 25 26, and a good response in 73% of patients compared to 50-55% reported by the Metha and Naismith studies11 26 included in the Hoffstein review. The AASM review reported a mean percentage of good response in 52% of patients and an average rate of optimum response in 42% of subjects; evaluating success on severe OSA, in this study 40% of patients obtained an optimum response and 50% a good response to MAD, compared to an average success of 34% referred by the AASM review10 (Fig. 4). The comparison between our study and above studies considering inclusion criteria are shown in Table IV.

Discussion

The efficacy of Somnodent® in MAS was demonstrated in the present study. The subjective evaluation of severity and frequency of snoring showed that both patients and their bed partners were satisfied. The design of the appliance allowed an excellent degree of freedom in execution of lateral and vertical movements, and the gradual protrusion enabled finding the therapeutic final advancement, reducing patient discomfort. Vanderveken et al. in 201223 demonstrated the tendency of airway patency to decrease when vertical dimension increase from 4 to 20 mm, suggesting that vertical elastics (Fig. 5), by preventing mouth opening, can improve MAD treatment in many subjects. An optimal treatment response was achieved in 53% of patients and a good response was attained in 73% of cases. Comparing the response rates to those reported in literature by Hoffstein11 and in the AASM review10, it can be supposed that the higher percentage of success in this study can be attributed to patient selection and to the fact that a multidisciplinary approach in diagnosis of OSA can improve the results of MAD treatment in subjects affected by severe OSAS26. In fact, the selection criteria for the majority of the studies included in the reviews listed above were polysomnographic values and dental, functional and periodontal contraindication. In this study, an obstruction site evaluation was performed and only patients with a low tonsillar grade, low nasal resistance and prevalent

Table IV. Comparison of inclusion criteria between the present study and studies included in mentioned reviews.

<table>
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<th>Our study</th>
<th>Studies included in mentioned reviews</th>
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<td>OSAS severity</td>
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retroolingual obstruction were included. Tonsillar hypertrophy represents a recommendation for their surgical removal and nasal congestion may reduce patient tolerance to the oral appliance treatment; in 2006, Marie Marklund demonstrated that patients with nasal congestion experienced a lower rate of occlusal modifications, which may be related with a lower adherence to oral device treatment. Two years later, Cistulli et al. estimated the impact of high nasal resistance, demonstrating its negative influence on MAD treatment outcome. Regarding the significance of a preventive obstruction site assessment, in 2006 Ng et al. evaluated upper airway pressure during natural sleep and demonstrated that retroolingual collapse was associated with a higher grade of response. In a review on oral devices published in 2007, Cistulli et al. included primary retroolingual collapse during sleep and larger retropalatal airway space as predictors of a favourable response to MAD treatment. The potential limitation of this study was that nasendoscopy with the Muller manoeuvre determined obstruction sites and the pattern of collapse during obstructive events, although the effect of sleep on pharyngeal size is significant. An improvement on outcome of MAD therapy can be offered by sleep endoscopy with advancement simulation. In the study of Jojahl on sleependoscopy performed with a MAD simulator to improve patient selection, treatment success, as defined by a follow-up AHI < 10 events per hour, was achieved in 79% of patients. In 2011, Vanderveken and Braem described a technique to obtain an individual protrusion simulator with a metal bitefork to perform, during sleep endoscopy, an advancement as similar as possible to that reproducible by the oral device.

Conclusions

It can be concluded that:
1. Somnomed MAS® is effective in reducing the subjective perception of snoring in all patients and in decreasing respiratory events.
2. The device is well accepted by patients and only transient poor short-term adverse effects occurred.
3. The success ratio was improved by multidisciplinary diagnosis and patient selection.

References


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Clinical techniques and technology

Ectopic lingual goiter treated by transoral robotic surgery

Gozzo della tiroide linguale asportato mediante chirurgia robotica transorale

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SUMMARY

Multinodular goiter in lingual thyroid is quite rare. Surgical removal is indicated in symptomatic patients and when cancer is suspected. An external approach is most often used, but is associated with morbidity and sequelae. In this study, we present for the first time the technique of transoral robotic surgery (TORS) for removal of a massive lingual goiter. Prospective patient data were collected, including demographics, medical history, symptoms, comorbidities and drugs prescribed. The da Vinci Surgical System was used for a transoral approach to the oropharynx. The technique was validated in a 31-year-old woman with signs and symptoms of multinodular goiter presenting since childhood. The procedure required 115 min, with intervals as follows: tracheotomy, 25 min; robot setting time, 20 min; and console time, 70 min. TORS is feasible in cases of multinodular goiter in a lingual thyroid. The procedure appears to be safe, with quick recovery of swallowing and speech.

KEY WORDS: Lingual thyroid goiter • Transoral robotic surgery • Thyroid ectopias

INTRODUCTION

Lingual thyroid results from the failure of descent of the thyroid gland from the foramen cecum to a definitive position in the anterior neck. Normally, migration of the gland starts during the fourth embryonic week. The gland initially is attached to the foramen cecum by the thyroglossal duct, which atrophies beginning in the seventh embryological week. The pathogenesis of the migration defect is unclear; some Authors postulate that maternal anti-thyroid antibody inhibits growth and migration of the embryonic thyroid.

The lingual thyroid, first described by Hickman in 1869, is the most common location for thyroid ectopias, with 400 previously reported cases, and a reported prevalence of about 1 in 200,000, with a female predilection. Lingual thyroid is usually asymptomatic, and its malignant transformation is no more common than that of a normally placed thyroid gland, with an estimated incidence of 1% . Multinodular goiter in a lingual thyroid is quite rare, with very few cases described in the literature. In about 70% of cases, lingual thyroid is the only functioning thyroid tissue that shows symptomatic enlargement or inflammation. Diagnosis is based on physical examination and imaging. The management of lingual thyroid includes observation, suppressive therapy, radioactive iodine treatment and surgery. Surgery is indicated in symptomatic patients presenting with dyspnea, dysphagia, speech impairment, throat fullness, or obstructive sleep apnoea. In most cases, a transcervical or transmandibular approach is required, with...
consequent morbidity related to the splitting of the lip, tongue and mandible. A minimally-invasive endoscopically
guided technique for lingual thyroidectomy has been proposed by Terris, but no case of large ectopic
multinodular lingual goiter treated with a transoral approach has been reported in the literature. We present the
first case of ectopic lingual goiter treated by transoral robotic surgery (TORS).

Clinical techniques and technologies

Prospective patient data were collected, including demographic information, medical history, symptoms, comorbidities and drugs prescribed. Preoperative assessment included physical examination, transnasal video endoscopy, blood tests for thyroid function assessment and head and neck magnetic resonance imaging. The local ethics committee approved the use of transoral robotic-assisted surgery for oropharyngeal tumours. The da Vinci Surgical System (Intuitive Surgical Inc, Sunnyvale, California) was used for a transoral approach to the oropharynx. Surgery was performed by a trained attending surgeon experienced in endoscopic and robotic surgery. The feasibility of the technique was validated in a 31-year-old woman who presented with the following symptoms from childhood: croaky voice, sensation of a foreign body in the throat and dysphagia. She had been on suppressive therapy (100 mcg of levothyroxine daily) since the age of 20 years. Thyroid function test results were normal, and no comorbidities were reported. Fibre-optic nasal endoscopy revealed a mass arising from the base of the tongue. MRI showed a 5.6 × 5.4 × 4.6 cm mass localized in the base of the tongue with areas of necrosis and heterogeneous contrast enhancement (as seen in large goiters) completely occluding the oropharynx (Figs. 1, 2). No thyroid tissue was present in the anterior neck.

The patient was placed on the operating table in a supine position. A tracheotomy under local anaesthesia was performed to secure the airways during conventional intubation. A cuffed tracheostomy tube was positioned using the da Vinci Surgical System. The surgeon was seated at the console and a second surgeon worked at the head of the patient. Access to the pharynx was achieved with a suspended 645001 FK retractor (Olympus®). Three 5-mm robotic arms were employed, with a 30-degree stereoscopic high-definition video camera on the central arm, Maryland forceps to grasp and retract on the left, and a spatula cautery for dissection and coagulation on the right. The incision of the mucosal layer started from the cranial aspect of the mass at the level of foramen cecum (Fig. 3), and the goiter was progressively detached from the lingual muscles using cautery dissection. Lateral retraction of the partially detached mass allowed visualization and dissection of the lateral border of the goiter. The procedure was completed upon reaching the glossoepiglottic vallecula, with removal of the specimen in one block (Fig. 3). Adequate haemostasis was performed with an estimated blood loss of 130 ml. No reconstruction was performed, leaving the surgical bed to heal by secondary intention. The procedure required 115 min, with intervals as follows: tracheotomy, 25 min; robot setting time, 20 min; and console time, 70 min. The FK retractor was removed with no signs of tongue damage. A nasogastric feeding tube was installed, and short-term antibiotics and analgesics were delivered. The tracheostomy tube was removed 48 hours after surgery. The postoperative period was uneventful, and the nasogastric feeding tube was re-
Ectopic lingual goiter treated by transoral robotic surgery

The patient was discharged on the fourth postoperative day, and complete healing of the surgical bed was accomplished within 3 weeks. The final pathology report confirmed the diagnosis of ectopic lingual multinodular goiter.

Discussion

Degeneration of goiter in an ectopic lingual thyroid is a rare event. Surgery is the common option for large masses, and several external approaches to the pharynx have been proposed, including transcervical or transmandibular with or without splitting the lip and tongue. These procedures allow wide exposure for safe removal of the lesion, but lead to substantial functional and aesthetic sequelae and, in most cases, prolonged hospitalization. A transoral approach has been proposed by some authors.

Visual access was provided, in most cases by endoscopic viewing, and dissection was performed using traditional instruments, CO2 laser, or harmonic shears. TORS is presently used for different otorhinolaryngologic areas. To the best of our knowledge, TORS for the treatment of ectopic lingual thyroid has not yet been described. As reported by Terris, a transoral approach for removal of the ectopic lingual thyroid reduces hospitalization times, bleeding, and morbidity related to the procedure, in comparison to external approaches. In addition to being minimally invasive, TORS provides the following advantages:

- better view of the surgical field due to high magnification, three-dimensional visualization and optical orientation;
- four-handed surgery (including the assistant), which allows tissue manipulation and retraction comparable with open surgery; and
- six degrees of motion due to wristed instruments that allow the surgeon to reach, under direct vision, areas around the corner.

The absolute local contraindication is related to the difficult exposition of the oropharynx, due to a limited opening of the mouth or the patient’s habitus. TORS for treatment of ectopic lingual goiter is feasible, requires a short learning curve, and appears to be safe. Temporary tracheotomy can be useful for airway management at the induction of anesthesia, avoiding the use of a nasotracheal tube in the pharynx during surgery. TORS can be considered an effective treatment for surgical removal of ectopic lingual goiter.

References


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Sudden clinical course of an unusual ENT tumour: clinical pictures of extramedullary plasmacytoma secondary to multiple myeloma

Case series

Introduction

Extramedullary plasmacytoma (EMP) is a rare monoclonal plasmacytic proliferation occurring in an extraskeletal site. EMP comprises 3-5% of all plasma cell neoplasms and accounts for less than 1% of all malignant head and neck tumours. The upper airways are involved in 80% of cases, although the heterogeneous pattern of frequency leads to consider exceptional some of the specific sites where the disorder appears. Its natural history is still unpredictable: EMP tends to be solitary, or it may be multiple at diagnosis in 10% of patients; it may occur at disease onset (15-20%) or develop (15%) in course of multiple myeloma (MM). Depending on the mass effect of the neoplasm, the clinical features are linked to the site of the illness, tumour size and involvement of the surrounding structures. As EMP does not show either distinctive clinical or radiologic features, diagnosis is provided by deep biopsies, and a multidisciplinary haematological approach is mandatory to complete the diagnostic-therapeutic work-up. The marked sensitivity to irradiation has led to consider radiotherapy the elective treatment, but up to now both a widely accepted consensus and an international guideline are still missing. The presentation and management of two suggestive clinical pictures characterised by unusual and sudden development are discussed herein.

Case series

Case 1

A 74-year-old Caucasian male with a 3-year pre-existing stage I IgGκ multiple myeloma (MM), came to our attention due to acute onset of diplopia with daily retro-orbital headache. Magnetic resonance imaging (MRI) and computerized tomography (CT) scans showed a left sphenoid sinus mass with ipsilateral cavernous sinus invasion, superior extension to the sinus roof, clivus erosion and imprint of the pituitary gland. Carotid artery impairment without lumen damage was also described (Figs. 1, 2). Fiberscope nasal inspection revealed only diffuse mucosal crusting without any evidence of tumour. After transnasal endo-
scopic sphenoidotomy, a biopsy of the lesion was performed: the histopathologic study was consistent with the diagnosis of EMP. No lytic lesions were found by bone radiograph survey. Bone marrow plasmacytosis was 30%. After radio-chemotherapy, complete regression of the tumour was achieved. The patient died 8 months later due to an intestinal perforation, without evidence of local or systemic relapse.

Case 2
A 62-year-old Caucasian woman was presented with a previous medical history significant for stage IIIa IgGλ MM that completely resolved after chemotherapy (bortezomib plus dexamethasone). Two years later the patient developed lung, chest-wall and vertebral relapses. Due to marked dysphonia, she was submitted to head and neck CT with evidence of a left hemilaryngeal mass extended from pharyngoepiglottic fold to the paraglottic homolateral area. Thyroidal shield was not involved and a normofunctional goiter was also observed. Bone marrow biopsy identified a plasma cell infiltration of 50-60%. Chemo- and radiotherapy led to a complete regression of the disease except for the laryngeal involvement. Neck imaging did not demonstrate any treatment response and a rapid progressive dysphagia plus dyspnoea quickly addressed the patient to ENT evaluation. Upper airway endoscopy showed a smooth red mass probably originating from the left aryepiglottic area and extended to the glottic region, piriform sinus, pharyngoepiglottic area. Cricoarytenoid motility was absent and the airway was severely compromised (Fig. 3). Emergency transisthmic tracheostomy unexpectedly revealed a pathologic tissue inside the thyroid gland. Laryngeal and thyroidal biopsies detected extramedullary spreading of MM. Despite chemotherapy, the patient died two months later due to the EMP.

Discussion
The common EMP presentation in the upper airways strongly relates to the importance of ENT examination. The heterogeneous pattern of frequency in the head and neck area may result in insidious clinical expressions that are potentially lethal. In their review of 400 publications, Alexiou et al. point out the topographic preference of EMP. The occurrence in the sphenoid sinus (2.0%), larynx (11%) and thyroid gland (1.4%) is confined to very few cases, indeed considered rare, but the finding of a cavernous sinus syndrome and upper airway blockage is exceedingly rare.4 11-13 These dramatic clinical complications reflect a highly aggressive tumour where any predictions about its natural history remain difficult. Classified as secondary or primary depending on whether there is evidence of systemic MM or not, EMP might suggest the presence of disseminated disease, and a multidisciplinary haematological evaluation is mandatory.
to exclude myelomatous lesions. Developing late in course of MM, both described cases share the same rapid extramedullary growth with a different and independent progression from MM. Extramedullary MM spreading is commonly associated with poor outcome, and the survival rate strictly depends on the myelomatous behaviour, chemotherapy side effects and any comorbid disorders. In our experience, the watershed of the prognostic perspectives was defined by EMP clinical progression rather than by MM growth. In the first case, an unexpected EMP lesion extending into the middle cranial fossa occurred in the context of a pre-existing stationary stage I MM, under no therapy. In the second patient, relapses of a stage III MM appeared with an extramedullary involvement of two crucial structures of the respiratory tree. Whereas myelomatous lesions resolved completely after chemotherapy, EMP expanded, regardless of MM. This led to a severe dyspnoea and a subsequent emergency tracheostomy was required.

Currently, there are no criteria to predict the sudden appearance of EMP during the course of MM. Its pathophysiology is poorly understood: EMP and MM might be considered two independent entities but simultaneous expressions of a unique disease, with different plasma cell families following a different natural history.

Conclusions

Despite the exceptionality of the two cases described, careful follow-up is recommended in patients with a history of MM, with particular regard to ENT symptoms. Long-term and well-controlled MM does not exclude the development of a highly aggressive EMP with sudden clinical course. Non-specific clinical and radiological presentations stress the importance of a multidisciplinary approach to achieve early correct diagnosis and prompt treatment.

References


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**Case report**

**Intramuscular haemangioma of the levator anguli oris: a rare case**

Angioma intramuscolare del muscolo elevatore dell’angolo della bocca: un raro caso clinico

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**SUMMARY**

Intramuscular haemangiomas are benign malformations of blood vessels occurring in skeletal muscles. Because of the rarity of these lesions, their deep location and variable clinical presentation, they often pose diagnostic difficulties. We herein present the first reported case of intramuscular haemangioma occurring in the levator anguli oris muscle. A 26-year-old man was referred to our Department for evaluation and management of a progressive swelling of the right cheek. Based mainly on the imaging findings, a preoperative diagnosis of intramuscular haemangioma was made and surgery was performed. During intervention, a highly vascular soft tissue mass was identified within the levator anguli oris muscle. The lesion was completely removed via an intraoral approach, and histopathological examination showed an intramuscular haemangioma.

**KEY WORDS:** Intramuscular haemangioma • Levator anguli oris

RIASSUNTO

Gli emangiomi intramuscolari sono malformazioni benigne di origine vascolare che si localizzano all’interno della muscolatura scheletrica. A causa della rarità di queste lesioni, la loro profonda localizzazione e la loro variabilità nella presentazione clinica, pongono spesso difficoltà diagnostiche. Il caso presentato in questo articolo è il primo emangioma intramuscolare del muscolo elevatore dell’angolo della bocca, riportato in letteratura. Trattasi di un uomo di 26 anni valutato presso la nostra clinica per progressiva tumefazione in corrispondenza della guancia destra. Sulla base dei reperti clinico-radiologici, è stata posta diagnosi pre-operatoria di emangioma intramuscolare e per tale motivo è stato sottoposto a eseresi chirurgica. Durante l’intervento, è stata identificata una massa altamente vascolarizzata di tessuto molle all’interno del muscolo elevatore dell’angolo della bocca. La lesione è stata completamente escissa tramite approccio intraorale e l’esame istopatologico ha confermato la diagnosi di emangioma intramuscolare.

PAROLE CHIAVE: Emangioma intramuscolare • Muscolo elevatore dell’angolo della bocca

Acta Otorhinolaryngol Ital 2013;33:350-352

**Introduction**

Intramuscular haemangiomas (IMHs) are relatively uncommon angiomatous malformations. They appear most often in the trunk and extremities, while their occurrence in the head and neck region is rare. In the head, the masseter muscle is the most frequently involved site. Clinically, diagnosis of IMHs is difficult. As a result, inappropriate treatment planning is a common problem that can lead to incomplete excision and unnecessary risk to the facial nerve. IMHs usually present in childhood or early adult life, are treated by complete surgical excision and carry an excellent prognosis.

To the best of our knowledge, the present case is the first intramuscular haemangioma within the levator anguli oris reported in the literature.

**Case report**

A 26-year-old man was referred to our Department for evaluation and management of a painless swelling of the right cheek (Fig. 1). The lesion had been present for 10 years and had gradually increased in size. The patient complained of cosmetic deformity. Clinical examination showed a diffuse mass situated about 2 cm superior to the right side of the upper lip. The lesion was soft, compressible, mobile and not adherent to skin. The overlying skin was slightly erythematous. No pulsation, bruits or thrills were noted. There was no evidence of neck lymphadenopathy.

A subsequent computerized tomography (CT) scan revealed a 4.6 x 1.9 cm soft tissue mass of the same density as muscle, arising from within the muscles of the cheek (Fig. 2). There was no underlying bone involvement of the
Intramuscular haemangioma of the levator anguli oris: a rare case

upper jaw. Magnetic resonance imaging (MRI) showed heterogeneous, intramuscular lesion at the same location (Fig. 3). The mass was hyperintense to the masseter muscle on T2-weighted images. The imaging findings, history of long duration of the swelling and the clinical finding of discolouration of the overlying skin raised suspicion of a vascular lesion. On that basis, angiography was performed, and the patient underwent bilateral common carotid arteriography via the right femoral artery that confirmed the vascular nature of the lesion. In particular, the right common carotid injection showed that the mass consisted of a collection of tortuous vessels of varying calibre. Two main feeding vessels were detected, one originating from the right facial artery and another from the right internal maxillary artery (Fig. 4). Based on these findings, a provisional diagnosis of intramuscular haemangioma was made and surgery was scheduled. The lesion was removed via an intraoral approach under general anaesthesia. During intervention, a highly vascular soft tissue mass was identified within the levator anguli oris muscle. The lesion was excised together with a margin of the normal surrounding muscle to prevent recurrence. Several small feeding vessels were individually ligated by bipolar diathermy. Blood loss during the procedure was minimal, allowing for complete excision. The postoperative period was uneventful. The histopathological examination showed small vessels growing between fibres of skeletal muscle, consistent with a diagnosis of intramuscular haemangioma of small vessel (capillary) type. The patient remains free of symptoms and there is no evidence of postoperative recurrence at 6 months (Fig. 5).

Discussion

Intramuscular haemangioma is an uncommon vascular malformation, accounting for less than 1% of all haemangiomas. It affects mainly the trunk and extremities where the muscle volume is larger. Approximately 13% of these lesions present in the head and neck region. In the head,
the masseter muscle is the most frequently involved site. Rarer sites include the orbicularis oris, depressor anguli oris and orbicularis oculi muscle. To the best of our knowledge, our case is the first reported of IMH within the levator anguli oris muscle. Intramuscular haemangiomas generally present as progressively enlarging and often painful lesions. Because of their deep location, they rarely display any clinical signs or symptoms that suggest a vascular nature, such as pulsations, thrills or bruits. Overlying skin discoloration is also uncommon. The absence of pathognomonic clinical findings and the rare incidence of these lesions make accurate pre-operative diagnosis difficult. Namely, only 8% of all cases of intramuscular haemangioma are diagnosed before surgical intervention. A variety of muscle neoplasms, benign muscular hypertrophy, congenital cysts and lymphadenopathies are commonly confused in differential diagnosis. In our case, the discoloration of the overlying skin in combination with the imaging findings led to the presumptive diagnosis of intramuscular haemangioma. For preoperative diagnosis of intramuscular hemangioma, plain radiographs, CT scan, MRI and angiography may be helpful. Plain soft tissue x-ray views occasionally demonstrate phleboliths within the lesion. MRI is thought to be more helpful than CT as it provides better detection and delineation of the extent of the IMH. The lesions are characteristically much brighter on T2- than T1-weighted imaging due to the increased free water present within stagnant blood in the vessels. Angiography usually clarifies the vascular nature of the lesion, demonstrates feeding vessels and identifies its extent. In our case, pre-operative diagnosis of IMH was strongly guided by the findings of arteriography. However, angiography should be performed if there is a strong suspicion of a vascular deformity. Various treatment methods have been used in the management of intramuscular haemangioma including steroid injections, radiation therapy, injection of sclerosing agents, cryotherapy and electrocaugetiuation. However, the optimal management is the surgical resection with wide margins of surrounding normal muscle because of the infiltrative nature of the IMH. The choice of surgical approach depends on the extent and location of the lesion. In our case, intraoral excision was used to achieve the best possible cosmetic result. Preoperative embolisation is indicated for large tumours with multiple or large calibre feeding vessels to minimize blood loss.

In conclusion, the possibility of an IMH should be included in the differential diagnosis of any facial mass. The appropriate radiologic examinations can enhance accurate preoperative diagnosis and optimal treatment planning. Surgical resection, well beyond the gross limits of the lesion, is generally considered the ideal therapeutic approach for IMH.

References

Case report

Palliative combined treatment for unresectable cutaneous basosquamous cell carcinoma of the head and neck

Trattamento palliativo combinato di un carcinoma basosquamoso cutaneo non resecabile del distretto testa-collo

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SUMMARY

A case is presented of a patient with a skin basosquamous cell carcinoma of the frontal region infiltrating the cerebral tissue and with a widespread unresectable regional metastatic ulceration of the left parotid region. The patient underwent combined palliative treatment: surgical coverage of the ulceration by means of a pectoralis major flap transposition and radiotherapy. After 18 months of follow-up, no signs of tumour progression were noted, the patient is currently free from pain, no increase in trismus was seen, and a slight gain in weight was recorded. Unresectable cancer is mainly treated by concurrent chemoradiation; radiotherapy, however, is contraindicated in deep neoplastic ulcerations with exposure of large vessels. The data reported suggest that surgical coverage of an unresectable neoplastic ulcer is feasible, and combined with early administration of radiation permits a palliative approach in an otherwise untreatable condition.

KEY WORDS: Basosquamous cell carcinoma • Palliative surgery • Palliative radiotherapy • Head and neck cancer

Introduction

Basosquamous cell carcinoma (BSCC) is a rare malignancy with features of both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (Fig. 1). The recent World Health Organization (WHO) classification of head and neck tumours defines BSCC as an aggressive subtype of SCC. The incidence of BSCC among BCC has been estimated to be 0.4-12% and its higher metastatic propensity compared to SCC, is clearly highlighted in the literature. Rare cases of BSCC with either leptomenigeal carcinomatosis or infiltrating cerebral tissue have been reported. Disease onset usually occurs between the sixth and seventh decade, with the skin of the head and neck being the sites most involved. A more aggressive behaviour has been recorded in patients with recurrence, and male sex has been statistically correlated with likelihood of recurrence.

Palliative treatment in head and neck cancer aims to improve the patient’s quality of life. In some cases, palliative treatment can prevent life-threatening complications (such as rupture of vessels) thus prolonging patient survival.
Herewith the case is presented of a patient with BSCC of the supraorbital skin, infiltrating the cerebral tissue and with widespread regional metastatic ulceration of the left parotid region. The patient underwent palliative treatment with surgical coverage and radiotherapy.

Case report

A 54-year-old male patient consulted our first aid unit on account of moderate bleeding from the neck. Upon physical examination, on the left side, a $3 \times 2$ cm non-bleeding ulceration of the frontal skin was found and a wide (approximately $10 \times 5$ cm) ulcer involving the left parotid area from the zygomatic arch to the level of the hyoid bone, eroding the external ear canal, disrupting most of the pavilion and causing complete peripheral facial nerve paralysis (Fig. 2). The patient also presented a moderate trismus with 1.5 cm maximal mouth opening. Upon visual inspection, it was possible to clearly perceive the carotid pulse at the jugulo-digastric level.

Laboratory tests revealed a haemoglobin value of 12 mg/dl with normal electrolytes.

Discussing the medical history, the patient reported having undergone surgery abroad (Albania) for BCC of the frontal skin. Unfortunately, earlier detailed charts were not available, and relatives could not provide exhaustive information about previous surgical treatment. It was certain, however, that the patient had never received either radiotherapy or chemotherapy and that, abroad, no further treatment options were advised besides pain control. From these findings, it was assessed that the disease appeared 2 years before as a left-sided frontal skin lesion for which the patient had undergone local excision. Six months later, the patient developed a left parotid-cervical mass that was treated with parotidectomy and lymph-node excision (no codified type of neck dissection was performed). Furthermore, 6 months after parotid-cervical surgery, a non-healing ulceration, which became progressively enlarged, appeared in the parotid region with concomitant facial paralysis. Moreover, a necrotic sore developed from the operated frontal skin. Since then the patient experienced progressive fatigue with consistent limitation in his daily activities, increasing pain that required morphine patches, and weight loss (8 kg in the last 6 months). He never experienced either seizure or any other kind of cerebral symptom.

Contrast enhanced CT scan of the head and neck and thorax showed infiltration of the meningeal and cerebral tissue of the left frontal lobe, infiltration of the mastoid middle ear, complete encasement of the left internal and external carotid arteries with involvement of the pterygoid muscles and skull base (Fig. 3). No evidence of distant lung metastasis was observed. After appropriate counseling and multidisciplinary evaluation, the patient underwent surgery. Extensive biopsies of the parotid ulceration’s borders were submitted for frozen section analysis that revealed BSCC (tumour staging rT4N1M0). The edges of the skin were resected until macroscopic healthy tissue was found. A generous undermining of the cervical skin, reaching the superior border of the clavicle, was carried out in order to avoid further incisions in the neck. A pectoralis major flap with a skin paddle of $20 \times 8$ cm...
was transposed to cover the defect. The external auditory canal was obliterated.

The post-operative course was uneventful, flap viability was optimal and no wound dehiscences occurred. The patient was discharged on the 4th post-operative day having been advised to undergo palliative radiotherapy that was started on the 15th day. External beam three-dimensional conformal radiotherapy was carried out using 6-MV photons (linear accelerator) equipment. Planning CT scan was performed in treatment position with a customized head mask. The gross tumour volume (GTV), the clinical target volume (CTV), the planning target volume (PTV) and the organs at risk (spinal cord, lens, eyes, etc.) were delineated on each slice. Radiotherapy was delivered to the cervico-parotid region with standard fractionation (2 Gy per day, 5 days a week) using three coplanar converging wedged beams (Fig. 4) and was stopped, at a total dose of 44 Gy, when a neck abscess developed at the operated neck side. The abscess was treated with surgical evacuation by means of simple pen rose drain introduction and antibiotic administration. Since GTV, at this site, was strictly related to the spinal cord, it was not possible to achieve a higher total dose. The supraorbital frontal skin recurrence was treated with electron beam radiotherapy with standard fractionation until a total dose of 44 Gy was reached.

Adjuvant chemotherapy was planned and advised, after the end of radiation, but the patient refused. After 18 months of follow-up, no signs of tumour progression were noted, the patient is currently pain free, no increase in trismus was observed, and a slight gain in weight was recorded (4 kg since the end of radiation) (Fig. 5).

Discussion

In the literature, there are no reports giving guidelines for the management of unresectable neoplastic head and neck ulcerations with vessel exposure.

Unresectable cancer is mainly treated by radiotherapy with concomitant chemotherapy, the setting of which is designed for a curative or a palliative intent based on the realistic chances of tumour control. Several host/tumour factors must be taken into consideration in treatment planning: patient’s general conditions (performance status) and specific comorbidities that might prevent withstanding of the treatment, the possibility of delivering curative doses of radiation without damaging vital structures, the locoregional volumetric extension of the disease, the presence or absence of distant metastases.

In the present case, due to cerebral involvement, it was not possible to offer the patient a chemoradiation protocol with curative intent.

In the case presented, the need for surgical coverage arose from the evidence that radiotherapy is contraindicated in deep neoplastic ulcerations with exposure of great vessels, on account of the serious risk of blow-out with fatal haemorrhage. Regional and distant tissue transfer techniques have increased the possibility of covering vital organs with well vascularised tissue allowing otherwise impossible radiation delivery. Nevertheless, we were unable to predict whether flap transposition would have efficiently covered the defect without dehiscence and without an immediate neoplastic colonization of the transposed tissue from the neoplastic recipient. This was our major concern, but we had to face the fact that no other options were available and that carotid rupture is such a catastrophic event that its exposure represents a surgical priority in itself. We felt that the transposition of a pectoralis major flap was more appropriate than reconstruction with a microvascular free flap, since the quality of the donor vessels for microvascular anastomosis was questionable.

In head and neck cancer, it is recommended to start post-operative adjuvant radiation, within 4-6 weeks after surgery to maximize loco-regional control. Our prompt onset of post-operative radiation within 2 weeks after surgery, despite the development of a neck abscess, might have been a crucial factor in successful palliation. Even if, however, we obtained a pathologic assessment only of the parotid-neck ulceration, we believe that the frontal lesion had to be considered the primary tumour, while the parotid ulceration was the regional metastatic extension.
Since the frontal ulceration appeared as a non-bleeding necrotic sore, we felt that it was not appropriate to take biopsies that could have worsened the local status and delayed the possibility of radiation delivery. In fact, necrotic tissue frequently hides cancer proliferation, therefore thus preventing the diagnosis. This slight likelihood of obtaining the correct diagnosis with a single bite biopsy leads the surgeon physician to perform multiple biopsies that could jeopardize the clinical condition. Furthermore, confirmation histology of the primary lesion would not have changed our treatment strategy in this particular patient. In the sixth edition of the TNM classification 8 (the only one available at the time the patient was treated), a giant unresectable metastatic involvement of the neck and parotid was classified N1 like a single small lymph node metastasis. Recently, in the seventh edition of the TNM classification 11, a more accurate N classification for non-melanoma skin cancer has been introduced, accordingly our case would now be classified N3: N0 no lymph node metastasis; N1 single < 3 cm; N2 single ≥ 3 to 6 cm, multiple ≤ 6 cm; N3 > 6 cm. These changes certainly improve the hazard consistency (homogeneity within the group) and hazard discrimination (heterogeneity between the groups) of the classification. However, we feel that a further discrimination between resectable and unresectable regional neck disease might be helpful, considering that treatment and prognosis of these conditions differ consistently. Furthermore, parotid disease, facial nerve involvement and tumour size greater than ≥ 6 cm within the parotid, had less favourable prognosis in terms of survival in several studies 12-14. Based on this concept, several years ago, a new staging system was introduced that separates parotid involvement from cervical lymph node involvement 10-12. Parotid disease was more prognostic of poor survival than neck involvement; in particular, facial nerve involvement and tumour size ≥ 6 cm within the parotid 11,13. These studies were conducted on cutaneous SCC but probably the same findings might be valid also for BSCC.

**Conclusions**

In cases of unresectable neoplastic head and neck ulceration, the combination of surgical coverage with postoperative radiation radiotherapy offers a valid treatment option to achieve a palliation in an otherwise untreatable situation. This report indicates that surgical coverage of vital organs with well vascularised tissue is feasible even in the case of neoplastic recipient ulceration; the authors believe that, in these conditions, early administration of palliative radiation radiotherapy is mandatory.

**References**


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The discovery of stapes

La scoperta della staffa

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SUMMARY

Giovanni Filippo Ingrassia revisited and redefined some of Galeno’s reports, and was recognized as one of the leading Italian Physicians of the 16th century. Ingrassia principally studied the skull, and gave very important contributions to otorhinolaryngology, including the discovery of the stapes. He also isolated the inferior nasal concha from the maxillary bone, described the frontal sinus, the pterygopalatine fossa and several foramina of the skull. Ingrassia firstly attributed a sensorial function to the middle ear bones, which he called fifth particular function. He also added some details to the description of the VIII cranial nerve, which introduces the concept of bone conducting sound. The most important discovery in Ingrassia’s study about the hearing organ was the first description of the third bone of the ossicular chain that he called “staffa”. Ingrassia should thus be reconsidered under a new light for his important discovery and for his intuitions about the stapes and its role in hearing. It is appropriate for a Sicilian physician to be placed at his rightful place side-by-side with Eustachio and Valsalva in the history of otology.

KEY WORDS: History • Otology • Stapes • Hearing • Ingrassia • Ear

INTERO

Giovanni Filippo Ingrassia riconsiderò e ridefinì alcune descrizioni di Galeno e fu riconosciuto come uno dei principali Medici Italiani del XVI secolo. Ingrassia studiò principalmente il cranio e diede un contributo importante per la moderna otorinolaringoiatria, come la scoperta della staffa. Egli descrisse l’osso del turbinato inferiore isolandolo dall’osso mascelare; descrisse inoltre: il seno frontale, la fossa pterigopalatina e diversi tra i fori cranici. Per primo, Ingrassia attribuì una funzione sensoriale agli ossicini dell’orecchio medio, funzione che chiamò quinta funzione particolare. Aggiunse anche alcuni dettagli alla descrizione dell’VIII nervo cranico, introducendo il concetto di conduzione ossea del suono. La scoperta più importante di Ingrassia, durante lo studio della funzione uditiva, è stata la prima descrizione del terzo ossicino della catena che chiamò “staffa”. Ingrassia deve quindi essere riconsiderato sotto una nuova ottica per le sue importanti scoperte e per la sua intuizione sulla staffa e sul suo ruolo nella funzione uditiva. Sarebbe appropriato per il medico Siciliano essere posto accanto ad Eustachio e Valsalva nella storia dell’otologia.

PAROLE CHIAVE: Storia • Otologia • Staffa • Udito • Ingrassia • Orecchio

Acta Otorhinolaryngol Ital 2013;33:357-359

Around the year 200 AD, the island of Sicily (Italy) saw the physician-philosopher Galeno landing on its coasts nearing the end of his life (in Misilmeri, Palermo, Italy), as Ibn Jubayr tells us in his chronicles¹. About 13 centuries later, the Mediterranean island gave birth to another, although less noted, great physician-philosopher of early medical history, Giovanni Filippo Ingrassia, who revisited and redefined some of Galeno’s reports. He was born in Regalbuto (province of Enna, Sicily) in 1510 and died in Palermo in 1580 (Fig. 1).² He was recognized as one of the leading Italian Physicians of the 16th century³. Ingrassia’s work was done under a new scientific approach of studying anatomy introduced by Vesalius, utilizing human cadaver autopsy as the main method to teach anatomy. Ingrassia acquired this method during his frequent visits to Vesalius’ lessons at Padua University. At that time, study of medicine was a mix of science and philosophy, and the latter allowed theoretical speculation about the evidence in medical practice; in today’s world this is represented by the – more scientific – statistical analysis of data. Most of the anatomical descriptions and discoveries of Ingrassia were reported in his book titled “In Galeni librum de ossibus doctissimae et expertissimae commentaria” ² (Fig. 2). This ancient anatomic book was a commentary to “De Ossibus” of Galeno. In his work, Ingrassia wrote 24 chapters about human bones introducing his discoveries, intuitions and criticism regarding some incorrect ideas of Galeno and Vesalius (his teacher). This great collection of his work was published posthumously by his nephew Nicola Ingrassia (also a physician).
Ingrassia studied principally the skull and provided some very important contributions for future otorhinolaryngological disciplines. Galeno identified the upper and lower jaws, and the parietal, temporal, frontal and occipital bones. Several centuries later, Vesalius and Realdo Colombo illustrated two additional segments, namely the ethmoid and sphenoid bones. Contemporary to these descriptions, Ingrassia added several details about these two bones: he described the lesser wings of the sphenoid, the crista galli, the cribriform plate, and the perpendicular plate of ethmoid, as well as describing for the first time sutures of the skull.

Furthermore, Ingrassia isolated the inferior nasal concha from the maxillary bone, described the frontal sinus, the pterygopalatine fossa and several foramina of the skull. Additionally, he hypothesized that the paranasal sinuses may exert a function in phonation (theory that is not widely accepted today), rather than “attracting air for healthful vital spirits, as well as in purging blood flowing to the brain”, as Realdo Colombo had previously asserted.

One of the most important intuitions of Ingrassia was the attribution of a sensorial function to the middle ear bones, which he called *fifth particular function* (“quintusigitur usus est trium ossicularum auditus”). The old scientific method implemented by Ingrassia starts from the anatomy (description of the structures), passing through pathological anatomy and then making a hypothesis about function. Adopting this approach to medicine, he was able to hypothesize the “fifth function” of the ossicular chain, an early intuition of a sensory function confirmed later.

Ingrassia added some details to the description of the VIII cranial nerve (V in the ancient Galeno’s classification) and in this description introduces the concept of bone conducting sound: “if one closes the external ear canal […] keeping between the teeth or accosting near the mouth the hand of a guitar […] he can hear sound, if after this he turns away the instrument no sound is then perceived”. Although the intuition of the Sicilian physician was brilliant, the mechanism that he thought of was different from the physiologic actual model, as he believed that the VIII nerve directly conducted the sound from the skull bones. However, Ingrassia described in detail the cochlea, the semicircular canals and the stapedius muscle. Also, the first description of the auditory tube, in the opinion of some authors, should be attributed to Ingrassia rather than Eustachio, but the evidence for this is not clear.

The most important discovery in Ingrassia’s study about the hearing organ was the first description of the *third bone of the ossicular chain* that he called “stapes”. In this regard, we would like the Sicilian physician to narrate his own story of the discovery. For this, we provide an excerpt from the original version of his scripts: “I want to tell now how this little bone was discovered by me for the first time. In the year of world redemption 1546, while I was teaching in Naples the theory and...”
The discovery of stapes

practice of medicine and also anatomy, I didn’t intend to find, but I discovered (by chance) this third bone: I didn’t search for it, because I had no notion or suspicion of it being there. While I was chiselling the ear bones to demonstrate to the students the little internal cavities and the substances contained within them, after I showed the first two little bones, there was, I don’t know how, this third little bone I saw on the table. After having considered and observed it with precision, I realised that it did not appear by chance, but by an act of the Nature. […] I then started to dissect heads of several animals, the cow in particular and started observing one by one the parts of the bone in which resides the hearing. In the end I found this third bone remaining and linked to one of the two sticks of the incus, namely the longer and thinner one. Immediately I returned to human head dissection, straight almost with the eyes closed I found that ossicle, which, due to its analogy, I called it “stapede” (stapes): effectively it is more similar to the stapes than the other two to a malleus or to an incus…”

Ingrassia wrote in the same pages the reason behind the name chosen. He compared the third ossicle to a stirrup made of wood used in Sicily to ride horses and donkey at that time. This was different in shape from the classical iron stirrups used in other parts of Italy in order to comply with a law forbidding the use of metal stirrups in the Sicilian island. Indeed, the shape of the third ossicle is closest to the Sicilian stapes than to other kinds known elsewhere.

This important discovery in the anatomy of middle ear had a long and hard polemic dispute in its attempt to attribute the merit among several anatomists of that time. The first person to attempt a claim on the discovery was Realdo Colombo, successor of Vesalius at the anatomy school of Padua, followed by Eustachio and the two Spanish physicians Collado and Ximeno. However, Vesalius himself eventually re-established the truth by attributing the first description of the stapes to Ingrassia.

Subsequently, Fallopio also acknowledged the Sicilian anatomist for this important discovery.

In our opinion, Ingrassia should be reconsidered in a new light for his important discovery and for his intuitions about the stapes and its role in hearing. It would be appropriate for the Sicilian physician to be placed at his rightful place side-by-side with Eustachio and Valsalva in the history of otology.

References

2 Ingrassia GF. In Galeni librum de ossibus doctissima et expertissima commentaria. Panormi (Palermo): Ioannem Maringum; 1604.
12 Fallopio G. Observationes anatomicae in libros quinque digesta. Venetiae (Venezia); 1561.
Calendar of events – Italian and International Congresses and Courses

Acta Otorhinolaryngol Ital 2013;33:360-365

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

In accordance with the Regulations of S.I.O. and Ch.C.-F. (Art. 8) Members of the Society organising Courses, Congresses or other scientific events should inform the Secretary of the Association (A.U.O.R.L., A.O.O.I.) within the deadlines set down in the respective Statutes and Regulations.

OCTOBER 2013

VII INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN RHINOSINUSITIS AND NASAL POLYPsis
October 4-6, 2013 • Matsue city, Shimane – Japan
Website: www.npcg7.umin.jp – E-mail: npcg7@med.shimane-u.ac.jp

FINESSE IN FACIAL PLASTIC SURGERY • October 10-14, 2013 • Regensburg – Germany
Website: www.facial-plastic-surgery.eu

2nd INTERNATIONAL SYMPOSIUM - AROUND THE LABYRINTH: AUDIOLOGICAL AND VESTIBULAR REHABILITATION • October 11-12, 2013 • Perugia – Italy
President: Giampietro Ricci. Organizing Secretariat: Grifoviaggi, via Marconi 51/53, 06121 Perugia, Italy. Tel. +39 075 5730081 – E-mail: incoming@grifoviaggi.it

27° CORSO “RINOPLASTICA – FONDAMENTI E TECNICHE ESSENZIALI DI RINOPLASTICA CHIUSA”
October 15-19, 2013 • Florence – Italy
Direttore del Corso: Alberto Scattolin, Centro Studi Micheli Pellegrini. Segreteria Organizzativa: Nord Est Congressi. E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

EUROPEAN UNION OF HEARING AID ACOUSTICIANS (EUHA) 58th INTERNATIONAL CONGRESS OF HEARING AID ACOUSTICIANS (EUHA) • October 16-18, 2013 • Nuremberg – Germany
Website: www.euha.org

XXXIV CONGRESSO NAZIONALE SIAF – DISABILITÀ UDITIVA FIGURE PROFESSIONALI E SERVIZI SANITARI • October 16-19, 2013 • Venice – Italy
Website: www.congresso-siaf2013.it

XXXVII CONVEGNO NAZIONALE DI AGGIORNAMENTO AOOI
October 18-19, 2013 • Feroletto Antico (CZ) – Italy

THE 2nd MEDITERRANEAN FESSION COURSE - FROM BASICS TO ADVANCED ENDOSCOPIC SINUS SURGERY • October 18-19, 2013 • Malta
Coordinators: Mario Said, Alberto Dragonetti. Contact information: E-mail: info@maltime.com – Website: www.maltime.com

SECONDO CORSO “LIVE-SURGERY” DI CHIRURGIA ENDOSCOPICA TRANS-NASALE, DALL’ANTROSTOMIA MEDIA ALL’ODONTOIDECTOMIA • October 21-23, 2013 • Brescia – Italy
Direttore del Corso: Piero Nicolai. Segreteria Scientifica: Andrea Bolzoni Villaret, Davide Lombardi. Segreteria Organizzativa: Katia Gissi - E-mail: k.gissi@servizicec.it – Website: www.servizicec.it
### Calendar of events

#### 8th SURGICAL ANATOMY IN HEAD & NECK CANCERS PROCEDURES
**October 23-25, 2013 • Paris – France**

Directors: Marco Benazzo, Department of Otorhinolaryngology, University of Pavia; Fausto Giuseppe Chiesa, Department of Head and Neck Surgery, IEO Milan; Piero Nicolai, Department of Otorhinolaryngology, University of Brescia; Antonio Pastore, Department of Otorhinolaryngology, University of Ferrara – Scientific Secretariat: N. Mevio, F. Mura, D. Scelsi, M. Tagliabue – E-mail: m.benazzo@smatteo.pv.it. 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-

#### 2nd BULGARIAN-ITALIAN MEETING ON RHINOLOGY & 6th ENDOSCOPIC SINUS SURGERY COURSE
**October 24-26, 2013 • Trieste - Italy**

Directors: Alessandro Varini, ENT Dept, Casa di Cura Salus Trieste, Italy – Dilyana Vicheva, ENT Clinic, Plovdiv, Bulgaria. Scientific Secretariat: A. Varini – Tel. +39 040 3171111 – E-mail: a.varini@salustrieste.it. Organizing Secretariat: The Office Trieste – Tel. +39 040 3688343 – Fax +39 040 368808 – E-mail: rhinology2013@theoffice.it – Website: www.theoffice.it

#### STATE OF THE ART ENDOSCOPIC SKULL BASE SURGERY A HANDS ON COURSE
**October 31- November 3 2013 • Columbus, Ohio – USA**

Course Directors: Ricardo L. Carrau – E-mail: Ricardo.Carrau@osumc.edu; Bradley A. Otto; Daniel M. Prevedello

#### NOVEMBER 2013

##### 2013 ANNUAL MEETING OF THE ISRAELI SOCIETY OF HEAD AND NECK SURGERY AND ONCOLOGY
**November 6-7, 2013 • Dead Sea – Israel**

Website: www.ishnos.com

##### 32nd ISIAN, 15th IRS, 19th ORL EGYPT • November 6-9, 2013 • Sharm El Sheikh – Egypt

President: R. Kamel. Secretary General: A. Atef. International Coordinator: H. Negm. Website: www.isian.irs-pars2013.org – E-mail: info@isian-irs-pars2013.org

##### CONVEGNO AOIG: I SENSI E L'INVECCHIAMENTO • November 8, 2013 • Milan – Italy

Presidente: Matteo Richichi. Website: www.aiog.it

##### 1st GLOBAL OTOLOGY RESEARCH FORUM • November 13, 2013 • Antalya – Turkey

Scientific Secretary: Armağan Incesulu, scientific@politzer2013.org, scientific@glorf.org – Organization Secretary: Tuncay Özçelik – E-mail: tozcelik@bayindirhastanesi.com.tr – Website: www.glorf.org

##### 29th WORLD CONGRESS POLITZER SOCIETY MEETING • November 13-17, 2013 • Belek-Antalya – Turkey

Info: Contact Information: to02-k@tr.net – Website: www.politzer2013.org

##### II CORSO “SCUOLA DI DISSEZIONE ANATOMICA CERVICO-FACCIALE”
**November 18-23, 2013 • Florence – Italy**

I sessione
- Ringiovanimento non chirurgico del viso – D. Draganic, R. Polselli, A. Rusciani, Y. Saban
- Chirurgia endoscopica seri paranasali (base) – P. Bossolesi, E. Emanuelli, F.G. Pagella
- Rinoplastica – L. D’Ascanio, G. La Fauci, R. Polselli, A. Scattolin
- Chirurgia del collo – A. Camaioni, M. Radici, G. Spriano, L. D’Ascanio
- Chirurgia endoscopica orecchio medio – D. Marchionni, L. Presutti

Direttore del Corso: Alberto Scattolin. Segreteria Organizzativa: Nord Est Congressi – E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

##### SVUOTAMENTO DEL COLLO - CORSI PRATICI MONOTEMATICI • November 20-22, 2013 • Rome – Italy


##### WORKSHOP 2013 - CHIRURGIA ENDOSCOPICA FUNZIONALE NASO-SINUSALE
**November 28-29, 2013 • Bologna – Italy**

Direttore del Corso: Ernesto Pasquini. Segreteria Organizzativa: CSR Congressi Srl, via G. Matteotti 35, 40057 Cadriano di Granarolo E. (BO). Tel. +39 051 765357 – Fax +39 051 765195 – E-mail: info@csrcongressi.com – Website: www.csrcongressi.com
### DECEMBER 2013

**PSO-HNS 57th ANNUAL CONVENTION – CURRENT OTOTOLOGICAL CONCEPTS AND FUTURE TRENDS**  
**December 1-3, 2013 • Manila – Philippines**  
E-mail: www.pso-hns.org

**RHINOFORUM 2013 • December 6-7, 2013 • Warsaw – Poland**  
President: Antoni Krzeski. Website: www.RhinoForum.pl

**22° CORSO DI LARINGOLOGIA • December 9-12, 2013 • Vittorio Veneto – Italy**  
Direttori del Corso: M. Lucioni, A. Bertolin, Chairman: G. Rizzato. Info: Andy Bertolin, Tel. +39 0438 665231, E-mail: andy.bertolin@ulss7.it. Segreteria Organizzativa: Nord Est Congressi, via Portanuova 3, 33100 Udine. Tel. +39 0432 21391 – Fax +39 0432 506687

### JANUARY–DECEMBER 2013

**THE INTERNATIONAL SOCIETY OF SURGICAL ANATOMY • CORSI 2013 • Nizza – France**

- **February 27 - March 1**: Chirurgia dei seni paranasali FESS. Direttori: E. Emanuelli, F. Pagella  
- **June 26-28**: Anterior skull base. Direttori: S. Chibbaro, P. Pasquis  
- **June 28-29**: Estetica del volto. Direttore: M. Sabbalini  
- **December 4-6**: Chirurgia dei seni paranasali FESS. E. Emanuelli, F. Pagella  
- **December 6-7**: Rinosettoplastica. Direttori: R. Polselli, Y. Saban

**1° CORSO INTERNAZIONALE (2013): ENDOSCOPIA NASO-SINUSALE DI BASE**  
**February 28 - March 1**: Rome – Italy  
**May 2-3**: Siena – Italy  
**September 21-22**: Foggia – Italy  
**November 14-15**: Udine – Italy

Coordinatori: Gaetano Paludetti, Desiderio Passali, Marco Piemonte. Anatomia radiologica e chirurgica naso-sinusale. Clinica della patologia naso-sinusale. Terapia medica e chirurgica della patologia naso-sinusale. Ricerca scientifica in ambito naso-sinusale. Dissezione su testa di agnello. Con il patrocinio della Società Italiana di Rinologia Comitato Educational. Segreteria Organizzativa: E-mail: info.educational.sir@gmail.com

**CORSI DI VIDEOCHIRURGIA ENDOSCOPICA NASO-SINUSALE E DEL BASICRANIO • Milano – Italy**  
**March 4-8**: Corso base  
**June 10-15**: Corso avanzato  
**November 25-29**: Corso intermedio

Direttore: Alberto Dragonetti – E-mail: a.dragonetti@fastwebnet.it. Segreteria Scientifica: Gabriella Mantini, Valentina Casoli – Tel. +39 02 64444545 – Fax +39 02 64444003 – E-mail: gabriella.mantini@ospedaleniguarda.it. Segreteria Organizzativa: Eurocompany Srl, via Canova 19, 20145 Milano. Tel. +39 02 315532 – Fax +39 02 33609213 – E-mail: corsieconvegni@eurocompany.mi.it

**THE MODERN SINONASAL SURGERY: ANATOMY, DIAGNOSTICS AND OPERATIVE TECHNIQUES**  
Varese – Italy  
**Basic Course • April 8-10 and October 14-16**  
**Advanced Course • July 3 and November 18-20**

Segreteria Organizzativa: Attingo – Tel. 377 3217150 – E-mail: corsi@attingo-edu.it

**TEMPORAL BONE SURGICAL DISSECTION COURSE • Barcelona – Spain**

- **Course n. 110 • April 10-12**  
- **Course n. 111 • July 3-5**  
- **Course n. 112 • November 27-29**

Information: Instituto de Otología García-Ibáñez, Conchi Castilla, C/ Dr. Roux 91, 08017 Barcelona, Spagna. Tel. +34 93 205 02 04 – Fax +34 93 205 43 67 – E-mail: entsecretaria@hotmail.es, info@iogi.org
### CORSO DI RINOLOGIA “FULL IMMERSION” ANNO 2013 • Imola (BO) – Italy

**Corso Basico** • June 17-21

**Corso Avanzato** • October 7-11

Direttore dei Corsi: Ignazio Tasca – E-mail: i.tasca@ausl.imola.bo.it – Website: www.associazionerinologia.it

Segreteria del Corso: Filippo Sorace – Tel. +39 051 695 5251 – E-mail: f.sorace@ausl.imola.bo.it. Giacomo Ceroni Compadretti – Tel. +39 051 695 5251 – E-mail: g.ceronicompadretti@ausl.imola.bo.it. Cristina Di Lieto – E-mail: cristianadilieto@hotmail.it

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### CURSO DE DISECCIÓN ENDOSCÓPICA DE LOS SENOS PARANASALES – ENDOSCOPIC SINUS SURGICAL DISSECTION COURSE

Instituto de Otologia Garcia-Ibáñez, C/ Dr. Roux 91, 08017 Barcelona, Spain. Tel. 93 205 02 04 – Fax 93 205 43 67 - E-mail: fundacion@iogi.org

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### CORSI DI DISSEZIONE ANATOMO-CHIRURGICI 2013 • Malta

- **Rhinoseptoplasty, mentoplasty, tip and profile correction** • September 23-24
- **Reconstructive laringectomy; CHEP, CHP, SOVRAGLOTTIC** • September 24-25
- **FESS dissectional course (English course)** • October 18-19


### JANUARY-DECEMBER 2014

#### CORSO DI CHIRURGIA OTOLOGICA, OTONEUROLOGICA E IMPLANTOLOGIA UDITIVA – Dissezione dell’osso temporale e del basicranio • January 7-9, 2014 • Paris – France

Direttore del Corso: Olivier Sterkers. Info: Daniele Bernardeschi, Reparto di Otorinolaringoiatria e Chirurgia Cervico-facciale, Ospedale Pitié-Salpêtrière e Università Paris Diderot - Paris VII, France. E-mail: daniele.bernardeschi@psl.aphp.fr

#### II CORSO “SCUOLA DI DISSEZIONE ANATOMICA CERVICO-FACCIALE”

**January 20-24, 2014 • Florence – Italy**

**II sessione**
- Blefaroplastica e otoplastica – P. Persichetti, R. Polselli, A. Rusciani, Y. Saban
- Chirurgia endoscopica seni paranasali (avanzato) – P. Bossolesi, E. Emanuelli, F.G. Pagella
- Rinoplastica – L. D’Ascanio, G. La Faucci, R. Polselli, A. Scattolini
- Anatomia chirurgica della laringe – M. Lucioni, G. Rizzato, G. Succo, L. D’Ascanio

Direttore del Corso: Alberto Scattolin. Segreteria Organizzativa: Nord Est Congressi – E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

#### THREE-DIMENSION TRANSNASAL ENDOSCOPIC TREATMENT OF SKULL BASE DISEASES

**January 23-24, 2014 • Brescia – Italy**

Organizing Secretariat: Katia Gissi, Servizi C.E.C. Srl, Via G. Verdi 18, 24121 Bergamo, Italy. Tel. +39 035 249899 – Fax +39 035 237852 – E-mail: k.gissi@servizicce.it – Website: www.servizicce.it

#### 4th ANNUAL NORTH AMERICAN RHINOLOGY & ALLERGY CONFERENCE (NARAC)

**January 23-26, 2014 • Puerto Rico**

E-mail: info@NARAconference.org – Website: www.NARAconference.org

#### I CORSO – RINGIOVANIMENTO NON CHIRURGICO DEL VISO

**January 30 - February 1, 2014 • Florence – Italy**

Faculty: D. Draganic, A. Rusciani, R. Polselli, Y. Saban. Segreteria Organizzativa: Nord Est Congressi. E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

#### TEMPORAL BONE DISSECTION COURSES 2014

**February and June 2014 (dates to be announced) • Brazil**

Website: www.forl.org.br/courses
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<td><a href="http://www.meetandwork.com">www.meetandwork.com</a></td>
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<td><a href="http://www.entcourses.it">www.entcourses.it</a></td>
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<td><a href="http://www.asohns.consec.com.au">www.asohns.consec.com.au</a></td>
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<td><a href="mailto:isella.linda@hsr.it">isella.linda@hsr.it</a></td>
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<td><a href="http://www.otosclerosis2014.com">www.otosclerosis2014.com</a></td>
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<td>May 10-12, 2014</td>
<td>Tehran, Iran</td>
<td>IRANCI 2014 Secretariat: Tel. - Fax 098-21-8860-0006 – E-mail: <a href="mailto:info@irancochlear.com">info@irancochlear.com</a> – Website: <a href="http://www.irancochlear.com">www.irancochlear.com</a></td>
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<td>June 17-20, 2014</td>
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<td>Directors: Marco Benazzo, Department of Otolaryngology HN Surgery, University of Pavia, Italy; Fausto Giuseppe Chiesa, Department of Otolaryngology HN Surgery, IEO Milan, Italy. Organizing Secretariat: Bquadro Congressi srl, via S. Giovanni in Borgo 4, 27100 Pavia. Tel. +39 0382 302859 – Fax +39 0382 27697 – E-mail: <a href="mailto:bolla@bquadro-congressi.it">bolla@bquadro-congressi.it</a>.</td>
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<td>24th CONGRESS OF EUROPEAN RHINOLOGIC SOCIETY (ERS) and 32nd INTERNATIONAL SYMPOSIUM OF INFECTION AND ALLERGY OF THE NOSE. THE NOSE AS INTERFACE</td>
<td>June 22-26, 2014</td>
<td>Amsterdam, Netherlands</td>
<td>President: W.J. Fokkens. Website: <a href="http://www.ers-isian2014.com">www.ers-isian2014.com</a> – E-mail: <a href="mailto:ers-isian2014@kenes.com">ers-isian2014@kenes.com</a></td>
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<td>BEST EVIDENCE ENT 2014</td>
<td>August 2-5, 2014</td>
<td>Wisconsin, USA</td>
<td>Course directors: John S. Rhee, David R. Friedland, Charles J. Harkins. Department of Otolaryngology 9200 West Wisconsin Avenue Milwaukee, WI 53226</td>
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<td>40° CONGRESSO CONVENTUS SOCIETAS ORL LATINA</td>
<td>September 1-5, 2014</td>
<td>Baia de Luanda, Angola</td>
<td>Info: Departamento de ORL da Faculdade de Medicina da Universidade Agostino Neto Hospital Josina Machel-Maria Pia Av. 1º Congresso do MPLA. Tel. 00244-923784901/914381304 – E-mail: <a href="mailto:mfilipe@snet.co.ao">mfilipe@snet.co.ao</a>, <a href="mailto:drmartuba@gmail.com">drmartuba@gmail.com</a></td>
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<td>Website: <a href="http://www.eaono2014.org">www.eaono2014.org</a></td>
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