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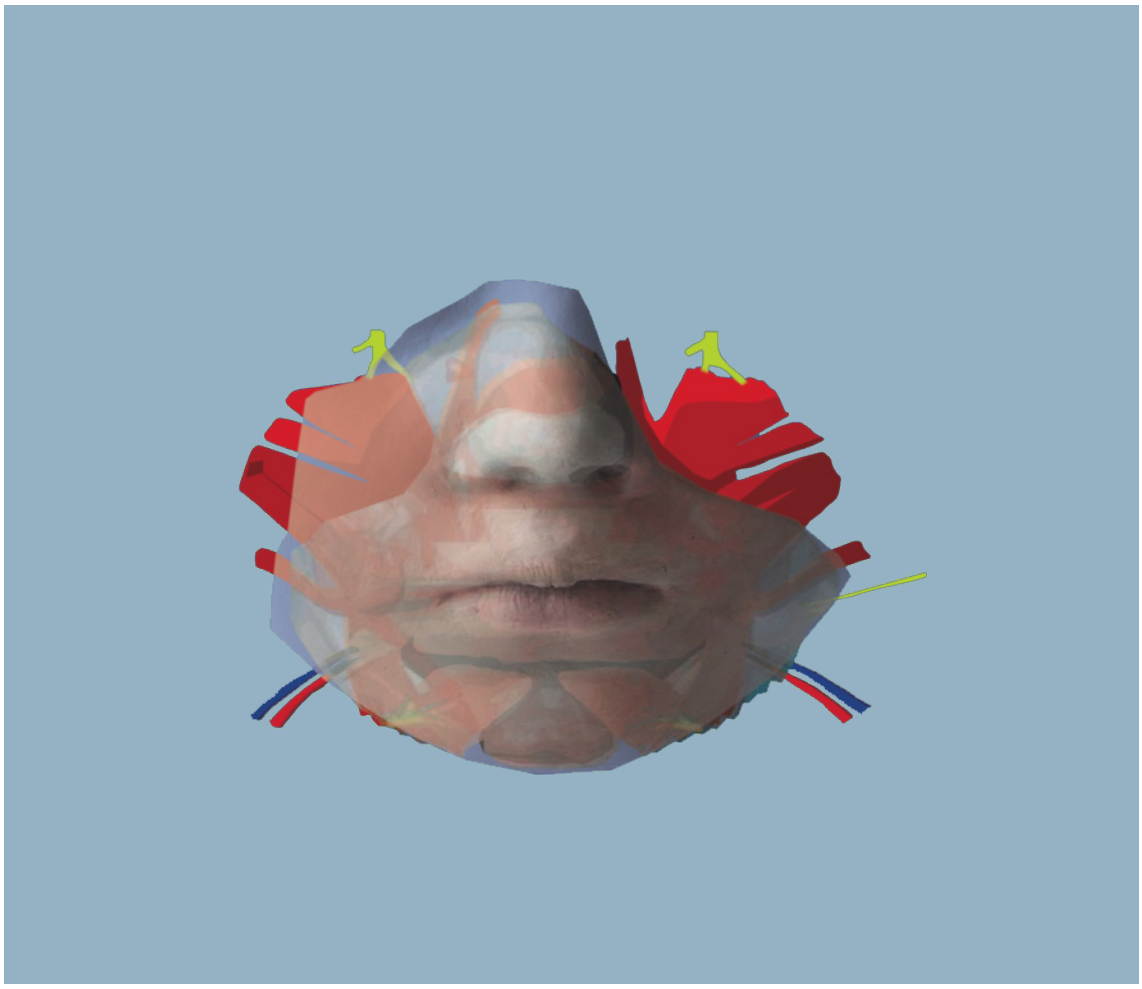
FACIAL DISFIGUREMENT: MICROSURGICAL AUTOLOGOUS RECONSTRUCTION OF SEVERE DEFECTS AND FACIAL TRANSPLANTATION

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FACIAL DISFIGUREMENT: MICROSURGICAL AUTOLOGOUS RECONSTRUCTION OF SEVERE DEFECTS AND FACIAL TRANSPLANTATION



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To my Fathers and Sister

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To Diana Teixeira

To my Masters

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ABBREVIATIONS

ALT	Anterolateral thigh flap
ASDC	Adipose-derived stem cells
ATG	rabbit antithymocyte globulin
BRONJ	Bisphosphonates induced osteonecrosis of the jaws
CD	Cluster differentiation
CMV	Cytomegalovirus
CN VII	Facial nerve (cranial nerve VII)
CT	Computed tomography
CTA	Composite tissue allotransplantation
d_LCFA	Descending branch of lateral circumflex femoral artery
DPL	Deep-planes lift
EBV	Epstein-Barr virus
ECA	External carotid artery
FT	Facial transplant
FCTA	Facial composite tissue allotransplantation
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HLA	Human leucocyte antigen
HTLV	Human T-cell lymphotropic virus
IO	Infraorbital nerve
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MSC	Mesenchymal stem cells
NIR	Near-infrared fluorescence
NF1	Neurofibromatosis type I
NK	Natural killer cells
ORN	Osteoradionecrosis
SO	Supraorbital nerve

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2. ABSTRACT

Disfigurement is more common than is generally realised. It can be consequence of trauma, cancer, radiotherapy, facial paralysis, birthmarks, vascular malformations, neurofibromatosis, cleft lip/palate and other craniofacial conditions.

Facial disfigurement can be physically, emotionally, and socially distressing, and some people whose faces have been disfigured can suffer a so-called “social death” which may instigate death by suicide. All the efforts should then be undertaken by reconstructive surgeons to improve the facial appearance and function.

In the **chapter I**, the social-psychological impact and common causes of disfigurement are analysed. Experimentally, we investigate different methods to evaluate patients with facial disfigurement, combining morphological analysis, functional and dynamic evaluation, as they may provide a measure of severity, progression of deformity and recovery of normal function (avatars and thermographic analysis).

In the **chapter II**, microsurgical autologous reconstruction of massive head and neck defects is first considered in a true clinical perspective, in parallel with new concepts of flap vascularization and harvesting principles. The role of chimeric free flaps and “their variations” in the context of limited vasculature and immediate oncological reconstruction is discussed. Regarding radiation and bisphosphonate induced mandible osteonecrosis, we describe different clinical situations related to several grades of osteonecrosis, where different options of free transfer should be considered based on patient-specific physiopathologic mechanisms. We propose a simple clinical grading system to predict the best treatment option. Facial reanimation of long-standing facial paralysis is also reviewed with focus on free muscle transfer. For the first time in the literature we describe facial reanimation in a blind patient. A new method for precise quantification of the characteristics of facial excursion pre-and postoperative is presented-facegram, with emphasis on smile analysis. This method focuses on the assessment of the trajectories of specific anatomical landmarks during rest and facial expressions. Measures based on the trajectories (position over time) of the anatomical landmarks cannot only evaluate abnormalities of spatial nature / topological, but can also assess temporal characteristics.

In the most extreme cases, conventional reconstructive options may be insufficient, and in **chapter III**, facial transplantation is investigated as a possible alternative. The definition and indications of Composite Tissue Allotransplantation (CTA) and technical aspects of facial allotransplantation are clarified. Adequate perfusion is crucial, but one of the most important aspects is related to allograft reinnervation; successful coaptation of as many major sensory and motor nerves is a key to optimize functional outcomes. Mock cadaver dissections are described and a new conceptual model for facial allotransplantation procurement is investigated; a transparotid dissection was not attempted before.

Finally, in **chapter IV** future perspectives in head and neck reconstruction are discussed, as well as the potential of facial transplantation to become clinical routine instead of experimental.

3. RESUMO

O desfiguramento facial é mais comum do que geralmente se acredita. Pode ser consequência de trauma, tumores, radioterapia, paralisia facial, lesões congênitas, malformações vasculares, neurofibromatose, fendas labiopalatinas e outras condições craniofaciais.

A desfiguração facial pode ser penosa de ponto de vista físico, emocional e social, e algumas pessoas cujos rostos foram desfigurados podem sofrer a chamada "morte social", que pode instigar à morte por suicídio. Todos os esforços devem então ser realizados pelos cirurgiões reconstrutivos para melhorar a aparência e função faciais.

No **capítulo I**, o impacto psicosocial e as causas mais comuns que levam ao desfiguramento são analisadas. Experimentalmente, investigamos diferentes métodos para a avaliação de pacientes com desfiguramento facial, combinando análise morfológica, avaliação funcional e dinâmica, que podem fornecer uma medida da gravidade, progressão da deformidade e recuperação da função normal (avatares e análise termográfica).

No **capítulo II**, a reconstrução autóloga microcirúrgica de grandes defeitos da cabeça e pescoço é primeiramente considerada numa perspectiva verdadeiramente clínica, em paralelo com os novos conceitos de vascularização e dissecção de retalhos. Discute-se o papel dos retalhos livres quiméricos e "suas variações" no contexto de vascularização limitada e reconstrução oncológica imediata. Relativamente à osteonecrose da mandíbula induzida pela radiação e bifosfonatos, descrevemos diferentes situações clínicas relacionadas com diversos graus de osteonecrose, onde diferentes opções de transferência livre de tecidos devem ser consideradas com base nos mecanismos fisiopatológicos específicos. Propomos um sistema de classificação clínica simples para prever a melhor opção reconstructiva. Posteriormente, a reanimação facial da paralisia facial de longa duração é também analisada com foco na transferência muscular livre. Pela primeira vez na literatura é descrita a reanimação facial em um paciente cego. Um novo método para quantificação precisa das características de excursão facial no pré-e pós-operatório é apresentado-facegram, com ênfase na análise do sorriso. Este método incide na avaliação das trajetórias de pontos anatómicos específicos durante a realização de várias expressões faciais e em repouso. As medidas baseadas nas trajetórias (posição ao longo do tempo) de referências anatômicas, não só permitem avaliar anormalidades de natureza espacial/topológica, como também avaliar características temporais.

Em situações extremas, as opções reconstrutivas convencionais podem ser insuficientes, e no **capítulo III**, o transplante facial é investigado como uma possível alternativa. A definição e as indicações da *Composite Tissue Alotransplantation* (CTA), assim como alguns aspectos técnicos do alotransplante facial são esclarecidas. Uma perfusão adequada é fundamental, mas um dos aspectos mais importantes está relacionado com a reinervação do alotransplante; a coaptação com sucesso de vários nervos sensoriais e motores é a chave para optimizar os resultados funcionais. São descritas disseções dissimuladas de cadáveres e um novo modelo conceptual para a colheita de um alotransplante facial é investigado; uma dissecção transparotídea não foi tentada préviamente.

Finalmente, no **capítulo IV** são discutidas perspectivas futuras na cirurgia reconstructiva da cabeça e pescoço, bem como o potencial da transplantação facial em se tornar uma prática clínica de rotina em vez de experimental.

CHAPTER I

FACIAL DISFIGUREMENT

1. SOCIO-PSYCHOLOGICAL IMPACT

No other part of the body is as unique and aesthetical significant as the face. Facial appearance influences individual's self-image and self-esteem, and any disfiguring injury affecting these features requires particular attention.

The face has a remarkably complex function in humans. Facial tissues receive and transmit tremendous amounts of information each day. The cranial nerves receive information from all five senses. Muscles of the face respond to stimuli with complex expressions, and are responsible for rapid movements of the eyes and forceful movements of the jaw in mastication. In addition, skull bones protect the brain and orbits. Facial appearance is a fundamental component of individuality. Facial disorders lead to abnormalities in a wide range of patients that disrupt these functions. These problems can be physically, emotionally, and socially disabling.[1]

Disfigurement can affect anyone, at any time, from any age, from any social and ethnic background. The psychosocial sequelae associated with facial disfigurement should not be underestimated, as they result in unacceptable facial appearance and functional inability to send symbolic facial messages. Stigmatisation, social anxiety and avoidance, poor self-image, and substance abuse[2] are frequent, leading to severe psychological morbidity. People are subjected to visual and verbal assaults, and a level of familiarity from strangers, startled reactions, whispering, remarks, furtive looks, curiosity, personal questions, advice, manifestations of pity or aversion, laughter, ridicule and outright avoidance. This perceived hostility from other people was also emphasized by McGrouther[3] to describe facial disfigurement as "the last bastion of discrimination".

Partridge[4] emphasized the role of the disfigured individual in managing the success or failure of social situations. Patients have high levels of social anxiety, low self-esteem or expectations, and low employment prospects. First meetings are particularly difficult as well as longer-term difficulties in forming friendships. Bullying at school, and lowered parental expectation can constitute additional problems for children.[5] Specific impairment in the ability to smile may also elevate the risk for depression.[6]

2. COMMON CAUSES OF FACIAL DISFIGUREMENT

Disfigurement is frequently caused by trauma. Traumatic facial injuries should be first treated in accordance with American Trauma Life Support (ATLS) protocols. Once immediately life–threatening issues such as uncontrolled bleeding and airway compromise have been addressed, or other potentially associated injuries have been excluded (cervical spine injuries, closed head trauma), attention should be turned to the treatment of the facial injuries. Trauma causes include accidents, burns, violence (for example acid and knife injuries), or animal attacks.

Facial trauma may also involve severe soft tissue damage or amputation of relevant anatomic structures such as the lips, nose, and ears, with subsequent aesthetic or functional problems, and psychological sequelae. Most amputations result from dog or human bites that produce gross defects and replantation of amputated facial tissues has been sporadically reported in the literature. Microvascular replantation is the best method for reattaching an amputated ear, giving excellent esthetic results and requires primary repair of the vessels.[7] However, suitable vessels for microanastomosis may be absent, and nonmicrosurgical methods can be an option, such as temporoparietal fascia flaps, retroauricular pocket procedures, or staged-costal cartilage reconstruction.[8]

A microsurgical replantation should also always be attempted in nasal amputations even if venous anastomosis and drainage cannot be restablished. The resulting venous congestion can be treated with medical leech (*Hirudo Medicinalis*) until venous neovascularization has been achieved.[9,10]

Dog bites to the face are common, and usually involve amputation of the lip resulting in a devastating facial injury. Lip replantation has been reported with good results in what concerns to color matching, return of sensibility, and stomal continence (orbicularis muscle contraction).[11-15] Revascularization of the lip segment is achieved by anastomosis to a single labial artery, however, reestablishment of venous outflow remains the most problematic technical issue, and if no veins are available, leech therapy can be employed, but may result in permanent visible scarring as a result of the leech bite.

Total upper eyelid replantation after dog bite avulsion injury was also reported using microsurgical techniques.[16]

The successful replantation of a traumatically amputated midfacial segment was descibed, comprising the entire nose, most of the upper and lower lips, the nasal boney and cartilaginous complex, based on microvascular repair of the labial arteries and glabellar veins.[17]

Others reported successful microsurgical primary replantation of an amputated cheek [18], as well as after total avulsion of most of the upper lip, cheek and alar rim [19], with good aesthetic and functional results. Venous congestion was overcome by multiple needle punctures and local application of heparin.

A great challenge to the plastic surgeon is to perform replantation of small pieces of facial tissue, because of the extremely small size of the arteries and lak of suitable veins for drainage, however, even nasal tip and eyebrow replantation have also been described.[20] Arterio-venous fistula, chemical leech (intrareplant heparin injection) and pin pricks have been used to improve venous outflow.

Total scalp avulsion is a rare, but potentially devastating event and every attempt should be made for replantation. Larger avulsion defects have higher success rates after replantation than smaller defects (< 300 cm^2), and the most commonly used recipient vessels are the superficial temporal artery and vein.[21] When multiple arterial anastomosis are not possible, one artery may be sufficient to reperfuse the replantated scalp and achieve good aesthetic results. [22,23] If replantation is not possible, microvascular tissue transfer remains a mainstay of treatment for scalp defects, especially latissimus dorsi flaps (alone or combined with serratus or parascapular muscle). Successful combined replantation of total scalp, forehead, left ear, eyebrows and upper eyelids was also described.[24]



Figure 1. Severe facial disfigurement caused by trauma (motocycle accident). Note near total absence of left superior and inferior eyelids, and brown disruption. There was also fracture of left frontal sinus which was reconstructed with a titanium mesh. Several surgeries were subsequently performed to improve the eyelids (including ectropion repair) and facial scarring, but further revisions are still needed.

Trauma often resulted in aesthetic and functional defects, however, management of trauma patients have been significantly improved concomitantly with the advances in the reconstructive surgery.

Facial disfigurement can also be consequence of birthmarks, vascular malformations, neurofibromatosis, cleft lip/palate and other craniofacial conditions.

Head and neck cancer can lead to massive facial defects. Radiation and bisphosphonate induced mandible osteonecrosis can constitute a serious problem and lead to functional impairment and facial disfigurement.

Facial paralysis, following Bell's Palsy, strokes or other clinical situations is another important cause. Skin conditions such as severe acne, eczema, vitiligo, psoriasis, and eye conditions such as loss of an eye (enucleation) are also potential etiologies.

Being part of a team working in a metropolitan hospital we usually deal with the most complex situations, related with facial trauma. Great part of these situations are caused by motorcycle accidents (Fig. 1), burns (Fig. 2) or animal bites.



Figure 2. Facial disfigurement caused by burns; severe ectropion was corrected with wide undermining and full-thickness skin grafts. Flexion contractures of the fingers have also been released.

Even rare situations such as human bites can be present. Traumatic auricular amputation due to human bite is not a common event, but it constitutes a difficult challenge for the reconstructive surgeon. Microsurgery can be performed in some cases, but replantation of a severed ear without microsurgery can be a safe alternative. We have previously reported in the **Journal of Craniofacial Surgery** [25] a case of a 44-year-old male individual who was involved in a fight and sustained a human bite, resulting in almost a complete amputation of his right ear; no suitable vessels for microsurgical anastomosis were found. Baudet's technique was used with success (Fig. 3). It is a simple technique and very reliable because it allows a great surface of contact between the graft and the vascular bed, substantially increasing its odds of survival in cases presenting with high risk of infection such as human bite injury. It also produces excellent aesthetic results. If ear replantation is not possible or has failed, a prelaminated free flap may be selected for posterior reconstruction.[26]

We also have made efforts for the reconstruction of massive defects following head and neck cancer ablative surgery-see chapter II, and to improve the functional sequelae, including microstomia.[27]

Finally, we had contact with the most extreme cases, in what conventional reconstructive options were not enough to deal with such forms of severe facial disfigurement, and we started to consider facial transplantation as an alternative.



Figure 3. Ear replantation after human bite avulsion injury (Baudet's technique).

3. AVATARS AND THERMOGRAPHIC ANALYSIS IN PATIENTS WITH FACIAL DISFIGUREMENT

INTRODUCTION

The application of 3D face reconstruction in the movies and gaming industry has gained recent popularity.[28] Daily human interaction and communication involves facial expression. Any disfiguring condition that takes away facial expressiveness leads to physical, psychological, and social disability.

Reproducing facial movements that look convincing, realistic and appealing, requires deep understanding of the morphologies and behaviors of the complex system that lies beneath the face and good knowledge of animation principals to perfectly reproduce facial movements that look realistic.[29] A high-quality avatar may achieve an increase in self-identification and a more complete representation of the patient's behavior, which may be beneficial for inducing virtual embodiment.

On the other hand, thermography has been used for numerous purposes within medicine such as a diagnostic complement of pain and for monitoring the course of peripheral vascular disorders.[30] Its use on the diagnosis of temporal joint disorders and nerve injuries has been widely tested.[31] Previous studies have measured heat emission differences between the left and right side of different areas of the head but have focused solely on healthy people, or in patients with specific facial pathologies.[32-33]

The aim of this study was to investigate how these two technologies could be useful in plastic surgery, namely in cases of facial disfigurement.

MATERIALS AND METHODS

This study was divided in two different parts, in order to analyze the potential applicability of thee two different technologies.

- **Avatars Technology**

On first part of this study, we conceived a look-alike 3D facial avatars application using two different approaches: i) a moving low-cost RGB-D device for low resolution results (ex. Microsoft Kinect), and ii) a single-shot method taken from multiple high resolution cameras synchronized and configured in stereoscopic pairs.

This system creates an animatable 3D facial model that resembles a real person. The process is divided in three steps: i) *acquisition*, ii) *retopology,* and iii) *texture transfer* (Fig. 4). The first deals with the 3D data gathering, which allowed us to create the subject virtual face model. The second (retopology) is the conversion process of the aforementioned facial model to a *"ready-to-animate"* model, fitting the template of a generic mesh to the acquired 3D mesh, in other words, a model with the required technical features to be used in

an animation movie, 3D game or virtual environment. Last, the *texture transfer* method computes the new texture, which is adjusted to the avatar's mesh. It is expected that the avatar's mesh best matches the person's representation. The 3D models were analyzed with MeshLab® v.1.3.2.

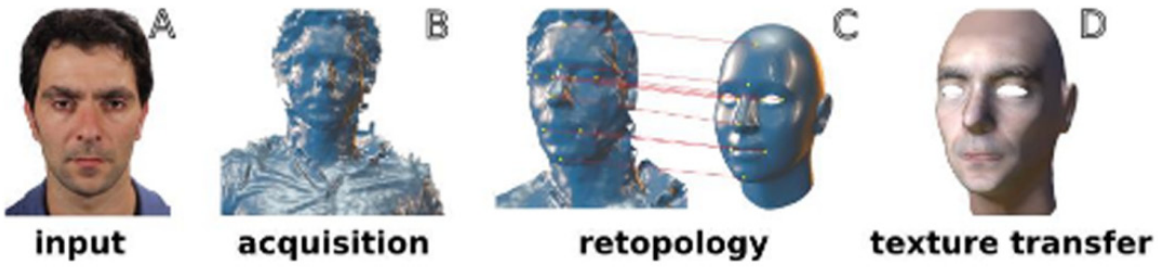


Figure 4. Overview of the pipeline. A) input RGB and depth maps B) 3D mesh reconstruction C) alignment of the scanned mesh with our template D) texture computation.

Our methodology uses a videogame based approach, where the avatars can adopt different morphologic appearances (like gender, age and race parameters). It may contain a set of exercises embedded in the gameplay that reinforce the learning process and generate a real time avatar response based on direct physician input, or on a set of predefined rules. We can also include a facial expression editor capable of displaying 3D characters in real-time. This allows the user to adjust or create new exercises on the fly, without the need of artistic or technical skills.

For an easier understanding, we have chosen a representative case of a 17 year-old male patient with history of congenital glaucoma and sequelae of facial trauma (motorcycle accident without a helmet (Fig. 5). He was submitted in the emergency room to upper and lower eyelid reconstruction, and frontal sinus reconstruction (anterior table) with a titanium mesh. Three months later, dermabrasion was attempted to improve facial scarring simultaneously with low-eyelid reconstruction with a full thickness skin graft. Despite these attempts, a disfigured face remains and further surgeries are needed. A corneal transplantation is also anticipated.



Figure 5. Severe facial trauma in the context of motorcycle accident without helmet. Severe disfiguration in the scalp, frontal area, brow, eyelids and middle third of the face was present.

- **Thermographic Analysis**

On the second part, in order to evaluate the potential use of thermography on facial disfigurement, we have first analysed 28 healthy subjects (14 females, 14 males, mean age 21, range 19-23 years - Table 1). This group control was characterized for posterior comparison with two patients with facial disfigurement.

Table 1. Control group characteristics.

Control group	N	Age	Weight (kg)	Height (m)
Male	14	22±1	73,21±10,06	1,77±0,06
Female	14	21±2	58,43±5,53	1,64±0,06
Total	28	21±2	65,82±10,96	1,70±0,09

The first patient (Patient 1) was the same that was studied on the first part (avatars technology), and the second (Patient 2) was a 24 year-old male with severe cosmetic and functional facial burn sequelae (Fig. 6). He was submitted to several surgeries before, including skin grafts and use of dermal regeneration templates, in order to improve his appearance.

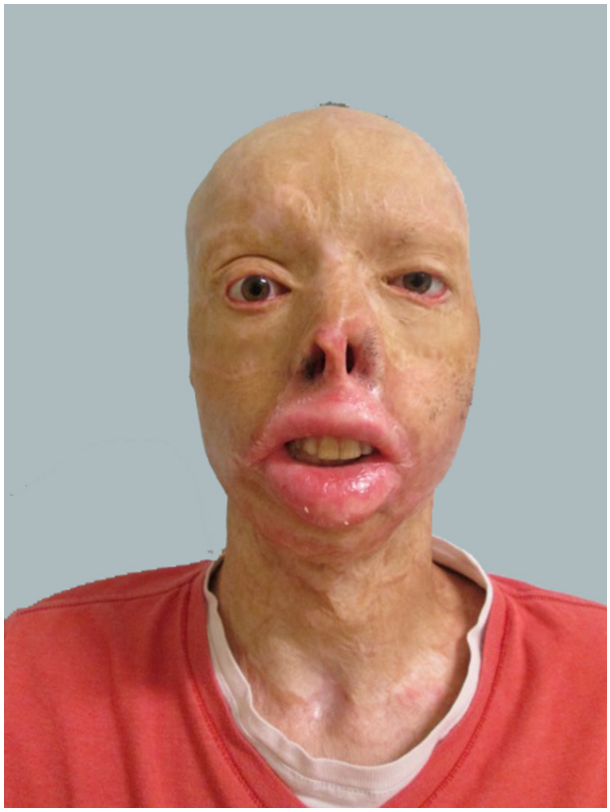


Figure 6. Male patient, 23 years-old, with severe sequelae of thermal burns (55 percent total burn surface area).

The measurements took place in a standardised room with a constant temperature of 24º C. The thermography camera used was a FLIR SC7000 (FLIR Systems, Wilsonville, Oregon, USA) with a Hot Metal colored lens filtre which was previous configured to a 30-40º C temperature range. The subjects sat on a chair at a distance of 1.5 m from the camera. They were asked to perform four facial expressions in the following order: facial expression at rest, with eyes closed, eyes wide open and smile.

Data management was performed with Altair 5.91.010 software (FLIR Systems, Wilsonville, Oregon, USA). An analysis mask was established over the facial areas of interest: 1 - Right forehead; 2 - Left forehead; 3 - Right orbit; 4 - Left orbit; 5 – Nose; 6 - Right labial commissure; 7 - Left labial commissure; 8 - Mouth (Fig. 7). For each area the mean temperature and its standard deviation were calculated, as well as the maximum and minimum values (Table 2).

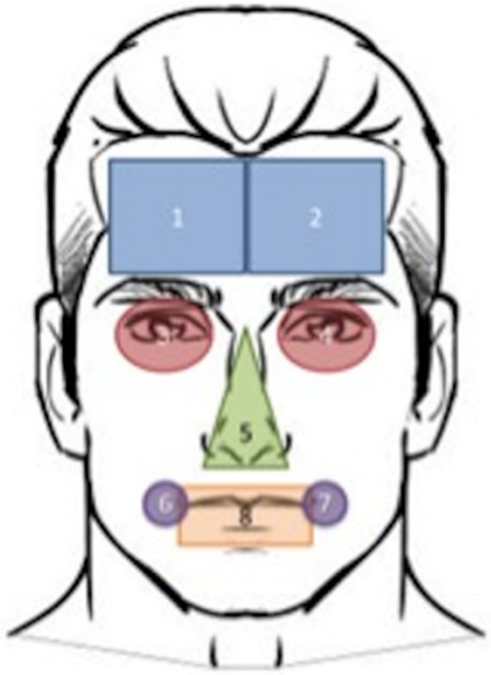


Figure 7. Presentation of the eight areas of thermal analysis and its geometric shape.

Table 2. Average, minimum, maximum temperatures and standard deviation recorded in each area represented by its order number during the facial expressions. All values are shown in Celsius degrees.

		1	2	3	4	5	6	7	8
At rest	Average	36,84	36,77	37,34	37,20	35,45	37,00	36,80	36,60
	Min.	33,64	34,02	34,91	34,80	33,40	35,66	35,59	34,89
	Max.	37,79	37,74	38,73	38,67	37,90	37,94	37,78	37,94
	SD	0,67	0,62	0,72	0,73	1,03	0,49	0,51	0,57
Eyes closed	Average	36,93	37,06	36,92	36,89	35,48	36,95	36,82	36,56
	Min.	33,79	34,53	34,59	34,66	33,42	35,50	35,57	34,63
	Max.	37,99	37,96	38,57	38,57	37,98	37,92	37,79	37,92
	SD	0,76	0,54	0,85	0,82	1,10	0,53	0,52	0,60
Eyes wide open	Average	36,60	36,66	37,52	37,39	35,36	37,02	36,83	36,67
	Min.	32,56	33,85	35,45	35,36	33,33	35,54	35,53	34,85
	Max.	37,81	37,78	38,76	38,72	37,98	38,03	37,86	38,04
	SD	0,88	0,69	0,65	0,68	1,03	0,52	0,54	0,58
Smile	Average	36,69	36,70	37,29	37,22	35,40	37,16	36,93	36,88
	Min.	33,55	33,95	34,81	35,04	33,41	35,63	35,57	34,62
	Max.	37,71	37,68	38,70	38,67	37,97	38,68	38,33	39,06
	SD	0,68	0,64	0,74	0,80	0,93	0,60	0,65	0,81

RESULTS

- **Avatars Technology**

In addition to a detailed analysis of the facial dynamics, 3D models analyzed with MeshLab allowed for a morphological study and direct measurements such as maximal extensions or eyelid aperture measurements. In our patient, this high-quality avatar showed persistent ectropion and a significant change on vertical height of palpebral fissure on the left side (Fig. 8). In the frontalis muscle contraction exercise, we have observed asymmetry and gross brow hairline distortion (Fig. 9). When ordering palpebral voluntary closure, the patient could not completely close his left eyelid (Fig. 10). Scar release, skin grafting and eventually lower eyelid tightening or lateral canthopexy will be necessary to improve the aesthetic and functional results. The problems seem to affect mainly the upper and middle thirds of the face, as good excursion of the oral commissures was seen (Fig. 11).



Figure 8. Creation of a 3D face avatar and analysis with MeshLab® v.1.3.2.; direct measurements such as maximal eyelid aperture are possible.



Figure 9. Task: frontalis muscle contraction.



Figure 10. Task: Palpebral voluntary closure.

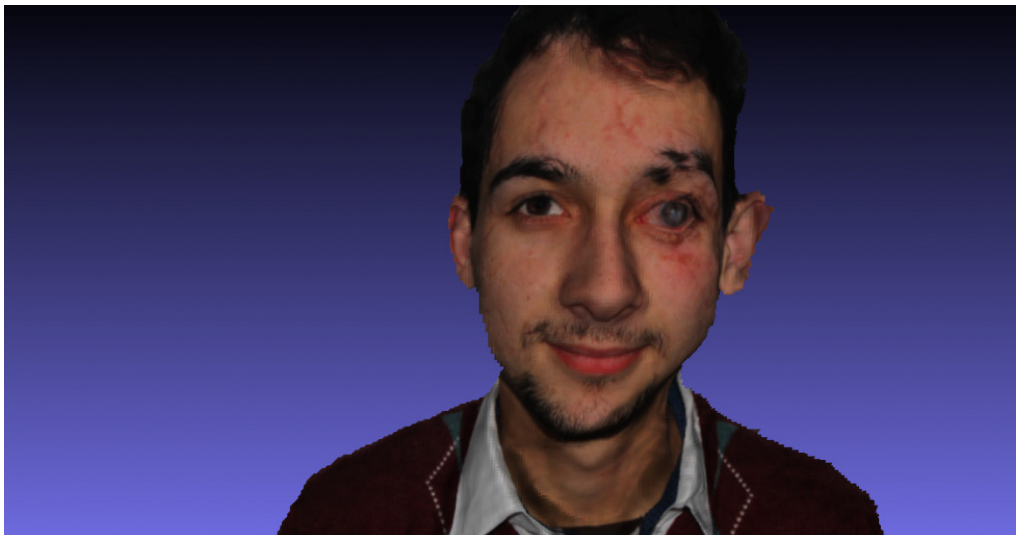


Figure 11. Smiling analysis.

- **Thermographic Analysis**

Concerning thermographic analysis, when comparing the measures of normal healthy subjects with the two patients, some important aspects must be highlighted: **Patient 1** showed a persistent tendency for contralateral thermal asymmetries with highest values of surface temperature on the right side, and highest temperature values on the right forehead area (Figs. 12 and 13); a tendency for surface temperature reduction on the left labial commissure was also seen (Fig. 14). The results showed that the facial temperature distribution was altered, probably in consequence of muscular damage, fibrosis, facial nerve paralysis (lesion of the frontal branch since there was absence of frontalis muscle contraction), and decrease of the regional blood flow.

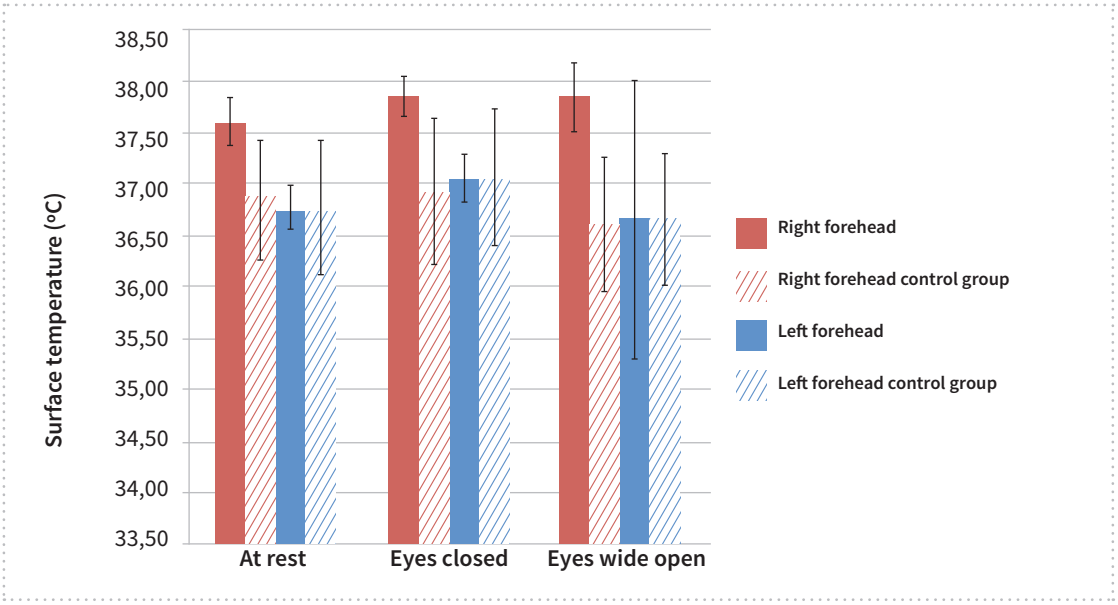


Figure 12. Average temperature and standard deviation in the right (area 1) and left (area 2) forehead areas during the four facial expressions (Patient 1). The hatched bars represent the mean values and standard deviations of the control group for the same task.

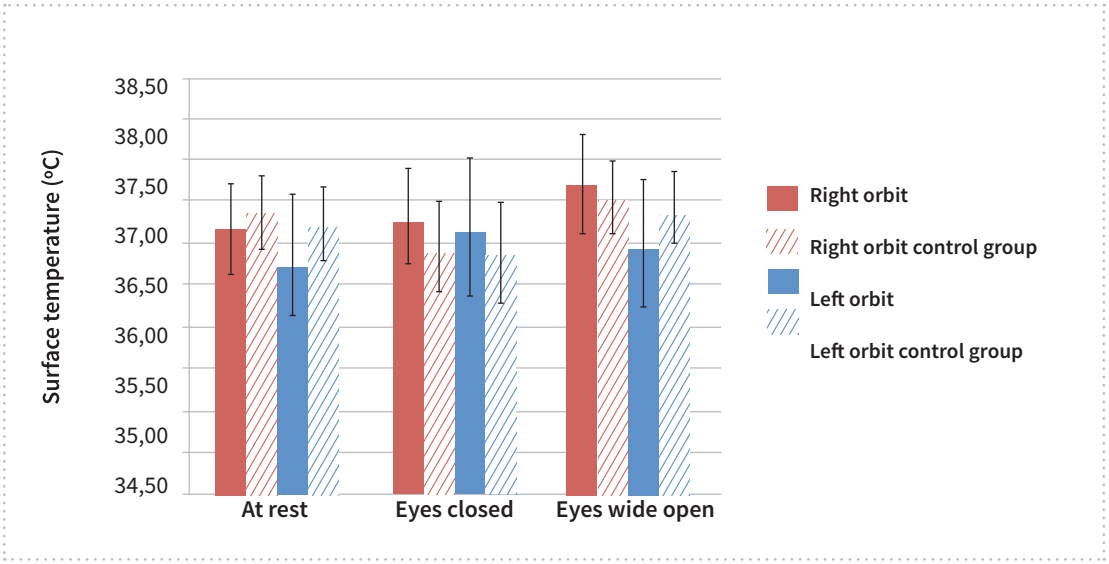


Figure 13. Average temperature and standard deviation in the right (area 3) and left (area 4) orbital areas during the four facial expressions (Patient 1). The hatched bars represent the mean values and standard deviations of the control group for the same task.

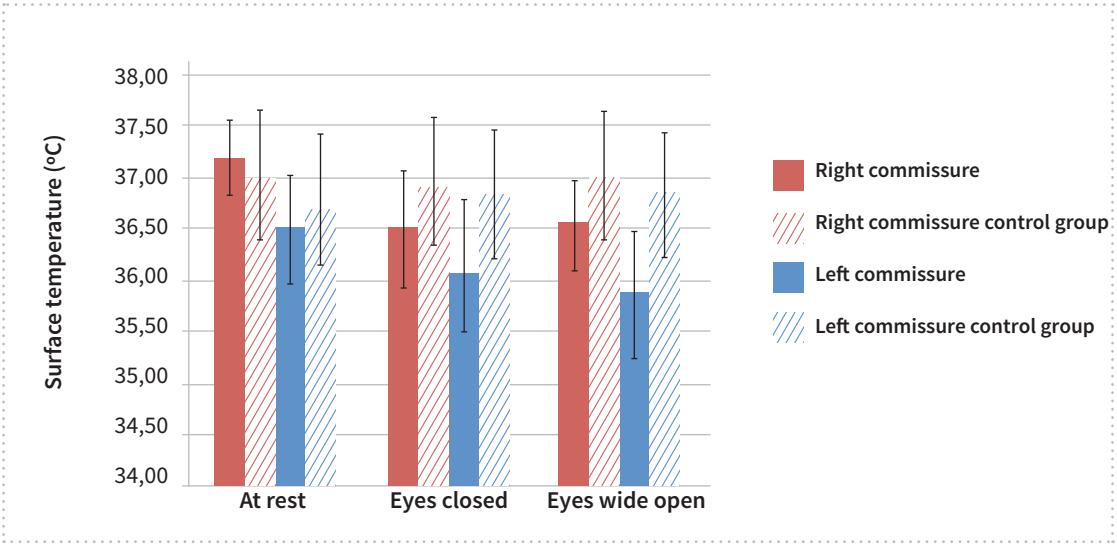


Figure 14. Average temperature and standard deviation in the right (area 6) and left (area 7) labial commissures areas during the four facial expressions (Patient 1). The hatched bars represent the mean values and standard deviations of the control group for the same task.

The **Patient 2** showed a tendency for balanced contralateral surface temperature values, as well as low bilateral forehead values, and high right and left commissure surface temperature values (Figs. 15-17). The extension of the commissures excursion in this patient is clearly superior to that of the midpoints or Cupid's bow, which may be explained by cicatricial retraction of the central part of the patient's lips. This fact may be responsible for the higher surface temperature values comparatively to the remaining central and inferior face, where minimal muscular activity was detected. High temperature values of the nose were also detected when compared to normal population, and the surface temperature rose during air passage (Fig. 18). This may be explained by the partial nasal destruction (burns sequelae), and lack of normal anatomical structures, including mucosa, cartilage and bone.

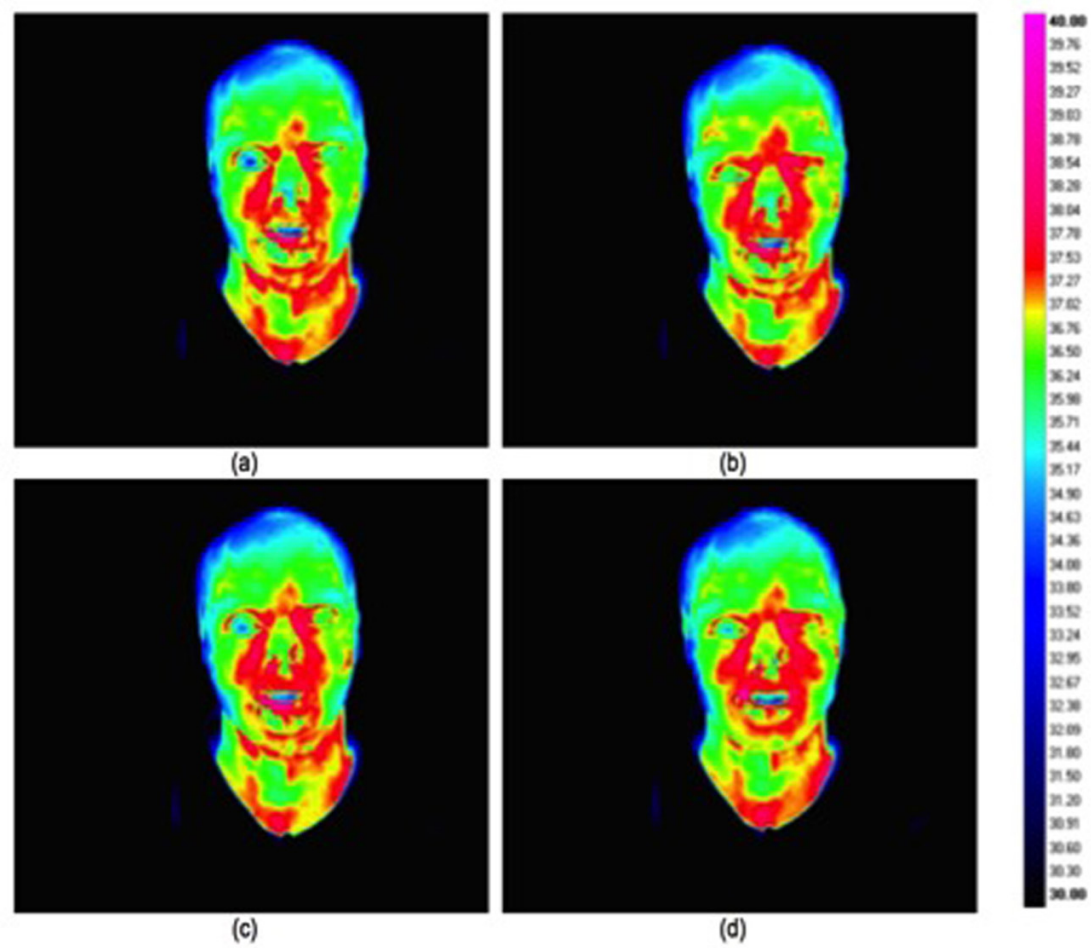


Figure 15. Facial expressions of Patient 2: (a) at rest, (b) eyes closed, (c) eyes wide open and (d) smile.

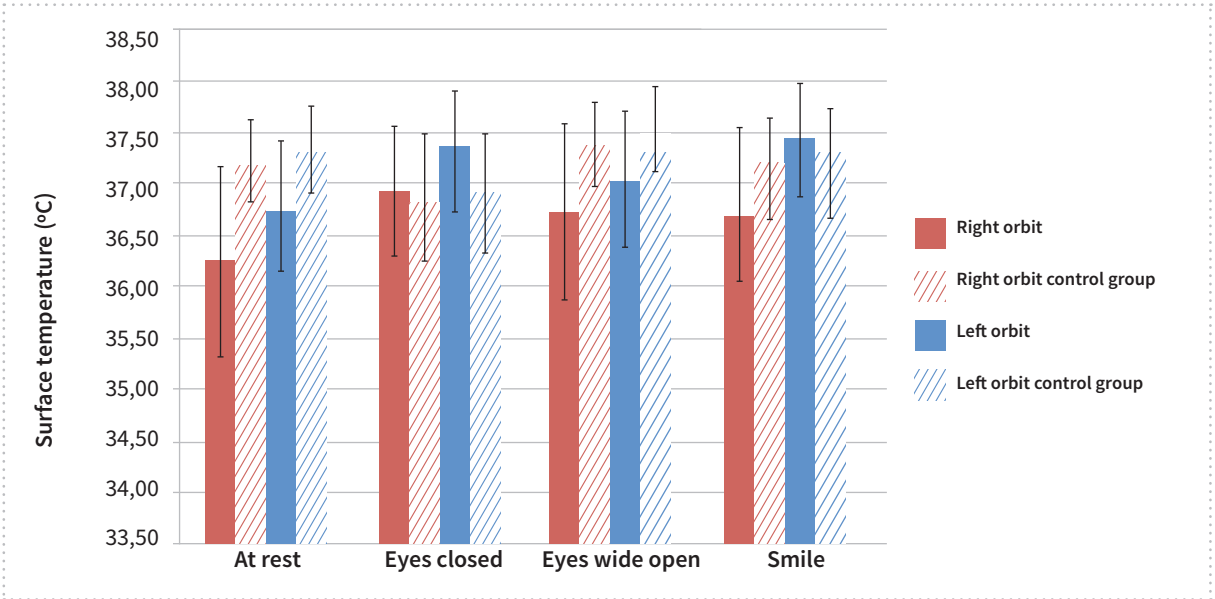


Figure 16. Average temperature and standard deviation in the right (area 1) and left (area 2) forehead areas during the four facial expressions (Patient 2). The hatched bars represent the mean values and standard deviations of the control group for the same task.

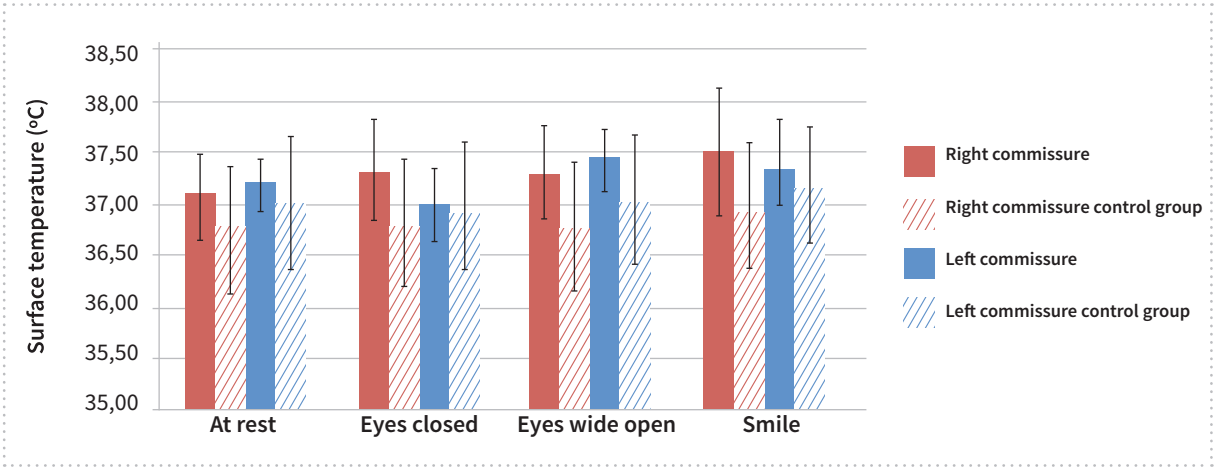


Figure 17. Average temperature and standard deviation in the right (area 6) and left (area 7) labial commissures areas during the four facial expressions (Patient 2). The hatched bars represent the mean values and standard deviations of the control group for the same task.

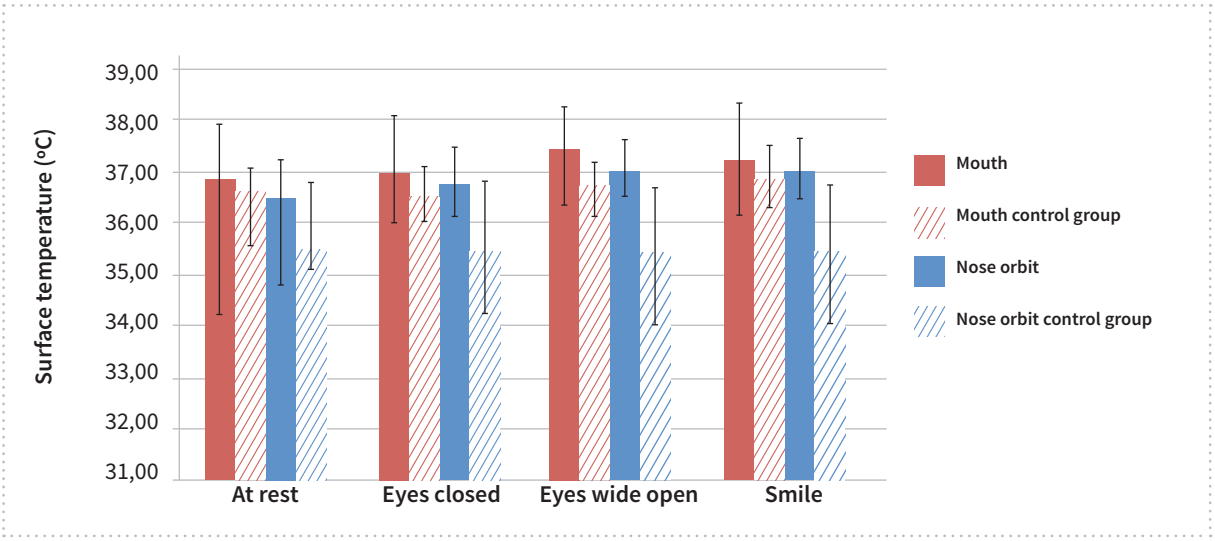


Figure 18. Average temperature and standard deviation in the nose (area 5) and mouth (area 8) areas during the four facial expressions (Patient 2). The hatched bars represent the mean values and standard deviations of the control group for the same task.

DISCUSSION

Several methods have been previously described to evaluate patients with facial disfigurement, as they may provide a measure of severity, progression of deformity and recovery of normal function. An ideal method should combine morphological analysis, functional and dynamic facial evaluation.

Avatars Technology acquires a high-quality face mesh and texture using low-cost capture hardware. It allows the common user to create a self-3D face avatar using a home computer with a RGB-D (depth camera). The interest of this study for Plastic Surgery could be justified by the general potential advantages of the facial models creation: the morphological study allows the establishment of relationships between the different facial elements and the study of the facials dynamics allows a detailed analysis of the face biomechanical movements; it also allows a greater embodiment of the subject in the virtual environment. It has applicability in facial disorders and facial disfigurement analysis, in all types of reconstructive surgery of the face, particularly oncologic defects or post trauma, facial paralysis, burned patients, or even in the field of cosmetic surgery. For example, avatars technology may be useful to study facial volume and movement, being incorporated into preoperative planning and used to improve patient communication in relearning facial movements, following temporomandibular joint (TMJ) surgery and other craniofacial procedures. It may be considered in the evaluation of patients with facial palsy, after direct neurotization with a hypoglossal nerve transfer or a cross-face graft, and after free muscle transplantation for treatment of long-standing facial paralysis.

It also may improve the quality of the direct measurements, and provides a tool that permits comparison of results between different surgical approaches. For example, facial palsy is often characterized by a severe dysfunction of the eyelids, leading to corneal ulceration and even blindness. A precise and quantitative evaluation of the exposed ocular surface is very important in order to estimate the risks of these ocular symptoms

Taking the example of people with autism spectrum disorder (ASD), these patients find it difficult to recognize and respond to emotions conveyed by the face. Most existing methodologies to teach people with ASD to recognize expressions use still images, and do not take into account that facial expressions have movement. An approach based on an avatar-user interaction model with real time response, which builds upon the patient-physician relationship may be designed to be used by the doctor/therapist and the patient, using state of the art technology to solve the problem and to improve interactivity.[34,35] The same strategy may be used in patients with facial disfigurement.

The user interface may include: a 3D avatar on the main window, the facial expression the user needs to match, the score and the level of difficulty of the task (facial movement). The avatar displays a sequence of expressions and the user needs to match the expression display on the upper right part of the screen. These expressions are generated randomly at the beginning of each exercise. Different types of exercises can be employed: matching the facial expression on all of the face, matching the facial expression on the upper part of the face or the facial expression on the lower part of the face.

This technology could also have a role in forensics. Computational forensics involves computer-based modeling, computer simulation, analysis, and recognition in studying and solving problems posed in various forensic disciplines. Forensic animation is a branch of forensic science in which audio-visual reconstructions of injuries or accidents are created to aid investigators, and its application in courtrooms today is becoming more popular. It may be used by the prosecution to explain to the jury the details and consequences of a complex trauma and related injuries, or shooting incidents, showing the positions of the victim, the impact points, and the path taken by bullets.

We argue that current technological advances in character animation can substantially improve the way we teach people with disfigurement and facial disorders to recognize facial expressions and emotions, through a novel and sophisticated interaction model that allows for a morphological study and enables patients to learn by imitating the avatars' movements.

Future work includes a field test with therapists and patients for further validation of the methodology, and suggestions for new exercises to be integrated in the system.

Thermographic Analysis, is being studied and has already been used in different medical conditions, such as the diagnosis of inflammatory processes of the head and neck.[36]

The skin temperature of a healthy human body exhibits a contralateral symmetry. This study was performed to determine the usefulness of thermography in the evaluation of facial skin temperature changes during the accomplishment of different facial expressions in healthy subjects and compare them with patients with facial disfigurement. We saw differences between healthy subjects and disfigured patients, that can be used for better pathophysiology understanding and therapeutic proposes. A relationship exists between the facial blood flow and the skin temperature, and thermal imaging has been used to identify perforators in different anatomic regions.[37] A thermal dysfunction may be noted in the presence of muscular disarrangment/ damage, facial paralysis, scarring, or inflammation. Therefore, facial thermography is an efficient clinical indicator with respect to the diagnosis and assessment of facial disfigurement.

This technology could also be used to assist in timing of scar revision surgery for example, or indeed the predictability of wound healing. It can be applied for assisting laser treatment of keloids and Hypertrophic Scars,

to determine the depth to which the laser heat-inducing influence penetrated. The laser will not reach the deep layer of scars if the scar has a thick collagen layer. Notably, it is known that temperatures above 54°C are required to thermally denature collagen fibers.

Thermography can detect physiological changes such as increased blood flow or heat. A small, pinhead size tumor that has been growing for about two years is large enough to develop its own blood supply (angiogenesis). While some screening exams, such as a mammogram, can detect anatomical changes in the breast tissue, thermography is the only technology currently in place that can detect such changes, and although it is not approved as a replacement cancer detection method, thermography has been approved by the FDA as an adjunct diagnostic tool to mammograms. It can be effective in other types of cancer screening and for detection of recurrences.

This method has several advantages: it is easy to perform, non-invasive and relatively cheap to achieve and manage. The essential drawback of thermography is the incapacity to measure temperature changes within deep tissues as it only measures heat emission from the skin. The combination of thermographic and ultrasonographic assessments is expected to increase the accuracy of the early detection of deep tissue injuries.[38]

Another limitation of thermography is the low temperature readings in fat tissue which can limit its use in obese subjects.[32]

This very preliminary study has, however, some limitations. Only two patients with facial disfigurement are included, and the facial injuries are different. It would make more sense to just look at one specific disfigurement like: all facial burns, or only eyelid deformity. In further studies, avatars should eventually be compared with videographic techniques, and CT or MRI for volume analysis. Regarding thermography, we know from prior studies that results tend to vary from males to females, and they have significant difference in the same patient from session to session. It seems that thermography has asymmetric registry in the face with a circadian rhytm. By including more sessions for thermograhic analysis, a more meaningful comparison of normal to abnormal patients would be able to be completed.

CONCLUSION

These two technologies could have a place in the management of facially disfigured patients, with diagnostic and therapeutic implications. Further studies have to be done, in order to validate the innovative methodology here proposed.

4. AIMS OF THIS THESIS

The objectives of this thesis are:

- Explore different options for reconstruction of severe facial defects, caused by cancer, radiotherapy, facial paralysis, burns or trauma;
- Clarify the role microsurgical autologous reconstruction in a true clinical perspective;
- Develop different methods to evaluate patients with facial disfigurement, combining morphological analysis, functional and dynamic evaluation;
- Clarify the role and indications of Composite Tissue Allotransplantation (CTA) as an alternative to autologous reconstruction;
- Discuss some technical aspects of facial allotransplantation;
- Investigate a new model for facial allotransplantation procurement based on mock cadaver dissections;
- Evaluate the potential of facial transplantation to become clinical routine instead of experimental.

CHAPTER II

MICROSURGICAL AUTOLOGOUS RECONSTRUCTION OF SEVERE FACIAL DEFECTS

1. DIFFERENT OPTIONS FOR RECONSTRUCTION OF MASSIVE FACIAL DEFECTS

The reconstruction of massive head and neck defects is a difficult challenge, requiring restoration of bone, skin and oral lining. The complex three-dimensional nature of compound defects often dictates the need of more than a single osteocutaneous flap for intra and extra-oral reconstruction. In addition, these patients may do not have reliable vascularity for separate arterial and venous anastomosis, due to extensive scarring in consequence of previous surgeries or radiation.

The primary goals for reconstruction of extensive defects are adequate oral continence and swallowing, satisfactory bone healing, obliteration of dead space and the best aesthetic result as possible.

Different options are available for the reconstruction of combined intra and extra-oral defects, depending on the extent of the deformity and surgical team experience. These options include:

1. Pedicled flaps with or without reconstruction plate;
2. Musculocutaneous free flaps (e.g., anterolateral thigh - vastus lateralis flap);
3. Free flaps with double skin island;
4. Double free flaps (e.g., fibula + ALT);
5. Prefabricated/prelaminated flaps;
6. Chimeric free flaps;
7. Flow-through sequentially linked free flaps.

For the past twenty years, there has been an ongoing search for new reconstructive options to restore functional and aesthetic deficits of patients with severe facial deformities, extremities, hands and other parts of the body for which application of currently available reconstructive options resulted in less-than optimal outcomes.[38]

One of the major problems with reconstruction of complex deficits on the face and extremities is the lack of available tissues that resemble the injured or missing parts, and with no vessels available in the proximity of the recipient area.

Conventional reconstructive treatments for massive facial defects may achieve significant improvements in swallowing, retaining saliva, chewing, and speech capabilities. However, they can lead to short outcomes, including infection, rejection (prosthesis), poor functional recovery, and poor aesthetic results. They often require multiple revision surgeries and prolonged hospitalization and rehabilitation, with a significant negative impact on patients, health care system and society.[39]

Osteocutaneous free flaps such as the scapular, radial forearm, iliac and fibula free flaps have been extensively reported. The fibula osteoseptocutaneous flap is the most widely used. It is adequate for

reconstructing oromandibular defects, as well as for inner and outer lining. Since 1975, when Taylor *et al* [40] first described the fibula flap as a source of vascularized bone graft, the procedure and the clinical applications have undergone significant evolution. Hidalgo and Fu-Chan Wei [41-43] demonstrated the reliability of the fibula osteoseptocutaneous free flap in 1980s and it gained popular use in mandibular reconstruction. However the two determinants of success for large facial defects reconstruction are the amount/quality of bone and soft tissue required. In some cases, the fibula osteocutaneous flap may not provide sufficient soft tissue for dead space obliteration.

Double free flaps were advocated by many renowned reconstructive surgeons [44 - 47], however, they need two separate pairs of recipient vessels in the neck for both flap revascularization, and they are time consuming.

Flap prefabrication and prelamination are evolving, new techniques that are useful in reconstructing complex defects of the head and neck. Flap prefabrication involves the introduction of a new blood supply by means of a vascular pedicle transfer into a volume of tissue. After neovascularization, this volume of tissue may be transferred, based only on its implanted vascular pedicle by local transposition, or microsurgical transfer. Flap prelamination refers to a technique in which additional tissue (e.g., grafts of skin and cartilage) is added to an existing flap (without manipulation of its axial blood supply) to make a multilayered flap that may be used for complex, three-dimensional multilayered reconstructions. This technique may be used locally or at a distance, requiring microvascular transfer.

Despite all the tailoring, and planning of these multiple flap and multi-stage reconstructions, these interventions never quite recapitulate the face. The reconstructive surgeon should then consider other options for reconstruction of extensive three-dimensional defects.

2. CHIMERIC FLAPS AND "THEIR VARIATIONS" FOR IMMEDIATE RECONSTRUCTION OF MASSIVE FACIAL DEFECTS

INTRODUCTION

The head and neck region presents a significant challenge for the reconstructive surgeon, due to its complex anatomy and essential functions.

Conventional reconstructive options can be considered for reconstruction of massive head and neck defects, but there is no single ideal osteocutaneous free or pedicled flap providing an unlimited length of bone and skin paddle, or that could orient three-dimensionally the skin paddle independently of the vascularized bone.[48] The surgeon should then be aware of more complex options for reconstruction of extensive three-dimensional defects namely chimeric free flaps and “their variations” in the context of limited vasculature and immediate oncological reconstruction, where facial transplantation is not applicable.

MATERIAL AND METHODS

Here we briefly review the indications, technical aspects, advantages and disadvantages of these reconstructive options.

RESULTS AND DISCUSSION

According to the most recent classification of compound flaps purposed by Hallock, chimeric flaps, also called polyflaps, refer to multiple otherwise independent flaps that have an independent vascular supply, but in turn all pedicles are linked to a common large vessel. They can be stratified in three types, either based on their intrinsic vasculature – perforated-based, branch-based, or whether they are prefabricated (surgical junction by microanastomosis). This last type can also be subdivided according to the fabricated component as a sequential type (anteriorly known as “flow-through sequentially linked flap”) or internal type, when the prefabricated component is attached to an indigenous branch within the flap (Fig. 19).[49,50]

Concerning “branch-based” chimeric flaps, the classical type, they allow inclusion of multiple skin paddles for intra/extra-oral coverage and a muscle or osseous component, for obliteration of dead space/plate or bone coverage, based on individual septocutaneous and musculocutaneous perforators.

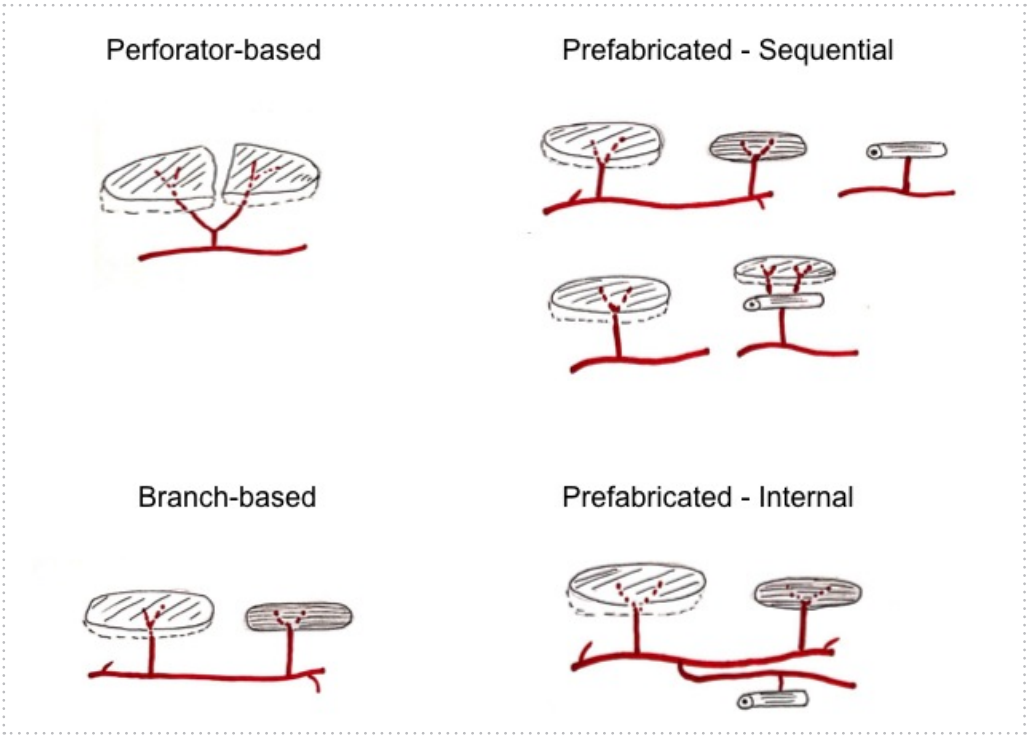


Figure 19. The anatomical and dynamic concept of chimeric flaps. They can be perforator or branch-based (depending on their intrinsic vasculature), or prefabricated (i.e., surgically joined together by means of a microanastomosis). The fabricated component can be attached to the terminus of the source vessel to the combination (sequential type) or to a branch indigenous within the flap (internal type).

Various refinements of the fibula flap were reported including the double-barrel flap and the chimeric fibula flap, to include multiple skin paddles and a muscle component, based on individual septocutaneous and musculocutaneous perforators. Septocutaneous perforators are predominantly located at the middle and distal thirds of the fibula, whereas the perforators of the lateral proximal third of the leg are mostly musculocutaneous perforators. The perforator of soleus muscle cuff, that nourishes the lateral aspect of soleus muscle, pierces the deep fascia between the peroneous longus and soleus muscles. It is then possible to harvest a modified fibular flap with two different fasciocutaneous and muscle paddles.[48,51]

To harvest a chimeric fibula flap, the skin paddle should be centered at the posterior border of the fibula at the junction between the middle and lower third of the donor leg. Usually we perform a modification of the surgical procedure proposed by Chih-Hung Lin for harvesting a osteocutaneous fibula flap.[52] After dissection of the osteoseptocutaneous component, the lateral soleus muscle is exposed by a posterior retraction of the gastrocnemius muscle, and then performing a longitudinal split at midline. A segment of soleus muscle is included, based on a constant musculocutaneous perforator, originating from the main source of peroneal vessels. The peroneal artery and venae comitantes are dissected at their origin and traced to their course to the fibula. The dissection is then completed harvesting the osteoseptocutaneous flap with a muscle segment as two separate components (Figs. 20 and 21). The osteocutaneous segment is further adapted to a reconstruction plate, and the muscle can be an option for dead space obliteration or plate coverage. The skin paddle can be used for extra or intra-oral reconstruction.

A chimeric anterolateral (ALT) flap can also be a good option for massive defects, incorporating two different fasciocutaneous and muscular components without bone reconstruction. The parascapular/scapular/latissimus dorsi muscle/serratus anterior muscle (thoracodorsal vessels based) chimeric flaps may also be considered for these reconstructions.[53]

The "perforator-based" type, which relates to the flap division according to branches of a perforate vessel, has the ALT flap as the prototype. Allowing division of the flap in smaller flaps, it is useful for simultaneous reconstruction of intraoral and cheek defects, avoiding infolding and deepithelialization.



Figure 20. *Above, left:* Extra-oral recurrence of squamous cell cancer with mandibular invasion (previous pelvi-glossectomy and reconstruction with a radial forearm free flap).
Above, right: The fibula free flap incorporating soleus muscle as a chimeric flap.
Below, right: The bone was shaped to a reconstruction plate; the muscle was used for dead space obliteration.
Below, right: Immediate postoperative period.



Figure 21. *Above, left:* Extensive squamous cell carcinoma of tongue with mandibular bone invasion and destruction following pelvi-glossectomy, segmental mandibulectomy, and bilateral modified radical neck dissection.
Above, right: The fibula free flap incorporating soleus muscle as a chimeric flap.
Below, right: The bone was adapted to a reconstruction plate; the muscle was used for coverage of the mandibular plate and the fasciocutaneous flap for reconstruction of the tongue and floor of the mouth.
Below, right: Good intra-oral coverage and external contour after 2 months.

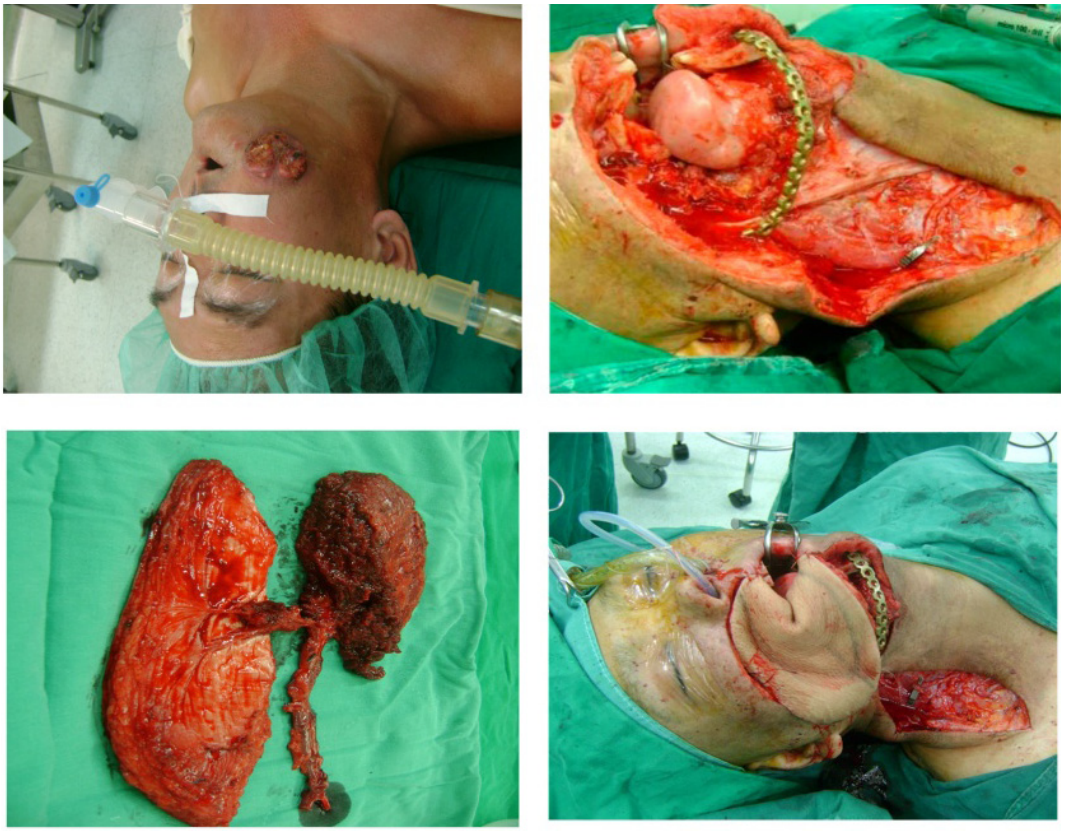


Figure 22. *Above, left:* Buccal through-and-through carcinoma.
Above, right: Large defect following wide resection with mandibulectomy and inferior maxillectomy.
Below, left: Perforator-based anterolateral thigh (ALT) chimeric flap can be harvested including a large skin paddle and an independent muscular flap supplied by one mother pedicle-descending branch of lateral circumflex femoral artery (d-LCFA).
Below, right: The skin paddle can be inserted both extra and intra-orally. The muscle is a good option for coverage of a reconstruction plate and for dead-space obliteration.

Chimeric flaps have advantages in reconstruction of large and compound defects, allowing easier 3D insertion and require only one pair of recipient vessels, not affecting major vessels. The thin skin paddle of fibula osteocutaneous flap may be adequate for intra or extra-oral coverage, but is often inadequate for augmenting submandibular, mouth floor or cheek massive defects. The dead space, if not obliterated, usually accumulates fluid and hematoma, and then cause secondary infection and flap failure, which can be aggravated by radiotherapy. Unreplaced soft tissues losses following tumor ressection, can lead to contraction, a sunken apperance, trismus and plate exposure.[48,51] The principal advantage of a free fibula osteocutaneous flap with soleus muscle as a chimeric flap is that soleus muscle can obliterate dead space in mouth-floor and neck area, and prevent saliva accumulation if orocutaneous fistula occurs. It provides improved coverage of the fibula and the reconstruction plate, and achieves high patient satisfaction with chin and submandibular contour. It presents low morbidity, decreased operative time and acceptable aesthetic results. In some series of chimeric branch-based fibula flaps, patients could stand on the balls of their feet without difficulty postoperatively.[48] Minor complaints included occasional ankle pain, hallux weakness, and sensory disturbance, but none related to gait.

However, despite the advantages of a chimeric fibula flap, the dissection of each septocutaneous or myocutaneous perforator can be time-consuming and extremely problematic for less experienced surgeons; a learning curve is necessary and anatomical variations can be present.

Transplantation of multiple free flap components can meet the requirements of three dimensional reconstruction. For instance, a perforator-based anterolateral thigh (ALT) chimeric flap can be harvested including a skin paddle and a muscular flap supplied by one mother pedicle-descending branch of lateral circumflex femoral artery (d-LCFA).[54] Using chimeric concept, free anterolateral thigh myocutaneous flap transplantation is safe and reliable, and it has the advantages of the better result at the recipient site, the less morbidity at the donor site, fewer postoperative complications and excellent tolerance to radiotherapy. The dimension of skin and the volume of muscle can be tailored as adequate as desired, so it is an ideal flap to repair soft tissue defects following the en block resection of oral cancer (Fig. 22).

Perforator and branch-based chimeric flaps constitute a good option for the most complex bone and soft-tissue head and neck reconstruction, afford more degrees of freedom, allowing for combined reconstruction of three-dimensional soft-tissue and bone defects, exceeding 6 cm in length.

The concept of an uninterrupted arterial flow-through flap was developed by several authors.[55-58] A flow-through flap is most commonly used in limb salvage procedures, when vascular reconstruction is required, in addition to soft-tissue reconstruction, but this concept was also adapted to the head and neck region. Bullocks *et al* [59] proposed a classification of flow-through flaps into three types, based on their inflow, outflow and the nature of the vascular conduit that traverses the flap: type I - the conduit is a single artery; type II - the conduits are two different arteries that communicate via “choke-vessels” within the flap, and the inflow and outflow arteries can be reversed; and type III- a single vein is used as a conduit that is incorporated into a vascular gap in a reverse orientation.

Most frequently, the radial forearm or the anterolateral thigh flap (ALT) flaps are used as flow-through flaps for revascularization of the free osteocutaneous flaps (fibula/iliac crest), or the ALT pedicle (Fig. 23). The proximal stumps of the radial artery and cephalic vein may be anastomosed to branches of the external carotid artery and jugular vein to revascularize the new composite tissue transfer. [47,57]

With two-three teams working simultaneously, the osteocutaneous flap (free fibula or iliac crest) and the fasciocutaneous free flap (e.g., radial forearm) are harvested. Closing wedge osteotomies are performed to shape the new mandible. Adequate lengths of the distal radial artery and chepalic vein should be attempted for microvascular anastomosis, and the radial forearm flap is elevated and allowed to perfuse. The distal stumps are end-to-end anastomosed to the vascular pedicle of the osteocutaneous free flap and both flaps are allowed to revascularize for 20 minutes.

The new composite tissue transfer is then transferred to head and neck region. The fasciocutaneous flap is inset into the oral cavity defect and the osteocutaneous flap is used for mandible reconstruction and external coverage, allowing three-dimensional reconstruction. It is crucial to avoid pedicle torsion or compression. The proximal stumps of the radial artery and cephalic vein are used for flow-through revascularization to the major neck vessels, without restrictions in terms of vessel length and caliber.

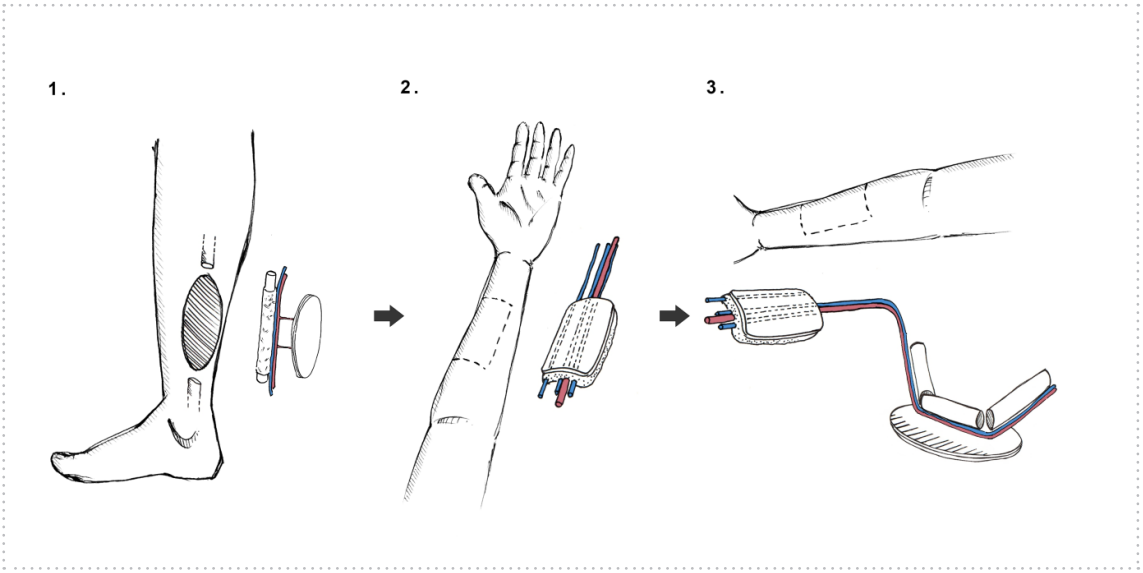


Figure 23. The anatomical and dynamic concept of flow-through sequentially linked free flaps.

Their great advantage is the possibility of inclusion of two different skin paddles repositioned three-dimensionally independently of the vascularized bone component provided by the osteocutaneous free flap.[59] The long proximal stumps of the radial artery and cephalic vein (or the ALT pedicle), are anastomosed inside the neck, without the need of interpositional vein grafting, overcoming the limited vasculature in the multioperated and scarred necks.

As disadvantages, both free flaps may be lost, in consequence of proximal thrombosis, requiring strict postoperative monitoring. It may be time-consuming (average 8 hours), unless two-three teams are involved. Another important consideration of the "prefabricated type" for dealing with such massive defects and to overcome the limited neck vasculature, is the reconstruction using end-to-side anastomosis of one free flap pedicle into the other free flap proximally, or end-to-end anastomosis of one free flap pedicle into a side branch of another free flap.[60,61] This technique – "chain-link flaps" has the advantage of utilizing only one set of recipient blood vessels, while being technically easier than anastomosis of the distal pedicle in flow-through flaps, where the caliber of the distal blood vessels (especially the veins) can be small. In some cases, this strategy also allows a greater degree of insetting freedom, avoiding the need to bend a flap pedicle 180 degrees.

In conclusion, despite morbidity and not perfect matching in terms of skin texture and pliability, these techniques are a good alternative in the presence of partial defects, especially in the context of immediate oncological reconstruction, where facial transplantation is not considered.

3. MICROSURGICAL RECONSTRUCTION FOR RADIATION AND BISPHOSPHONATE INDUCED MANDIBLE OSTEONECROSIS BASED ON PATIENT-SPECIFIC PHYSIOPATHOLOGIC MECHANISMS

INTRODUCTION

Radiation and bisphosphonate induced mandible osteonecrosis have distinct underlying physiopathologic mechanisms but both constitute a serious problem and lead to functional impairment and facial disfigurement.

Although radiotherapy can increase cure rates, the irradiated patient is susceptible to secondary effects and a series of potential oro-facial complications (table 3), and one of the worst complications is the osteoradionecrosis (ORN).

Table 3. Oro-facial complications of Radiotherapy

1. Xerostomia
2. Dental caries
3. Mucositis
4. Periodontitis
5. Dysphagia
6. Loss or change in taste
7. Opportunistic infections
8. Lock-jaw
9. Osteoradionecrosis (ORN)

Obliterative endarteritis, hyperemia, hyalinization, cellular loss, hypovascularization, thrombosis, and fibrosis are the most common histologic findings in ORN, who may result in metabolic and tissue homeostatic disturbances that decrease the diffusion of oxygen into the tissues (Fig. 24). Bone cells are damaged as a result of acute inflammation, free radicals, and the chronic activation of fibroblasts. It should be emphasized that osteoradionecrosis is not only a disease of the bone, and also affects surrounding soft tissue. Sometimes, after radical osteoradionecrosis resection, composite through-and-through defects exist, which require a second free flap for reconstruction of the external skin defect of the lower face or neck.

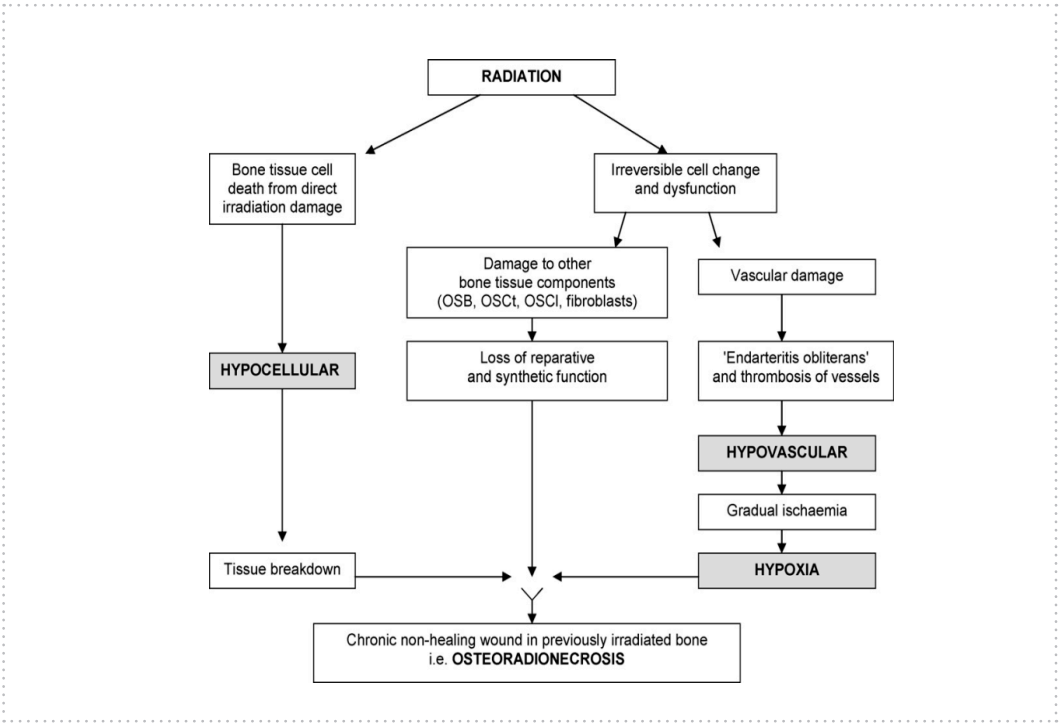


Figure 24. ORN a sore that does not heal - hypoxic, hypocellular and hypovascular (3H) - Marx (1983).

Osteonecrosis of the jaws was also more recently described as an adverse side effect of bisphosphonate therapy. Bisphosphonates are inhibitors of bone resorption by osteoclasts, and patients with multiple myeloma and osseous metastasis from carcinomas, who are receiving nitrogen-containing bisphosphonates, are at greatest risk for osteonecrosis.

In both clinical situations, wide radical resection of necrotic bone with immediate replacement with healthy vascularized tissue is often the best option for the treatment of advanced osteonecrosis. Several free flaps such as the scapular bone flap, iliac crest flap or soft tissue only flaps (rectus abdominis and latissimus dorsi myocutaneous flaps) have been used, but the fibula osteoseptocutaneous free flap is usually preferred, because it allows two surgical teams to work simultaneously, to perform multiple osteotomies, to obtain adequate length of bone up to 25 to 27 cm, and a vascular pedicle up to 12 to 15 cm. This is important because identification of adequate recipient vessels may be difficult in the presence of an irradiated neck [62] and may have to be selected outside the irradiated field, or in the opposite neck.[63,64]

For patients with advanced refractory disease, pathological fracture, oro-cutaneous fistula and severe osteolysis, ressection associated with microvascular reconstruction seems to be a valid option that stops the underlying pathophysiology of overinfected avascular bone necrosis.

METHODS AND RESULTS

We describe different clinical situations related to several grades of osteonecrosis, where different options of free transfer should be considered based on case-specific physiopathologic mechanisms. We propose a simple clinical grading system to predict the best treatment option.

GRADE I (FIG. 25)

Description: no clinical evidence of necrotic bone, but with early non-specific or radiographic findings, or with exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.

Required reconstruction: No specific reconstruction is required.

Treatment plan: Oral hygiene measures, chlorhexidine 0.12 % mouthwashes, treatment of pain, frequent clinical evaluations (6/6 months), consider suspension of oral bisphosphonates.



Figure 25. Early exposure of necrotic bone in an asymptomatic patient without evidence of infection; conservative treatment is often the best option.

GRADE II (FIGS. 26-28)

Description: Mandible osteonecrosis with or without pathological fracture.

Required reconstruction: Bone.

Treatment plan: Free fibula transfer.

Example: A 54 year-old-male patient was diagnosed with squamous non-small cell lung cancer with bone metastasis (left hip). He was submitted to surgery, radiotherapy, chemotherapy, followed by a 3 years treatment with intravenous bisphosphonate (Zollendronic acid). One year later, he presented with painful bone exposure at the level of the alveolar ridge of the right body of the mandible, associated with pathological fracture and without history of tooth extraction. He underwent previous treatment with antibiotics, antiseptics and conservative surgical debridment. A maxillofacial CT showed a complex lytic lesion in the right body of the mandible, with 42x 11 mm, bone sequestrum and pathological fracture. The patient was submitted to a right segmental mandibulectomy (symphysis to the right angle) including 1 cm margin of macroscopically healthy bone, through a transcervival approach. The defect was reconstructed using a free fibula flap, and the microvascular anastomosis were completed with an end-to-end technique to the right facial vessels. The fibula

flap was divided into 2 segments in an attempt to reestablish the mandibular contour, and each segment was fixed with 3 locking screws to the mandibular reconstruction plate. Because there were no significant skin or mucosal defect, no skin paddle was used. The oral mucosa was closed in a watertight manner over the fibula flap. No infection, delayed healing, or compromise to the vascularity of the flap was noted. The patient had complete resolution of symptoms and complications (including pain, infection and pathogical fracture) and was satisfied with the esthetic and functional results. An ortopantomography showed proper conformation of the flap and reconstruction plate and no recurrence of osteonecrosis in the resection margins after 12 months.

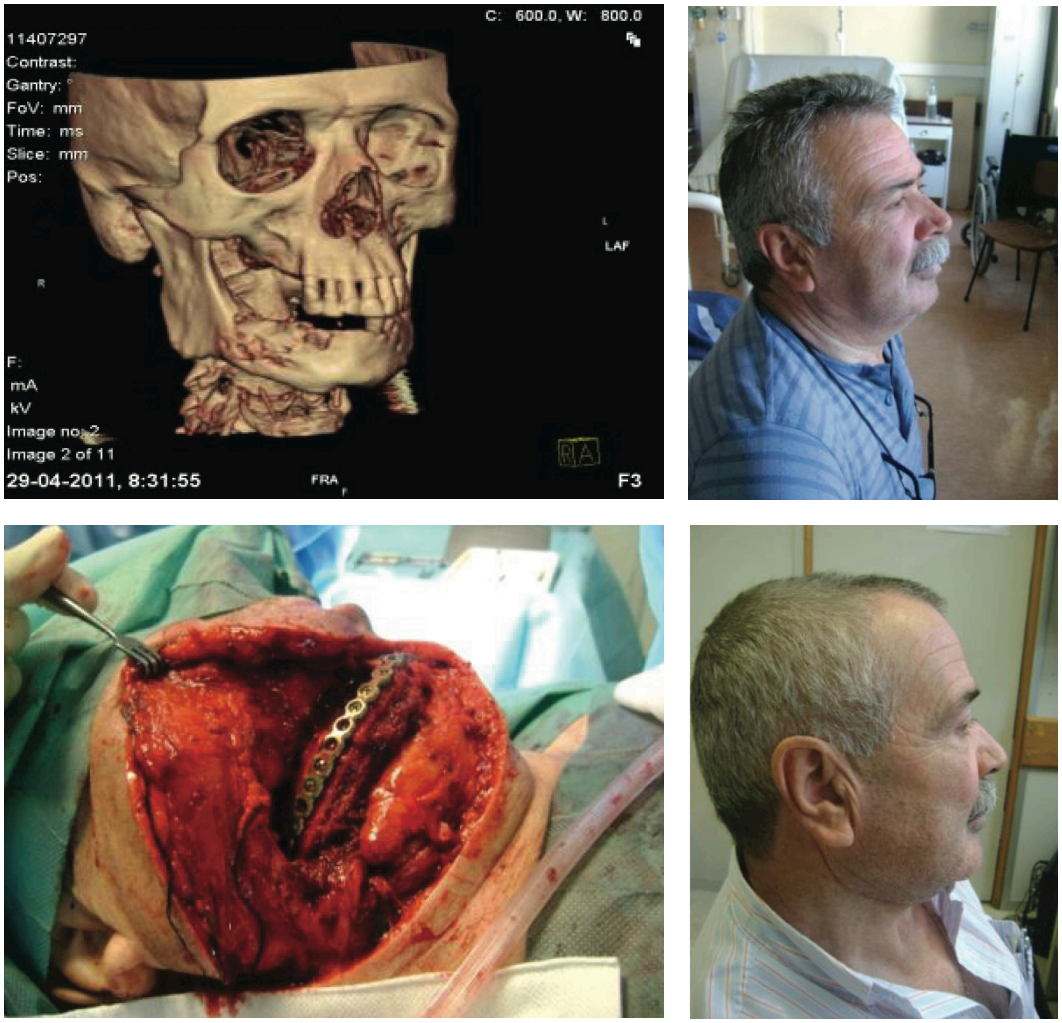


Figure 26. *Above, left*: Bisphosphonates induced osteonecrosis of the jaws (BRONJ).
Above, right: Preoperative: absence of orocutaneous fistula.
Below, left: The fibula flap was divided into 2 segments in an attempt to reestablish the mandibular contour and was fixed to the mandibular reconstruction plate.
Below, right: Postoperative appearance after 12 months: good contour.

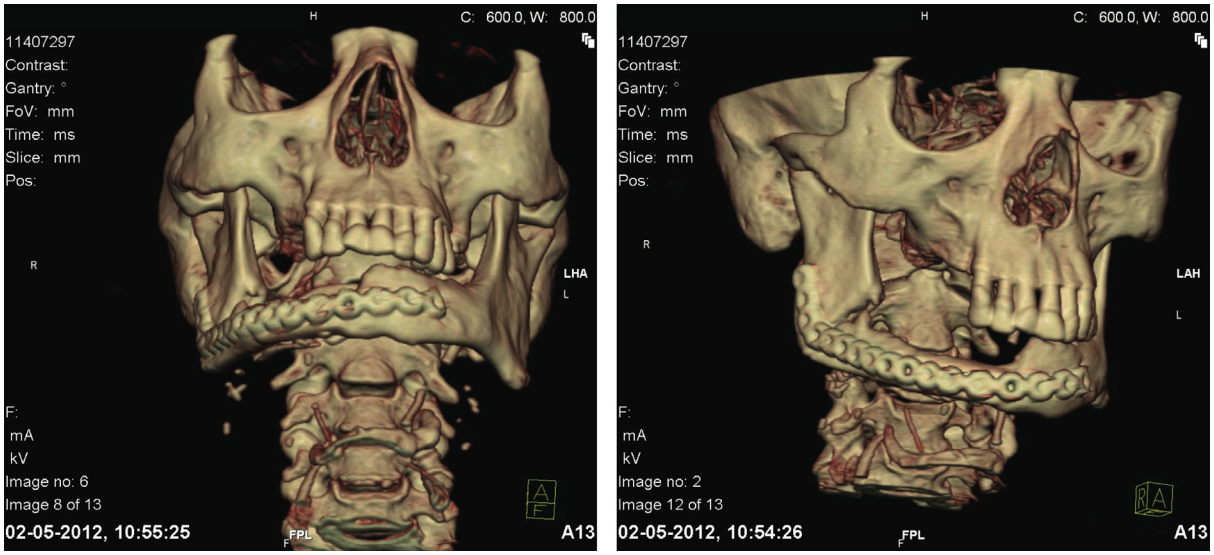


Figure 27. Bone consolidation was successfully achieved.



Figure 28. Postoperative appearance after 12 months: no bone exposure was subsequently seen.

GRADE III (FIG. 29)

Description: Mandible osteonecrosis + orocutaneous fistula.

Required reconstruction: Bone + internal/ external coverage.

Treatment plan: Fibula osteoseptocutaneous free flap.

Example: A 57 year-old-male patient was diagnosed with squamous cell carcinoma of the hypopharynx (clinical staging, T2 N0 M0). He underwent radiotherapy (2 Gy in 36 fractions with 6-MV energy) with concurrent radio-sensitizing chemotherapy (cisplatin100 mg/m^2, 3/3 weeks, for a total of 3 cycles), with clinical remission and no signs of locoregional recurrence. Later, he reported progressive “burning-like” pain radiating to the ear and making it difficult to open his mouth. The pain was controlled with gabapentin 300 mg for 8-8 hours, Tradorec XL® of 100 mg (tramadol) at night, and Zamadol (tramadol hydrochloride) for 6-6 hours in SOS, but despite conservative treatment, he had great difficulty in opening the mouth and chewing, with impaired quality of

life. During his radiation treatment, he developed an orocutaneous fistula on the left angle. A CT scan was performed and showed abnormal trabeculation of the mandible consistent with osteonecrosis (angle and left body). He was submitted to segmental mandibulectomy and reconstruction with a fibula osteoseptocutaneous free flap. Despite good coverage and healing, concomitant with pain relief and improvement of mouth opening, the patient died later as a consequence of cardiorespiratory arrest.



Figure 29. *Above, left:* Mandible osteoradionecrosis (ORN).
Above, right: Associated orocutaneous fistula.
Below, left: Fibula osteoseptocutaneous free flap.
Below, right: Immediate postoperative appearance; good contour and coverage.

GRADE IV (FIGS. 30-35)

Description: Mandible osteonecrosis + orocutanous fistula + irradiated external soft tissue.

Required reconstuction: Bone + external soft tissue replacement + separation of bone and soft tissue (guided bone regeneration).

Treatment plan: Fibula + anterolateral thigh flap (ALT) chimeric flaps.

Example: Persistence of poor coverage in the context of an extensive irradiated area, and inadequate barrier surrounding the bone were identified as the two main problems preventing adequate bone healing in a 41 year-old female patient with severe ORN and deficient bone consolidation after a fibula free flap. Despite flap viability with patent microvascular anastomosis and normal radiological bone density, there was no effective consolidation. Extrusion of mandibular reconstruction plate and persistent orocutaneous fistula were subsequently seen. A modified ALT flap was used incorporating two independent fasciocutaneous and muscular components. The skin paddle was placed for external coverage and contour, whereas the muscular segment was used for dead space obliteration and coverage of the reconstruction plate. A collagen biomatrix dura mater substitute (TissuDura®; Baxter, Vienna-Austria) membrane was then employed to act as a barrier to prevent soft-tissue invasion into the fibula, and to form a “chamber” to “guide” the bone regeneration. It is composed of colloidal collagen from equine Achilles tendon, has been recently used in neurosurgical procedures with no local or systemic toxicity, low incidence of inflammation, and has demonstrated elasticity and good anatomically adaptablility.[65] A bone substitute was also added in rebuilding mandible bonestock (Repros® granules, JRI Orthopaedics Ltd, Sheffield - United Kingdom), as a temporary scaffold to fill the osteotomy gaps and to provide biomechanical stability.
Initial bone consolidation was seen after 3 months, and closure of orocutaneous fistula was achieved.

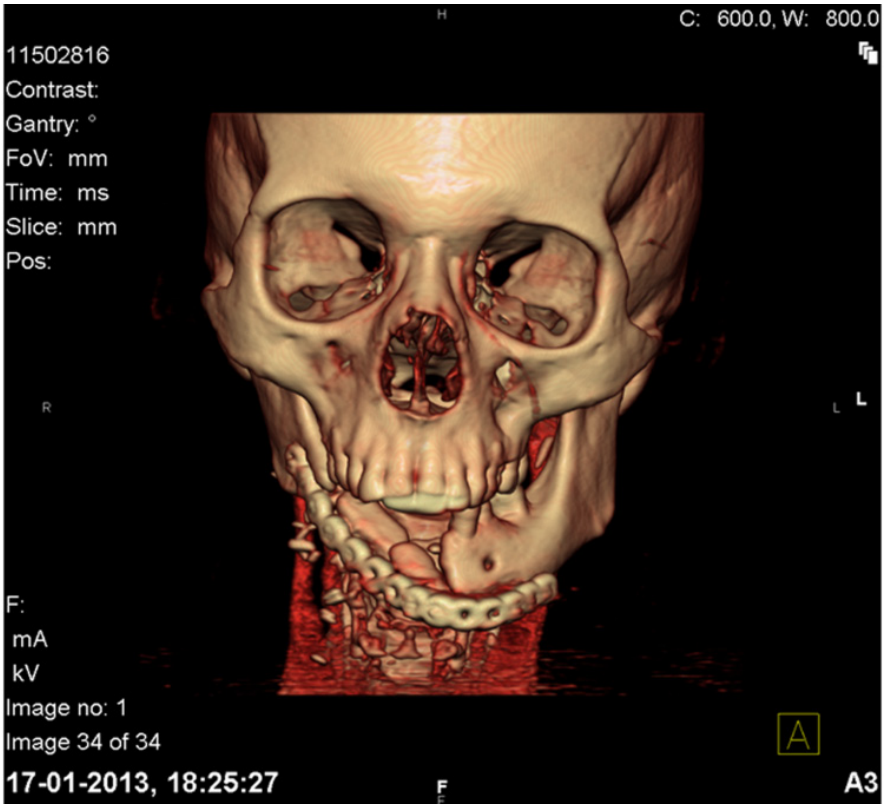


Figure 30. The fibula free flap despite bone viability and normal density was not incorporated in the remaining mandible. This resulted in extrusion of the reconstructed plate.



Figure 31. Extrusion of mandibular reconstruction plate and persistent orocutaneous fistula.

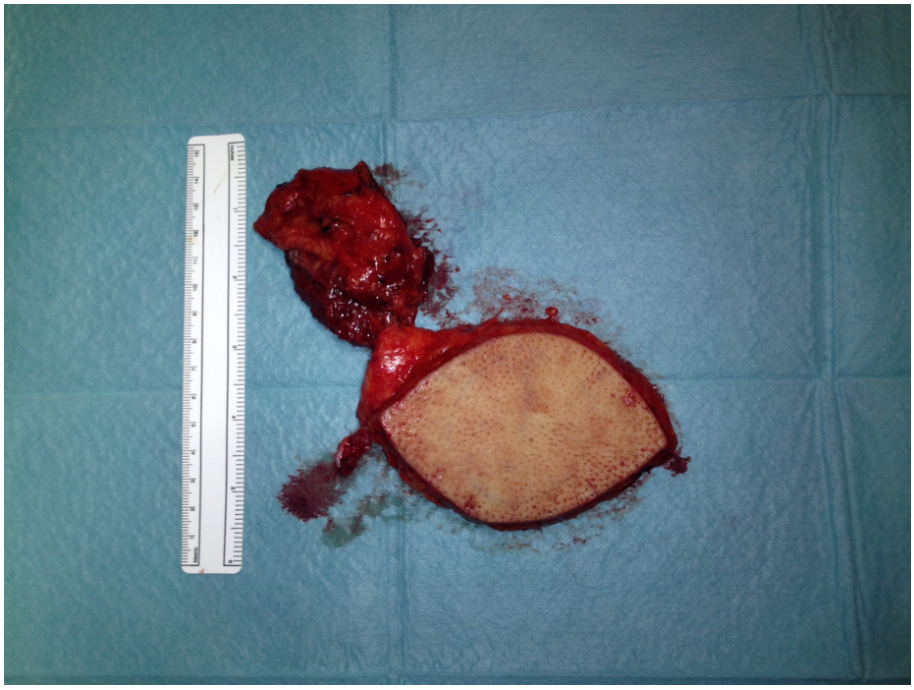


Figure 32. ALT chimeric flap: the skin paddle is independent of the muscle component. The skin paddle was inserted extra-orally. The muscle was used for coverage of the reconstruction plate and for dead-space obliteration.



Figure 33. A collagen biomatrix dura mater substitute (TissuDura®; Baxter, Vienna, Austria) membrane and a bone substitute (Repros® granules, JRI Orthopaedics Ltd, Sheffield, UK) were used to "guide" the bone regeneration process and in rebuilding bonestock.



Figure 34. Postoperative appearance after 3 months: good contour and absence of orocutaneous fistula.

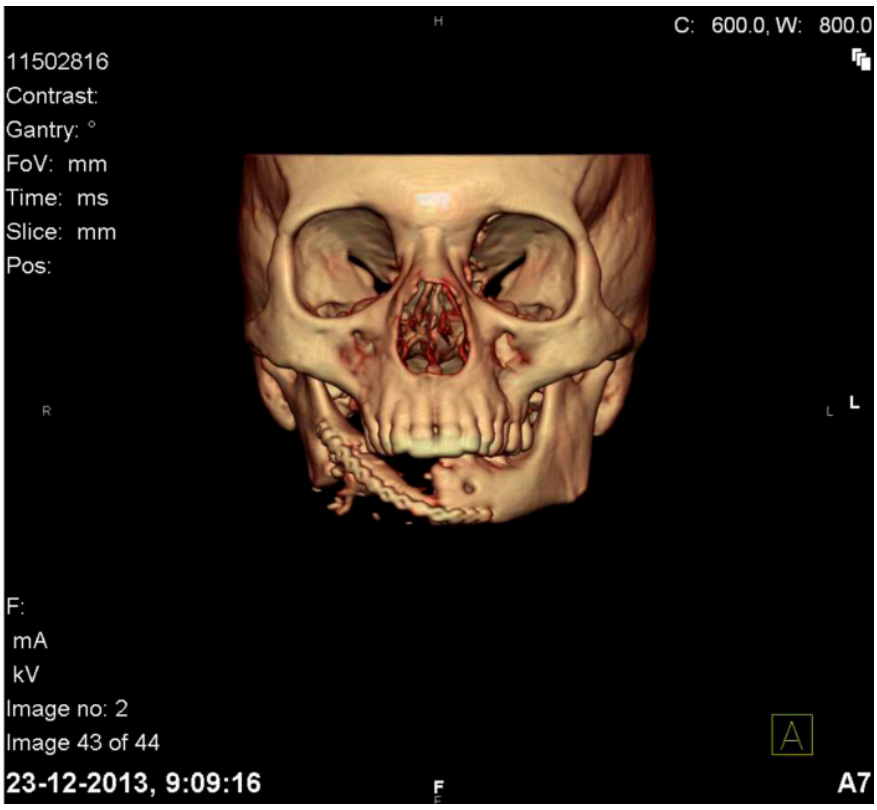


Figure 35. The previous fibula flap was finally integrated into the remaining mandible.

DISCUSSION

The incidence of osteoradionecrosis varies widely in the literature ranging from 1% to 37%.[66] The definition of osteoradionecrosis is generally accepted as the presence of exposed bone in an irradiated field, which fails to heal within a 3-month period.[67] Early presentation, within 2 years, is thought to be related to high doses of radiotherapy (>70 gray), whereas late presentation is usually secondary to trauma and delayed wound healing within compromised tissue.

In an irradiated field, even a minor insult such as a dental procedure can result in delayed healing and some cases develop into ORN. Signs of radiation may include pigmentary changes, lack of hair and telangiectasis. Intraorally, the mucosa may be dry with frothy sputum in the acute phase. The patient may have a nonresolving painful mucosal ulcer, inability to open the mouth (trismus), usually 3 to 6 months following radiotherapy. The initial effects of radiotherapy to the oral tissues such as mucositis and loss of taste are troublesome but usually resolve within a few weeks. Xerostomia may be long-standing but can be managed with supportive therapy such as sialogues and artificial saliva.[68] Exposed bone inside the mouth can be seen (sequestrum), usually in the posterior mandibular region. There may be exposed bone seen through the skin, in the form of an orocutaneous fistula or the patient may present with a pathological fracture, and transfer of microvascularized bone, eventually associating a skin paddle, is often the best reconstructive option.

As previously mentioned, osteoradionecrosis affects surrounding soft tissue and is not only a disease of the bone. A modified ALT flap can also improve local tissue vascularization, allowing for coverage of both a reconstruction plate and external/internal soft tissue, and closure of an orocutaneous fistula in the presence of severe osteoradionecrosis. It can also been used as a salvage procedure after deficient bone consolidation with a fibula free flap, in addition to a collagen biomatrix substitute, to act as a barrier to prevent soft-tissue invasion into the fibula, and to guide the vascularized bone transfer for effective consolidation.

Bisphosphonates such as alendronate (Fosamax), pamidronate (Aredia), and zolendronate (Zometa) are commonly used to manage the hypercalcemia associated with malignancies such as multiple myeloma or metastatic breast cancer and more recently, to prevent osteoporosis. They are analogs of endogenous pyrophosphates with substitution of 1 atom of oxygen for 1 atom of carbon and they have high affinity to the bone, being accumulated for long periods. Bisphosphonates are inhibitors of bone resorption by osteoclasts, which help reduce calcium levels and preserve bone, and also have anti-angiogenic properties. They can lead to decreased bone turnover, hypermineralization (target of the therapeutic use) and bone hypovascularization. This results in a combination of a compact and avascular bone, and osteonecrosis by a mechanism of ischemia and secondary infection.

Like ORN, bisphosphonates induced osteonecrosis of the jaws (BRONJ) presents as painful exposed bone in the maxillary or mandibular alveolus with intra or extraoral drainage and is usually refractory to conventional non-operative and operative surgical treatment.

The current literature advocates a conservative treatment of bisphosphonate related osteonecrosis of the jaws, using antibiotics and limited surgical debridment. Antibiotics, conservative debridements, irrigations and topical application of anti-infectives are seldom curative but may useful in the first stages and permit the patients to live with their disease. Hyperbaric oxygen does not seem to be effective. Patients who have responded poorly to conservative treatment may require segmental mandibulectomy or maxilectomy. Several

authors [69,70] have argued against bone reconstruction of segmental defects among patients with BRONJ, owing to the perceived high risk of perioperative complications, risk of transferring malignant cells from the donor site, recurrence of BRONJ at resection margins, and nonunion. Patients often have poor survival and health status. “Skeptics” of microvascular reconstruction report good results with segmental resection without reconstruction.

“Defenders” of microvascular reconstruction[71-75] state that microvascular reconstruction allows for restitution of bone continuity with vascularized tissue with functional and esthetic advantages. There is a reduced risk of exposure of the reconstructed plate and minor recurrence of osteonecrosis. In addition, fibula is rarely involved by bone metastasis or multiple myeloma, and the use of autologous fibula bone transfer in patients with a history of cancer, poses a minimal risk of transfer of metastatic lesions from the fibula to the mandible. Bisphosphonate-induced osteonecrosis primarily affects the jaw bones and usually follows dental trauma with exposure of bone to oral secretions. Therefore, transferring the fibula does not likely transfer bone adversely affected by systemic bisphosphonate therapy.

In fact, most cases reported of vascularized bone reconstruction of segmental mandibulectomy defects showed minimal perioperative complications, no transfer of malignant cells to the recipient site, improved cosmesis and oral function, decreased complications related to plate exposure and benefit from the establishment of union of the native mandible with the fibula flap.

We believe that segmentar ressection and microvascular reconstruction may be a valid option in specific advanced cases of ORN and BRONJ, interrupting the underlying pathophysiology of overinfected avascular bone necrosis.

Clinicians who understand the specific physiophatologic mechanisms of each case, can incorporate them into the assessment of the required reconstruction and treatment plans.

4. MICROSURGICAL FACIAL REANIMATION FOR TREATMENT OF LONG-STANDING FACIAL PARALYSIS

4.1. Irreversible facial paralysis: definition

Nonverbal communication includes our facial expressions, gestures, body posture, eye contact, and tone of voice. Facial expressions are crucial to social interaction, relay feeling and emotions.[76] There are 18 muscles of facial expression, each contributing to create the distinctive appearance of an individual's facial animation, which are arranged in layers.[77] The most superficial are the depressor anguli oris, zygomaticus minor, and orbicularis oculi. Nerves entering their deep surface innervate the superficial and middle layer muscles. The deepest layer is comprised of the buccinators, mentalis, and levator anguli oris and are innervated on their superficial surface, so that they are in the same plane as all the other nerve branches.

The facial nerve or cranial nerve (CN) VII, begins at the level of the pons, then exits the skull base at the petrous portion of the temporal bone, courses through the internal auditory meatus within the facial canal, and exits the skull base at the stylomastoid foramen which lies anterior and deep to the mastoid process.[78] Upon exiting, the main trunk of the nerve continues anteriorly and inferiorly and divides further within the parotid gland into the cervicofacial and temporofacial divisions. Finnaly, it then divides into five peripheral branches to supply the muscles of facial expression:

- Temporal: runs across the undersurface of the temporal-parietal fascia after crossing over the zygomatic arch; it innervates the frontalis, corrugator, and upper orbicularis oculi muscles;
- Zygomatic: supply the lower eyelid, nasalis, zygomaticus major and minor, levator labii superioris, orbicularis oculi, orbicularis oris, and buccinators;
- Buccal (frequent overlap with zygomatic branch);
- Marginal: passes caudal to the angle of the mandible and then arches upward to cross the mandibular body to innervate the depressor anguli oris, depressor labii inferioris, mentalis, and sometimes the upper platysma and lower orbicularis oris;
- Cervical (the most caudal and innervates the platysma).

Facial paralysis has often an idiophatic etiology but it can be caused by tumor surgery (e.g., acoustic neuroma, preauricular or infra-auricular tumour excision), trauma, or be part of a congenital anomaly.

In the treatment of facial paralysis, the best results are seen when facial nerve function is reestablished. Because the consequent atrophy of the mimic muscles is considered permanent after approximately 2 years, it is possible to reestablish muscle contraction from other nerve sources during the first 18-24 months after the onset.

In 1971, Smith [79] described the use of cross-facial nerve grafts from selected branches of the facial nerve of the unaffected side (contralateral) to reinnervate muscles on the paralysed side. In 1978, Spira [80] used the trigeminal nerve, and the hypoglossal nerve was introduced by Conley and Baker in 1979 [81] for replacing the facial nerve.

Concomitant hypoglossal-facial nerve neurotization and cross-facial nerve grafts were described by Terzis in 1984 [82], as a babysitter procedure, and other techniques were posteriorly developed using temporary and permanent nerve substitution.

Faria *et al* [83] has more recently used the masseteric branch (trigeminal nerve) to substitute the facial nerve in cases of paralysis persisting up to 18 months, as consequence of the high success rates in treatment of long-standing unilateral or bilateral facial palsy with gracilis muscle transplantation using this nerve. They suggested masseteric-facial nerve coaptation, whether temporary (baby-sitter) or permanent, to improve facial balance at rest and symmetry of the voluntary smile.

When a long-standing facial paralysis is present (for more than 24 months), the inability to contract the atrophied musculature results in distortion of facial morphology, especially during activation of the contralateral musculature. In the treatment of established facial paralysis, transposition of new musculature (dymamic facial reanimation) leads to the best morphological results.

4.2. Physical, social and psychological impact

Facial paralysis can have a tremendous impact on the affected individuals (Fig. 36). They deal with physical, psychological and social disability daily. The impact of facial disfigurement on social interactions, includes psychological and physical fatigue.[84] Patients can experience staring, bullying, discrimination, which can affect their quality of life, affecting their private relationships, as well as school and work interaction.

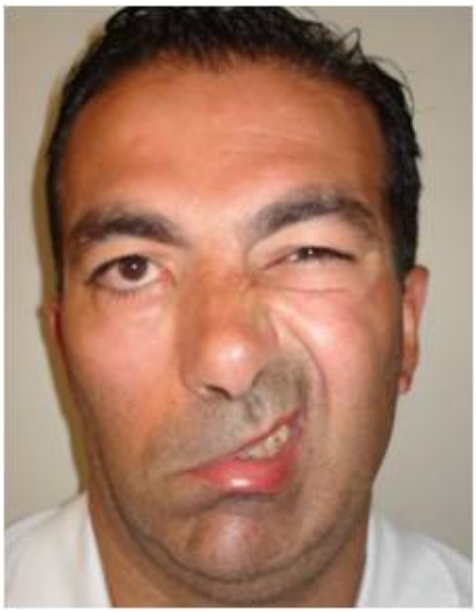


Figure 36. Gross disfigurement in severe forms of facial palsy.

In addition to the disfiguring condition that takes away facial expressiveness, facial paralysis is associated to functional problems such as speech impairment, drooling, problems with eating, drinking or

rinsing the mouth, and closing or sustaining eye closure for moistening and protection.

Facial neuromuscular reeducation is a process of facilitation the return of intended facial movement and expresion patterns, eliminating unwanted patterns.[85] Surface-electromyographic (EMG) biofeefback or mirror feedback serves as adjunts, providing accurate information about facial muscle function and the timing of activation.

All efforts should then be taken to enhance the recovery of facial expression and function in these patients by means of neuromuscular reeducation, or facial reanimation surgery in long-standing paralysis.

4.3. Surgical options for treatment of facial palsy

4.3.1. Static reanimation

Static techniques are currently mainly used for older patients or debilitated individuals with a poor prognosis. They are also indicated for those without nerve or muscle available for dynamic procedures, or as secondary procedures after failed dynamic reanimation, because they not lead to facial movement recovery.

The major advantages of static procedures include immediate restoration of facial symmetry at rest and relief of nasal obstruction caused by alar collapse. They also enhance mastication and speech production through correction of oral commissure ptosis, and cornea protection by restoring eyelid competence. Inadequate corneal protection can cause exposure keratitis, corneal ulceration, and blindness and since most dynamic procedures do not provide adequate reanimation and protection of the eye, static techniques can be important to address this issue.

Static procedures include the following:

- Facial sling suspension with sutures, tendon or autograft (fascia lata strips);
- The use of injectables or implants;
- Rejuvenation techniques – Brow lift, open and endoscopic facelift; rhytidectomy and blepharoplasty;
- Ocular protection – Lower-lid shortening or tightening (Kuhnt-Szymanowski procedure), gold weight implantation, tarsorrhaphy, canthoplasty, and canthopexy;
- Upper and lower-lip shortening or thickening;
- Repositioning of the nasal alar base;
- Facial musculature plication or shortening;
- Nasolabial fold recreation or lifting.

Aggressive and disfiguring tarsorrhaphies for cornea protection should be avoided. The use of eyelid weights continues to be the mainstay in rehabilitation of the paralyzed eye [86]; traditional gold weights were associated to a high complication rate including extrusion and a visible bulk on the upper lid and have been

replaced, with the availability of new materials, by thin profile implants and springs.[87]

Today, a variety of materials can be utilized to create static slings. Materials such as Gore-Tex® (PTFE-polytetrafluoroethylene), AlloDerm®, palmaris longus tendon and fascia lata have all proven successful. Both tendon and fascia lata grafts are easily harvested and provide adequate length and strength; the fascia lata is preferred because multiple strips can be acquired. Gore-Tex® and Alloderm® avoid donor site morbidity; however, because alloplasts are foreign material, a higher risk of infection and extrusion has been reported compared to fascia lata and tendon grafts.

4.3.2. Dynamic reanimation

Static techniques generally are unsatisfactory as a single modality for rehabilitation of the paralyzed face and thus, should not be used as a primary modality of reconstruction.

When facial nerve dysfunction has exceeded 18 months and neurofibrosis/myofibrosis in the distal neuromuscular unit preclude successful reinnervation, or in patients with congenital facial paralysis where neuromuscular units never developed, regional muscle transposition and free-muscle transfer are the 2 best modalities to reanimate the face.

Regional muscle procedures are technically less demanding, provide immediate reanimation and can be appropriate in debilitated patients or who cannot wait for a 12-24 month period of neurotization of a free muscle transfer. However, they are limited by anatomic constraints of size and vectors and results are not consistent.

Examples of regional muscle flaps:

Temporalis muscle

- Improve the symmetry of the commissures and reestablish a voluntary smile.
- The vector of the temporalis muscle resembles that of the zygomaticus major and thus, results in a lateral smile.
- Transposition will not produce spontaneous mimetic function. The patient must consciously contract the transposed muscle in conjunction with the smiling.
- Temporalis muscle transposition can also reanimate the eyelids. However, reanimation of the eye with the temporalis transfer can produce eyelid distortion.
- Most common complications: infection and implant-related complications, failure of attachment, pulling away of the temporalis muscle from the commissure, and overcorrection of the upper lip. The transfer may also generate excessive muscle bulk and a facial deformity, particularly over the zygoma.

An orthodromic temporalis tendon transfer can be performed in a minimally invasive manner, eliminating the facial asymmetry typically produced by the classic technique.[88] A short incision (3-4 cm) is extended into the temporal hair, the muscle is dissected deep to the periosteum, the coronoid is transected along the attached temporalis tendon, and the flap is tunneled to a separate incision, made at the melolabial crease. The tendon is inserted in the perioral region, with overcorrection of the lateral commissure. The temporalis muscle can also be extended with the use of fascia lata or acellular dermis to allow recruitment of the contralateral orbicular oris and lip.[89]

Masseter muscle transposition

- Can be used either alone or in conjunction with the temporalis muscle.
- Unlike the temporalis, the vector of smile of the masseter muscle is in the buccinator-risorius direction, which produces a less natural smile.
- The muscle is quite bulky and can create facial irregularity or surface deformity, such as a bulge at the commissure.

Digastric muscle transposition

- It can be achieved by transposing the tendon of the digastric muscle to the orbicularis of the lower lip.
- The blood supply and nerve to the anterior belly remains intact, and dynamic depression of the lower lip border is achieved.
- Ideal for isolated palsy of the marginal mandibular nerve only, since it can create oral incompetence in patients with more extensive palsy of the lower face.

Microneurovascular muscle transfer is the best strategy for facial reanimation when a patient has long-established facial paralysis (>24 months). Other approaches leave residual asymmetry, an unnatural appearance, and unwanted facial movements while eating.

Free muscle transfer powered by either the ipsilateral trigeminal nerve or a cross-face nerve graft, supplies a new neuromuscular unit to the face and establishes more precise vectors in addition to spontaneous mimetic facial expression. In recent years, microsurgical gracilis muscle transplantation has been the most widely used technique in the dynamic rehabilitation of the smile, but multiple transfers were described.[90-101]

In unilateral cases, the muscle is often powered by a cross-face graft from a buccal or zygomatic branch of the healthy facial nerve, which can provide a spontaneous smile. However, a 9 to 12-month waiting period is necessary for axonal extension through the cable graft before free muscle transfer. An exception to this is the case of bilateral facial paralysis, in which there is no contralateral nerve to be used as a donor. In these cases, it is necessary to use other nerve sources such as the masseteric branch of the trigeminal nerve, hypoglossal or the accessory nerve, which eliminates the need for a regeneration phase and a second operative procedure. These donor nerves can then be used in single-stage facial reanimation by direct muscle neurotization.

The muscles suitable for transfer, and motor donor nerves available for microsurgical facial reanimation are listed as follows:

Muscles suitable for transfer

- Gracilis.
- Serratus.
- Pectoralis minor.
- Latissimus dorsi.
- Platysma.
- Rectus abdominis.
- Rectus femoris.
- Extensor digitorum brevis.
- Abductor hallucis.
- External oblique.

Donor nerves available for neurotization

- Contralateral facial nerve (cross face graft).
- Masseteric branch of trigeminal nerve.
- Hypoglossal nerve.
- Acessory nerve.

Gracilis free-muscle transfer

The gracilis flap is nowadays the most popular muscle and the author's first choice for facial reanimation.

It has also been used as a pedicled or free flap, for anal sphincter reconstruction, vagina, perineum, ischium, groin or lower abdomen wound coverage, for bone, tendon or major vessel coverage in the limb, and for arm and forearm muscles replacement because of major muscle loss and denervated atrophy.

The gracilis muscle[102] is a flat, thin strap muscle located in the medial thigh. It functions to adduct the thigh, and to flex and rotate the leg medially at the knee. The gracilis muscle lies just posterior to the adductor longus, whose tendon of origin is easily palpated. The origin of the gracilis muscle is the body of the pubis and the adjacent ramus of the ischium. Its insertion is at the medial upper surface of the tibia, below the condile. The width of the muscle is about 5–8 cm in adults and 3–4 cm in children (at the level where the pedicle enters the muscle). Its thickness ranges from 2 to 4 cm (average: 3 cm).

The gracilis is a class II vascular pattern muscle (based on Mathes & Nahai classification), having both

dominant and minor vascular pedicles. The dominant nutrient pedicle arise mostly as the terminal branch of the medial circumflex artery, or sometimes directly from the profunda femoris artery. The single dominant pedicle includes a sizeable artery (average 1.5 mm diameter, 6 to 8 cm length) and two venae comitantes (average 2.0 mm diameter). Minor pedicles are usually two in number, upper and distal, branches of the profunda femoris artery and superficial femoral artery, respectively.

The muscle is innervated by a single motor nerve, the anterior branch of the obturator nerve (L2-4), which runs between the adductor longus and brevis and divides into the motor and sensory nerves in the vicinity of the main vascular pedicle. The nerve enters the muscle 1-2 cm superior to the point of entrance of the vascular pedicle. It contains an average of three fascicles: one fascicle group (supplies the posterior portion) and one small single fascicle (supplies the anterior 25 % or more of the muscle).[103]

The gracilis flap can be harvested in different ways:[104-106]

- Short muscle (proximal one-third of thigh) for facial reanimation.
- Whole muscle (proximal and middle third of the thigh with short tendon) for arm and forearm muscles replacement.
- Extended long muscle (whole muscle and whole tendon) for “one muscle with two functions” reconstruction as originally reported by Doi *et al* [107] for complete avulsion of the brachial plexus, using one muscle and along tendon for simultaneous reconstruction of finger extension and elbow flexion, and the spinal accessory nerve for reinnervation. This usually requires two separate incisions: the upper medial thigh incision, and a second incision over the medial knee to expose the gracilis tendon.

In what concerns to the components required, the gracilis muscle can be harvested as a muscle, musculocutaneous, compound or conjoint flap. The medial circumflex femoral artery perforator and gracilis muscle coinjoint flap was reported by Geoffrey Hallock [108] with separate muscle and skin components but is not currently used. A skin paddle can be designed centralized at the vessel pedicle in the proximal one-third as reported by David Chuang et al.[109] The skin paddle can also be designed in a transverse direction (transverse gracilis musculocutaneous flap), determined by the amount of skin in the upper medial thigh centered over the main pedicle of the gracilis muscle, as reported by N John Yousif.[110]

Advantages of gracilis muscle trasfer in facial reanimation:

- Consistent anatomy;
- Long single innervated motor nerve;
- Good size for facial functional restoration;
- Good excursion;
- Reliable overlying skin flap if simultaneous wound coverage is required;
- Allows two teams to work simultaneously;
- No functional deficit;

- Donor site can usually be closed directly;
- Well concealed scar on the medial aspect of the thigh.

Disadvantages of gracilis muscle in facial reanimation:

- Not good in strength; usually it can achieve M2–3 muscle power in upper lip movement;
- Skin island over the distal half of the thigh is no reliable.

Brief summary of the facial reanimation procedure with gracilis transplantation

To harvest the gracilis muscle flap, the patient is placed supine with the lower limb in abduction and knee and hip in flexion. An upper medial thigh incision is made at the anterior border of the gracilis (posterior border of the adductor longus), and once encountered, the neurovascular pedicle is dissected (Fig. 37). It enters the muscle on its deep surface about 8 to 10 cm distal to its origin, at the junction of its upper quarter and lower three-quarters, in the space between the adductor longus and adductor magnus. The vascular pedicle is mobilized to its origin from the profunda vessels by dividing all branches to the overlying adductor longus muscle. The nerve to the gracilis, which arises from the anterior division of the obturator nerve is usually traced up proximally up to 5 to 6 cm, for coaptation to a sural nerve graft or the masseteric branch (Fig. 38). If a long nerve is required, retrograde dissection of the motor nerve up to the bifurcation of the anterior and posterior branch is required, or extra dissection of 10 to 12 cm of the nerve can be harvested with intraneural dissection up to the obturator foramen. This allows to reach the contralateral side of the face without requiring a nerve graft in a single-stage procedure.[111]

The size of the transplantated muscle is individualized to the patient, but usually measurements of the distance from the oral commissure to the tragus are made. If the distance is 9 cm (average functional length required), additional 1cm on each on each end for suture placement should be considered, that is, a length of 11 cm will be required. About 60-75 % of the circumference of the muscle should be harvested to reduce bulk.

In the recipient site, a facial incision is done starting near the upper pole of the ear, courses downward through the preauricular area and follows anteriorly a neck crease parallel and below the mandibular body to about its midpoint. The cheek flap is elevated above the parotid fascia to the anterior border of the masseter muscle, and superiorly onto the body of the masseter and temple. Facial vessels are identified at the level of the anterior border of the masseter muscle, coursing upward toward the body of the mandible.

The flap is positioned and secured to the commissure and the orbicularis oris of the upper and lower lip. Placement of these sutures is critical as they must recreate a normal nasolabial fold; the muscle is sutured with sufficient tension to produce a slight degree of movement at the corner of the mouth and is anchored superiorly to the temporal fascia and preauricular region. Nerve coaptation and vascular anastomosis are then performed (Fig. 39). The cheek flap is repositioned and the incision is closed.

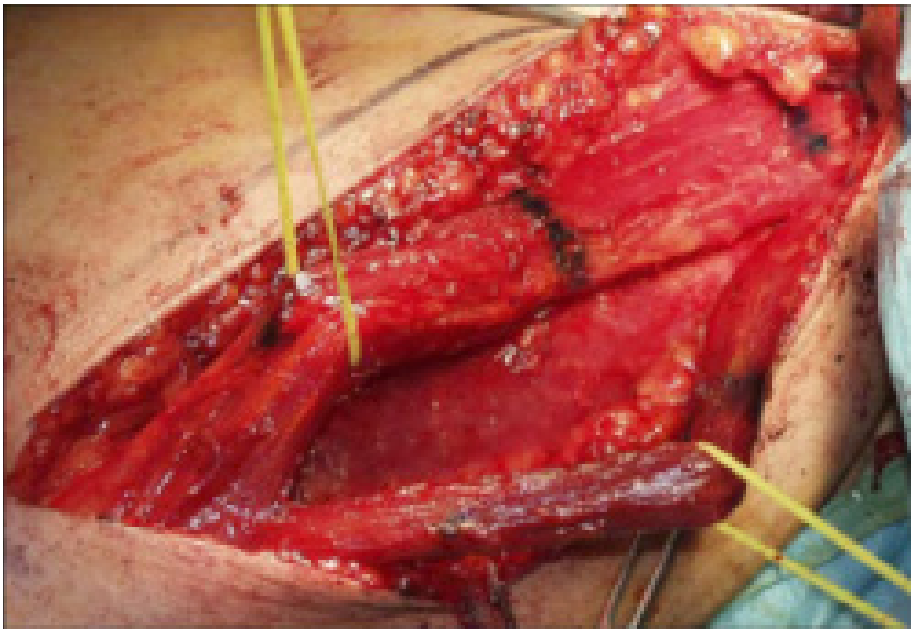


Figure 37. Gracilis muscle isolated.



Figure 38. Gracilis muscle divided with the vascular pedicle and the anterior branch of the obturator nerve sectioned for posterior transfer.

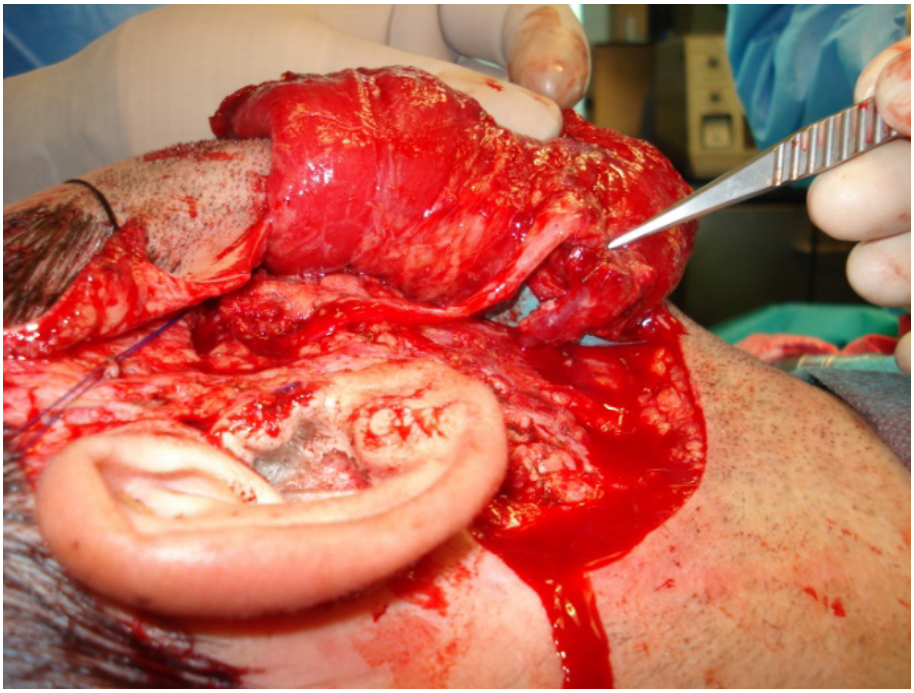


Figure 39. Anastomosis to the facial vessels and nerve coaptation are performed before completing muscle insertion.

Technical refinements in smile reconstruction

Modern goals of facial reanimation include achieving commissure excursion that matches the contralateral nonparalyzed side, avoiding bulk, shortening operative time, decreasing scar length, and improving the reliability of reanimation correcting the lower lip deformity. Inherent to dynamic procedures is the need for secondary revisions to augment functional faculties and aesthetic results (Fig. 40).[112]



Figure 40. A moderate result with free gracils transfer requiring secondary revision: excessive bulk, assymetry at rest and during animation.

To reduce the needs of secondary procedures, technical refinements have been developed by surgeons familiar with facial reanimation.[89,106,113]

To reduce bulk, the soft tissue from the infrazygomatic margin down to the lip can be removed to create a pocket for the muscle placement, improving facial symmetry (Figs. 41 and 42). The buccal fat can be also partially removed to make the surface of the pocket smooth. The gracilis muscle may be trimmed into a mini-trapezoid shape based on the outside face or through an inside face measurement.

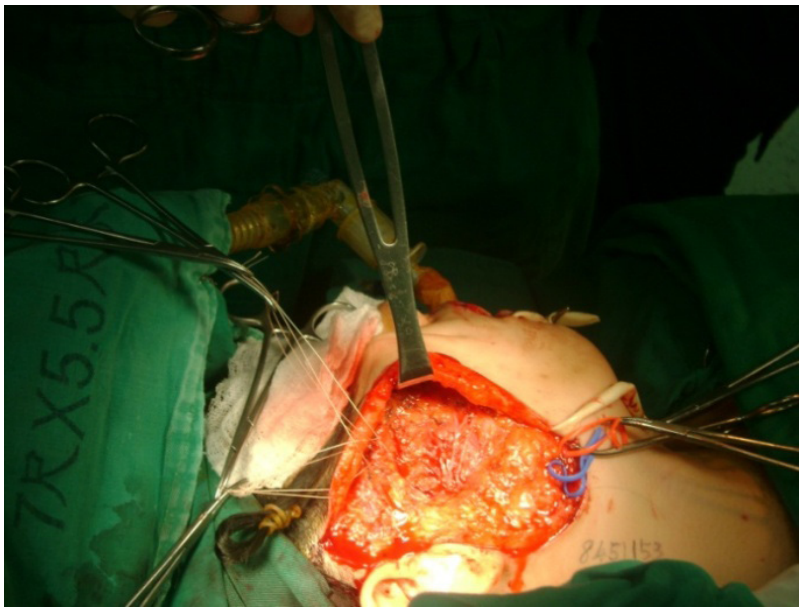


Figure 41. Superficial parotidectomy to reduce bulk after free muscle transfer.

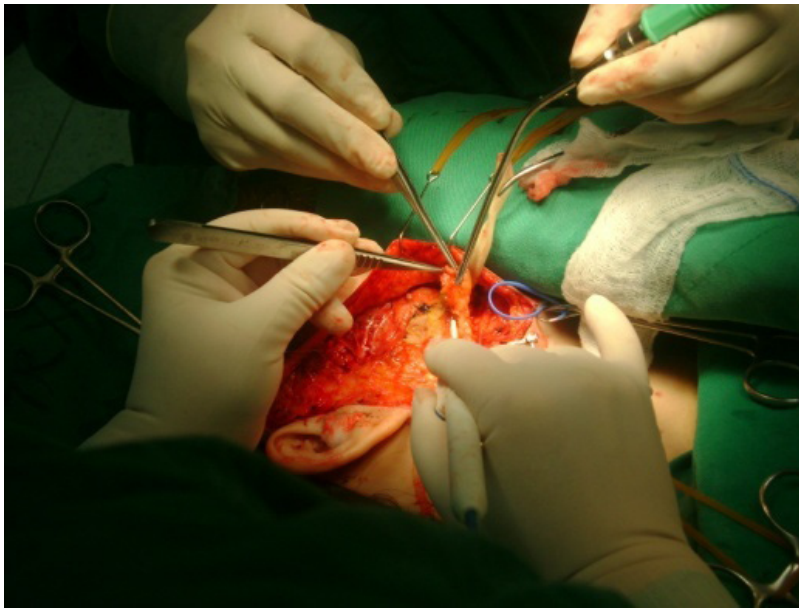


Figure 42. Soft tissue removal to create a pocket for muscle placement (cont.).

David Chuang [106] also advocates placement of the muscle infra-zygomatically, not above the zygomatic body or fixed to the suprazygomatic fascia, to reduce postoperative bulkiness (Fig. 43). The muscle should be placed in retrograde fashion and facial vessels should be used as the first choice as recipient vessels because they have greater length and larger diameter; superficial temporal vessels are more suitable for anterograde placement. The proximal tendinous aponeurosis is anchored to the orbicularis oris, and the distal muscle is fixed to the periosteum of the zygomatic muscle. The distal cut edge can be closed by interrupted locked sutures with 3-0 nylon to avoid bleeding before insertion. If the muscle is anchored to the dermis of the nasolabial fold rather than the lips, weak elevation and poor exposure of teeth during smiling will result.

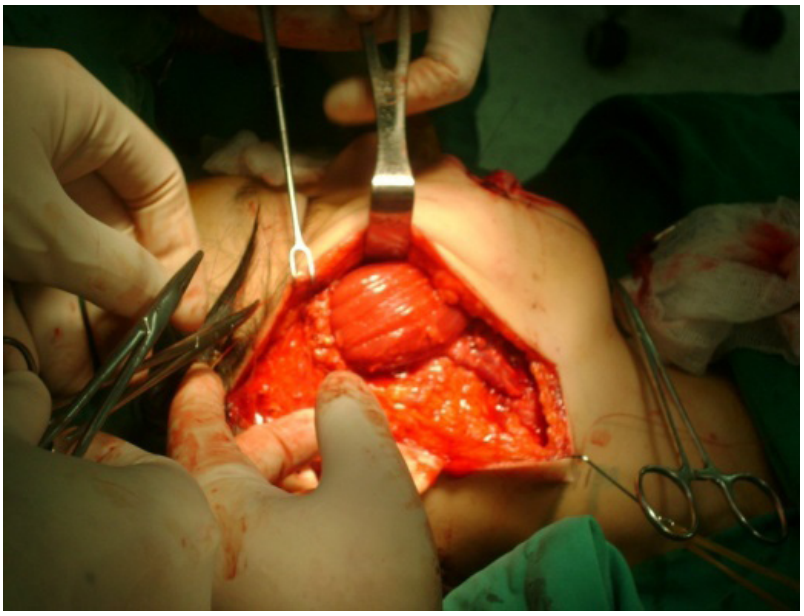


Figure 43. Infrazygomatic attachment of the gracilis muscle

Despite these refinements, upper lip contracture and deformity can remain the most frequent sequelae, and need revision. To avoid this, additional length should be added to the outside or inside face measurement: 3 cm in the outer side (neurovascular side or lateral margin of the gracilis), and 2 cm in the inner side (medial margin- Fig. 44).

Asymmetry of smile can also be caused by lip depressor inactivity due to marginal mandibular paralysis. In the normal resting position, the deformity is not usually noticeable because the lips are closed and the depressor on the normal side is relaxed. With speech, the paralyzed side remains elevated while the nonparalyzed side moves inferiorly and away from the teeth. This deformity is particularly accentuated when the patient attempts a full smile, because there is overpulling of the depressor muscles which aren't countered by the muscles on the paralysed side. Dynamic procedures have been described to correct this [114], including transfer of the anterior belly of the digastric muscle, transfer of the platysma muscle, mini-hypoglossal nerve transfer to the cervicofacial branch of the ipsilateral facial nerve, facial-to-facial nerve transfer, and direct neurotization of the depressor muscles. These approaches are complex and have not become widespread. Selective weakening of muscles on the side that appears overactive can be done medically with Botox®, or

surgically with a myomectomy [115], and by a marginal mandibular neurectomy [116] to produce a permanent result. Resection of the depressor labii inferioris on the normal side through a buccal sulcus incision has been the described as the most effective procedure (Fig. 45).[117] Depressor myomectomy can be preceded by an injection into the normal depressor labii inferioris muscle of local anesthetic or botulinum toxin to give the patient a chance to evaluate what the effectiveness would be of a depressor resection.[118]

However, contralateral lower lip myomectomy can be insufficient to resolve asymmetry of the lower lip when smiling. Placing additional tendon graft from the gracilis muscle belly to the lower lip muscle was suggested by David Chuang, with improved results (Fig. 44). The graft can be harvested from the distal gracilis tendon, palmaris longus or plantar tendon and will augment the lower lip more dynamically and symmetrically during smile. Recently, the same author harvested an additional length (2x1 cm) from the proximal tendinous aponeurosis, avoiding a scar in the knee (distal gracilis tendon harvest), or in the forearm (palmaris longus tendon graft). Alternatively, the plantar tendon can be harvested from a small incision over the medial Achilles tendon.

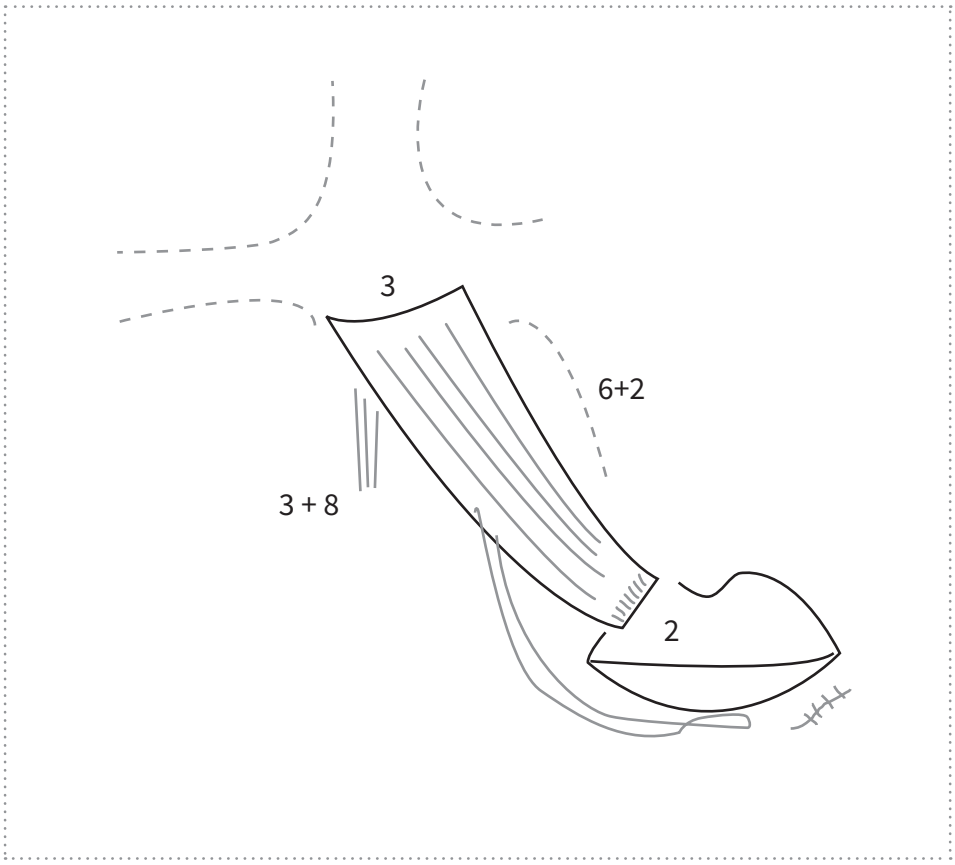


Figure 44. Additional lengh (3 cm in the inner side and 2 cm in the outer side of the gracilis) is added through the outside face measurement. A tendon graft from gracilis muscle belly to the lower lip muscle is placed for augmentation of lower lip pulling, in addition to contralateral lower lip myomectomy.

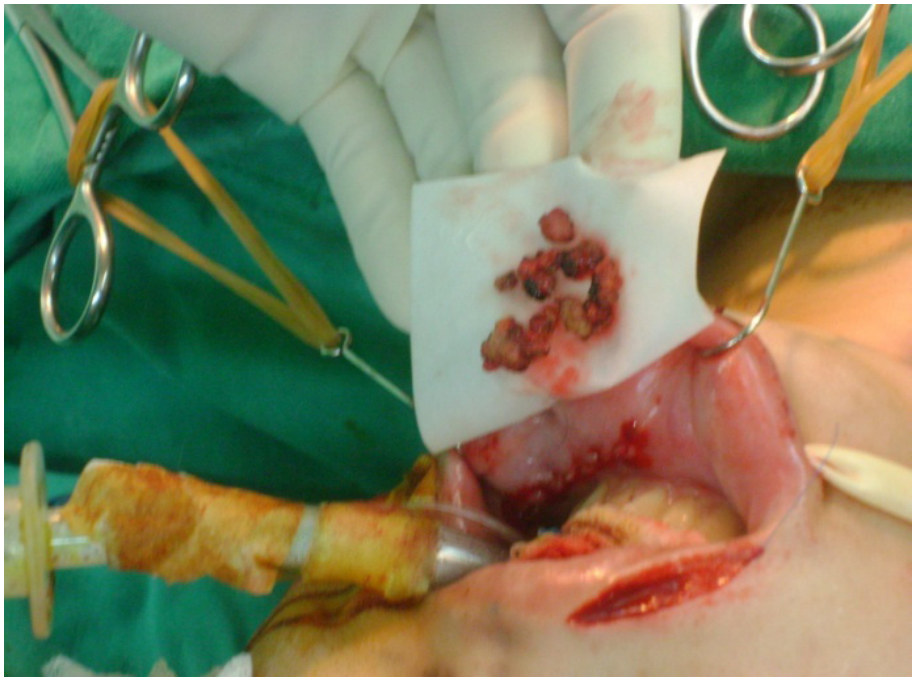


Figure 45. Depressory myomectomy.

4.3.3. Association of static and dynamic procedures

Static procedures are often used after dynamic reanimation failures or to refine a satisfactory result. Static procedures can also be used as adjunct procedures to dynamic techniques to provide immediate benefit.

Dynamic muscle transfer may be performed in conjuction with lateral canthopexy, tarsal strip canthoplasty, brow-lift, face-lift and selected nerve grafting or crossovers.

Recently Biglioli *et al* [119] described the association of deep-planes lift (DPL) with free flap surgery for facial reanimation (latissimus dorsi free flap). DPL consisted of harvesting a flap compound by superficial musculoaponevrotic system antero-inferiorly and parotid fascia postero-superiorly. The flap is lifted and fixed to the periosteum of the zygomatic arch. DPL in association with facial reanimation allows immediate symmetry of the face at rest, in consequence of restoration of the nasolabial fold, correction of soft tissue ptosis and labial philtrum deviation.

Static procedures at the time of facial reanimation provide an immediate result, improve long-term postoperative follow-up outcomes and patient satisfaction.

4.4. MICROSURGICAL FACIAL REANIMATION

4.4.1. Two-stage reanimation

Surgical treatment of unilateral long-standing facial paralysis requires transposition of new musculature to restore function and a microneurovascular free-muscle flap is the procedure of choice.[120–122] The gracilis muscle has been used with success but one of the critical factors of this procedure is the selection of a motor nerve to innervate the transplanted muscle. To achieve synchronous and spontaneous activity, the contralateral facial nerve is used by means of a cross-facial nerve graft when available.[123] This procedure is usually performed in two stages, involving a cross-face nerve graft in the first stage and free-muscle transfer in the second stage. The second stage is done 6 to 12 months later, which means that the main disadvantage of the two-stage procedure is the delay between the stages.

A sural nerve graft is usually harvested and reversed in the face so that the regeneration axons will not dissipate. Sural nerve harvesting was traditionally performed through open approaches. Subsequent modifications permitted harvesting through series of shorter incisions, or nerve “stripping” with 2 small incisions.[124,125] Recently, a endoscopic technique, originally designed for vein harvesting during coronary bypass grafting surgery, was developed with decrease in operative time and involving a single incision.[126,127]

The graft is coaptated to the donor facial nerve branches (a sizeable buccal or zygomatic branch) and is tunneled across the upper lip or under the chin through a small submental incision.[111] The progress of Tinel sign along the course of nerve graft helps to monitorize nerve regeneration, as this sign usually reaches the contralateral side in 4 to 8 months. The cross-face nerve graft is posteriorly coaptated to the gracilis muscle nerve, and microvascular anastomosis are done to the facial vessels.

A tendency toward increase in motor nerve conduction velocity can be seen even 3 years after the sural nerve graft, suggesting that existence of another distal suture is a factor limiting motor nerve conduction velocity recovery, although the nerve graft has the potential to recover over a long period of time.[128] The condition of nerve coaptation or scarring are other influential factors.

Research was focused on addressing the efficiency of axonal transversing of nerve grafts, improving target accuracy in the regenerated nerve, and decreasing detrimental neural oversprouting in branched motor nerves.[129-131] Strategies to deliver nerve growth-promoting factors and inhibitors of inflammation and rejection have been investigated. Direct visualization of traversing axons expressing fluorescent proteins in vivo will help us to understand what causes axonal misrouting (synkinesis).[132]

4.4.2. Single-stage reanimation with crossface nerve grafting

The single-stage procedure involves one nerve coaptation instead of two, as required by the two-stage technique with cross-nerve grafting, and theoretically this can guarantee the passage of a larger number of nerve fibers. A vascularized nerve graft produces also more rapid axonal regeneration and myelination.[133]

In addition, the procedure spare the patients the deficit associated with sural nerve grafting and reduce the time required for recovery.

1. Single-stage reanimation with nerve coaptation to contralateral facial nerve

In this procedure, the donor nerve is kept long and tunnelled across the upper lip to be connected to the contralateral intact facial nerve. The ideal donor muscle should have a reliable vascular and nerve pattern, no functional deficit at the donor site, a similar excursion compared to the normal side of the face and should be distant enough to allow 2 different surgical teams to work simultaneously.[134]

Several muscles have been used:

Extensor digitorium brevis free flap

It was first described for incomplete facial paralysis by Thompson in 1971 [135] as a nonvascularized and denervated muscle transfer, and was dependent on neurotization from the recipient bed. The motor nerve to the muscle was posteriorly included by Thompson and Gustavson [136] and O'Brien *et al* [120], tunnelled to contralateral side and coaptated to the normal facial nerve, but results were inconsistent, failed to produce symmetric movement and this technique was abandoned.

Lastissimus Dorsi Free flap

Harii *et al* [137] first reported the one-stage segmented latissimus dorsi free flap for facial reanimation. Single-stage facial reanimation with a microsurgical latissimus dorsi free flap seems to achieve similar results to those obtained with the classic two-stage reconstruction, reducing morbidity and the time required for recovery.[122] To avoid excessive bulk, the distal and particularly thin portion of the latissimus dorsi should be harvested. However, a long pedicle is necessary (15-16 cm with proximal dissection of the thoracodorsal nerve from the posterior chorda of the brachial plexus and muscle parenchyma), and reinnervation may be incomplete or take a long time. Denervation of a long muscle is another disadvantage.

Rectus femoris free flap

In 1994, Koshima *et al* [87] proposed a single stage procedure with free-muscle transfer using the rectus femoris muscle. Despite the functional problems related to the donor site, and the short vascular pedicle, it has a robust arterial supply and a long femoral nerve (more than 20 cm).

Gracilis Muscle

The gracilis free muscle transfer is actually the preferred option by most surgeons because of its reliable vascular anatomy, similar and parallel excursion to the face, does not result in significant donor-site morbidity, and allows two teams to operate at the same time, without the need to reposition the patient.

In a single-stage procedure, the contralateral gracilis is harvested, and the nerve to the gracilis is traced up the obturator foramen with intraneural dissection, so that 10-12 cm of nerve is obtained. The muscle is reversed when is moved to the face, allowing the neurovascular pedicle to be closer to the nasolabial fold and reach the contralateral side without requiring a nerve graft.

2. Single-stage reanimation with nerve coaptation to masseteric branch

In 1995, Zuker *et al* [138] successfully used the nerve of the masseter muscle, branch of the trigeminal nerve, in the treatment of Moebius syndrome (bilateral palsy), and the results suggested that this technique could be an option for treating unilateral facial paralysis as well. In these patients cranial nerve defects can be isolated or multiple, related to prenatal ischemic events which cause brainstem lesions. 85 % of patients have bilateral facial paralysis. Abducens palsy is also common (68 %), followed by glossopharyngeal, hypoglossal and oculomotor involvement.[139-142] The cranial nerve least likely to be involved in Moebius Syndrome is the accessory nerve, suggesting that this nerve can be available for reanimation procedures. However, it is precluded because it is far from the face and may require a nerve graft to activate the muscle, and its activity is not synergistic with smile.[138] Trochlear and trigeminal (motor) palsy is also unusual.[143]

The masseteric nerve is identified on the undersurface of the masseter muscle, coursing vertically downward at the posterior margin of the muscle. Ocasionally it may be seen coursing obliquely or even transversely. It is a whitish structure, usually 2 mm in diameter, with one large fascicle, although it may have small branches, and often bifurcate or trifurcate. It enters the muscle after 1 cm course. The origin of the masseter muscle is cleared from the zygomatic arch, and the nerve is identified spreading the muscle fibers vertically (Fig. 46). The gracilis motor nerve generally has one small fascicle and one large fascicle, which is accurately approximated to the single fascicle of the motor nerve of the masseter.[138]

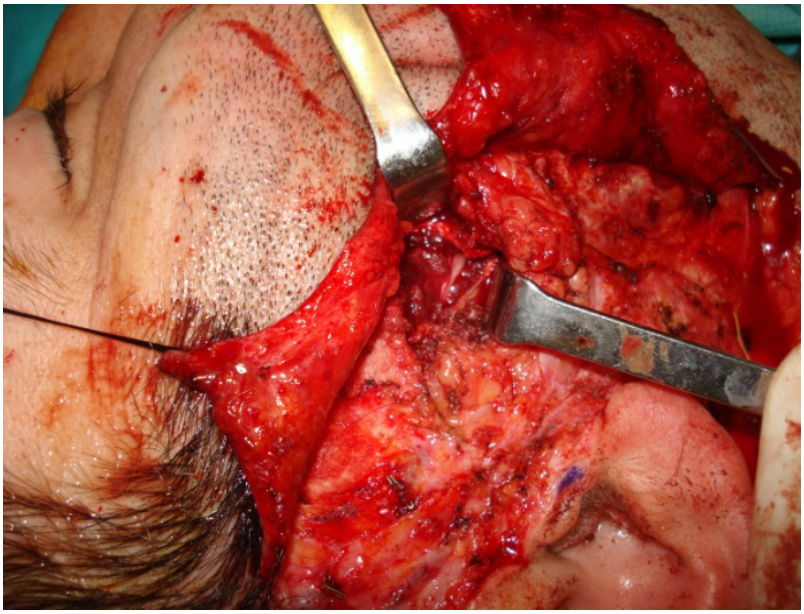


Figure 46. To find the masseteric branch, the origin of the masseter muscle is cleared from the zygomatic arch, and the nerve is identified spreading the muscle fibers vertically. It usually courses vertically downward at the posterior margin of the muscle. Ocasionally it may be seen coursing obliquely or even transversely like this case.

A comparison of commissure excursion following gracilis muscle free flap with a cross-face nerve graft versus the motor nerve to the masseter muscle was performed by Young-Chan Bae *et al* [144], and showed that the extent of movement was greater using the masseteric muscle. Clinical analysis of different techniques [145], also found that one-stage unilateral facial reanimation with gracilis muscle innervated by the motor nerve to the masseter produce more predictable and consistent results and the extent of movement is greater. However, the cross-face nerve graft provides a more spontaneous movement which is crucial in producing a normal appearing smile, but there is usually less movement and it is not suitable for the older patient (reinervation is difficult). Manktelow *et al* [146], speculated that there may be a larger role for the masseter motor nerve in innervation of patients with unilateral paralysis. Although the trigeminal nerve does not include emotional movements, the patients can achieve some degree of automaticity of movements (mastication and smiling). After the muscle transfer, the patient initially learns to simulate a smile by biting, but the majority of patients develop the ability to smile spontaneously and without jaw movement. In a review of 45 muscle transfers innervated by the masseter nerve, Manktelow [146] concluded that a spontaneous smile occurred routinely in 59 percent and ocasionally in 29 percent of patients. Eighty-five percent learned to smile without biting.

Cerebral cortical reorganization is seen in many clinical situations, including stroke, Braille reading, limb amputations, or nerve transfers for treatment of brachial plexus injuries.[89] After biceps reinnervation with transfer of the intercostal nerves to the musculocutaneous nerve, the patient initially has to take a deep breath to flex the elbow, but after 1 to 2 years they can maintain muscle contraction without respiratory movements. Functional magnetic resonance imaging showed that after nerve transfer, the respiratory center controls elbow flexion, but it is replaced by the biceps cortical center after 6 months.

In the face, the centers controlling the jaw musculature and facial movement are in close proximity. A similar process, with the facial nerve taking control by connections to the trigeminal nerve can cause muscle contraction and produce a smile.

Cortical reorganization is possible through activation of preexisting inactive or latent horizontal connections in the cortex, between the cortical centers and/or development of new synaptic connections.[148] It has been speculated that the adaptability of the cerebral cortex deteriorates with increasing age and might not be possible in the Moebius syndrome, in consequence of the nuclear agenesis in the brain stem. However older patients and congenital patients with complete facial palsies can develop a spontaneous smile.[146]

The enormous advantage of the masseter nerve-free tissue transfer technique is that, unlike the cross-facial nerve, the masseter nerve donor produces muscle excursion (in relation to smile and commissure excursion) in normal range with consistent movement (Figs. 47 and 48).



Figure 47. Left side facial palsy secondary to otitis media (preoperatively).



Figure 48. Excellent commissure excursion following free gracilis transfer and nerve coaptation to the masseteric branch.

4.4.3. Simultaneous facial reanimation and reconstruction of soft tissue defects

Simultaneous reconstruction of defective tissues with facial reanimation can be required in cases of facial paralysis due to ablative surgery. In the presence of complex facial paralysis, the deficits include soft-tissue, mucosa, and/or skin defects, requiring not only facial reanimation but also aesthetic correction of intraoral or external face defects. The intraoral defect is usually a consequence of contracture release, or after tumour excision. Defects can also be external and present as a countour deformity in the temporal area, infra-auricular, and retroauricular regions, or in the cheek.[109] However, few options are available for using simultaneously the muscle and the overlying skin paddle. Rectus femoris, rectus abdominis, latissimus dorsi, vastus lateralis and gracilis are the potential flaps that can be considered for simultaneous correction of complex facial paralysis.

A compound flap, consisting of gracilis muscle with its overlying skin paddle separated into two components can be transferred for correction of both problems. The muscle is used for facial reanimation and the skin flap is used for correction of intraoral or extraoral defects. Both components are supplied by the proximal pedicle with its septocutaneous and musculocutaneous perforator skin vessels which are present in the upper third of the gracilis muscle.[149] The dissection between the skin paddle and the gracilis muscle is performed toward the intermuscular septum between the gracilis and the adductor longus muscles and is stopped once the septum is met to preserve the septocutaneous and some musculocutaneous perforators, so its is crucial to preserve the intermuscular septum to achieve a reliable skin paddle.[105] This technique can be done in a classic two-stage procedure: cross-face nerve grafting and posterior transfer of the compound free flap. It can also be applied for immediate reconstruction following tumor ablation and facial muscle/ nerve sacrifice.

The latissimus dorsi muscle can be also elevated as a compound flap of various types incorporating

a skin paddle overlying the latissimus dorsi muscle/serratus anterior musculocutaneous flap or as a latissimus dorsi perforator-based flap with a small muscle cuff. It offers a good option when facial reanimation requires simultaneous soft tissue reconstruction.[150]

4.4.4. Personal experience with microsurgical treatment of facial palsy

The author has experience with both static and dynamic procedures for facial reanimation.

The temporalis flap (and its rarely used counterpart, the masseter muscle transfer) is unique among these choices in that we see the immediate return of dynamic movement. Other techniques such as free tissue transfer, similar to other nerve crossover procedures, requires a period of reinnervation, which invariably requires many months. In our experience with the temporalis flap for reconstrution of midlle third defects of the face, published in the journal **Annals of Plastic Surgery**, there are additional advantages using this flap.[151] No distant surgical site is required and the technique limits the surgical field to the involved hemiface. The temporalis flap is easily harvested and transferred. The area of the face most amenable to this muscle transfer is the perioral region, where the primary goals are to restore symmetry of the smile and improve oral function. Possible complications include infection, seromas, alopecia, trismus, depression of the donor zone, and the protuberance at the level of the zygomatic arch. The rotation arch is a limitative factor, and the temporal muscle does not get defects in the middle line.

The author has preference for gracilis free muscle transplantation. Initially we preferred to use the cross-face nerve graft for reinnervation, although we had previous experience with the motor nerve of masseter muscle in a case of bilateral palsy (Moebius Syndrome). We also found it interesting as a salvage procedure in cases of an unreliable cross-nerve match due to technical problems (insufficient length, fibrosis).[152] This was published in the **Microsurgery** journal. The author actually prefers to use the masseteric branch, because produces more predictable and consistent results, and the extent of oral commissure movement is greater. Time of onset of contraction (reinnervation) is approximately 3 months without difficulty in coordinating flap function with contralateral mimetic musculature; a full contraction with symmetrical smile and teeth showing is generally seen (Figs. 49-53).



Figure 49. Established facial paralysis as sequelae of surgery for eighth nerve neuroma (*Left:* at rest; *Right*: during smiling).

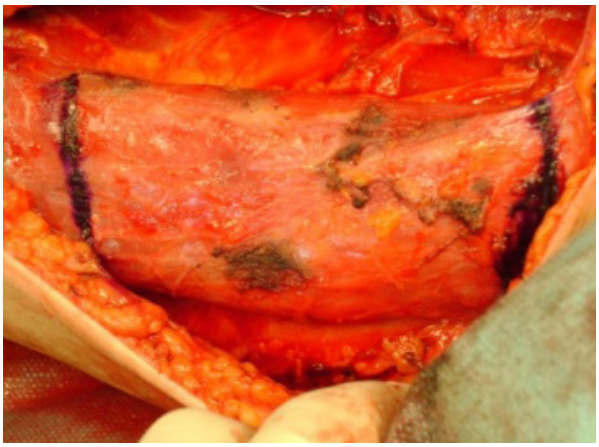


Figure 50. Identification of the gracilis muscle.

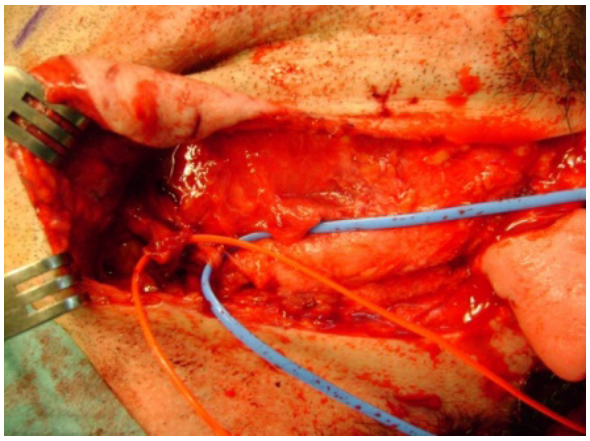


Figure 51. Dissection of the flap.

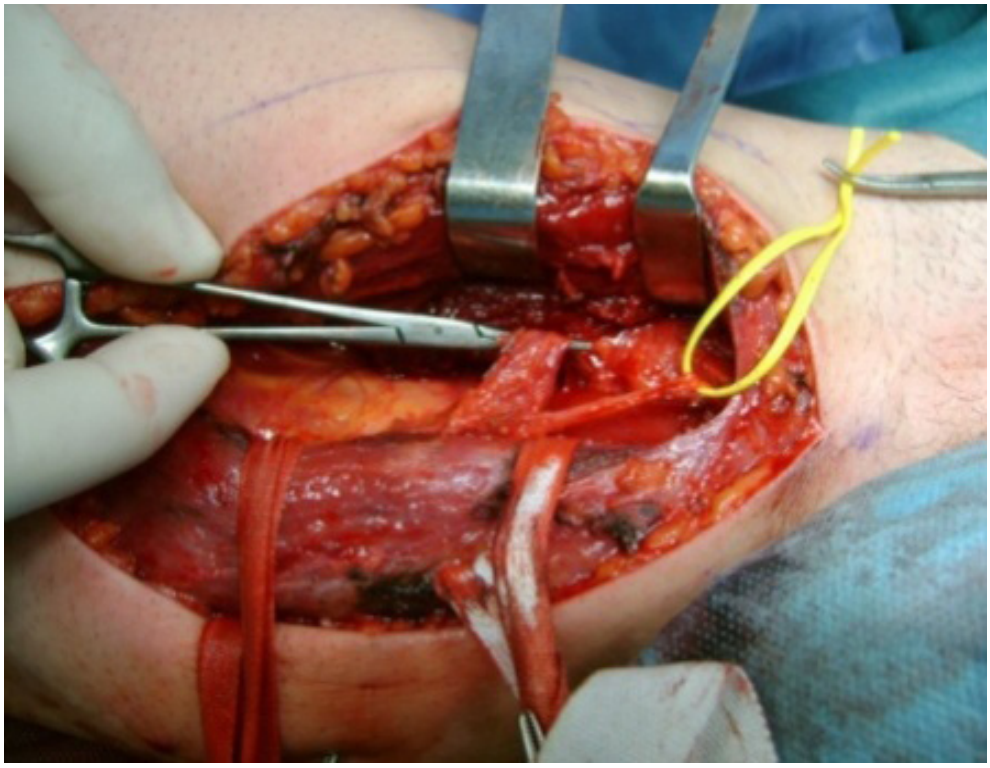


Figure 52. Dissection of the neurovascular pedicle.



Figure 53. Symmetry with good tone at rest and full contraction with symmetrical smile (*Left:* at rest; *Right*: during smiling).

Effective rehabilitation after muscle transfer requires training and physical therapy to achieve optimal function. The concept of neural plasticity supports that there is central plasticity and reorganization. After a certain training period, patients with gracilis transfers driven by the masseteric branch of the trigeminal nerve into the face are able to achieve movement without initiating a clenching of teeth.

This rehabilitation process may be more problematic in blind patients. Patients visually-impaired suffer from reduced social interaction in part due to reliance upon others to initiate social contact and they have smaller social circles usually with a corresponding reduction in self-esteem or well-being. The isolation and emotional pain that a blind and visually impaired person experience in association with facial paralysis can be distressing and constrictive in regular public interaction, and may also elevate the risk for depression.

We described for the first time in the literature (**Journal of Reconstructive Microsurgery**) the treatment of facial paralysis in a blind patient.[153] The facial reanimation program combined microsurgical facial reanimation, acoustic, and sensorial rehabilitation. This patient, a 37 year old woman with established facial paralysis as sequelae of surgery for eighth nerve neuroma was referred to our department (Fig. 54). She had undergone right suboccipital craniectomy, removal of acoustic neuroma in 2005 and radiosurgery as an adjunct treatment, which was complicated with bilateral blindness secondary to optic atrophy, paralysis of the right oculomotor nerve, right facial palsy and hydrocephalus managed with ventriculoperitoneal shunt. A year after removal of the tumor, she was submitted to a cross-face with the sural nerve, retaining obvious asymmetry at rest (grade V of the House-Brackmann scale), without frontal function, no function of the orbicularis oculi and minimal excursion of the oral commissure. In 2012, she underwent facial reanimation with gracilis free transfer (Figs. 55 and 56); microneurovascular anastomosis were performed to the facial vessels, and to the motor nerve of masseter muscle. Time of contraction onset (reinnervation) was 3 months.

The patient then initiated a rehabilitation program that was designed to reinforce the desired facial movement patterns. The patient was taught how to exercise the transferred gracilis muscle and the first stage of exercises included individualized muscle contractions of the contralateral part of the face only, then with the transferred gracilis contracting. The program consisted of 5 to 20 repetitions of 3 to 5 exercises to be done three times daily. Her mother was used for acoustic feedback during exercise, helping to coordinate facial movements for the construction of different facial expressions. Further, other tasks were added, such as sucking, and saying words containing “f”, “p” or “b”, which facilitates lip movements. She was also educated to evaluate the degree of muscle contraction through the tactile sense, that is, through a sensory feedback. The patient manifested interest in her reeducation process, relearning facial movements and expressions.

The patient was further evaluated with a novel quantitative method, which accurately assesses the fundamental aspects of the facial excursion (see next section). Good vertical excursion of the commissure marks was noted as well as symmetry of the commissures at rest. On the functional aspect, drooling and fluid loss with drinking are eliminated. Speech was significantly improved. After successful facial reanimation she could develop social skills to start and carry on conversations, to play games effectively, and to join in and feel part of a group. This patient lives in an institution of support/solidarity. The difficult relationship with the children, who do not understand the nature of such deformity, also comes out strongly enhanced, and was one of the great achievements reported by the patient.

Microsurgical muscle-free transplantation in association with acoustic and sensorial feedback rehabilitation achieves good results in blind patients, improving their levels of self- esteem and expectations, and allowing greater social interaction by means of the ability to smile.



Figure 54. Established right-side facial paralysis in a blind patient as sequelae of surgery for eighth nerve neurinoma and radiotherapy. Preoperatively (6 years from the onset of paralysis): *Left*- at rest; *Rigth*- during smiling.

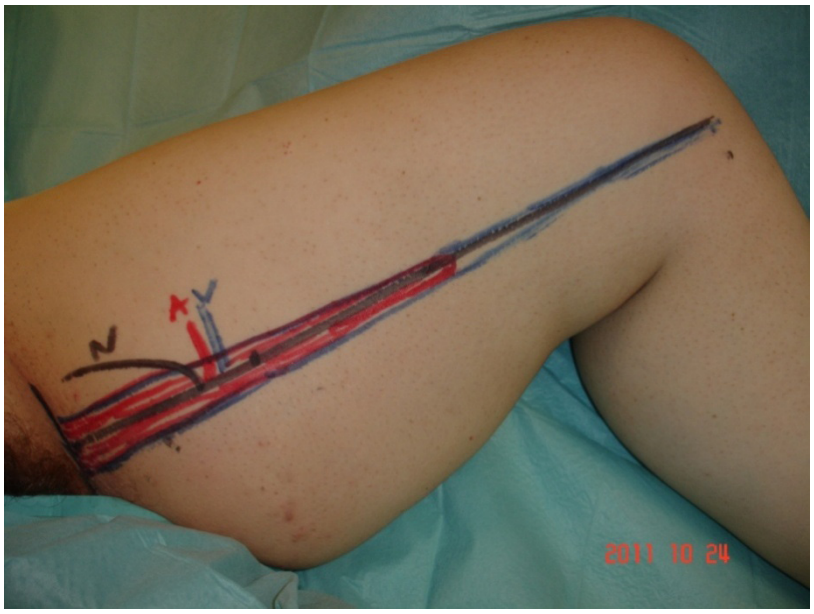


Figure 55. Design of the flap.

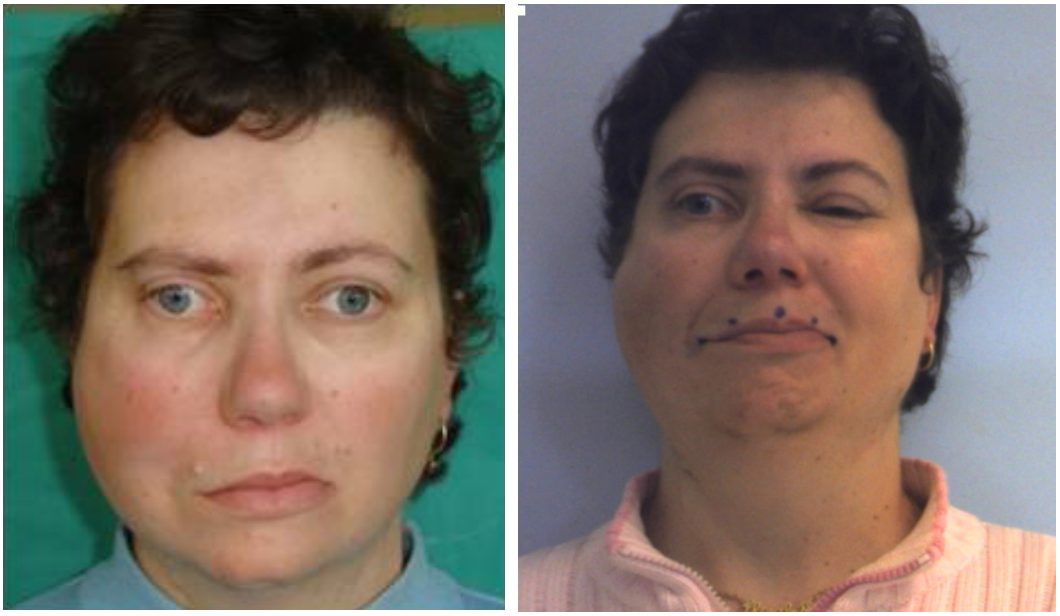


Figure 56. Postoperatively (6 months); *Left*- at rest; *Right*- during smiling.

4.5. A facegram for spatial-temporal analysis of facial excursion

4.5.1. The concept of facegram

Unilateral facial paralysis results in the inability to contract the mimetic musculature and, in long-term cases, to coarse distortion of facial morphology, especially during activation of the contralateral musculature and when the effects of gravity become apparent.

The goal of facial reanimation is restoration of both a symmetric face at rest and a spontaneous smile. There are several techniques available for facial reanimation. These includes reinnervation techniques, muscle transfers, and static procedures.

An essential element to support and, more importantly, assess the reanimation techniques is the precise measurement of static and dynamic facial features. There are simple methods to assess oral excursion, but lack some objectivity and standardization.[154] Quantitative methods have been developed but require equipment that usually includes video cameras, a complex calibration device, a computer customized software, IR lightings to illuminate the face and minimise the effect of varying lighting conditions.[155,156] Although three-dimensional tracking can provide enhanced information, analysis is time-consuming, expensive, requires complex equipment such as special lighting, the use of reflective markers a dense array of cameras, and the personal operating the system has to have a thorough education and experience, which may reduce the utility of these methods for clinical assessment.

Clinicians do not have a simple tool providing an objective and quantitative analysis of facial movement in order to compare medical, surgical and physical therapy. Such a tool necessarily involves the acquisition of two-dimensional (2D) or three-dimensional (3D) recordings of patients while carring out a standard set of facial expressions, and the processing of these spatial-temporal data in order to facilitate analysis and interpretation.

A new method for precise quantification of the characteristics of facial excursion pre-and postoperative is presented here, with emphasis on smile analysis. This method focuses on the assessment of the trajectories of specific anatomical landmarks during rest and facial expressions. Measures based on the trajectories (position over time) of the anatomical landmarks cannot only evaluate abnormalities of spatial nature / topological, but can also assess temporal characteristics.

4.5.2. Material and methods

A group of 20 normal patients (without paralysis), 10 men aged between 14 and 50 years and 10 women aged between 18 and 57 years, was used as control group to set up the canonical trajectories for specific anatomical landmarks.

This method was applied and tested in different clinical situations: one normal subject, 3 patients with facial palsy and one patient with severe burns sequels (Table 4).

Table 4. The Facegram was applied and tested in different clinical situations

PATIENTS/ SUBJECTS	SEX	AGE	ETIOLOGY	SIDE	SURGERY PERFORMED
1*	Female	18	-	-	-
2	Female	71	Facial palsy (Idiopathic)	Left	Fascia Lata Suspension (S)
3	Female	37	Facial palsy (Acoustic neuroma)	Right	Gracilis transplantation(D)
8	Male	33	Facial palsy (Cholesteatoma)	Right	Gracilis transplantation(D)
5	Male	22	Burns (55 % TBSA)	Bilateral	-

(*: Standard subject; D: Dynamic procedure; S: Static procedure; TBSA:Total burn surface area)

Video tracking of anatomical landmarks and the construction of facegrams

In order to reliably capture the dynamics of the smile movements, we developed specialized software capable of simultaneously tracking the position over time of a number of anatomical points. This is accomplished using video recordings of the subject while controlling the process of smiling. Detailed quantifications of the spatial-temporal properties of the muscular dynamics are presented using our newly proposed facegrams. The programming environment MATLAB (R2011a, MathWorks, Natick, Massachusetts, U.S.A.) was used to develop the tracking software, and for computing the facegrams.

Video recordings

In the video recording sessions, the subject is placed with his/her face centered in the camera frame, and with the camera's optical axis perpendicular to the face plane. Using a color pen, a number of small dots are marked on specific anatomical landmarks. In this work five points were marked: commissures, mid-points and Cupid (Figs. 57 and 58).

The lighting conditions and the pen color are chosen in order to provide a high contrast between the markers and the subject's skin. During the video recording, the subject is asked to smile, while keeping his/her head still, in a series of 5 stages: rest, contract, hold, relax, rest. This is done in a total period of roughly 10 seconds, with the rest and hold stages lasting 3 seconds each. It is important to notice that the speeds of the contraction and relaxation stages are not affected by the observer: once the recording session starts, only two voice commands are given - "contract" and "relax". During the recording session, a picture of the subject holding horizontally a ruler in front on his mouth is taken. This picture is later used by the tracking software for space calibration purposes.

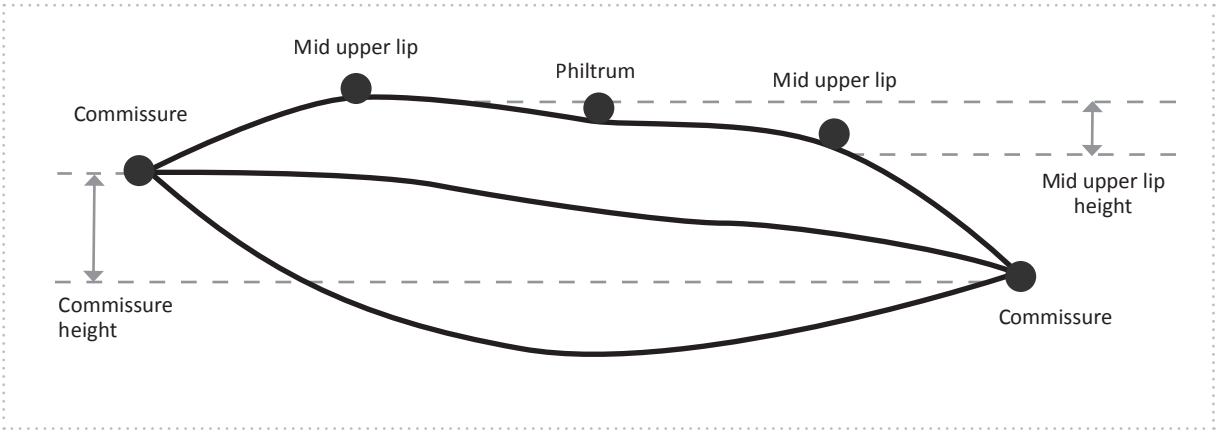


Figure 57. The selected points (commissures, philtrum, mid upper lip), are placed symmetrical on the vermilion margin; measurements of commissure height and mid upper lip height diferences are also performed.

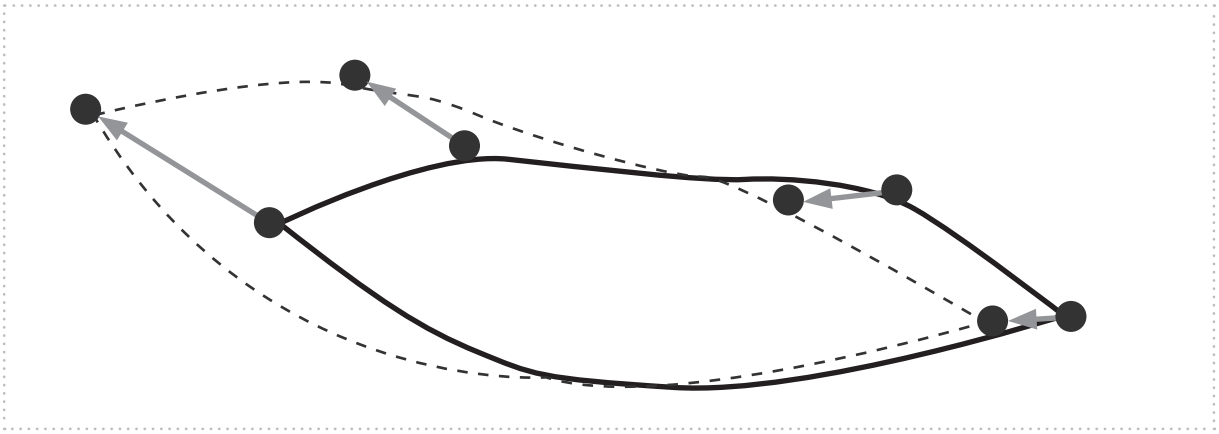


Figure 58. Movement of the commissures and mid upper lip in a patient with facial paralysis.

Tracking software

Our tracking software is used to convert the video recordings of the subject, acquired under the above mentioned constraints, into lists of (x,y,t) points capturing the movement of the markers associated with the subject's smiling dynamics. The movement is captured in 2D, in the projection of the face's surface into the camera's place. Even using standard, non-expensive HD webcams (50 USD), it is possible to have high resolution in both time (close to 0.03 seconds, from 30 frames-per-second) and space (close to 0.25 mm). The facial landmark points can have a diameter of 1-2 mm and the spatial precision still be sub-millimetre. This is possible because the tracking algorithm locks on the area of the coloured spot and tracks its centroid. The spatial resolution is therefore largely determined by the resolution of the camera (px/mm) and by the contrast between marker colour and skin colour, not by the area of the spot itself: in high contrast conditions the algorithm is capable of clearly identifying the boundary of the spot/marker and obtaining precise measurements bellow 1 mm.

The tracking system starts by first presenting the initial frame of the video sequence. Here the user is asked to use the mouse to: 1) draw a line setting the face's vertical axis of symmetry and 2) point and click on

the colored dots marking the anatomical landmarks. The software provides a graphical user interface (GUI) to assist the user in this task. The GUI provides tools such as zooming, and the line axis, together with the marker points, can be edited and visualized over the subject's face. The facial vertical axis is usually defined as the line connecting the midglabellar area to the menton. Once line axis and points have been set, an automatic tracking algorithm analyses the video stream, frame-by-frame, extracting the positions of each marker as a function of time. The algorithm uses the "block matching" strategy to track the position of each marker in the sequence of frames. The positions in pixel-space are converted to real-space (in millimeters) using the calibration picture. The scaling factor px/mm is obtained from the length of several centimetres in the ruler. It is therefore possible to estimate the scaling factor with an error which allows sub-millimetre resolution. Nevertheless we impose a lower bound for this error and have set the spatial error at 0.25 mm. The positions also suffer a coordinate transformation where the new axes are the face's vertical axis and its perpendicular axis which passes through the central marker (Cupid). This new coordinate system provides immediate evidence for possible asymmetries in the mouth anatomical landmarks with respect to the facial vertical axis.

Facegram

A precise assessment of the muscular dynamics associated with the control of smiling requires inevitably analysis in both spatial and temporal domains; the complexity and dynamical nature of the smile control simply cannot be captured using static examination. In order to deal with the challenge of quantifying spatial-temporal properties of smile control, we developed novel strategies to present/visualize the dynamics data. Using the positions time-series of all anatomical markers we compute several traces, each emphasizing different aspects of dynamics. Collectively we call these traces *facegram*, as they are an invaluable tool for assessing quantitatively, the normal and pathological behavior on the dynamics of the system. The main element in the facegram is the plot, in scale, of the paths followed by each anatomical landmark. In every pathway, 6 points mark important times: 1) start of recording (T1); 2) start of contraction (T2); 3) end of contraction (T3); 4) start of relaxation (T4); 5) end of relaxation (T5); and 6) end of recording (T6). A large amount of quantitative information can be extracted directly from these plots such as symmetry assessment in the contraction and relaxation trajectories. The fact that this plot is on scale allows also direct measurements such as maximal extensions. The facegram also contains other elements which help to highlight more subtle properties of the dynamics:

- The horizontal (and the vertical) displacement of each point as a function of time – these traces provide information regarding the temporal coordination/consistency between each anatomical point, and are useful in some forms of paralysis where horizontal or vertical components of the movement are affected;
- The differential horizontal (and the vertical) displacement of each point as a function of time – these traces correspond to the difference between the position of (supposedly) symmetrical anatomical points, and are useful for detecting asymmetries on both spatial and temporal domains.

The facegram implies a projection from a 3-Dimensional object (face) to a 2-Dimensional space (camera plane). The anatomical landmark locations which can be more affected by this projection are the

commissures' positions, as a result of the face curvature. In order to estimate the error associated with this projection the following procedure was followed. In a group of 5 individuals, the distance between Cupid and left/right commissure was measured at the maximum extension of a smiling expression, using a flexible ruler placed over the face curvature. These maximal extensions were compared with the equivalent measurements on the facegram (therefore measured in 2D). The difference between the maximal extensions in 3D and in 2D was 0.7 ± 0.5 mm (STD); this value can be used as the projection error and it should be taken into account that is was calculated for the worst-case scenario.

RESULTS

FACEGRAM ANALYSIS

1. Standard subject

A normal Facegram should reveal a symmetrical movement of the face. The vertical axis of the face is assessed drawing a line from midglabellar area to the menton. This line should bisect nasal ridge, upper lip, Cupid's bow and central two incisors if there is no deviation (Fig. 59). Coordination between the movement of the five standard landmarks is seen in these subjects and relaxation movement overlaps well with contraction movement (Fig. 60). Temporal symmetry is also observed. Note that even a 0.5 mm of horizontal displacement (x) can be revealed in a facegram analysis of a normal subject with an essentially symmetrical smile. Vertical movement (y) shows good amplitude and is consistent through the time (seconds). Commissure movement length was close to 2.5 mm. These lengths may be determined by examining on the curve at points corresponding to a rest situation and maximal contraction and calculating the differences between the coordinates x, y (Fig. 61). Commissure points can also show small differences in vertical assessement.

Even smiles that at the macro-scale are essentially symmetrical, show at the micro-scale allowed by this method small asymmetries and a large degree of variability. The precise quantifications of the landmarks trajectories provided by this method allow the establishment of spatial and temporal boundaries for the magnitude of the asymmetries that define a "symmetrical" smile in the macro-scale.

The software also allows the amplification of each landmark separately and with great detail (Fig. 62). Start and end points (T1 and T6; rest position) can also show a difference in both horizontal (x) and vertical (y) assessement (0.6 mm in this facegram).

A normal excursion should be recorded in a smooth line through the time.



Figure 59. Facegram analysis in a normal subject.

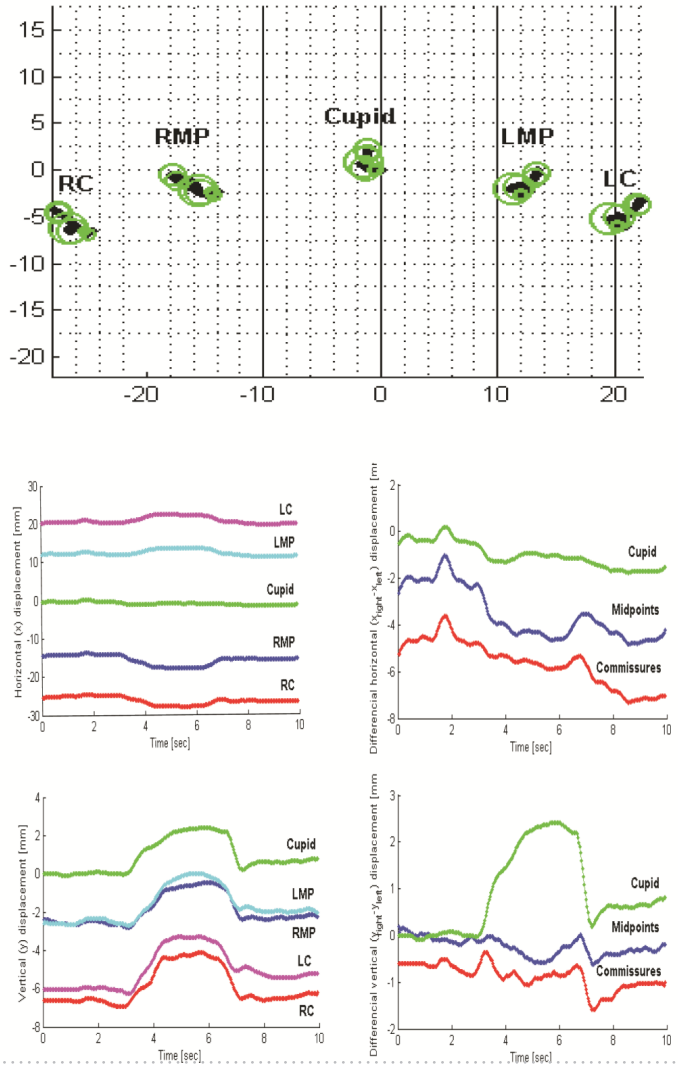


Figure 60. Coordination between the movement of five points; relaxation movement overlaps well with contraction movement. Note that even a 0.6 mm of horizontal displacement can be revealed in a facegram analysis of a normal subject with a symmetrical smile.
RC: right commissure; LC: left commissure; RMP: right midpoint; LMP: left midpoint

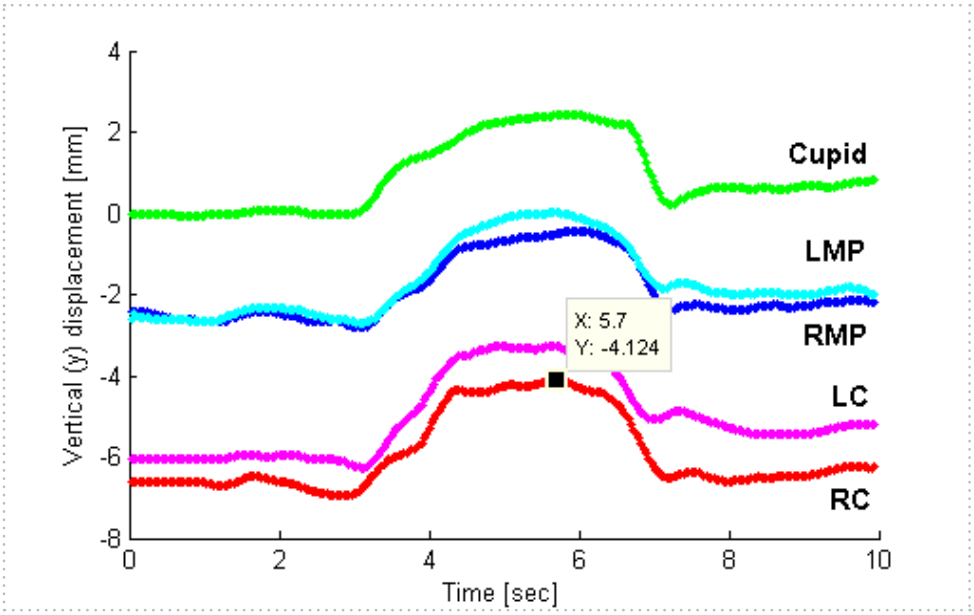


Figure 61. Differences in facial excursion may be determined by examining on the curve at points corresponding to a rest situation and maximal contraction and calculating the differences between the coordinates (x, y)

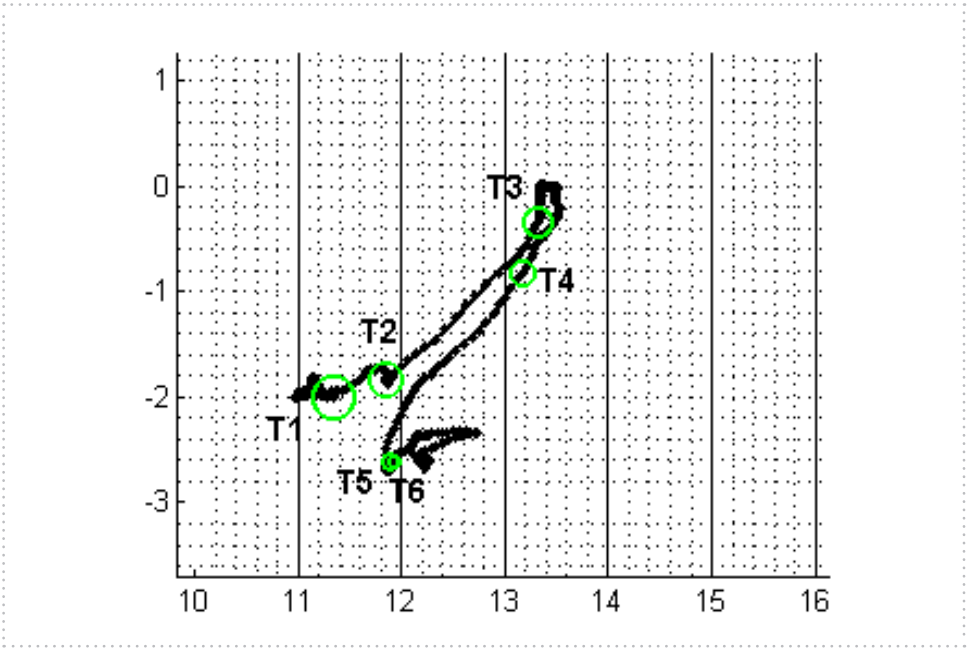


Figure 62. In every pathway, 6 points mark important times: T1- start of recording; T2- start of contraction; T3- end of contraction; T4- start of relaxation; T5- end of relaxation; and T6- end of recording.

2. Static reanimation (fascia lata suspension)

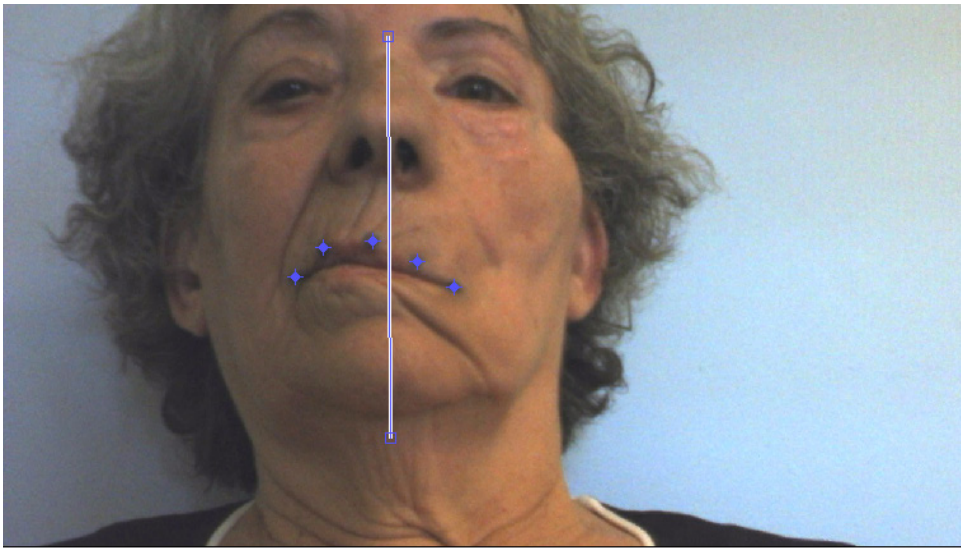


Figure 63. Facegram analysis in a patient submitted to static reanimation (left palsy).

In this patient we can observe a Cupid deviation to the right in relation to the vertical axis (Figs. 63 and 64) and significant horizontal and vertical asymmetry between the points at rest. Minimum movement of the midpoints and commissures is detected. Unbalanced distension, almost unilateral (with maximal extension above the normal) or exaggerated compensatory contralateral contraction is noted. We can conclude that this result is very unsatisfactory and a dynamic procedure should be proposed.

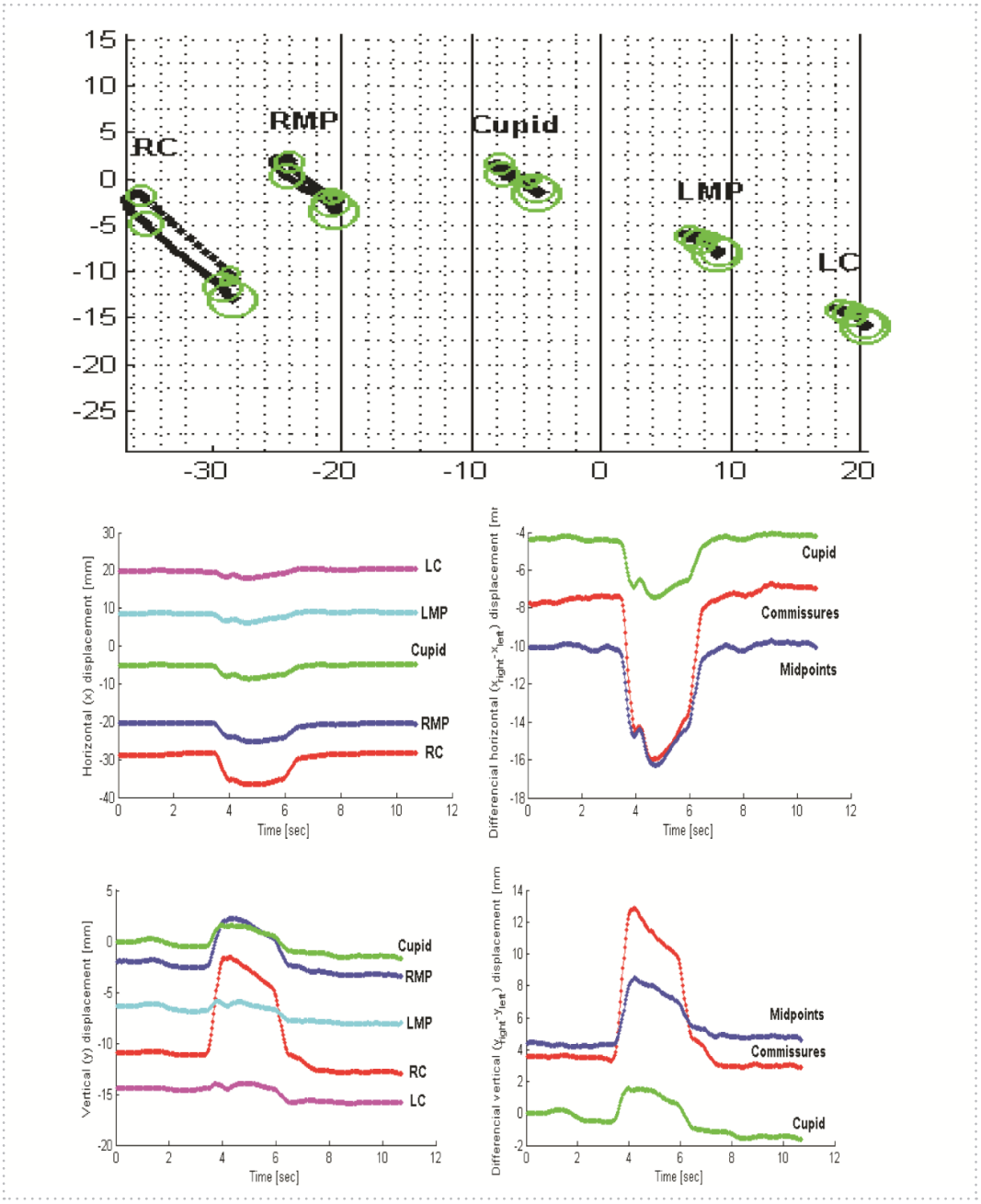


Figure 64. Unbalanced distension, almost unilateral (with maximal extension above the normal).

3. Dynamic reanimation (gracilis transplantation)



Figure 65. Facegram analysis in a patient submitted to dynamic reanimation - gracilis muscle free transplantation (right palsy).

The movement is almost exclusively horizontal (Figs. 65 and 66). There is symmetry of midpoints at rest, but the right commissure remains in a lower position than the contralateral. The amplitude of excursion is greater at the right side and predominantly horizontal. This probably reflects the patient's concern on initiating the gracilis muscle contraction (cerebral adaptation) and some incoordination.

This patient will need a revision of the tension and commissure insertion of the flap.

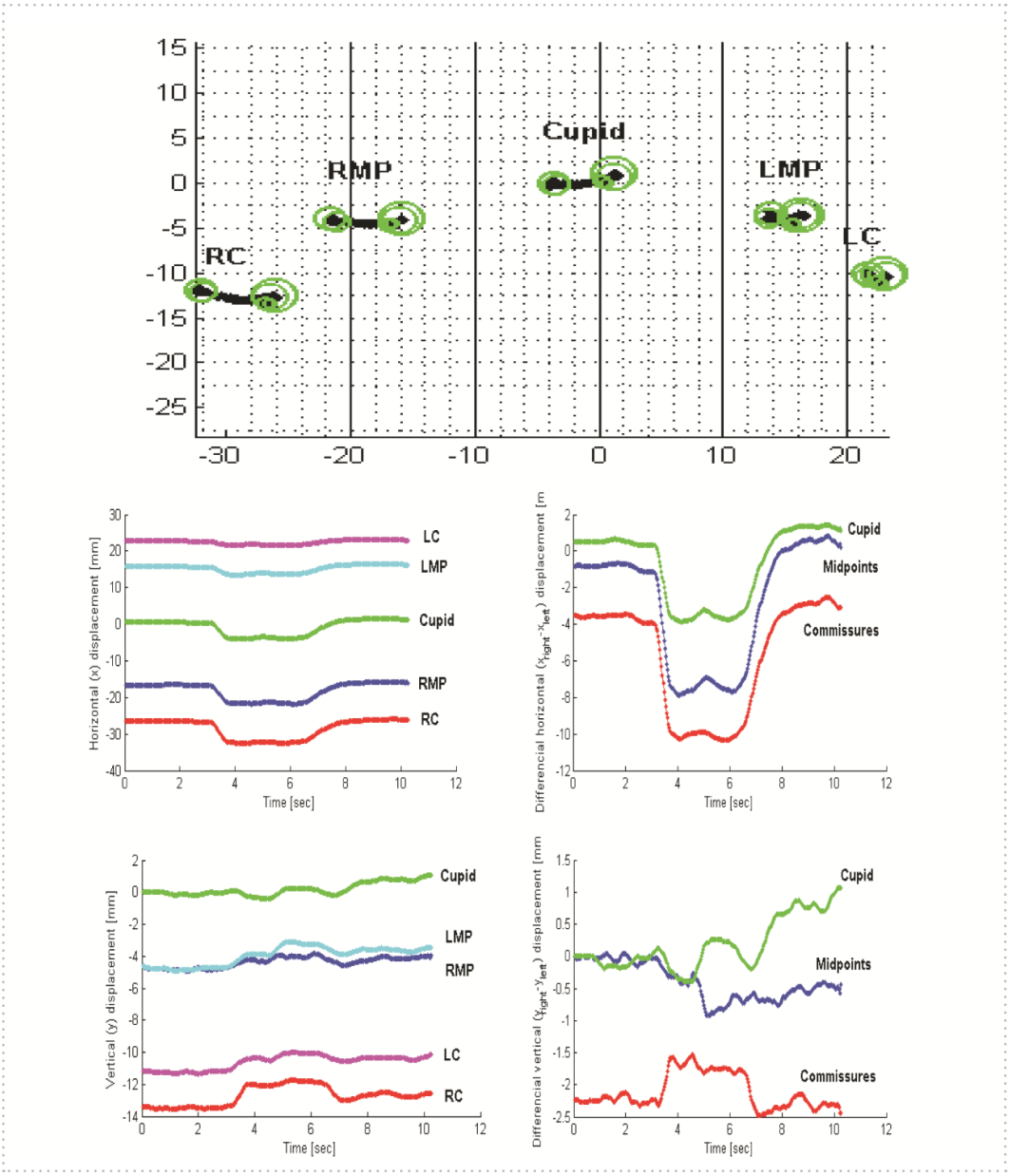


Figure 66. The movement is almost exclusively horizontal.

4. Blind patient submitted to dynamic reanimation (gracilis transplantation)

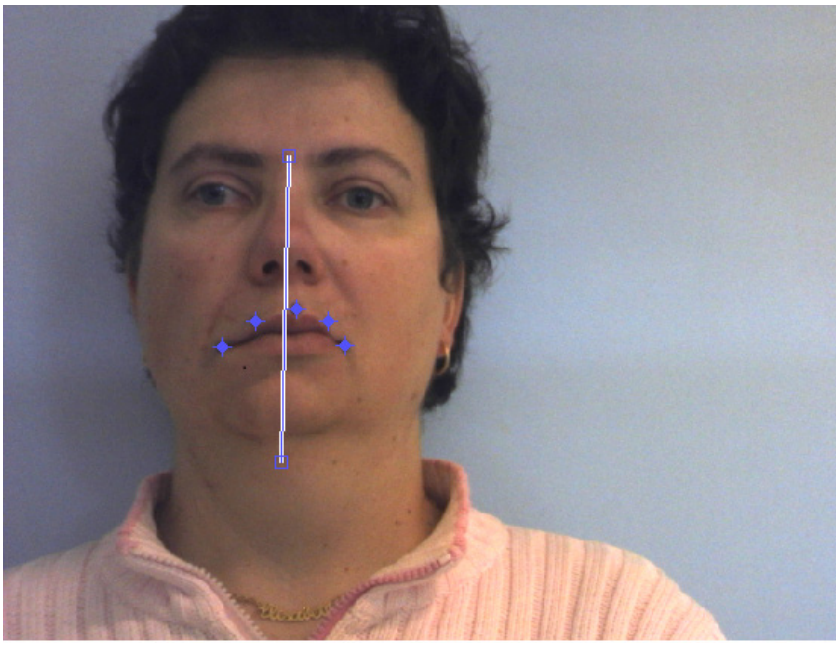


Figure 67. Facegram analysis in a blind patient submitted to dynamic reanimation - gracilis muscle free transplantation (right palsy).

Cupid mark does not exactly intersect the vertical axis of the face, despite improved symmetry of the face at rest after surgery (Figs. 67 and 68).

Some imbalance between contraction and relaxation is observed: the movement is not very consistent. Horizontal movements are abrupt at the right side and less coordinated. However, good vertical excursion of commissure marks is noted (4.8 mm). There is symmetry of the commissures at rest.

This should be considered as a good result in a blind patient after facial reanimation associated to acoustic and sensorial feedback rehabilitation.

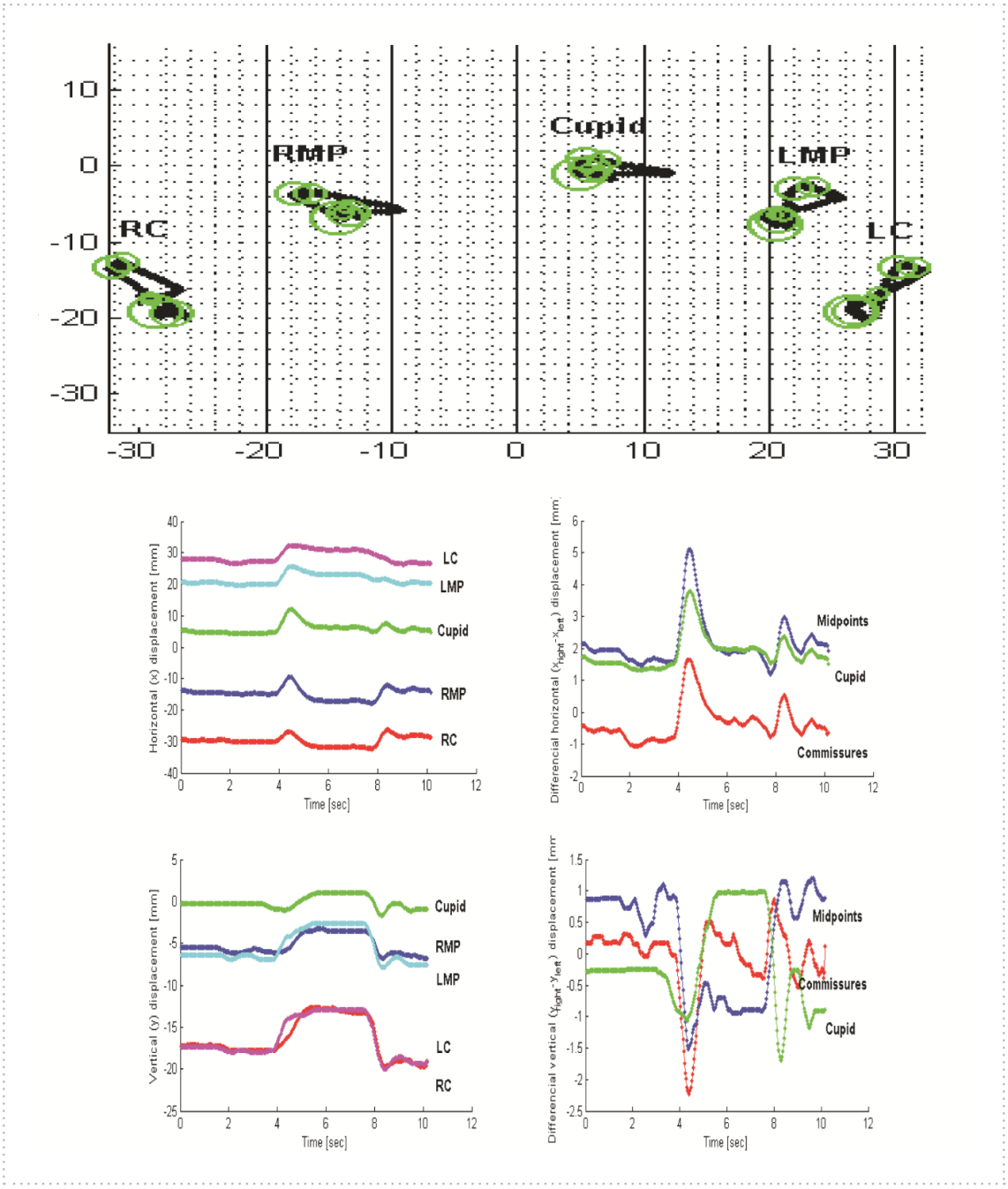


Figure 68. Some imbalance between contraction and relaxation. However, good vertical excursion of commisure marks is noted (4.8 mm). There is symmetry of the commissures at rest.

5. Burn patient candidate to facial transplantation

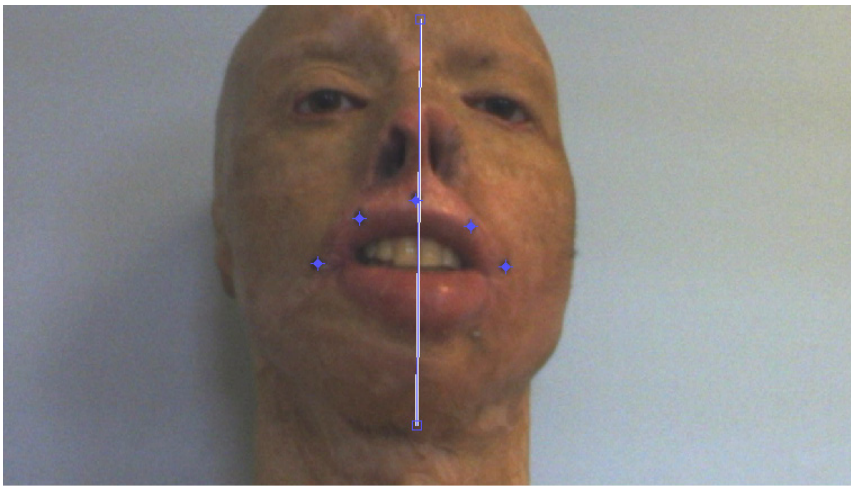


Figure 69. Facegram analysis in a burn patient candidate to facial transplantation.

Facegram shows symmetry/balance and temporal consistency (Figs. 69 and 70). Hold period is not properly maintained (there is a progressive loss of extension). The extent of horizontal movement is very similar to the normal individual, with consistent and coordinated movements over time. Vertical movement appears to be superior in relation to horizontal movement. The extension of the commissures is clearly superior to that of midpoints or Cupid's bow compared to a normal individual, which may be explained by cicatricial retraction of the central part of patient's lips. Despite the reduction in range of motion over time this patient has acceptable muscle function and innervation, even in the presence of severe scarring, and facial movement approaches the normal compared to a standard population. After facial transplantation, it will be difficult to recover motor function that will achieve the same degree of muscle contraction. In this case the facegram can be useful to provide a baseline pattern, which will be important to accompany functional recovery.

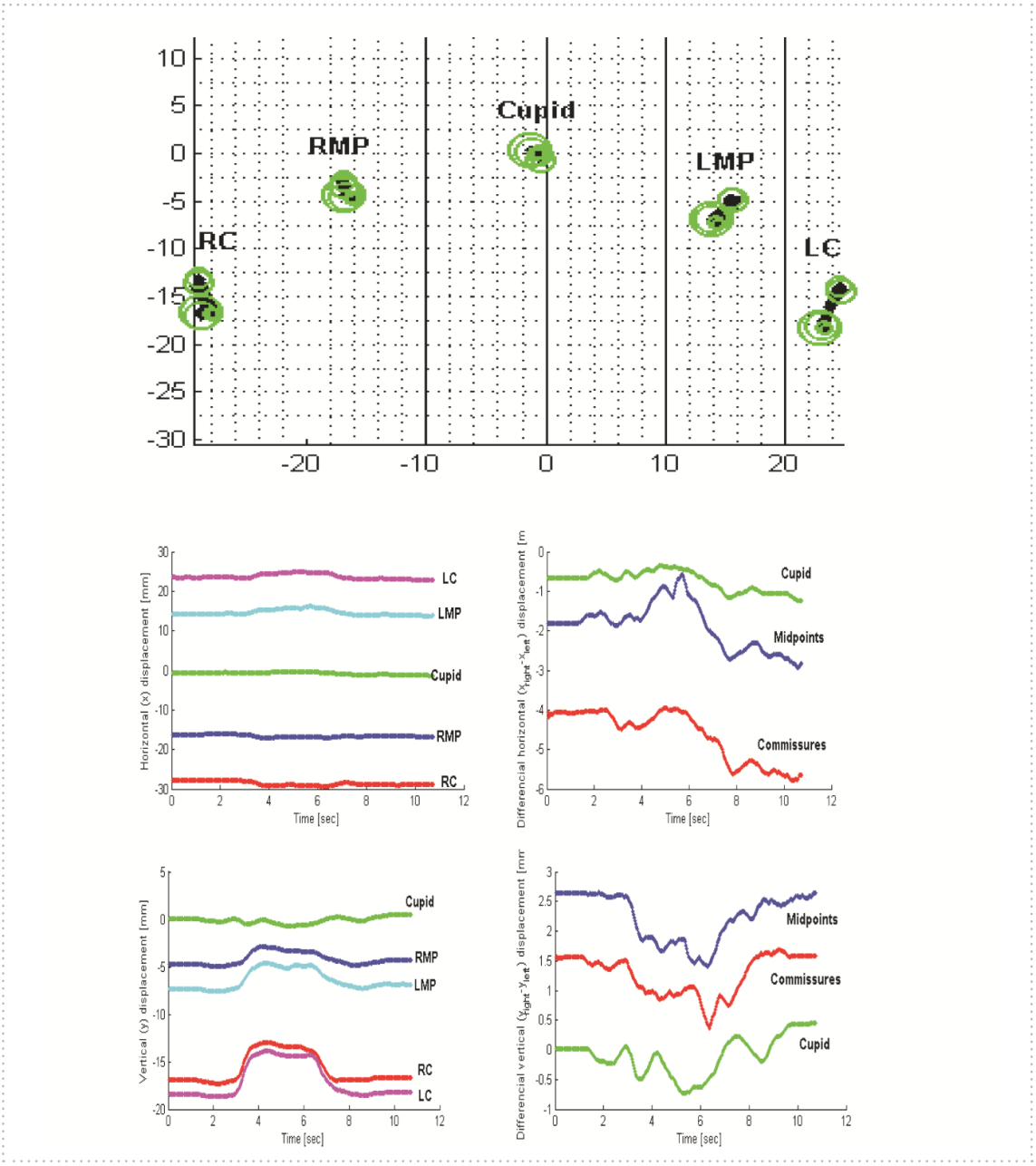


Figure 70. Facegram with symmetry/balance and temporal consistency. Hold period is not properly maintained (there is a progressive loss of extension).

DISCUSSION

The objectives of facial reanimation are a symmetric face at rest and with voluntary motion, corneal protection, restoration of oral, nasal and ocular sphincter control, and controlled balance when expressing emotion with no loss of other significant functions.

Early repair of facial nerve paralysis when cortical neural input cannot be provided by the facial nerve nucleus, may be achieved anastomozing the extracranial stump of the facial nerve to a motor donor nerve, such as the hypoglossus, or the masseteric nerve.[157,158]

When facial nerve dysfunction has exceeded 18 months, neurofibrosis and myofibrosis in the distal neuromuscular unit preclude successful reinnervation, or in patients with congenital facial paralysis where neuromuscular units never developed, regional muscle transposition and free-muscle transfer are the 2 best modalities to reanimate the face.

Many clinicians and researchers working in the field of mimic muscle evaluation have underlined the need for objective, quantitative ways to evaluate facial excursion as a supplement to subjective assessments. In addition, there is a strong relation between lip contraction, lip force, eating ability, speech and saliva control.[155]

Numerous subjective facial grading scales have been proposed.[159,160] These include House-Brackman Scale, Sunnybrook system, Yanagihara system, Burres-Fisch, Nottingham system, Terzis and Noah classification, “Rough” Grading System, etc.

Rating scales provide a measure of severity, progression of deformity and recovery of normal function. However, they are subjective, lack precise description of facial impairment, and are susceptible to drift among raters. There are differences between individuals, genders and age groups. It is also difficult to find a balance between exact descriptions and minimizing the number of groups in which patients are classified.[161]

There are no standard measurement techniques for the assessment of facial symmetry at rest and with movement.

The Maximal Static Response Assay [162] is a static assay, in which physical markers are place on facial landmarks and the coordinates of the center of each marker are manually recorded in the initial and final digitized frames (repose and maximal facial response) of a video sequence of facial expressions. The linear x,y displacement of each marker between repose and maximal response provides a quantitative measure of motion, but no information is given between repose and maximal response and nonlinear motion is ignored. It is time consuming for the operator and the patient.

In the automated face analysis (AFA)[163], motion of facial features is tracked automatically by computer vision using dense flow extraction (for motion detection of the overlying skin produced by muscle contractions), feature-based tracking and high-gradient component detection to detect wrinkles and furrow features. AFA automatically extracts and represents nonlinear motion across the image sequence.

Tessa Hadlock introduced the Facial Clinimetric Evaluation (FaCE) instrument.[164] Preoperatively and postoperatively, a resting still photograph and a photograph with the largest smiling effort are compared for the change in position of the oral commissure, related to smiling effort. The smile improvement (Δ z) is calculated as a ratio of preoperative to postoperative commissure excursion with smiling effort (Δ denotes the

change in position, and z denotes the distance from oral commisssure to midline of the lower lip).

Previously described methods [162-165] do not provide information between repose and maximal response, nonlinear motion and temporal components are ignored, or graphic analysis is not the most accurate.

A more practical system was described by Manktelow *et al* [154] for the evaluation of facial paralysis reconstructions, with a handheld ruler being applied to landmarks about the mouth, and quantitative assessment of their positions at rest and when smiling (static measurements). Despite being a simple, reliable and accurate technique, one of the limitations of this method is that it does not account for the direction of the measured movement, and does not provide temporal information.

Some authors suggest that three-dimensional analyses are more accurate [166,167], and motion systems were developed.[168-170] An interesting 3D capture system was developed by Hontanilla *et al* [171], providing not only distances but also velocities and areas. The FACIAL CLIMA involves placing special reflecting dots on the subject's face and video recording with three infrared-light cameras while performing facial movements. The lateral cameras are rotated 30º converging on the central camera (placed 20 cm higher).

Indeed, with multiple cameras (2 or more, with different view angles) the tracking of the anatomical landmarks would be more precise with respect to the problem of facial convexity. A single camera provides tracking in 2D while two cameras can achieve reasonable tracking in 3D. However, tracking with multiple cameras impose an important constraint: the relative position and orientation of the cameras need to be precisely known to be able to triangulate the movement of the points in space. This means that the system would require a non-trivial set up and calibration. A hallmark of our proposed method is instead the ability to very easily acquire the videos and calculate the facegrams, using an inexpensive webcam. That is, we chose to sacrifice precision in anatomical points distal to the central axis of the face in order to provide a portable system that every clinician can use at the cost of a standard webcam.

An ideal facial grading system should be simple, inexpensive, reliable, require minimal time and equipment, measure both static and dynamic components, and sensitive to changes over time, or following medical therapy and surgical reconstruction.

We have described a novel quantitative, reliable method which accurately assesses the fundamental aspects of the facial excursion, incorporating spatial and temporal components. This method allows the construction of what we call a facegram, likewise an audiogram which records auditory frequencies, or an electrocardiogram records cardiac electrical potentials.

This system is unique in the fact that it allows to visualize in scale the paths followed by each anatomical landmark. It includes the horizontal (and the vertical) displacement, and the differential horizontal (and the vertical) displacement of each point as a function of time. The software also allows the amplification of each landmark separately and with great detail.

The video sequences are not analysed frame by frame with manual point selection by the user on each frame. The user only identifies the markers' locations in the first frame. The algorithm then tracks automatically the markers independently in (x, y, t) coordinates for the entire video sequence. The process thus takes a few seconds, is reproducible, and reliable, since variability in the point selection of the markers (as long as within its central area) is not translated in variability in the markers trajectories. It is a simple tool, rather than a complex system, impractical in the clinical setting.

This study provided an objective analysis of facial movement, allowing in first instance to evaluate patients with facial paralysis in the perspective of disability, and postoperatively to conclude about the effectiveness of the reconstructive procedure (nerve grafts/ transfers, static and dynamic reanimation). It may also be important for progress in the field of physical therapy and rehabilitation, following the outcome of patients with Bell's palsy in order to assess spontaneous regeneration over time, recovery from acoustic neuroma surgery or some other surgery complicated with facial weakness/paralysis.

This facegram was initially developed for facial paralysis, however it has an enormous application potential in all types of reconstructive surgery of the face, particularly in oncologic defects or traumatic etiology, burned patients, or even in the field of cosmetic surgery.

The case studies presented in this paper focus on smile dynamics but our facegram method can be equally applied with different constellations of anatomical points. In other words, instead of the five landmarks to track the smile movement, a different number of points associated with other anatomical references could be used in order to produce a facegram such as the nose, palpebral aperture and for dynamic measurements of the eyebrows or eyelids.

It may also be an important contribution to the facial transplantation assay and for comparison of results from center to center, since the facial appearance of the recipient will have a direct relationship with the motor reinnervation and simultaneous development of alterations in the expression and nasolabial folds. [172]

CONCLUSION

In this work, we describe a novel quantitative, reliable method, which accurately assesses the fundamental aspects of the facial excursion, incorporating spatial and temporal components.

CHAPTER III

FACIAL TRANSPLANTATION

1. THE CONCEPT OF ALLOTRANSPLANTATION

1.1. Definition and indications of Composite Tissue Allotransplantation (CTA)

Conventional reconstructive treatments include free transfer (autologous tissues), retaching amputated body parts using microsurgical techniques, and by means of prosthetic materials. However, they can lead to short outcomes, including infection, rejection (prosthesis), poor functional recovery, and poor aesthetic results. They often require multiple revision surgeries and prolonged hospitalization and rehabilitation, with a significant negative impact on patients, health care system and society.[39]

Composite tissue allotransplantation (CTA) involves the transplantation of various tissues including integumentary or musculoskeletal, nerves, and vascular tissues, in contrast to visceral solid organ transplantation (SOT). CTAs are composed of ectodermal (nerves, nails, hair) and mesodermal tissues (tendons, bones, muscles, cartilage, dermis, connective tissue, vessels).

CTA was described in hands, face, larynx, abdominal wall, tongue, esopahagus, penis, lower limb, and knee.[173]

CTA in the form of hand and facial tissue transplantation is now a clinical reality. For such major and complex tissue defects, CTA can provide superior functional and aesthetic outcomes by restoring “like with like”.

Since the first face transplantation was successfully completed in November 2005 in Amiens (France)[174], facial transplantation has emerged as the most complex solution to restore a near-normal-apperance, and function on the reconstructive ladder for severe facial disfigurement. This can occur following a variety of events, including ablative surgery, neurofibromatosis, trauma and cancer.

Since 2005, 27 face transplantations have been performed to date in France (*n* = 9), the United States of America (*n* = 7), Turkey (*n* = 5), Spain (*n* = 3), China (*n* = 1), Belgium (*n* = 1), and Poland (*n* = 1).[175-177] 19 of these cases have been published on Medline. Tables 5 and 6 provide an overview on the main characteristics of all procedures. To date, face transplantation has been performed on patients with severe burns (*n* = 10, including chemical and electrical burns), gunshot injuries (*n* = 8), animal attacks (*n* = 3), neurofibromatosis type I (*n* = 3), severe radiotherapy side effects, and crush trauma (*n* = 1) The average age of the recipients was 34.6 ± 10.0 years, ranging from 19 to 59 years, and the average age of the donors was 39.7 ± 13.0 years (19 to 65 years). Age disparity between donor and recipient varied from 1 year to 36 years. Eight recipients were more than 10 years younger than their corresponding donor. The recipient male-to-female ratio was 21: 5. As far as reported, transplantation of the human face, including different anatomical structures, and requiring microsurgical anastomoses of nerves and vessels, as well as multiple osteosynthesis, took an average of 17.6 hours. Three deaths were associated with the procedure, representing 11.1% of all recipients. One patient died 27 months after surgery because of a lack of compliance considering the immunosuppressive therapy. The second case of death has occurred in the third French recipient due to prolonged anoxic cardiac arrest following multidrug-resistant infections and consequent graft necrosis.[178] The third patient deceased in July 2013 after suffering from recurrent cancer.[179]

To date, 14 different surgical teams harvested 17 partial and 10 full facial allografts. As far as published, there were at least 11 myocutaneous transplantations, whereas at least 16 explants included bone. Other tissues like septal cartilage and the parotid or lacrimal glands were transplanted in as many as 11 cases. There were at least 2 allografts that included the tongue (Table 6). So far, no case of graft loss, hyperacute or chronic rejection, or graft-versus-host disease has been reported. With exception of one case, all patients who underwent facial transplantation surgery returned to normal life.[180]

Face transplantation actually seems to have higher costs than heart or any other solid organ and represent twice the costs faced for a liver transplantation [178], but costs might decrease with teams' experiences, which may shorten postoperative intensive care and overall hospital stays. Despite short follow-up and adverse events related to immunosuppression, functional recovery after face transplantation is expected to be superior to that achieved with conventional reconstructive methods in restoring major deficits.

Table 5. Main characteristics of the first 27 face transplantations.

NUMBER	YEAR	CITY & TEAM LEADER	R SEX AND AGE	D AGE	ETIOLOGY	TYPE	SD (h)	FUP (y)
1	11/2005	Devauchelle Amiens, France	F, 38	46	Animal attack	Partial myocutaneous	15	7.8
2	04/2006	Guo Xian, China	* M, 30	25	Animal attack	Partial osteomyocutaneous	13	7.4
3	01/2007	Lantieri Paris, France	M, 29	65	NF 1	Partial myocutaneous	11	6.8
4	12/2008	Siemionow Cleveland, USA	F, 45	44	Gunshot injury	Partial osteomyocutaneous	22	4.8
5	03/2009	Lantieri Paris, France	M, 27	43	Gunshot injury	Partial osteomyocutaneous	19	4.6
6	04/2009	Lantieri Paris, France	* M, 37	59	Burns	Partial myocutaneous	13	4.5
7	04/2009	Pomahac Boston, USA	M, 59	60	Burns	Partial osteomyocutaneous	17	4.5
8	08/2009	Lantieri Paris, France	M, 33	55	Gunshot injury	Partial osteomyocutaneous	16	4.2
9	08/2009	Cavadas Valencia, Spain	* M, 42	35	Radiotherapy	Partial osteomyocutaneous	15	4.2
10	11/2009	Devauchelle Amiens, France	M, 27	—	Burns	Partial osteomyocutaneous	19	3.9
11	01/2010	Gomez-Cia Seville, Spain	M, 35	30	NF 1	Partial myocutaneous	22	3.8
12	04/2010	Barret Barcelona, Spain	M, 31	41	Gunshot injury	Full osteomyocutaneous	—	3.5
13	07/2010	Lantieri Paris, France	M, 37	—	NF 1	Full myocutaneous	14	3.3
14	03/2011	Pomahac Boston, USA	M, 25	48	Burns	Full myocutaneous	17	2.5
15	04/2011	Lantieri Paris, France	M, 45	—	Gunshot injury	Partial osteomyocutaneous	—	2.4
16	04/2011	Lantieri Paris, France	M, 41	—	Gunshot injury	Partial osteomyocutaneous	—	2.4
17	04/2011	Pomahac Boston, USA	M, 30	31	Burns	Full myocutaneous	14	2.4
18	05/2011	Pomahac Boston, USA	F, 57	42	Animal attack	Full osteomyocutaneous	19	2.3
19	01/2012	Ozkan Antalya, Turkey	M, 19	39	Burns	Full osteomyocutaneous	9	1.7
20	01/2012	Blondeel, Gent, Belgium	N/A	N/A	N/A	Partial osteomyocutaneous	20	1.7
21	02/2012	Nazir Ankara, Turkey	M, 25	40	Burns	Full face transplant	—	1.6
22	03/2012	Ozmen Ankara, Turkey	F, 20	28	Burns	Partial face transplant	—	1.5
23	03/2012	Rodriguez Baltimore, USA	M, 37	21	Gunshot injury	Full osteomyocutaneous	36	1.5
24	05/2012	Ozkan Antalya, Turkey	M, 27	19	Burns	Full face transplant	—	1.3
25	01/2013	Pomahac Boston, USA	F, 44	—	Burns	Full myocutaneous	15	0.6
26	05/2013	Ozkan Antalya, Turkey	M 27	19	Gunshot injury	Partial osteomyocutaneous	—	0.5
27	07/2013	Maciejewski Warsaw, Poland	M, 33	42	Crush trauma	Partial osteomyocutaneous	27	0.3

R = recipient, D = donor, D = difference, SD = surgery duration, FUP = follow-up period, and *= patient died.

Table 6. Transplanted tissues (25 reports to date).

Myocutaneous		Osseous		Other	
Mucosa	25	Maxilla	8	Parotid gland	10
Nose	24	Mandible	2	Septal cartilage	9
Cheek	23	Nasal bone	3	Tongue	2
Upper lip	23	Zygomatic bone	2		
Lower lip	19	Orbital floor	2		
Chin	16				
Lower eyelid	11				
Upper eyelid	10				
Forehead	10				

1.2. Technical aspects in facial transplantation

DONOR SELECTION

The inclusion criteria for FT programs vary from center to center, but to date only patients with extensive tissue damage and with poor functional and aesthetic outcomes after conventional reconstruction procedures were included. Donors were selected based on race, skin color, sex, blood type, age, HLA matching, and immunological status. Patients were excluded in case of significant medical comorbidity, missing guarantee for posttransplant follow-up, high risk of recurrent cancer under immunosuppression, and pregnancy.[181]

Lantieri and his team considered only defects including full destruction of orbicularis oris and/or orbicularis oculi muscles to be without a prospect of a successful reconstruction by conventional means.[182] The team in Boston only included patients with a defect comprising >25% of the facial area and/or loss of one of the central facial parts such as eyelids, nose, or lips.[181] In order to find the optimal candidates for FT, Siemionow *et al* developed a preliminary assessment tool called the FACES score.[183]

Several attempts have been made to match recipients with donors acoording to age, sex and skin phenothype. Baccarani *et al* [184] described the morphological matching process as comprising evaluation of gender, skin texture, special features (nose, eyes, ears), and size of head. Many of these factors are modifiable. The allograft is pliable and can be modified by draping or stretching of the facial graft for a small donor face, or by debridement of redundant tissue for a large donor graft, correcting head size discrepancy.

Computer simulation suggested that the donor's age should lie between 20 years below and 10 years above the recipient's age.[185] Skin texture differences might occur with a large age discrepancy. The facial graft can eventually stretch and distort considerably and any hair-bearing areas are likely to adapt to the recipient's hormonal environment, subsequently gender may be not so much important as might be expected.

Most donor facial features are likely to mould to the recipients underlying facial skeleton, and usually a hybrid chimeric face results which primarily resembles the recipient. This has been confirmed by cadaveric studies.[50] However, some pronounced and distinctive soft tissue features such as the nose, can cause the chimeric face to resemble the donor to an unacceptable degree. [184]

The outcome following facial transplantation needs to be considerably better than that achieved with conventional reconstructive techniques in order to justify its choice as a reconstructive modality. The impact

of a facial graft may be lessened if the transplant looks similar to the recipient, or has minor discrepancies.[187]

Skin colour distribution, independently of facial form and skin surface topography, seems to have a major influence on the perception of facial age and judgments of attractiveness and health.[188] Even small skin tonal mismatches following surgery (such as skin grafting) can cause psychological morbidity. Skin tone matching between the donor and the recipient may be important to increase the potential donor pool, usually restrained by the need for matching for gender and/or age.

Other dermatological conditions of donors should be considered as selection criteria, as the transfer of rosacea between donor and recipient was observed in the seventh face transplant. [189,190] Premature aging of the allograft has not yet been reported, but longer follow-up is required.

Serological screening of the donor for infectious disease status is essential, as well as a detailed history of potential exposure, "at risk" behavior and an accurate diagnosis of cause of death. In order to minimise the risk of transmission of significant infections to the immunocompromised recipient, the practice is to routinely screen for the following: human immunodeficiency virus (HIV) -1 and -2; hepatitis B virus (HBV) surface antigen and core antibody; hepatitis C virus (HCV) antibody; human T-cell lymphotropic virus (HTLV) -1 and -2 antibody; cytomegalovirus (CMV) delta agent; toxoplasma antibody; syphilis; and Epstein-Barr virus (EBV) antibody. Only donors with negative virology results should be considered, and even donors with a history of possible exposure to HIV should also be excluded, as there is a time lapse before the antibody appears.

CMV matching of donor to recipient is ideal, as severe CMV viraemia is a predictor of mucosa rejection.[191] Prophylaxis against CMV should be considered if either the facial transplant donor or recipient is positive. In the fourth facial transplant case (CMV donor-positive/recipient-negative status), maintenance of a high level of ganciclovir in the postoperative period was crucial and no CMV viraemia has been reported.[192]

EBV transmission may be associated with several clinical scenarios including asymptomatic viraemia, hepatitis and mononucleosis syndrome.[193] In addition, the risk of post-transplantation lymphoproliferative disorder can increase as much as 20-30 fold. Seronegative recipients at risk of EBV transmission from a seropositive donor should be monitored closely.

A type 1 human herpes simplex infection was reported on the lips of the first partial face transplant, and was successfully treated.[194] Transmission of human herpes virus 8 (HHV-8) from donor to recipient has been described in solid organ transplantation, leading to an increased incidence of Kaposi sarcoma. In areas of increased prevalence (such as the Middle East or Africa) may be prudent to test for this agent.[195]

The donor face in the third facial transplant performed worldwide was positive for *T. pallidum*; in consequence the *T. pallidum* negative recipient thus received treatment with methylpenicillin.[196]

RECOVERY FROM THE DONOR

Cold ischemia time following cardiac arrest is one of the most important aspects affecting the success rate in solid organ transplantation; fast harvesting, transport, and implantation are required. The ischemia time tolerated by a facial graft has not been tested in a clinical setting, but based on known effects of ischemia-reperfusion injury on its individual components, and ischemia time limitations of the muscle, the most sensitive part of the

allograft, Pomahac *et al* [197] recommended reperfusing within 4 hours of onset of cold ischemia. In order to reduce tissue damage and to avoid blood congestion during cold ischemia time, some surgical teams opted for allograft perfusion and storage in different organ preservation solutions at 4ºC as known from solid organ transplantation. As far as reported only ILG-1 (Institut Georges Lopez Organ Preservation Solution) and UWC (University of Wisconsin Solution) were used and suggested for cold perfusion after removal of the facial allograft.

In the majority of cases, the recovery of allografts was from brain-death heart-beating donors, and facial transplantation teams harvested the "face" in the first place in the case of multi-organ procurements. In order to reduce cold ischemia time the surgical teams harvested the allograft by dissection of greater parts of the face under maintenance of circulation before cross clamp time, so the final surgical steps could be managed within a short period of time. Bueno *et al* [190] performed half of the facial allograft dissection before removal of the solid organs, and the rest shortly after the cardiac death. Other teams [198] performed the entire allograft recovery following donor's cardiac death, after thoracic an abdominal organs removal.

In some situations, allograft recovery and insertion may have to be performed in different hospitals. Transport should be done safely and quickly to limit ischemia time, in an organ preservation solution inside a refrigerator with ice.[199]

ALLOGRAFT PERFUSION

Facial transplantation is a complex operation. Blood supply of the transplanted tissue was first suggested as requiring at least two arteries and veins from the donor's face.[200] In order to reduce the risk of postoperative thrombosis and potential transplant loss, most anastomoses were performed preferentially in large diameter vessels. The majority of surgeons opted for a bilateral connection of the facial or external carotid artery (Table 7-a). Venous drainage was mostly ensured via end-to-end connection of the external jugular vein (*n* =6), facial vein (*n* = 4), or junction to the thyrolinguofacial trunks (*n* = 4). With exception of two reported cases, all anastomoses were performed using conventional end-to-end microsurgical techniques. As with any microsurgical procedure, there is the possibility of thrombosis of the arteries or veins, but this is unlikely to occur beyond the second day and if this does happen, should be considered as technical failure and not immunological acute or chronic rejection. Failure of vascular anastomosis was identified as a potential risk, but thus far, all allografts have been grafted successfully and remained viable following surgery, which might be explained by good circulation in the head and neck region and the highly skilled surgeons in the respective transplant centers. Post-operative venous thrombosis has been reported by the Barcelona team, requiring reanastomosis on post-operative day three. [201]

In addition, relatively few anastomosis appear to be necessary for adequate reperfusion of facial allografts. Preliminar studies using intraoperative near-infrared (NIR) fluorescence imaging suggested that facial flap models can be adequately perfused from a single pedicle.[202] NIR fluorescence imaging is based on the deep photon tissue penetration of NIR light (700-900 mm) for rapid and quantitative assessment of local perfusion at depths of several millimeters. Upper facial composite tissue allotransplants were created by Nguyen *et al* [203] using the superficial temporal artery and external jugular veins pedicles in yorkshire pigs. Animals were injected with indocyanine green and imaged with NIR fluorescence. Unilateral arterial clamping was used to occlude all the perfusion to one side of the flap to simulate flap failure based on a single

pedicle during or after facial transplantation. Initially, there was a complete lack of indocyanine green on the ipsilateral side, but over time, it was seen entering the contralateral side, originating from the contralateral pedicle, crossing over the midline and eventually completed illuminating the flap, perfusing the pedicle on the clamped side in a different pattern. These findings suggested that single pedicle perfusion is possible. However the structure of the pig's skull and facial structures are somewhat different from a human as the flap is perfused mainly by the branches of the superficial temporal artery, and perfusion was based on NIR monitoring of the surface skin paddle, leaving us little information about the composite tissue below.

Complete facial vascularization is actually known to be possible by means of a single pedicle anastomosis of the facial vessels, as well as the re-vascularization of the maxilla, palate and mandible.[179,204,205] Preclinical cadaveric dissections have showed that small arterial connections exist between the deep branches of the facial artery and the distal branches of the maxillary artery.[206] The maxilla and hard palate can receive an adequate blood supply from the facial artery alone, and subsequently, midfacial allotransplantantion including the maxilla and zygoma was performed. The fourth and full face allotransplant, performed in the United States, containing maxilla and palate also received its vascular perfusion from just the facial artery alone.[207] A single external carotid artery was also enough for perfusion of the entire face as reported by the Barcelona group.

Harvesting the allografts in a single mono-block segment (e.g., facial osteo-myocutaneous tissues with mimic muscles, vessels, motor and sensory nerves) ensures complete revascularization by preserving musculocutaneous perforating vessels localized between the muscles and the cutaneous component.

In a study with three subjects with severe craniofacial injury who underwent full face transplantation[208], dynamic computed tomography (CT) identified adequate blood flow for facial allografts via extensive vascular reorganization for external carotid artery (ECA) angiosome; collateral flows from vertebral, ascending pharyngeal or maxillary arteries supplied the branches from the recipient ECAs distal to the ligation. While allograft tissue was slightly less perfused when the facial artery was the only donor artery when compared to an ECA-ECA anastomosis, allograft perfusion was higher than the recipient normal neck tissue. Venous drainage was also adequate for all subjects, even when the recipient internal jugular vein was anastomosed in end-to-end fashion.

Table 7. Microsurgical considerations as far as reported (16 reports to date). (b) Sensory and motor recovery (12 reports to date).

(a)

Arterial anastomosis		Venous anastomosis		Sensory nerve repair		Motor nerve repair	
External carotid artery	12	External jugular vein	6	Infraorbital nerve	10	Facial nerve	15
Facial artery	6	Facial vein	4	Mental nerve	8	Hypoglossal nerve	1
External maxillary artery	1	Internal jugular vein	5	Supraorbital nerve	5	Mandibular branch	1
CCA to SCA	1	Thyrolingual trunks	4	None	5		
		Retromandibular vein	3				
		Anterior facial vein	2				

(b)

Sensory recovery (months after transplantation)			Motor recovery (months after transplantation)	
Nerve repair	Touch	Temperature	Nerve repair	Motor recovery
Yes	4.1	4.5	Yes	7.8
No	7.3	12.5	No	—

VASCULAR PLANNING

Facial transplantation candidates have extremely complex vascular anatomy due to severe injury and/or multiple prior reconstructive attempts; thus, each procedure is uniquely determined by the defects and vascular anatomy of the candidate.[209]

High spatial and temporal resolution vascular imaging is required to determine those vessels appropriate for arterial and venous anastomoses and usually includes computed tomographic vascular mapping of the external carotid distribution.[210] Computed tomographic angiography should be used as the first-choice modality for preoperative imaging of facial transplant patients because, when compared with magnetic resonance imaging, the visualization of small vessels is far superior and images have fewer artifacts.[211]

Cine computed tomographic images were suggested by Sisk et al [212] because they provide data on direction of blood flow, which is important for preoperative planning. Cine loop analysis identified retrograde arterial filling not illustrated on the static images alone, but the static images depicted small vessels more clearly, particularly in the crowded vessel takeoffs. Combination of cine computed tomographic and the best static images was suggested for successful transplantation.

Color Doppler is simpler and can be used in the preoperative vascular assessment of both donor and recipient in facial transplantation. The diameter, course and the branching pattern of each facial vessel can be documented up to the level of the nasal ala.[213]

ORTHOGNATIC PLANNING

Facial transplantation represents one of the most complicated scenarios in craniofacial surgery because of skeletal, aesthetic, and dental discrepancies between donor and recipient. Facial allografts have varied in the composition of the involved tissues, conditioning the extent of the respective surgical procedure. As far as reported transplantation of bone, requiring open fixation, has been performed in at least 12 cases, most of which contained the mandible and/or maxilla including teeth. This can be achieved by means of a LeFort II osteotomy combined with the mandible anterior segmental removal, usually containing teeth.[192,214] Subsequent osteosynthesis and correct dental occlusion must be ensured. Gordon *et al* [215] advocate an orthognathic planning in the facial transplant (FT) bone components to achieve a Class I relationship and a functional occlusion. Some degree of malocclusion was reported in some situations, and a bilateral jaw osteotomy was then performed. Computer-assisted surgery solutions, such as the Computer-Assisted Planning and Execution (CAPE) workstation [216,217], have been developed in swine models and demonstrated that integration of computer planning and intraoperative navigation are possible with submillimeter accuracy, as needed for facial transplantation and other related craniomaxillofacial procedures.

Patients may also need oral rehabilitation with dental implants or prosthesis manufacture to achieve functional and aesthetic improvement.[218,219]

TRANSFUSION REQUIREMENTS IN FACIAL TRANSPLANTATION

A significant blood loss can be expected during the procedure. The second facial transplant performed in China resulted in 5 liters blood loss.[220]

Lantieri *et al* [221] described transfusion requirements of 10 or more units of packed red blood cells in each of their first four patients. Gomez-Cia *et al* [222] experienced as severe blood loss, as 24 units were transfused resulting in post-transplant dilutional coagulophaty, and rhabdomyolisis attributed to both massive blood loss and to an intra-operative immobilization period.[223]

PARTIAL *VS* FULL - FACE TRANSPLANTATION

Clinical updates of facials transplantation have been performed.[176,179,219,224] Twenty-seven face transplants have been performed to date, including 17 partial and 10 full-face transplants.

Initial experiences included the substitution of missing units, and started a new frontier for transplantation medicine, with the birth of restoration surgery in contrast to reconstructive surgery. However, facial transplantation is no longer a program of exchanging missing anatomy parts but creates a new face for a human being, and should be performed after a careful analysis of the defect. Outcome is more than ever defined in terms of a complex of function and appearance, rather than achievement in closure. After the first world's full-face transplant performed in Barcelona in March 2010, a true ablative surgery with a total restoration proved to be effective, and this experience has changed the reconstructive paradigm of facial transplantation.

Nowadays, facial transplants following strict aesthetic units should restore disfigurement extending to small central areas, whereas if many facial units are involved, ablative surgery extending to all esthetic units involved (with the sacrifice of normal tissues if necessary), and restoration should be implemented.[176] However, caution is necessary when considering the resection of the periorbital structures, as if the the transplant fails, vision will be at risk, and classical reconstructive options may be inadequate. It is important to preserve as much normal structures as possible (conjunctiva, muscles), to protect the eyes.

There are two main types of facial transplantation: [225]

1) **Partial Facial transplantation:**

- Comprises the nose and the upper lips with a vaying amount of chin and cheek;
- Includes muscle, mucosa, and skin and/or bone;
- If motor function failed to return, it would require static or dynamic procedures to restore movement.

2) **Full facial transplantation:**

- Include the possibility of using ears, nose or eyelids (depending on the individual's needs);
- In the case of failure: possibility of application of autologous skin grafts (the bed for skin grafting might be better than it was initially due to the formation of granulation tissue), the use of artificial skin (Integra®) or repeating the transplant (more likely to reject due to prior sensibilization).

Previously, it was thought that full face allografts must include bilateral superficial temporal and facial arteries, with need for inclusion of donor parotid glands.[226] This would lead to poor aesthetic outcomes and limit facial nerve coaptation to the level of the main trunk, which often results in synkinesias. The allograft harvesting technique has been improved during the last years in order to exclude parotid and submandibular glands and to increase the options for allograft reinnervation (see section 3- mock cadaver dissections for facial transplant procurement).

As of July of 2013, 27 facial vascularized composite allotransplantations have been performed. Mohan Raja *et al* [227] developed a classification system and treatment algorithm for facial defects that may be ideally suited for facial transplantation. Skeletal defects were defined by craniofacial osteotomies and soft-tissue defects by aesthetic facial subunits. The soft-tissue defect was subdivided into the following subunits: oral-nasal (type 1), oronasal-orbital (type 2), and full facial (type 3). The bony defects were subdivided into mandibular involvement (M), Le Fort 1 (A), Le Fort 3 (B), and monobloc (C) - Fig. 71. The mechanisms of injury included trauma ($n = 13$), burns ($n = 8$), congenital deformity ($n = 3$), oncologic resection ($n = 1$), and unreported ($n = 2$). According to the proposed classification system: one was type 1; one was type 1-M; one was type 1-MB; two were type 2; two were type 2-B; two were type 2-MB; six were type 3; one was type 3-B; and three were type 3-MB; eight could not be classified due to a lack of data. The treatment algorithm designed a vascularized composite allotransplantation that addressed the bony and soft-tissue components.

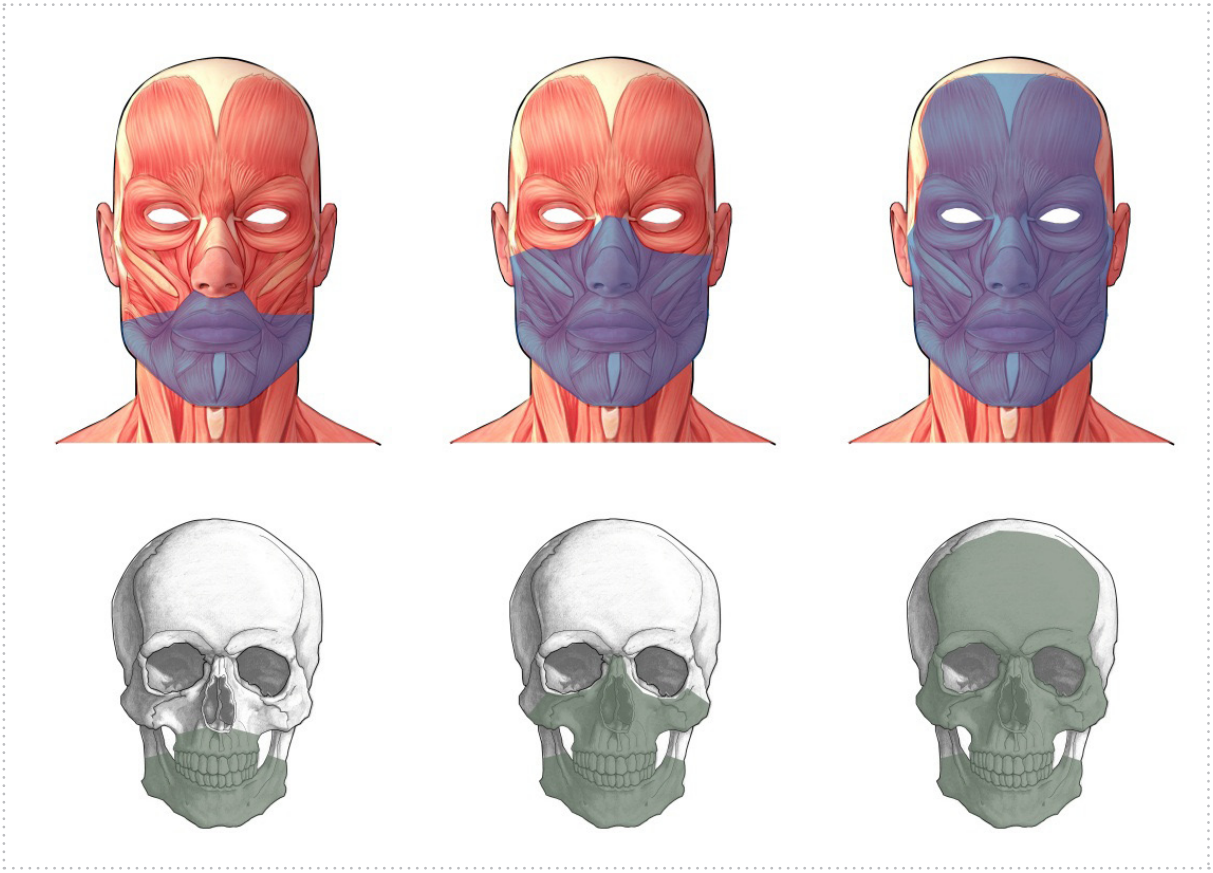


Figure 71. Classification system proposed by Mohan: Skeletal defects were defined by craniofacial osteotomies and soft-tissue defects by aesthetic facial subunits. The soft-tissue defect was subdivided into the following subunits: oral-nasal (type 1), oronasal-orbital (type 2), and full facial (type 3). The bony defects were subdivided into mandibular involvement (M), Le Fort 1 (A), Le Fort 3 (B), and monobloc (C).

2. ACTUAL PROBLEMS OF FACIAL TRANSPLANTATION

2.1. Immunosuppression

Organ or tissue transplantation engenders a recipient response directed against the donor and so, all patients who receive a transplant have to be treated with lifelong immunosupressive agents. The magnitude of response will be influenced by the tissue transplantated, previous sensibilization against histocompatibility antigens, age of the recipient, and degree of mismatching for major histocompatibility antigens (human leucocyte antigen-HLA).

HLA molecules are encoded by a set of highly polymorphic genes located within the major histocompatibility complex (MHC) on chromossome 6. There are three classical class I HLA molecules: A, B and C, expressed on most cell types and recognized by both CD8+ T cells and natural Killer (NK) cells. Class II molecules (DR, DQ and DP) are expressed mainly on B cells, macrophages and activated T cells; they are recognized by CD4+ T cells. HLA molecules present antigenic peptides to T cells.

Rejection occurs when HLA antigens on donor cells are recognized by recipient lymphocytes or antibodies, leading to destruction of the antigen-bearing graft. It can be hyperacute (antibody-mediated; within the first 48 hours), acute (cell and antibody-mediated; within days and months after transplantation), and chronic. Because skin and oral mucosa are well known to have high immunogenic properties and often comprise the largest part of a composite facial allograft, rejection is expected to be particularly problematic. Although no hyperacute graft rejection has been reported so far, acute rejections seem to be inevitable: each of the FT recipients who had a follow-up period of more than one year had at least one episode of acute rejection [180], manifesting itself in reddening of the skin, swelling, and the presence of nodules and papules.

HLA matching may reduce the doses of immunosuppression required and the risk of side effects.[228] HLA-A, B and DR matching may reduce the overall risk of rejection, but to date, there is not enough evidence to advocate a minimum level of class I and II matching between the donor and the recipient, and full HLA match might preclude widespread of facial transplantation as an option for severe facial disfigurement.

HISTOCOMPATIBILITY TESTING FOR COMPOSITE TISSUE ALLOGRAFT TRANSPLANTATION

The facial transplantation candidate and the donor should be HLA-typed pre-operatively. Assessement of the potential recipient HLA-specific antibody status is also important, and a pre-transplant crossmatching using donor lymphocytes and recipient sera is prudent, to determine the likely risk of rejection, since the candidate may have experienced a sensitizing event such as previous blood transfusion, pregnancy, deceased donor tissue transplants (tendons, vein, or heart valve grafts), organ transplant and even immunization. Historically, immunization has not been considered relevant because no HLA antigens are contained in vaccines, however, the more sensitive solid phase screening techniques have revealed that some patients will respond to vaccines with antibodies that apparently cross-react with HLA molecules. In general, transplant across a positive cytotoxic cross-match caused by even cross-reactive antibodies should be avoided to preclude the possibility of hyperacute rejection of the graft.

Various assays are employed for antibody screening, including complement-dependent cytotoxicity assays as well as the newer, more specific and sensitive solid phase assays. Solid phase procedures use purified HLA class I or II antigens as targets, and anti-HLA antibodies are detected by either enzyme linked immunosorbent assay or flow cytometric methodology. If antibody is present, the corresponding antigens would be avoided in the donor to eliminate the possibility of hyperacute rejection of the graft. The objective is to transplant a graft that possesses the maximum potential for long-term survival, because loss of a graft frequently results in the development of anti-HLA antibodies, which can severely restrict the patient's access to a second graft. A negative lymphocyte crossmatch using even the most sensitive technique does not absolutely preclude the possibility of hyperacute rejection because this can be caused by antitissue-specific or antiendothelial antibodies, but a negative cross-match is sufficient in the vast majority of cases to indicate a permissive donor–recipient combination.

Once a patient is accepted as a CTA candidate, mononuclear cells are collected at intervals and frozen for future use as baseline controls in immunologic monitoring assays such as mixed lymphocyte reactions or immune activation assays. When a patient is transplanted, large numbers of donor spleen cells are also archived for use as stimulator cells in these assays as well as a source of cells for posttransplant cross-matching to monitor for the development of donor-specific antibodies. If preservation of donor cells is not possible at the time of transplant, knowing the HLA type of the donor permits selection of appropriate surrogate cells for use in posttransplant cross-matches. Donor-specific cross-matches are often the method of choice for monitoring posttransplant antibody, but in the presence of therapeutic antibodies used for induction therapy or treatment of rejection, cross-matching may not be feasible. In these cases, the therapeutic antibody can sometimes be absorbed out of the serum before cross-matching or solid phase screening, or cross-match assays can be used. The presence of anti-HLA antibody that are not specific for donor antigens, commonly referred to as third party antibody, does not result in hyperacute rejection but does appear to correlate negatively with overall graft survival. Development of donor-specific antibodies post-transplant, either anticlass I or anticlass II, has been shown in kidney, heart, and lung grafts to correlate with decreased graft survival. If antidonor antibody is detected after transplantation in conjunction with an acute rejection episode, plasmapheresis may be necessary to reverse the rejection episode, and donor specific cross-matches are the preferred method of monitoring the effectiveness of the pheresis procedures.

Donor-to-recipient matching for major blood groups (ABO) is also probably the best approach to prevent hyperacute rejection. However, the fourth facial transplant was performed successfully despite different blood groups: A (donor) and AB (recipient), and if shown to be reproducible could rise the availability of donors.[207]

All solid organs require ABO compatibility but CTA carries several additional unique requirements that further limit the potential donor pool. These requirements include matching of bone size, gender, and skin color and tone. Some of these matching requirements are of course negotiable and depend upon the preferences of the recipient but if requested they significantly affect the number of potential donors. Adding HLA matching to this list of requirements was felt to restrict the donor pool to such an extent as to effectively preclude transplant. If HLA matching is pursued as a strategy, experience in renal transplantation indicates that class II matching is a priority and that zero-antigen mismatched grafts should have a statistically significant survival advantage.

DIFFERENCES BETWEEN COMPOSITE TISSUE ALLOGRAFTS AND OTHER SOLID ORGAN GRAFTS

The various solid organ grafts fall into a hierarchy of antigenicity with kidney being the lowest followed by pancreas, liver, heart, lung, and intestine. As a consequence, renal transplants generally require lower levels of immunosuppression than do heart or intestine transplants.

In contrast to solid organ allografts, composite tissue allografts may include diverse tissues (skin, muscle, tendons, nerves, bone, vessels) that express various levels of antigenicity and contain some immunocompetent tissues (bone marrow, lymph nodes) that may alter the immune response. In the case of a facial transplantation, and due to its highest antigenicity within all the tissues, skin has long been regarded as one of the major obstacles to the success, as evidenced by the robust cellular and humoral immune response elicited by skin grafts. It was anticipated that the skin component of composite tissue allografts would require high, possibly toxic, levels of immunosuppression to prevent rejection.

Composite tissue grafts differ from all other solid organ grafts in regard to bone marrow content. No other solid organ graft carries an intact bone/bone marrow component. Liver grafts do possess significant hematopoietic potential, and intestinal grafts carry a heavy mature lymphocyte burden because of the presence of the gut-associated lymphoid tissue, but neither contains functional bone marrow. Both of these organs have produced cases of graft versus host disease (GvHD) in transplant recipients, and with both organs, fatal cases of GvHD have been reported. When bone marrow or hematopoietic stem cells are transplanted for treatment of malignancy, GvHD is commonly seen and is a frequently severe, life-threatening disease. Composite tissue grafts containing bone marrow and lymph node components carry the potential for producing GvHD.

Another major difference between solid organ grafts and CTA is the relative level of exposure to the environment. Lung and intestine transplants are exceptional in that they are constantly exposed to environmental factors and both have proven to be highly prone to bacterial, viral, or fungal infections. These infections have compromised the survival of both of these grafts and appear to significantly limit success rates in these transplantation. However, this has not been the case. No CTA performed to date has reported any serious infection in the graft itself. Some infections have been reported in the recipients but these have most often been the infections encountered in all immunouppressed patients (e.g., cytomegalovirus (CMV) infection).

IMMUNOLOGICAL BASIS AND MECHANISMS OF ACTION OF IMMUNOSUPPRESSIVE DRUGS

In the early times of transplantation, few immunosuppressive treatments were available, agents had significant side effects and were inadequate to overcome the immunological rejection of any transplanted tissue or organ.

The introduction of cyclosporine in the early 1980s ushered in a new era of transplantation which was later followed by new immunosuppressive agents such as tacrolimus, monoclonal antibodies (anti-CD 25), antithymocyte globulins, mycophenolate mofetil, and rapamycin.

The successful use of this tacrolimus /MMF/corticosteroid combination therapy in hand transplants has led other groups that had performed laryngeal, bone, nerve, and more recently facial tissue allotransplants, to use this same drug combination. This is achieved through a comprehensive balance of multiple drugs and

methodologies that interfere with the immune response at various sites by blocking the formation, stimulation, proliferation, and differentiation of lymphocytes (Fig. 72).

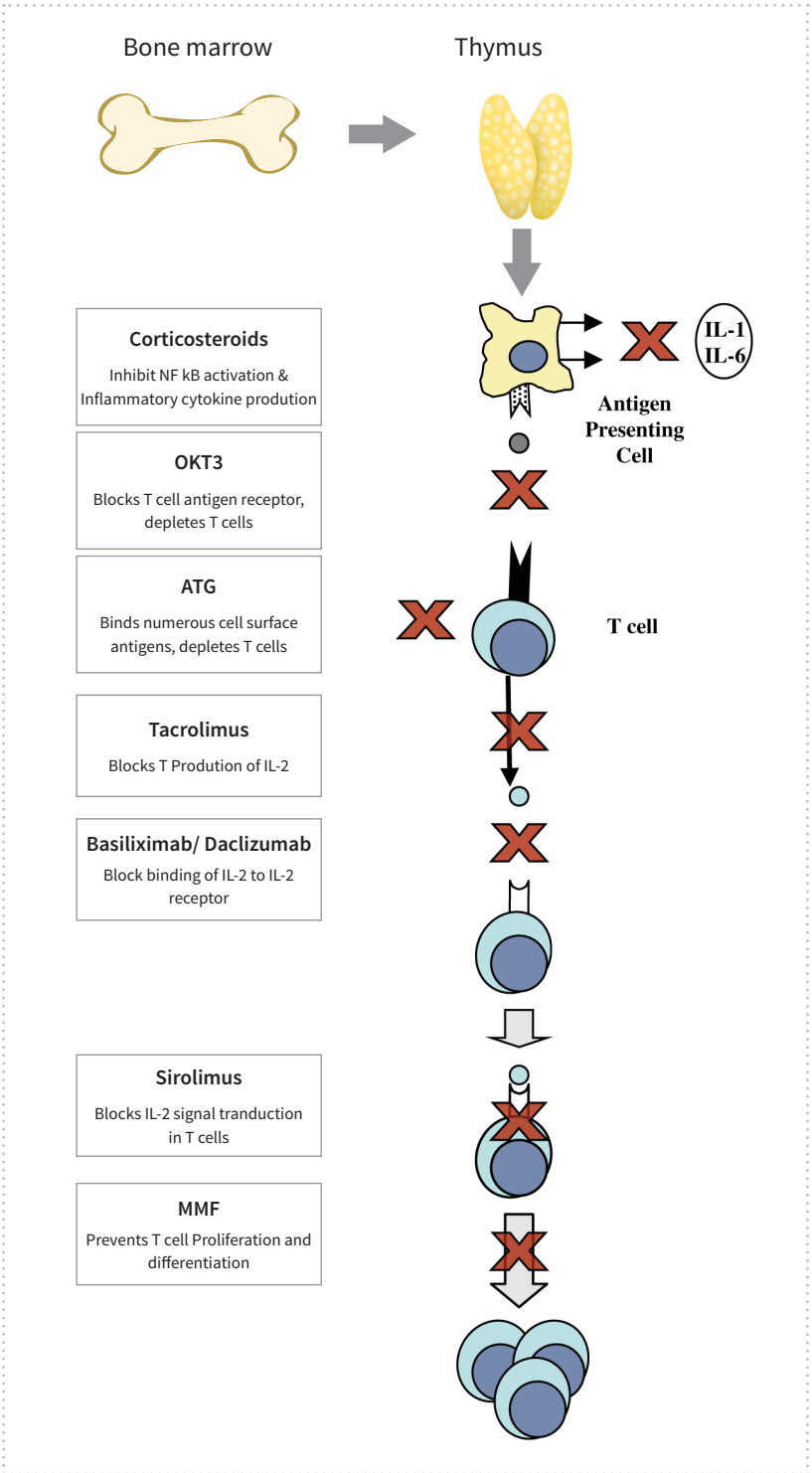


Figure 72. Mechanisms of actions of immunossupressive drugs.

COMBINATION THERAPY

Similar to regimen used in solid organ transplantation, immunosuppressive therapy in patients with a facial allograft consists of an "induction," started in an early stage during or even before surgery, and "maintenance" for as long as the transplant remains in the recipient. Although strategies of immunosuppression diversify slightly from center to center, most of the face transplantation groups employed an induction therapy with polyclonal antithymocyte globulins (ATG), anti-interleukin-2 (IL-2) receptor monoclonal antibodies such as daclizumab and basiliximab, anti-CD3 monoclonal antibodies, mycophenolate mofetil, methylprednisolone, and the calcineurin-inhibitor tacrolimus. Maintenance was typically a triple therapy comprising tacrolimus, mycophenolate mofetil, and prednisolone.[229,230] These drugs were also administered in response to rejection episodes (treatment or rescue therapy).

Steroids are cytokine gene expression blockers and, along with adrenal glucocorticoids have served as a mainstay in immunosuppressive regimens, but are unsuitable for use as solo agents due to increased side effects. However, they are useful in the initial phase of CTA because of their anti-edematous and anti-inflammatory effects.

Prednisolone, the prototype in this class, is analogous to the major endogenous corticosteroid, cortisol (hydrocortisone), but four times more potent in its action. The actions are mediated by subcellular hormone receptors that form steroid receptor complexes, bind to DNA and affect the expression of genes driving protein synthesis and cellular processes.

Tracolimus (FK506) is a macrolide antibiotic, derived from the soil fungus *Streptomyces tsukubaensis* that prevents T-cell activation, suppresses B-cell activation and like cyclosporine is a calcineurin inhibitor. Its main side-effects are hyperglycemia and nephrotoxicity. Tacrolimus (FK506) introduction in 1992 led to a decrease in 1-year acute rejection rates from the previous 50% with cyclosporine-based immunosuppression to approximately 30%. In vitro tacrolimus has been shown to be 100 times more potent than cyclosporine. It is of interest that tacrolimus has been shown to promote nerve regeneration in small animal models after nerve injury. These effects seem to be related to actions of multiple neuroimmunophilin ligands and may be of particular use in instances such as hand and facial CTA where motor and sensory function is crucial for overall function. In fact, this effect of promoting nerve regeneration is thought to be responsible for the 'better than expected' early functional outcomes reported in the clinical hand and facial tissue allotransplants performed.

Tacrolimus has also been used clinically in the form of a topical immunosuppressant for maintenance therapy and to reverse acute rejection episodes in both hand and face transplantation. Topical tacrolimus ointment is also used in the clinical setting to treat various skin conditions such as atopic dermatitis, psoriasis and pyoderma gangrenosum.

Mycophenolate mofetil (MMF) is a modern variant of azathioprin, is an antimitotic agent that interrupts lymphocyte division, by selectively inhibiting the rate-limiting enzyme inosine monophosphate dehydrogenase, required for *de novo* synthesis of guanosine nucleotide. This is essential for proliferation of T and B lymphocytes. Its main side effects are hematological and digestive toxicities.

Mycophenolate mofetil (MMF) introduction in 1995 resulted in the lowering of acute rejection rates. When combined with tacrolimus and corticosteroid, MMF provided 1-year acute rejection rates below 20%.

SIDE EFFECTS

Immunosupressive therapy has many risks and side effects (Table 8). Many are dose dependent metabolic disorders and may include diabetes, Cushing's syndrome, hypertension, renal toxicity, disturbances in blood lipids, thrombotic microangiopathy, and other side-effects [182,192,231], but long-term immunosupression also increases the risk of infection and cancer.[232] Cytomegalovirus (CMV) or Epstein Barr virus (EBV) infections, herpes virus recurrences and fungal infections are more frequent. Bacterial infections can also be expected. The sixth face transplant recipient developed multi-resistant *pseudomonas aeruginosa* on post-operative day 15, affecting the facial graft, requiring tapering of the immunosuppression and surgical excision of the infected tissue.[182]

The incidence of colorectal and lung cancer is increased, as well as cancers where a viral cause is suspected (non-Hodgkin's lymphoma, Kaposi's sarcoma and cervical cancer). Half of all patients receiving an organ transplant will eventually develop cutaneous squamous cell cancer which can be very local aggressive, metastasizing early. Cancer treatment usually includes reduction of immunosuppressive therapy and chemotherapy, which may lead to transplant rejection. In the second recipient of the Lyon/Amiens group, an EBV related B-cell lymphoma occurred affecting the liver, spleen, pancreas, lungs and lymph nodes. Treatment with rituximab resulted in full remission.[233] A pseudo-sarcomatous spindle-cell nodule at the base of the tongue was seen in the Valencia patient and removed surgically without signs of recurrence.[234] Finally, patient 9 was diagnosed with recurrent squamous cell carcinoma under immunosuppression. In this respect neurofibromatosis type 1 as an indication for facial transplantation should be critically questioned, as the development of malignant peripheral nerve sheath tumors may occur under immunosuppression, as already observed following solid organ transplantations.

Table 8. Complications reported in face transplant recipients.

Immunotherapy complications	n
Infections	
Viral (CMV, HSV, EBV, and Poxyvirus)	8
Bacterial (Pseudomonas, staphylococcal, and other) *	7
Fungal (Candida)	3
Rosasea	1
Metabolic	
Acute rejections	14
Renal failure	2
Glucose intolerance/diabetes mellitus	2
Transient leukopenia	1
Severe rhabdomyolysis	1
Neoplasia	
Cervical dysplasia	1
Monoclonal B-cell lymphoma	1
Secondary squamous cell carcinoma *	1
Other complications	
Acute respiratory distress syndrome	1
Right diaphragmatic paralysis	1
Transient thrombocytosis	1
Thrombotic microangiopathy	1

* Complication leading to death. N = number

REJECTION

In facial transplantation, 90% graft survival after 1 year was estimated using current immunosuppressive agents. It was thought that 10 % of facial allografts could fail as a result of acute rejection.[236] However, to date, gross loss of a graft due to acute rejection has not been reported. It was also predicted that chronic rejection could affect 30-50 % of facial allografts at five years [225], but it seems that had less impact than expected. There has been only one report of graft loss of due to intimal hyperplasia in the arteries in more than 80 composite tissue hand transplants, which may have resulted from chronic rejection.[237]

After a FT, episodes of acute and chronic rejection may occur.[238] Acute rejection of a transplant will be apparent within days or weeks. If early signs of rejection (erythema, rash, pinpoint swelling) are visible, skin biopsy, and an increase in systemic immunosuppression should be done. Topical tracolimus and steroids should also be considered. All FT recipients have experienced different acute rejection levels at some point [174,207,214], but were successfully resolved by increasing systematic immunosuppression.[239]

Current immunosuppressive agents do not prevent chronic rejection, which is the major cause of organ graft failure. The skin is also likely to be the principal target of chronic rejection and it will be progressively replaced by fibrous tissue leading to loss of transplant mobility and functional failure. Although a risk of chronic rejection exists, it is not known to what extent immunosuppressive treatment can cause CTA dysfunction over time and shorten life. Moreover, no clinical or histological evidence of chronic rejection has been reported in previous cases of FT. A systematical clinical monitoring is required regarding skin and oral mucosa biopsies.

Noandherence to immunosuppressive medication is well recognized and was possibly the cause of graft failure in the world's first hand transplant.[240] The second facial transplant mortality (in China) was also linked to interruption of immunosuppressant therapy rather than as result of acute rejection.[196] Nonadherence is more frequent in the young and in lower socioeconomic groups.

It's crucial the development of new agents and protocols, and to optimize the genetic matching of the donor and the recipient. New immunosuppressive agents and associations are being studied to reduce their doses and toxicity. Since skin is the most antigenic component, topical treatment with tracolimus and phototherapy have also been used.[179]

Development of more selective molecules with less toxicity to organs (kidney, liver), and strategies to induce specific tolerance are being evaluated and would allow a recipient to accept a graft from a particular donor without the need for continual immunosuppression by creation of a hematopoietic chimerism state. Some centers have used bone marrow infusion, extracorporeal photopheresis, anti-T-cell antibodies, anti-IL-2 receptor antibodies, and X-ray irradiation. Bone marrow was transplantated with the first face transplant, but multiple assessments during the 18-month post-operative period demonstrated haematopoietic microchimerism only on one occasion.

Mesenchymal stem cells (MSC) demonstrate immunoregulatory effects by regulating tissue damage inactivating T-Cells components.[241,242] Intra-arterial infusion of MSCs, seems to be effective to control the cellular immune responses. Conventional bone marrow transplantation [243] can create chimerism but a 28-day delay period is needed before transplantation, and although possible for living solid-organ transplantation this is not feasible for composite allotransplantation, because donors are cadavers. Vascularized bone grafts contained within composite tissue allotransplants can also induce mixed chimerism with partial

myeloablative conditioning.[244] The recent application in different fields of adipose-derived stem cells (ASDCs), created expectation that ASDCs in combination with immussuppression can prolong allotransplant survival, and induction of tolerance through T-Cell regulation.

BIOPSIES

Despite the fact that CTA can be monitored posttransplant by daily inspection of the donor skin, protocol biopsies are used to follow the health of CTA grafts. In most cases, biopsies have been small punch biopsies of the skin. In various cases, a sentinel free flap from the donor such as a conventional radial forearm was transplanted for monitoring the clinical and pathologic signs of graft rejection.[174,231] An example was the first world transplantation where it was transferred as a vascularised sentinel graft on the recipient's axillary vessels. Mucosa and skin biopsies were scheduled every week in the cheek mucosa and sentinel graft for 1 month, then monthly for 4 months. Although the skin of the forearm and face does not have exactly the same thickness, clinical and pathological changes appeared simultaneously on both during the rejection episode. These changes may also appear first on the transplantated oral mucosa which is easier to biopsy, offering another way to monitor rejection. If erythema, edema, or rash are visibly present in the graft, tissue from the affected areas should be sampled. Diagnosis of rejection by biopsy, although it remains the gold standard, can be sporadic because rejection reactions do not affect most grafts uniformly but rather tend to be patchy. Lymphocyte infiltrates are not always detectable even in samples taken directly from skin exhibiting a rash or other visible clinical indicators of inflammation.

INFECTIONS FOLLOWING FACE TRANSPLANTATION

The flora colonizing donor oral and respiratory mucosa, peripheral ganglia and lymph nodes are transferred and predispose recipients to donor-derived infections.

The facial transplantation team at Brigham and Women's Hospital evaluated more than 20 candidates and performed FT in four of these patients between April of 2009 and May of 2011.[245] All the FCTA recipients in their institution received induction immunosuppression with mycophenolate mofetil (MMF) 1 g before surgery, methylprednisolone 1.5 g over 3 days and rabbit antithymocyte globulin (AGT) 1.5 mg per Kg daily for 4 days. Initial maintenance immunosuppresion included MMF 2 g/day, tracolimus (adjusted to a trough level of 10-15 mcg/ml) and a prednisone taper discontinued 60-100 days posttransplant.[214,231,246] Perioperative antimicrobial prophylaxis included vancomycin, cefazolin and micafungin (except one patient) for at least 4 days after surgery, but this regimen was adjusted based on donor and recipient cultures obtained at the time of transplantation. Pneumocystis prophylaxis with trimethropim-sulfamethoxazole and cytomegalovirus (CMV) prophylaxis with valganciclovir were given for 6 months post-FCTA, or longer if acute rejection was observed.

Two other centers report adjustment of perioperative antimicrobial agents depending upon donor and recipient intraoperative culture results.[192,220] The duration of perioperative prophylaxis reported ranged from 2 to 14 days.[182,201]

Reported early infections occurring days to 1 month after transplantation included *P.aeruginosa* pneumonia, Gram-negative pathogens, catheter-related infection, *Enterobacter clocae* bacteremia, Candida stomatis, HSV, molluscum contagiosum and CMV.[174,182,246]

Gram-negative pneumonias were observed in the postoperative period and may be secondary to aspiration events during the prolonged procedures. Since colonization of the donor recipient or donor respiratory tract with Gram-negative pathogens is frequent, as a result of previous hospitalization, an antipseudomonal antimicrobial agent should be included. The patient who underwent full FCTA, and bilateral hand and forearm composite tissue allotransplantation in May 2011 (Boston), developed septic shock in the setting of a new pulmonary infiltrate. Sputum and tracheal aspirate cultures were positive to *Serratia marcescens*, *Proteus mirabilis*, and *P.aeruginosa.* The upper extremity grafts were removed day 5 posttransplantation due to irreversible ischemia that resulted from the low perfusion during the septic shock episode. The recipient completed 3 weeks of cefepime, ciprofloxacin, metronidazole and micafungin after transplant that targeted the pathogens causing pneumonia and donor maxillary sinus pathogens.

A superinfected sialocele can occur due to the remaining donor salivary gland tissue and be responsible for submental fluid collections.[201] It may be preventable by careful dissection of donor gland tissue and can be successfully treated with botulinum toxin injection.

Bacterial parotiditis episodes were observed months/years after transplantation but responded to treatment with cephalexin and dilation/ductoplasty of a stenotic parotid duct.[246]

CMV seronegative patients who received allografts from CMV seropositive donors developed CMV disease 1-2 months after discontinuation of prophylaxis, but recovered with valganciclovir, foscarnet or investigational CMX001(a lipid counjugate of cidofovir) [247] treatment and did not experienced subsequent rejection. In the future, CMV vaccination may have an important role to decrease the risk of disease in CMV donor seronegative/recipient seropositive recipients, in addition to frequent monitoring for CMV viremia and extension of the prophylactic valganciclovir course.

Late infectious complications included viral gastroenteritis, bacterial conjunctivitis, *Clostridium dificile*-associated diarrhea, molluscum contagiosum and HSV reactivation. [174,182,194,248]

Fungal infections were also observed, but may be prevented by inclusion of micafungin in the perioperative prophylactic regimen, as notably, a Candida surgical site infection developed in the only patient who did not receive it previously in the Brigham and Women's Hospital center. A patient also developed tender erythematous nodules on the dorsal surface of both feet, and skin scrapings of the nodules grew *Trichophyton rubrum*, consistent with Majocchi's granuloma, an invasive dermatophyte infection, which resolved with a 3 month course of terbinafine.[246]

An interdisciplinary team approach is necessary for optimal outcomes and to minimize the risk of infectious complications, involving plastic surgery, dermatology, infectious diseases, otolaryngology and radiology.

MORTALITY AFTER FACE TRANSPLANTATION

Three mortality cases have been reported to date after face transplantation. The first patient received concomitant face and bilateral hand transplantations, but postoperatively he developed a multiresistant *Pseudomonas aeruginosa* infection of the allograft which led to septic shock and pneumonia, and died on day 65 post-operatively despite intensive care therapy.[182]

Failure of concomitant bilateral hand transplants in a patient who received a facial transplant, was also described by the Boston team, which were subsequently removed. However, this patient may be considered again for further hand transplantation.

Due to the complexity of concomitant transplantation and the limited experience of facial transplants, Sieminonow *et al* [249] recommended staged reconstruction as the best option; teams will need to evaluate the benefits and risks of concomitant tissue allotransplantation [250,251] and to identify the complexities of cortical reorganization and rehabilitation in this setting.

The Chinese patient died 27 months after the transplant, and it is believed that he discontinued his immunosuppresion and consequently developed multi-organ failure.[191]

The third patient died in consequence of an aggressive recurrent squamous cell carcinoma of the tongue under immunosuppression and a predominant HIV infection. However medical details on the circumstances have not yet been reported. It is very controversial to include as candidates patients with predominant cancer or facial defects due to cancer or oncologic therapies. Due to the potential risks of immunosuppression, they should only be considered as candidates in case of an intact immune system.

2.2. Ethical and psychological issues

Devastating facial deformities can cause significant functional and psychosocial injury. Significant facial disfigurement with soft tissue and bone loss can preclude meaningful human interaction. Facial allotransplantation for reconstruction of devastating deformities has become a clinical reality, with 27 transplants performed at various centers around the world, in France, China, Spain, Poland, Turkey, Belgium, and United States.[176,252,253] Although currently facial CTA is still in an experimental stage, the functional and aesthetic results that have been reported are very encouraging. Patients have achieved, to a great extent, significant improvement in appearance and largely recovered motor and sensory facial functions. [219] This functional restoration has been superior to that achieved by conventional reconstruction, without the morbidity of multiple surgeries.[252] Unlike solid organ transplantation, which can be life saving, facial transplantation is considered by many to be life enhancing, highlighting the ethical argument against justification of these procedures, given the risks of lifelong immunosuppression. Meticulous patient selection is mandatory, and a multidisciplinary team approach is key for the program's success. The overriding goal of screening for candidacy is to identify and select subjects who have the best chance for a positive immunologic, functional, and quality-of-life outcome.[252] In addition, psychological implications for the patient, societal consequences, and ethical concerns, including valid informed consent, have to be discussed.[253] Results to date indicate that the clinical, technical, and immunological patient care issues in this emerging science appear to mirror

those of other reconstructive and organ transplantation procedures. The long-term physical, emotional, and psychological effects on the recipient patient, as well as long-term consequences to the donor's family, are yet to be validated.[253]

Several articles have already been published in order to evaluate the ethical and psychological concerns when performing facial transplantation, including rejection and drug toxicity rates, implications for donor population, correct patient selection and compliance, existence of other reconstructive options, functional recovery, psychological implications, valid informed consent with risks and benefits of the procedure, and the requirements/guidelines for establishing a FT Program.

Rejection rates and drug toxicity

It was the relative success of composite tissue allotransplantation for the hand that made consideration of facial tissue allotransplantation as a viable option.[254] The immunosuppression regimens are basically the same. Some reported one or more episodes of acute rejection that resolved with changes in the immunosuppression regimen. The current thought is that if the episodes of acute rejection are recognized and treated early, they are manageable, and no living recipients have developed chronic rejection, although there are no long-term data.[255]

Implications for donor population

Face transplantation has not been included in any national standard transplantation organization like Eurotransplant, and so, donor selection had to be performed individually and donor family consent had to be obtained. Organ donation relies on the generosity of a pool of donors that is far smaller than the list of potential recipients. The question is whether or not the practice of facial tissue transplantation will decrease the overall availability of organs. This depends on the public's perception of the appropriateness of the use of donated organs, which is closely tied to patient selection. For example, when Mickey Mantle (who developed liver failure from alcoholism) received a liver after being listed for a very short period of time, there was a public outcry regarding the criteria for the allocation of livers.[256] Although liver donations did not decrease after the Mickey Mantle case, the concern is that highly visible failures in facial transplantation may decrease the overall donor pool, affecting all those waiting on transplant lists. Currently there is no indication that face transplants have had an influence on organ donation overall.

Consideration must also be given to the appearance of the donor after the facial tissues have been removed. The appearance of the donor's body has to be respected. Removal must be undertaken by a trained team, but other staff not familiar with the procedure may be present in the theaters. A molded mask of acrylic resin or silicone [257] may have to be considered during graft procurement, particularly if the family wishes to view the deceased. Silicone masks have more natural texture but take too long to produce (10 hours); resin masks can be produced in 3 hours (additional 60 minutes for coloration).

Patient selection and compliance

The patient is the main variable in all considerations of the ethical appropriateness of facial transplantation. Beyond the functional considerations of patient selection for FT, there are psychological and ethical issues that have to be taken into account.

Concerns regarding rejection and drug toxicity must be understood in relation to the individual with the devastating facial defect. Choosing a patient who is relatively young and healthy, who is psychologically stable, and who has multiple reconstructive options left if the transplant fails (i.e., a "lifeboat" or "exit strategy") minimizes the possible risks, leaving possible benefits in the clear majority. An example is Pascal Coler, the 29-year-old French man who was horribly disfigured with a massive plexiform neurofibroma. He is young, healthy, and if his graft is rejected he still has many reconstructive options. The Chinese patient, who was unable to cope with continuing the necessary medications and who lived in a village more than two days' travel from his surgeon, was not so fortunate.

Multiple algorithms and safeguards have been proposed to try to ensure proper patient selection for face transplantation. Obviously the defects addressed should involve areas that cannot be adequately reconstructed with traditional techniques (e.g., eyelids, nose, mouth, and maxilla). Patients must be screened for psychological or psychiatric issues that might impede their complying with medication, or coping with a changed appearance and the rigorous follow-up and constant monitoring required. However, the character of the surgeons and the institutions involved in these operations cannot be downplayed. An algorithm for selecting a potential transplant candidate is only as good as those applying it. Francis Moore stressed this in 1988 when he wrote that innovations in transplantation should not be performed for purposes of institutional prestige or professional recognition.[258]

Individuals with facial disfigurement often experience social isolation and psychological suffering. Some issues are unique to facial transplant recipient patients, such as: [259]

- Difficulties integrating the facial transplant into existing body image and identity;
- Deficits of nonverbal communication;
- Possible lack of improvement in facial animation;
- Dealing with friends and family reactions to a different appearance;
- Anxiety and concern related to transplant failure.

The American Society for Reconstructive Microsurgery (ASRM) and the American Society of Plastic Surgeons (ASPS) proposed guiding principles to assist plastic surgeons before undertaking facial transplantation procedures:

- Facial transplantation should only be utilized in the presence of severe deformities;
- Such disfigurement cannot be helped through conventional reconstructive techniques;
- Facial transplantation should only be undertaken in institutions with appropriate Institutional Review Boards for approval and application of new clinical procedures;
- Should be performed in the context of a transplant team and having appropriate resources;

- The team should include specialists in plastic surgery, immunology/transplant, ethics, psychology, oncology, physical therapy, pharmacology and patient advocacy;
- Appropriate patient selection criteria should be established;
- A risk/benefit ratio must be considered for each patient;
- The patient should be informed with the latest and complete information associated with the facial transplant;
- The patient must demonstrate a thorough understanding of all the known risks and benefits;
- The informed consent should include an alternative solution in the event of transplant failure;
- Candidates should undergo a complete psychological evaluation as well as social support;
- Patients with psychological or psychiatry diagnoses are poor candidates;
- Peer review of the results of facial transplantation is mandatory to assure compliance with medical standards of care and outcomes assessment.

FT is not a "life saving" procedure. The risks of life-long immunosuppressive therapy may outweigh the benefits, however, all FT teams have reported a significant improvement in the quality of life. One of the unsolved issues remaining would be allograft total loss that could lead to a very few reconstructive options for the patient.

Psychological aspects

A thorough psychological evaluation of the recipient is essential, and affective, behavioral, cognitive or perception disorders should be considered as clear contraindications.[260]

In general, patients experience an improvement in the quality of life with a social reintegration, acceptance of a new body image, without psychocologial disorders.[182,261]

Some patients have returned to working life. Measurement of teasing in the fourth face transplant revelead that the patient suffered less teasing, verbal abuse and received more positive affirmations after the transplant.[262] Ratings of depression, body image, quality of life and societal reintegration showed improvements among recipients and were also reported by the the Boston and Spanish teams (Pomahac, Barret). The first recipient experienced psychological acceptance by the twelfth post-operative week, correlated to return of expressiveness.[174] He was able to walk in the street and meet new people without any problems.[194]

After facial transplantation, as predicted by computer simulation [257], the recipient's new appearance will be the result of a combination of both subjects, and different bony structures of each face. So far, there have been no problems regarding the transfer of identity among FT recipients. An age discrepancy due to restrictions on face donors was reported by Lantieri *et al* [182] in their first four transplants, where donors were on average 24 years older then recipients.

To date, three published reports on quantitative psychological testing have been published. Regarding three recipients, Chang and Pomahac found significant improvement on quality of life measures of physical

and mental health based on the MOS-SF 12.[264] Using different quantitative and nonquantitative, subjective quality of life assessments like the Short Form questionnaire 36 (SF-36) and the Derriford Appearance Scale 59 (DAS-59), Lantieri and his team showed quantitative improvements in the quality of life of his first patients, respectively. Three of his patients even returned to work, a fact facilitating their social reintegration.[182] Finally Coffman and Siemionow suggested the introduction of a standard psychological follow-up protocol for further examination after transplant surgery, raising the question of whether a significant improvement of quality of life may offset the risks and side effects of immunosuppression.[265]

Informed consent

The patient should understand the complexity of the procedure, the surgical risks, immunosupression therapy risks, and the likely possibility of CTA rejection.

Informed consent has become the foundation for the interaction between the surgeon and his or her patient and a legal and ethical requirement for invasive interventions. Beauchamp and Childress described seven key elements of informed consent: (1) competence to understand and decide, (2) voluntariness in choice, (3) physician's or researcher's disclosure of material information, (4) recommendation of a plan, (5) understanding, (6) patient decision in favor of a plan, and (7) authorization of a chosen plan. It is not difficult to see the challenges to satisfying these elements in the case of facial tissue allotransplantation. Anthony Renshaw and others had published a thoughtful analysis of informed consent in face transplantation and concluded that the ambiguities surrounding outcomes in this procedure did not preclude proper informed consent.[266] According to these authors much information should be discussed and understood by the patient to give an informed consent, including the following points:

1. **Identity**
   - The face will adapt to the shape of the underlying bony structure.
   - There will be some superficial characteristics of the donor.
   - A "third" face is likely which will resemble the recipient more than the donor.
   - The recipient will not take on the identity of the donor postoperatively.

2. **Immunosuppression**
   - The need for immunosuppression will be life-long.
   - Noncompliance will lead to graft rejection.
   - There are significant side effects of immunosuppression including cardiovascular, infectious and neoplastic complications.
   - Regular, thorough monitoring will be necessary for the rest of the patient's life.

3. Rejection

- Rejection may lead to complete graft loss.
- Graft loss can occur at any time.
- In that case of graft loss, different treatment options will have to be discussed with the surgical team.
- Options include altering medication, conventional reconstructive facial surgery according to an already prepared plan or another facial transplant at a later time.
- Graft loss may result in an outcome worse than the patient's preoperative condition.

4. Psychosocial issues

- Psychological acceptance of the donor face may take a long time.
- Relationships may be challenging, especially in the early stages when family and friends are adjusting to altered appearance.
- Psychological challenges are not yet fully understood.

5. Surgical issues

- The risk of technical failure is about 4%.
- Perioperative risks, including mortality, are similar to other free flap surgery.

6. Functional recovery

- Return of facial sensation and function will be variable and difficult to predict.
- Time frame for functional recovery is likely to be months/years.

7. Media issues

- Media interest is likely to be high, particularly for the first several patients.
- The donor family may become aware of the recipient's identity through the media.
- Because this type of transplant is so new, it is likely that the news media will be very interested in both the donors and the people who receive the transplants. Every effort will be performed to protect the privacy of patients, but it is not possible to guarantee complete confidentiality. The press may find out the names of both the donor and recipient. This may cause problems, including the stress and anxiety that come with such a loss of privacy.

8. General risks

All transplant patients face the following challenges:

- Difficulty following the strict medication dosing after the operation;
- Understanding the complicated side effects and risks of taking drugs that stop your immune system from working normally;
- Swings in emotions following transplant surgery;
- Stress related to study procedures, and other new feelings and thoughts.

9. Facial transplant risks

- Psychiatric support will be provided to all patients before and after facial transplantation. This support will help the patients to cope with this event and learn to live with the changes, both positive and negative, that it brings.
- Risks of taking transplant drugs for a lifetime.
- The medications suppressing the immune response, and thus preventing rejection of the transplanted tissue, have multiple side effects:

Infections:

- It is important that patients receive certain vaccinations prior to transplant (pneumococcal vaccine, flu vaccine, etc.);
- Medications that prevent the occurrence of infections will be given at the time of the procedure and for some time afterwards.

Diabetes:

- Some of the transplant drugs may give rise to diabetes. The blood sugar levels will therefore be monitored and, if needed, anti-diabetes medication will be given.

Cancer:

- Certain cancers are more common in people who have undergone transplantation. This is probably because the immune system after the transplant is not as effective at eliminating very early cancer cells. It is important to note that most transplant patients do not develop serious cancers. Some cancers that are more common after transplant are those of the: skin (especially in white people), lymph glands, and cervix (of the uterus) in women;
- To minimize the chances of having cancer, all patients should be screened before transplantation as follows:
    - Patients over 50 years have a colonoscopy (screening test for bowel cancer);

- All men over 50 years have a PSA (screening test for prostate cancer). Because prostate cancer is more common in African-Americans, they should have a PSA if aged over 40 years;
- All women over 40 years have a mammogram;
- All women have a Pap smear.

- The chances of developing skin cancer are best minimized by thorough protection from the sun. We can also detect other types of cancer early by following guidelines for the general population.

Kidney failure:

- Immunosuppressive medications have a negative impact on kidney function. A small number of transplant patients end up requiring dialysis because of kidney failure caused by these medications. It is therefore very important to test kidney function during the regular visits and change medications as needed to prevent kidney failure from happening. The lifetime risk of losing kidney function is unknown, but it is believed that it should not exceed 10%.

10. Benefits of FT

- We do not know if facial transplants will have more long-term success than standard reconstructive surgery for the face. Probably yes, but there is no guarantee. Although the early experiences have been good, further developments have to be done, specially related to immunossupression therapy.
- There may be less pain and discomfort after surgery (as compared to conventional reconstructive surgery). There will be no other surgical sites on the body where the patient's own skin was removed for use on the face.
- There will be only one large surgical procedure, instead of many smaller ones. The standard way of rebuilding a damaged face involves many surgeries, with time for healing in between.

Requirements/guidelines for establishing a FT Program

There are undoubtedly many institutions worldwide planning to establish composite tissue allotransplantation (CTA) centers in the near future capable of performing facial transplantation. Unfortunately, different countries require inconsistent protocols/approvals through an assortment of various government agencies. Therefore, providing a simple, generic recipe for program establishment would be both misleading and simply impossible. In addition, few previous publications on facial transplantation effectively describe the optimal sequence, timing and steps required for obtaining an Institutional Review Board (IRB)-approved face transplant protocol and/or establishing a program.[267]

M. Siemionow and C. R. Gordon have published in 2010 generic guidelines for establishing a FT program including the pretransplant requirements, such as the logistics of organizing a team (multi-team approach), essential program requirements, IRB protocol details, project funding, the organ procurement organization

(OPO) and the coroner.[268] Although this overview may be more applicable to the U.S. based institutions, they might have worldwide application and be of significant interest to many plastic surgeons pioneering this new transplantation procedure in their respective countries.

Complete evaluation of the current face transplant outcomes and further research in areas such as bioethics and immunology, are undoubtedly warranted prior to anyone considering this surgical procedure as nonexperimental.

2.3. Motor and sensitive reinnervation

FT aims to restore mimic musculature function, swallowing, speaking and to provide aesthetic improvements. Patients had been able to breathe through the nose, smell, eat, chew, recover phonatory function and speech intelligibility. Even with unsatisfactory facial nerve anastomosis, like in the Chinese transplant, the patient was still able to eat, drink and talk normally at two years.[220] Restoration of smell, ability to eat, drink and speak, was decribed in the absence of nerve coaptation by Siemionow et al by 8 months post-transplant.[207] There was also an important reduction of chronic pain levels from scarred and contracted tissues.[192] In the follow-up of four patients, Lantieri *et al* described recovery of intelligible speech between days 10 and 24 post-operatively.[182] Twelve months after the first Belgian facial transplantation for restoration of a severely injured face due to a ballistic injury [269], the speech intelligibility was normal in words, but slightly impaired in sentences due to moderate hypernasality; lip incompetence was also present. Facial expressiveness was present but decreased.

The allograft is initially viable after reperfusion, but its motor activity and sensitivity remain absent at the beginning. With the objective of full sensory nerve recovery, most transplant teams connected the infraorbital and mental nerve, whereas neurorrhaphy of the supraorbital nerve has been performed in 5 cases (Table 4-a). In one case each, connection of the buccal sensory nerve [231] and of the lingual and infra-alveolar nerve [234] has been performed. In 4 cases, sensory nerves were only placed near the corresponding nerve exit point (Table 4-a). The time of recurrence of sensation was thereby dependent on the fact whether sensory nerve coaptation had been performed or not.

Sensory recovery following facial transplant patients has been promising, possibly consequence of the accelerated nerve regeneration associated with the administration of tacrolimus.[270] Between 6-9 months after transplantation, patients returned to normal ranges in terms of warmth and cold, and recover the discriminative facial sensibility. Lantieri *et al* described thermal and sensory recovery in the third recipient by 3 months.[182] Dubernard *et al* [194] al reported that the entire skin surface and oral mucosa of the first allograft was sensate by the fourteenth post-operative week, with complete sensory recovery to light touch, heat and cold achieved by six months. Completed sensory recovery in forehead, eyelids, cheeks, and oral mucosa was noted in the third Spanish recipient by four months.[201] In their first patient, Pomahac *et al* described sensory recovery and two point discrimination to 15 mm by 6 months.[231] Function was comparatively diminished in regions not selectively reinnervated with nerve coaptation.

A successful face transplant will also depend on motor recovery. Recovery of the facial movements allows them to express their feelings and expression. Healing of the muscular sutures, and nerve regeneration along the facial nerve are important factors, but mobile facial expression also depends upon the depth of scarring before the operation. New mobile skin and subcutaneous tissue may move better than the pretransplantated face. Besides facial nerve coaptation, the Spanish team led by Cavadas even performed connection of the hypoglossal nerve.[234]

As far as reported, 12 patients regained their motor functions with varying success rates regarding early results. First contractions of single muscles have been observed as early as 2-3 months after surgery while complex movements appeared within the first year.[182,194,201,214,220,231] The recipient of the first near total FT was given back the ability to smell, drink from a cup, and eat solid food within a very short period of time following surgery. After 5 years the clinical results of the first FT patient exceeded expectations with the recipient being able to fully open her mouth, smile, speak, chew, and swallow again. As long-term results are still pending, a final assessment regarding sensomotorical outcomes cannot be made presently.

Functional recovery of the transplant in association with aesthetic appearance of the recipient will determine the success of such complex procedure.

3. MOCK CADAVER DISSECTIONS FOR FACIAL TRANSPLANT PROCUREMENT

3.1. Facial allotransplantation procurement using a transparotid approach: a new anatomical model

INTRODUCTION

Facial transplantation has emerged as the next step on the reconstructive ladder for severe facial disfigurement which can occur following a variety of events, including ablative surgery, trauma (including burns), and cancer. Full face transplantation is a complex procedure. Adequate perfusion and reinnervation of the allograft are essential, and a detailed plan is needed. In addition, facial anatomies are unique, depending on the extent of the initial injury and previous reconstruction procedures. Pre-clinical research about technical aspects of the facial allotransplantation procedure, including surgical harvesting options, have been investigated in cadaveric models to address different reconstructive needs.[271]

In what concern to functional recovery**,** return of facial sensation and function will be variable, difficult to predict and may take months/years. The facial appearance of the recipient improves gradually together with nerve regrowth, with the changes in expression and the appearance of nasolabial folds. Coaptation to the facial and infraorbital nerves has been particularly challenging because of incongruence between donors, especially in neurofibromatosis.[257]

Reorganization occurs after face transplantation through neuromuscular pathways and sensory and proprioceptive feedback, and successful coaptation of as many major sensory and motor nerves is a key to optimize functional outcomes.

Here we describe a new harvesting option for a face allotransplant procurement; a transparotid dissection was not attempted before.

3.2. Materials and methods

Three mock cadaver dissections were performed, procuring full face transplants with en bloc facial nerve dissection. The dissection was initially in the caudal-cranial direction, instead of cranio-caudal. Neck dissections were first carried out in the subplastismal plane. Facial vessels were identified by dissection from the carotid arteries and jugular veins distally (Fig.73). Submandibular glands were excluded. The bilateral facial vessels were dissected as the allotransplant main vascular pedicle.



Figure 73. Neck approach to find facial vessels.

Facial allografts dissection then followed cranio-caudal and lateral-medial directions as described by Pomahac *et al* [197], procuring allografts that included the fronto-temporo-parietal regions of the scalp to the coronal level, eyelids, nose, muscles of facial animation, lips, motor and sensory nerves, and vessels.

A coronal incision was continued in a cranial direction and in-continuity bilateral preauricular incisions were extended inferiorly to the neck.

Supraorbital dissection was first subgaleal and then subperiosteal, 1 centimeter above the supraorbital rim (Fig. 74).

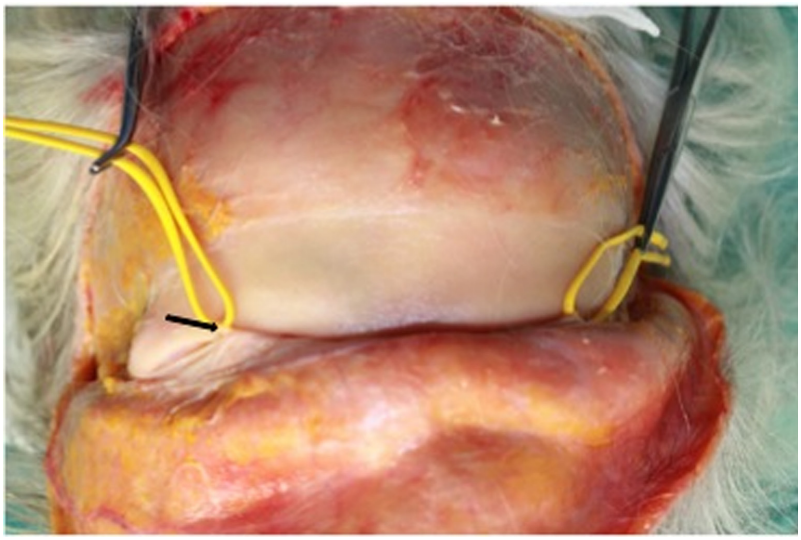


Figure 74. Cranio-caudal dissection was first subgaleal and then subperiosteal until visualization of the supraorbital nerves(black arrow).

Eyelids were included by performing release along the palpebral conjunctival reflection and canthal ligaments (Fig. 75).

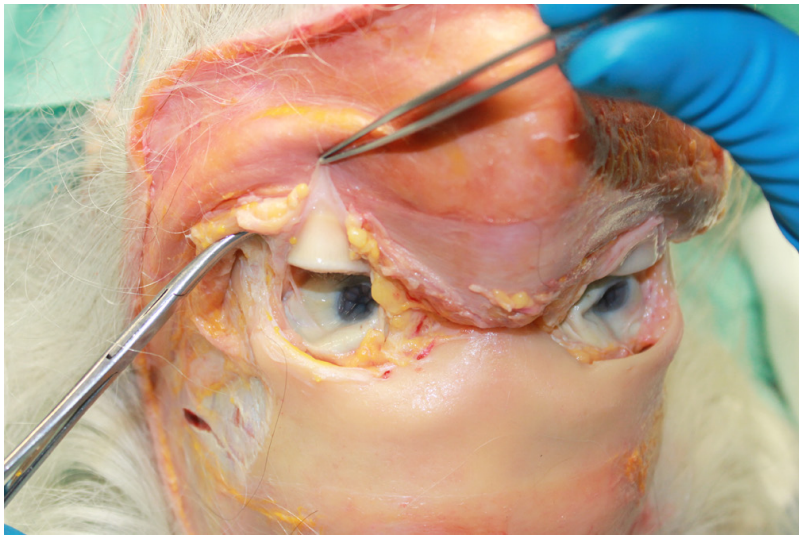


Figure 75. Release along the palpebral conjunctival reflection and desinsertion of the canthal ligaments allowed for eyelids inclusion

Infraorbital dissection was subperiosteal along the anterior maxilla and zygoma (Fig. 76). Osteotomies can be performed according to the recipient needs. In this dissection model, the nasal bone pyramid was included and separated from the malar eminence with an osteotome.

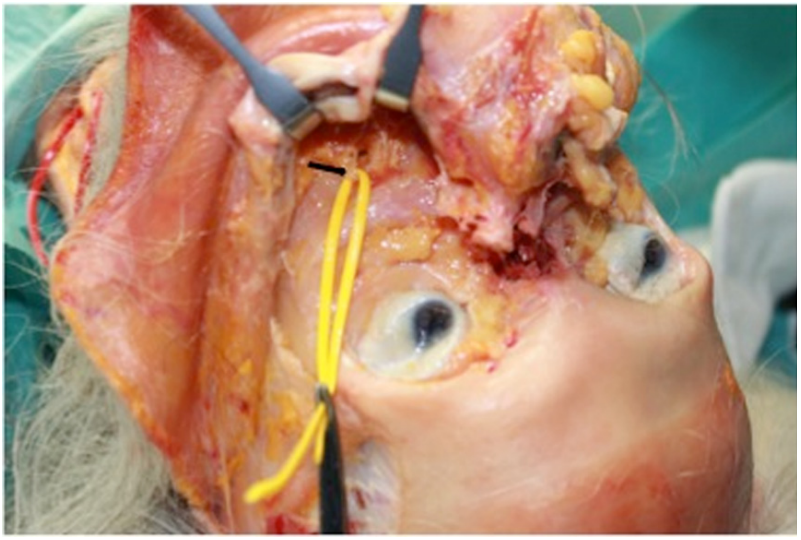


Figure 76. Infraorbital nerve visualization (black arrow).

Preauricular dissections were performed, and facial nerve main trunk was found at the tragal pointer (Fig. 77, *above*, *left*). Transparotideal dissection proceeded with identification of temporofacial and cervicofacial divisions (Fig. 77, *above*, *right*), until final division in temporal (frontal), zygomatic, buccal, marginal mandibular and cervical branches (Fig. 77, *below*, *left*). The extratemporal course of the facial nerve (main trunk, temporofacial and cervicofacial divisions, and individual facial branches) was then elevated en bloc as part of the allograft (Fig. 77, *below*, *right*). The nerves were dissected out from the parotid completely and left as loose attachments to the allograft specimen. Lengthening of all branches (up to 20 mm) was attained just by dissection and mobilization of the parotid gland. Parotid glands were not included in the allografts and the parotid duct was divided.

At the anterior edge of the masseter muscle, perioral tissues were raised in a subperiosteal plane, along the gingivobuccal sulcus and inferiorly to the mandibular border (Fig. 78). The mental nerve was identified at its exit from the mental foramen included in the allotransplant. Neck dissection plane was finally connected with the facial plane and the allograft dissection completed.

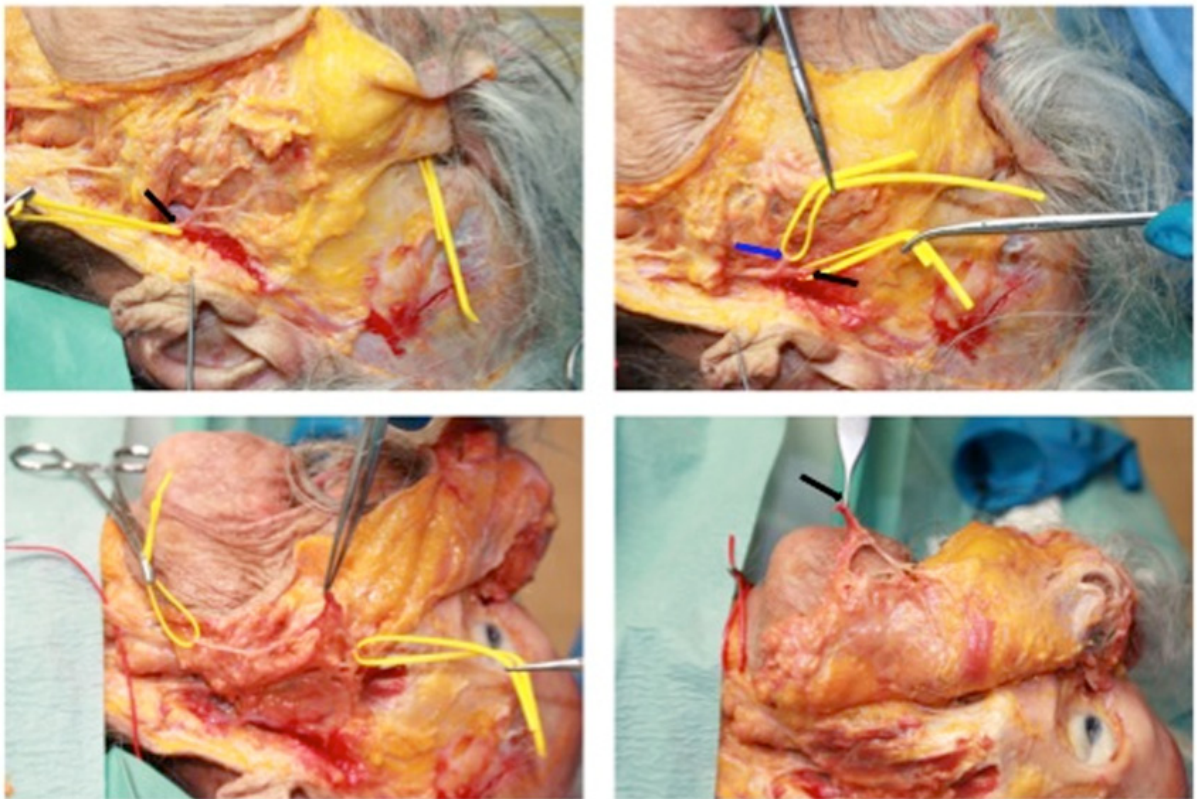


Figure 77. Facial nerve dissection.
Above, left: Exposure of the facial nerve trunk (black arrow).
Above, right: Identification of the temporofacial (black arrow) and cervicofacial divisions (blue arrow).
Below, left: Transparotideal dissection.
Below, right: The facial nerve (with all branches included) was elevated en bloc together with the allotransplant; the black arrow is pointing to the facial nerve trunk.

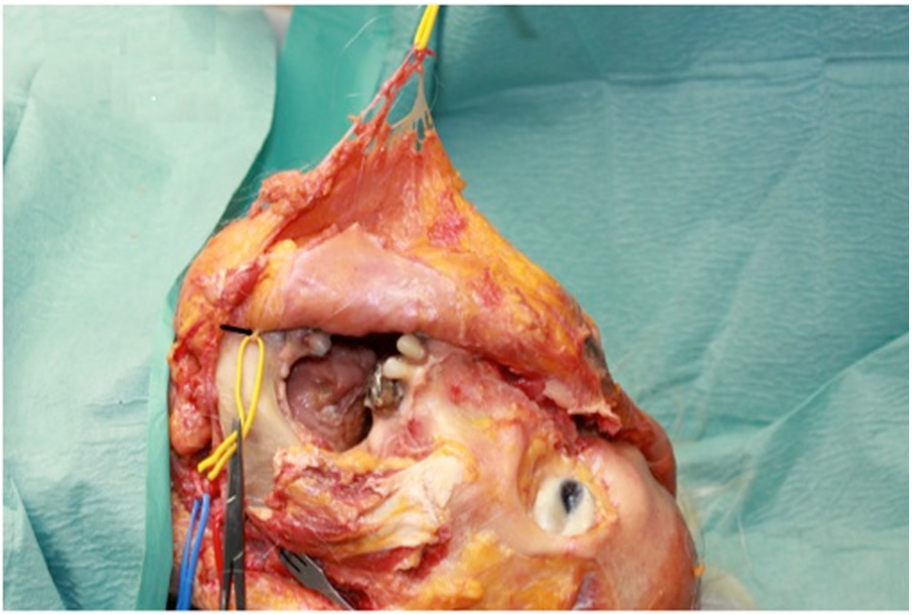


Figure 78. After subperiosteal dissection at the anterior edge of the masseter muscle, the gingival mucosa was cut; the mental nerve (black arrow) was identified and included in the allotransplant.

3.3. Results

We successfully recovered three full face allografts each under 3 hours. We found it easier and safer to connect neck and facial planes by preliminar dissection of the facial vessels, keeping them always protected and their course identified within the elevated tissues.

Full face transplantation with en bloc facial nerve dissection was technically feasible, allowing for more proximal or distal nerve section, and to achieve the desired length and diameter for appropriate matching during nerve coaptation. It also excludes parotid and submandibular glands, with the potential for best aesthetic outcomes.

DISCUSSION

Since the first face transplantation was successfully completed in November 2005 in Amiens (France) [174], facial transplantation has emerged as the most complex solution to restore a near-normal-apperance, and function on the reconstructive ladder for severe facial disfigurement.

Facial transplantation requires the acquisition of a suitable donor with a good tissue match as well as similar cosmetic features. In addition, the patients need to be placed on immunosuppressant medication to prevent rejection. Connecting just one artery and one vein on each side of the face can provide enough blood flow to the transplanted tissues. In an attempt to restore facial function, the surgical team should also connect all the main available nerves.

Adequate planning requires both complete sensory and motor nerve connection and should be part of each operation. The identification of healthy nerves for neurotization in the recipient is of particular importance for successful nerve regeneration within the allograft. However, due to the severity of the initial injury and resultant scar formation, a lack of healthy nerve stumps in the recipient is a commonly encountered problem. To reduce time constraints, Cavadas *et al* [234] performed an elective surgery 3 months before the transplantation to identify and tag the recipient nerves (including the lower divisions of the facial nerves); this approach can help the facial transplantation team.

The evidence for full neurological recovery following neurorrhaphy of facial nerves is generally poor.[272] Insufficient recovery has been attributed to poor pathfinding of regrowing axons, excessive collateral axonal branching at the lesion site, and polyneuronal innervation of the neuromuscular junctions.[273] Reports of the first seven facial transplants performed, claimed sensory recovery from between 3 and 6 months, with acceptable motor recovery commencing between 9 and 12 months.[196]

Sensory recovery of face composite tissue allotransplatation was reported in all patients as nearly perfect at 3 to 8 months after transplantation. In fact, nearly normal sensory recovery can be expected following facial transplantation with or without repair of sensory nerves, maybe because of regeneration from the recipient bed and allograft margins, trigeminofacial communications, nervi nervorum of the facial nerve, preservation of normal density of the receptors within the allograft and therapy with tracolimus (TAC).[271]

However, sensory function of the face graft is unpredictable in consequence to high-energy trauma and large defects. Rodriguez-Lorenzo *et al* [274] performed measurements of the maximum length of dissection for the infraorbitary nerve (IO) and supraorbital nerve (SO) and concluded that SO to IO tension-free nerve transfer is anatomically feasible and may improve the restoration of midfacial sensation by the use of a healthy recipient nerve if IO nerves are not available.

A successful face transplant will also depend on motor recovery. Motor recovery following composite tissue allotransplantation was slower and often less optimal when compared with the sensory recovery outcomes.[191,214,270] Active and passive lips movements were obtained between 6 and 12 months but differ between full and partial facial transplants.[180,194]

Muscles would regain motion through the facial nerve and if this nerve was being dissected proximally, regeneration would take a long time to enable muscular activity within the graft. Neurorrhaphy at the trunk of the facial nerve leads to less targeted postoperative reinnervation, and coaptation of motor nerves as close as possible of effector muscles is the best option, as it allows retention of greater native nerve length. [275] Inclusion of the parotid gland and limiting facial nerve coaptation to the level of the main trunk adds complexity, poor aesthetic outcomes with fullness to the cheeks and synkinesias. Coaptation of motor nerve branches at more distal sites as recently performed by the Brigham and Womans transplant team, is highly desirable allowing faster reinnervation and decreasing the likelihood of synkinesia. However, distal branches may be difficult to find, are thin, fragile and have limited length for safe, tension-free coaptation. In addition, nerve grafts may be necessary.

Recently, nerve transfers were described as an option that could theoretically be used in face transplantation either as a primary nerve reconstruction when there are no available healthy nerves, or as a secondary procedure for enhancement of functional outcomes.[276] The supraorbital nerve, branches of the

cervical plexus and the masseter nerve are usually located out of the zone of injury and can be selected as neurotizers for the infraorbital nerve, mental nerve and buccal branch of the facial nerve respectively.

All surgical team members should participate in a series of mock, fresh-cadaver facial transplants exercises to ensure all details are complete, to define each surgeon's role and for optimizing the team dynamics and effectiveness. This is essential to decrease potential delay, technical problems and post-operative complications.

Each case is unique and facial transplantation is an original work for each patient. The precise amount of tissue requested, has to be dissected from the donor, including salivary glands, muscle, bone, and even the whole maxilla. It is never the same block of tissue, further adaptation is needed, and a transparotideal approach can be a possibility only when indicated in each particular situation.

In this study, facial vessels were first identified by dissection from the carotid arteries and jugular veins distally. We decided to perform this modification, because we found it easier and safer to connect neck and facial planes by preliminar dissection of the facial vessels. In addition, and according to same clinical observations [197], in some cases there will be no time for the facial transplant recovery before aortic cross clamping and recovery of live-saving organs. In these situations, visualization of the vascular pedicle facial will be necessary before physiologic perfusion is lost. The bilateral facial vessels were dissected as the allotransplant main vascular pedicle.

The most important modification was introduced, and was related to the facial nerve approach. The transparotid approach can give to the surgeon the option of dissection to the level of temporofacial and cervicofacial divisions or final branches, avoiding section at the level of the main trunk, reducing the likelihood of occurrence of synkinesias (Fig. 79). This technique implies an anterograde dissection from the trunk which may be may be easier to perform in some circumstances than a retrograde dissection after finding the distal thin and fragile branches, medial to the parotid gland. It is quite versatile, as it allows to achieve the desired length and diameter for appropriate matching during nerve coaptation and adaptation to the preserved and remaining recipient's anatomic structures, so it can avoids the need for interposition nerve grafts (thoracodorsal, great auricular) that were required in previous cases of full face transplantation. It gives various neurotization possibilities (Fig. 80): direct division to division or branch to branch neurorrhaphy; cross-division neurotization; division to proximal branches coaptation; or division to distal branches with interpositional grafts (e.g. thoracodorsal, great auricular). It also excludes the parotid gland from the allograft (reduces bulk).

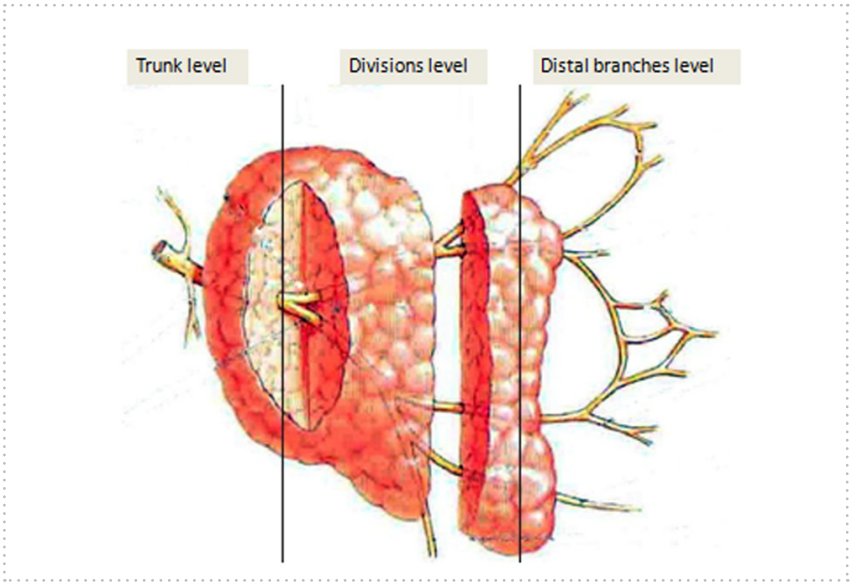


Figure 79. Options for nerve section in a transparotideal approach.

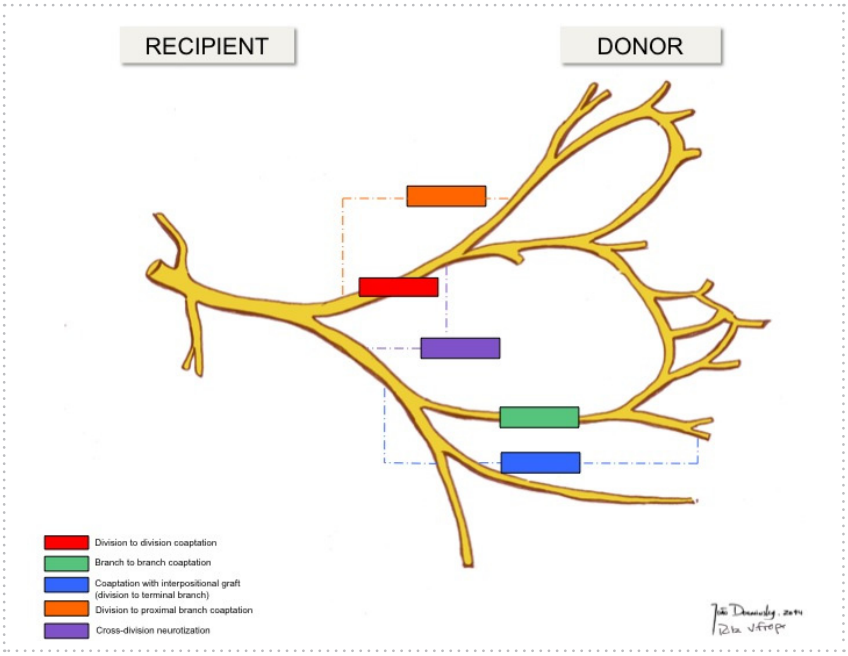


Figure 80. Neurotization possibilities in a transparotideal approach.

3.4. Conclusions

This technique follows principles of targeted nerve reinnervation. It allows to select the level of facial nerve section to the temporofacial and cervicofacial divisions or final branches, with further adaptation to the remaining recipient's anatomic structures, and avoiding the need for nerve grafts; it also excludes the parotid gland (reduces bulk). Despite a small increase in the time required for dissection, this approach may increase harvesting options for reconstructive surgeons who are interested on performing facial transplantation, or have already done but were not satisfied with their functional results.

CHAPTER IV

FINAL CONCLUSIONS AND FUTURE PERSPECTIVES

1. Autologous reconstruction in the head and neck

The goal of head and neck reconstruction is to restore normal form (aesthetic recognizable appearance), and function (restoration of normal eating, breathing, smelling, and facial expression for social interaction and communication). The reconstruction of acquired facial defects and deformities resulting from trauma, burns, and tumor resection has always been a great challenge for surgeons because of the complex facial anatomy, and its contribution to each patient's Identity formation providing the basis for social interaction. Surgical intervention should ideally result in both functionally and aesthetically satisfying results. A major difficulty is that we are dealing with highly specialized tissues and complex three-dimensional problems. The best results are obtained by repair using "like-tissue" but usually local tissue is not available, and regional or distant autologous tissue is necessary.

Conventional autologous reconstruction in the head and neck has undergone a revolution, as microsurgery has evolved and expanded our ability to reconstruct the most complex defects. Our work demonstrated an evolving perspective of head and neck reconstructive surgery that has developed in parallel with new concepts of flap vascularization and harvesting principles, microsurgery, prefabrication, and face transplantation. [25,151-153,172, 277-283]

Current reconstructive procedures never lead to complete functional restoration. This is highligthed in the rare instances where traumatically avulsed scalp and face are reattached using microvascular techniques, contrasted with the ocasions when the amputated parts are not available. Conventional reconstructions often involve multistage procedures, but despite our best efforts, which include tailoring and planning of these multiple flaps, these interventions never quite exactly recapitulate the facial features. A consistent plan is needed from the start so as not to "burn any brigdes" along the way. Facial subunits (hair bearing beard, sideburn, eyebrow, etc.) and mucosal surfaces (buccal, nasal, conjuntival) should be evaluated, as well as the volume and composition of the missing tissue.

However, these patients do not need to take immunosupressive medications and harbor the associated risk of immunosuppression for the rest of their lives. It is important to continue to develop and improve our methods of reconstruction, and offer acceptable alternatives to transplantation, or after failure or a complication of allotransplantation.

Use of newer techniques like using navigation during surgery, computer aided designing (CAD) and virtual surgery, stereo lithographic models, customized implants, robotic surgery, and tissue engineering, are searching solutions. The DaVinci Surgical System can reach inaccessible regions easily, while the surgeon performs the procedure in a comfortable sitting position at the consol, using 3D, endoscopic, microscopic image and sensitive controls from a remote place. Currently, robotic surgery is being used for resection and reconstruction of tumors at base of tongue and larynx, avoiding a mandibulotomy for access.[284]

Regenerative medicine techniques have the potential to restore facial functions while minimizing the risks associated with traditional reconstruction procedures. Tissues can be regenerated or replaced from specific biologic mediators or scaffolds. Progresses have been undetaeken in the understanding of cell-cell interactions, the selection of appropriate matrices (cell-matrix interaction) and chemical signalling (cytokines,

growth factõrs) for stimulation of cell proliferation and migration within a tissue-engineered construct. Natural collagen, demineralized bone matrix, acellular matrix; or polymers — polyglycolic acid or metal — titanium are used as a scaffold at present, followed by in-vitro growth and maturation, to produce tissue such as cartilage and bone.

Gene therapy and immune system targeting are being explored as a way to attack tumors at cellular/molecular level and will determine the role of surgery, chemotherapy and radiotherapy in cancer treatment.

The early experience with CTA has been very promising and yields results that are superior to those achieved using conventional methods of reconstruction. However, it will be synergistic efforts in both CTA and conventional reconstruction to take us to the next level of full face restoration.[285]

2. Facial transplantation in Portugal - are we ready?

Face transplantation has provided a new paradigm of options to restore in one stage what in the past has been performed in multiple stages with multiple combinations of free flaps and local/regional flap options. It couples the principles of microsurgical reconstruction with those of human organ transplantation, and has emerged as a new strategy for restoration of extensive damage, or loss of greater parts of the face.

The department of Plastic and Reconstructive Surgery - Centro Hospitalar São João, has always been a pioneer in Portugal in terms of research and has always followed the technical development of the specialty. The pioneering vision of Professor Jose Amarante also contributed, encouraging to visit and trainning programmes in world reference centers. In my particular case, I had the opportunity to receive training in a prestigious center, where I improved my technical and theoretical knowledge about complex reconstructions, mainly in the head and neck. There, I have also initiated my research in CTA (composite tissue allotransplantation). Actually, our department have some elements with good skills in microsurgery and experience in complex reconstructions. It now presents a more detailed knowledge regarding facial allotransplant procurement, after we have performed cadaver dissections. We have also developed a new method (facegram) for spatiotemporal analysis of the facial excursion and facial reinnervation. Other plastic surgery departments in Portugal certainly have the capacity to do it, if necessary.

Due to its inherent complexity, facial transplantation should only be performed by university-affiliated medical institutions capable of orchestrating a specialized multidisciplinary team with a long-term commitment and dedication to its success. A single staff member familiar with microsurgery and/or interested in CTA does not mean that a successful program will be achieved. It must be emphasized that face transplantation is still experimental and its therapeutic value remains to be validated. A detailed plan should be in place by months and years, given the possibility of a team leader moves or retires.

The team should incorporate a network of reconstructive microsurgeons, craniomaxillofacial surgeons, infectious disease specialists, radiologists, social worker, ethicist, transplant psychiatrists/psychologist and immunologists. The surgical team should be composed of at least 6 to 10 staff surgeons, with a combination of microsurgical-trained plastic surgeons, residents and maxillofacial surgeons for simultaneous dissection of the donor and recipient. They should be responsible for the evaluation of the facial defects and functional limitations, in order to estimate the potential aesthetic and functional benefits of facial transplantation. The donor team should work to recover the allograft, and the recipient team should be responsible for removing the overlying layers, and isolating relevant structures with emphasis on preservation of functional units.

Patients considered for facial transplantation should be evaluated by clinical inspection, Angio-TC-Scan and MRI examination. The candidates should be properly informed, and assume the risks attendant. The process should continue with the submission on a case-by-case basis to the Ethics Comittee. If accepted, it should be submitted to the regional and national transplant institutes for final administrative approval. During this period an individual reconstructive plan should be delineated.

We think that we are ready for such complex technical procedure, and more important, to restore patient's life and well-being, if no other options are available. However, the patient should constitute a good candidate, understanding the potential complications while desiring the procedure.

3. Facial transplantation - it will remain experimental or will become clinical routine?

Some facial defects can simply not be adequately restored using conventional methods. The patients with such deformities should be identified early, and have a minimum salvage type of reconstruction, as end results are likely to be disappointing, donor sites become depleted, and potential salvage options may become limited.

With the experience of 27 cases to date, demonstrating the feasibility of the procedure, face transplantation seems to have become a viable reconstructive option for severely disfigured patients. Clinical and psychological results are encouraging and to date there has been no case of transplant loss. However, with exception of the first case, there is a lack of mid-and-long-term reports analyzing functional, psychological, and aesthetic outcomes after a longer period of time. The risk of a potential transplant loss due to chronic rejection stays remarkable, and to date it is still unclear which treatment options would be applicable in this particular case. Post-operative revisions may be also necessary to achieve optimal functional and aesthetic results; these may include soft tissue revision, hard tissue mismatch, and craniofacial skeleton and dental occlusion. Although revising a facial transplant may potentially risk the integrity of the graft, appropriately chosen revisions may provide great benefit.[286]

Although early results are encouraging, there is still a lot of work to do until completion of this procedure could generally be recommended. The pioneers and newcomers in this surgical field should pool together their results and try to develop guidelines and standard protocols for the implementation of the procedure. Evaluating the chances and optimizing the process of FT might be easier, if all recipients were included in standardized follow-up protocols, making it possible to compare the results, and to work out unsolved problems with the objective of improving knowledge.

Regarding immunosuppressive therapy, research has to be done and alternative protocols should be tested. As long as the occurrence of side effects and complications due to the immunological therapy remains high, or until long-term survival of allografts and the patients has been proved, facial transplantation will stay experimental and will not be considered as a routine practice, leaving surgeons and patients in uncertainty on the final outcome.

FINAL CONCLUSIONS

Despite eight years of experience, facial allografts are still an exceptional reconstructive option that should only be considered for certain cases. Early results are encouraging, but there is still a lot to be done regarding immunosuppressive therapy, and to improve functional results (targeted reinnervation). In the long term, face transplantation may be replaced by more compatible reconstructive options reducing the risks and improving the results, possibly based on tissue engineering principles. Tissue engineering, which aims to create tissue-matched, prefabricated, prevascularised bony and/or soft tissue composite grafts, therefore has the potential to revolutionise the future of plastic and reconstructive surgery. In the future, we may have tissue banks to supply readymade body parts for reconstruction. But till such time, the reconstructive surgeon should use current methods of reconstruction, and have some kind of experience with microsurgical workhorse flaps in head and neck reconstruction (e.g., free radial artery forearm flap, free ALT, free fibula osteocutaneous flap), or even pedicled flaps such as pectoralis major myocutaneous flap.

Our work showed several options for the reconstruction of severe defects, in order to provide the best aesthetic and functional results, as well as different methods to evaluate patients with facial disfigurement. If autologous techniques are insufficient, facial allotransplantation may have to be considered as an alternative; the dissection technique here described may increase the harvesting options for reconstructive surgeons and gives various neurotization possibilities to optimize nerve coaptation and motor recovery. Furthermore alternative strategies for the reconstruction of severely disfigured patients should be considered.

CHAPTER V

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CHAPTER VI

ORIGINAL PUBLICATIONS

PUBLICATION I



HEAD AND NECK SURGERY

Reconstruction of Middle Third Defects of the Face With the Temporal Flap

Ricardo Moreira Horta, MD, Rui Barbosa, MD, Marisa Marques, MD, Marco Rebelo, MD, António Ferreira, MD, Jorge Cruz Reis, MD, and José Manuel Amarante, MD, PhD

Abstract: The temporal flap is of great interest in head and neck reconstruction when a skin graft or a local flap cannot be used. It has shown important results on the facial reanimation and in oncological surgery. We describe our experience with the pedicled flap in reconstruction of the middle third face defects in 8 oncologic patients. This flap allows the covering of bone and noble structures such as the periorbital, auricular, frontal, or parotid gland areas. Few major or minor complications were seen and good aesthetic results were achieved. It also can be done with or without adjuvant radiotherapy. The patient prognosis however, depends on the stage of the tumor.

Key Words: temporal flap, tumor, face, reconstruction

(*Ann Plast Surg* 2009;63: 288–291)

The temporal muscle gives a versatile and reliable flap, which has been regaining its interest on oncological surgery of the head and neck. It's particularly useful in reconstructions for which the ideal is a flexible muscle, moderately thick, adaptable to the dimensions and shapes of the defect. Its use as a pedicled flap is thorough documented, showing results confirmed on the facial reanimation and in the reconstruction of the orbit floor, the basis of the skull, middle third of the face, oral cavity, and oropharynx.[1,2]

We hereby describe our experience with the conventional pedicled flap of the temporal muscle in the reconstruction of side defects of the middle third of the face in 9 oncologic patients, from 1999 to 2007.

STUDY MATERIAL

The clinical processes of internment and appointment of 9 consecutive patients were reexamined, within a period of 8 years. These patients underwent a reconstructive surgery of the auricular, parotid, frontal, zygomatic, and orbital areas with the temporal muscle flap. The cases of reconstruction with the temporal muscle for nononcological causes weren't named in this article.

METHODS

The flaps were lifted according to the conventional technique. The temporal muscle has its origin in the temporal cavity and temporal fascia, it goes underneath the zygomatic arch and it is set in the coronoid apophysis and the preceding section of the jaw. It has 2 dominant pedicles, the deep temporal blood vessels, anterior and posterior, coming from the intern maxillary artery and the respective veins. The pedicles penetrate the deep surface of the muscle near the zygomatic cavity. The muscle was exposed by a hemicoronal scalp incision and the lifting of 2 dermoadipose flaps. After the division of its insertion in the temporal bone, the muscle is dissected to the subperiosteal level, with a dissector instrument in direct contact with the bone, to avoid the lesion of the pedicles, to the level of the zygomatic arch. The flap is lifted to the subperiosteal level of the deep surface of the zygomatic arch. Here, the muscle is transferred to the defect, folded over its inferior part. On case 2 the flap was transferred to the defect underneath the zygomatic arch. On case 6, the dissection of the flap included a margin of the pericranium. All flaps were covered with a split-thickness skin graft.

RESULTS

Nine patients, 5 men and 4 women, (average age: 71.67 years; limits: 66–88 years) underwent an oncological ablative surgery with immediate reconstruction, using a temporal muscle flap, between September 1999 and August 2007. The average area of the reconstructed defects was 39.56 cm^2 (limits: 20.4–55.3 cm^2).

In case 6, a 88-year-old patient, with basocellular carcinoma of the orbit did not survive the postoperative period, dying of myorcadium infarct. Other patient (case 8), died of cerebral metastization of the tumor. The average follow-up of the remaining cases was 30.5 months (limits: 12–70 months). Eight patients went through radiotherapy (pre- and postoperative on cases 1 and 2, preoperative on case 5 and postoperative on cases 3, 4, 7, 8, and 9—Table). No flap was lost. In case 5, it was noticed a partial necrosis with dehiscence of the flap after local infection, which demanded another surgery and coverage with a pectoral major myocutaneous flap. In case 1, we can see a depression in the alopetic area of the temporal zone with a protuberance at the level of the zygomatic arch, 5 years after the surgery (Figs. 1–6).

DISCUSSION

The temporal flap was initially described by Lentz in 1895. This flap has been used in the reconstruction of the periorbitary defects, mastoid, maxillar, basis of the skull, and oral cavity.[1]

When a skin graft or local flaps are not available options for coverage of face defects, the use of regional or distance flaps is necessary. The surgeon must consider the aesthetic and functional morbidity created by the selected flap. The regional muscular, myocutaneous or fasciocutaneous flaps used for reconstruction of the head and neck as the pectoral major, trapezius, latissimus dorsi, or deltopectoral flaps have some restrictions resulting from its volume and donor zone morbidity, which cause considerable aesthetic deformity as well as the inconvenient of being subjected to the induced traction by movements during the cicatrization phases. The free flaps are an excellent option, however, they may be connected to morbidity of the donor zone, increased surgery time and the need for a crew with microsurgery experience.

The temporal muscle has a reliable and constant vascularization, apart from the simplicity of the technique of dissecting the flap with the availability of a volume of well-vascularized tissue that can be cut so that the reconstruction of the defect with minor sequels on the

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FIGURE 1. Volumous right parotid gland carcinoma.

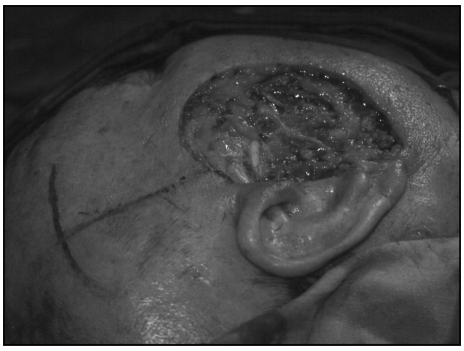


FIGURE 2. The defect after ablative surgery.



FIGURE 3. Dissection of the temporal flap.



FIGURE 4. The flap in place.



FIGURE 5. Final result after 1 year.

donor zone can be performed. The flap is available by a hemicoronal incision which is disguised on the scalp and the preauricular sulcus. The flap and the defect are approximately in the same surgical field, narrowing down the time of surgery and the concern with induced traction by movements, postoperatively. Its use may be extended by continuing the dissection to the pericranium, allowing more complex reconstructions.[3]

The rotation arch is a limitative factor.[3] The temporal muscle does not get defects in the middle line, just one small part of the muscle gets more medial defects and the most part of the volume remains in the pedicle.[4] This flap cannot be used when the intern maxilar vessels or the ipsilateral external carotid were sacrified.

The major complications include a permanent lesion of the temporal section of the facial nerve and the loss of the flap. The

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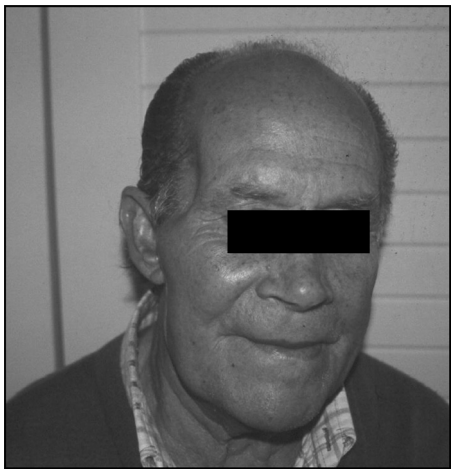


FIGURE 6. Temporal depression and zygomatic proeminence.



FIGURE 7. Frontozygomatic squamous cell carcinoma.



FIGURE 8. Large defect after tumor removal.

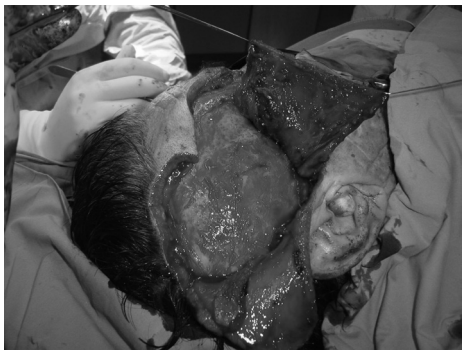


FIGURE 9. Dissection of the temporal flap.



FIGURE 10. The flap in place.



FIGURE 11. Split-thickness skin graft over the muscle flap.

minor complications include infection, seromas, a temporary nervous paralysis, alopecia, trismus, depression of the donor zone, and the protuberance at the level of the zygomatic arch.[1] In 2 cases, there

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FIGURE 12. Final result after 2 years.

was a lesion of the temporal branch of the facial nerve with definitive paralysis as a consequence of the tumor resection and not of the dissection of the flap. In the first case, in a bald patient, we can see a depression of the donor area of the flap and the moderate protuberance at the level of the zygomatic arch; these complications may be avoided by preserving the anterior 1/3 of the muscle in patients with temporal alopecia and by transferring the flap underneath of the zygomatic arch. In case 2, the flap was replaced underneath the zygomatic arch by the defect of the parotid gland area; in this way the zygomatic zone was avoided. In case 5, there was a partial necrosis with dehiscence of the flap; it was necessary to perform a second procedure and provide coverage with a pectoral major myocutaneous flap. There were no records of other complications and a good aesthetic result was in general seen (Figs. 7–12).

CONCLUSION

The flap of the temporal muscle may be a good choice for the reconstruction of the side defects of the middle third of the face after the ablative oncological surgery. This flap allows the covering of bone and the noble structures with well vascularized tissue and immediate placement of a split-thickness skin graft; it also may be done with pre and/or postoperative radiotherapy. The chance of complications is small and the results are aesthetically acceptable, although the final results and the patient prognosis are correlated with the tumor stage, size, and histologic aggressivity.

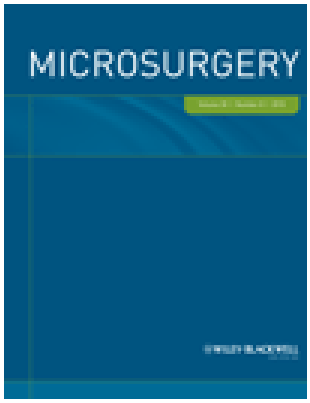
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PUBLICATION II



LETTER TO THE EDITOR

MICROSURGERY 31:164–166 2011

FACIAL REANIMATION WITH GRACILIS MUSCLE TRANSPLANTATION AND OBTURATOR NERVE COAPTATION TO THE MOTOR NERVE OF MASSETER MUSCLE AS A SALVAGE PROCEDURE IN AN UNRELIABLE CROSS-FACE NERVE GRAFT

Dear Editor,

Surgical treatment of unilateral long-standing facial paralysis requires transposition of new musculature to restore function and a microneurovascular free-muscle flap is the procedure of choice.[1–3] The gracilis muscle has been used with success but one of the critical factors of this procedure is the selection of a motor nerve to innervate the transplanted muscle. To achieve synchronous and spontaneous activity, the contralateral facial nerve is used by means of a cross-facial nerve graft when available.[4,5] In 1995, Zuker et al.[6] successfully used the nerve of the masseter muscle, branch of the trigeminal nerve in the treatment of Moebius syndrome (bilateral palsy), and the results suggested that this technique could be an option for treating unilateral facial paralysis as well. A comparison of commissure excursion following gracilis muscle free flap with a cross-face nerve graft versus the motor nerve to the masseter muscle was performed by Bae et al.,[7] showed that the extent of movement was greater using the masseteric muscle. Clinical analysis of different techniques,[8] also found that one-stage unilateral facial reanimation with gracilis muscle innervated by the motor nerve to the masseter, produced more predictable and consistent results and the extent of movement is greater. However, the cross-face nerve graft provides a more spontaneous movement which is crucial in producing a normal appearing smile, but there is usually less movement and it is not suitable for the older patient (reinervation is difficult). Manktelow et al.,[9] speculated that there may be a larger role for the masseter motor nerve in innervation of patients with unilateral paralysis. The majority of patients develop the ability to smile spontaneously and without jaw movement.

We report a case of a 32 years old man with established facial paralysis as sequelae of surgery for an acoustic neuroma (vestibulocochlear nerve tumor). (Fig. 1) We had chosen a cross-face sural nerve graft as we believed that the two-stage method provide better symmetry at rest and a spontaneous smile. During the first-stage a sural nerve graft (segment of 12 cm length) was harvested, coaptated to a buccal nerve of the facial nerve and transposed subcutaneously above the upper lip onto the contralateral hemiface. After 12 months, a second stage surgical procedure was planned for gracilis muscle transplantation. During the surgery, we found that the length of the sural nerve did not allow it to reach the contralateral facial side at the exact point for neurotherapy to the anterior branch of the obturator nerve and it was surrounded by fibrosis. After a rectangular portion of the gracilis muscle (7 × 6 cm) was settled into the cheek pocket, the obturator nerve was therefore coapted to the motor nerve of the masseter muscle, and microvascular anastomoses were done to the facial vessels. The postoperative course was uneventful.

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Figure 1. Established facial paralysis as sequelae of surgery for eighth nerve neurinoma.

Time of onset of contraction (reinnervation) was 3 months without difficulty coordinating flap function with contralateral mimetic musculature. Electromyographic analysis was not necessary due to clinical results and objective functional recovery. The facial and thigh surgical wounds healed normally.

Results were rated according to the classification of Terzis and Noah.[10] Symmetry with good tone at rest, full contraction with symmetrical smile and teeth showing was seen (Fig. 2) - grade V: excellent.

A tendency toward increase in motor nerve conduction velocity can be seen even 3 years after the sural nerve graft, suggesting that existence of another distal suture is a factor limiting motor nerve conduction velocity recovery although the graft nerve has the potential to recover over a long period of time.[11] The condition of nerve coaptation or scarring are other influential factors. The enormous advantage of the masseter nerve-free tissue transfer technique is that, unlike the cross-facial nerve, the masseter nerve donor produces a movement and muscle excursion (in relation to smile and commissure excursion) in normal range with consistent movement. This is the reason why we believe that this salvage procedure can ensure better results than neurolysis, nerve graft elongation or a new cross face nerve graft.

We found it interesting as a salvage procedure, in cases of an unreliable cross-nerve match due to technical problems (insufficient length, fibrosis) and in our experience in unilateral and bilateral patients, the masseter nerve provides a powerful and reliable innervation to a free muscle transfer. Although the trigeminal nerve does not include emotional movements, the patients can achieve some degree of automaticity of movements (mastication and smiling).



Figure 2. Full contraction with symmetrical smile.

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PUBLICATION III



TECHNICAL STRATEGY

Ear Replantation After Human Bite Avulsion Injury

Ricardo Horta, MD, António Costa-Ferreira, MD, Joana Costa, MD, Pedro Silva, MD, José Manuel Amarante, MD, PhD, Álvaro Silva, MD, and Rita Filipe, MD

Abstract: Traumatic auricular amputation due to human bite is not a common event, but it constitutes a difficult challenge for the reconstructive surgeon. Microsurgery can be performed in some cases, but replantation of a severed ear without microsurgery can be a safe alternative.

We present a case of a 44-year-old male individual who was involved in a fight and sustained a human bite, resulting in almost a complete amputation of his right ear. The Baudet technique has been used successfully. It is a simple technique and very reliable because it allows a great surface of contact between the graft and the vascular bed, substantially increasing its odds of survival in cases presenting with high risk of infection such as human bite injury. It also produces excellent aesthetic results.

Key Words: Ear, amputation, human bite, replantation

(*J Craniofac Surg* 2011;22: 1457–1459)

Traumatic auricular amputation due to human bite is not a common event, but the morbidity of a total or near-total ear amputation is severe. It constitutes a difficult challenge for the reconstructive surgeon to salvage an amputated ear segment.

Microsurgery can be performed in some cases, but even in the presence of a clean-cut amputation, most microsurgical techniques are complex because of vessel damage. Replantation of a severed ear without microsurgery can be a safe alternative as long as a proper technique is selected. The Baudet[1] fenestration technique of ear reattachment, with partial burial of the amputated part in the retroauricular region, is still one of the best options to consider in these challenging traumatic injuries.

CLINICAL REPORT

A 44-year-old male individual was involved in a fight and sustained a human bite, resulting in almost a complete amputation of his right ear associated with severe crushing injury of the amputated segment. Only the ear lobe was left intact. The patient was transferred to our institution for an attempt of replantation. The amputated auricle was placed in a plastic bag with saline, surrounded by ice, and brought to the emergency room with the individual (Figs. 1 and 2). The patient was immediately administered intravenous antibiotics (amoxicillin/clavulanic acid 1.2 g 3 times a day plus metronidazole 500 mg 4 times a day) and was led to the operating room approximately 4½ hours after the accident. Both the amputated segment and the amputated stump of the ear were meticulously cleaned with normal saline and povidone-iodine 10%. There, a debridement was performed under general anesthesia, and no suitable vessels for microsurgical anastomosis were found. It was decided to remove the posteromedial skin from the amputated part and to enhance the "take" of the reattached ear's recipient vascular surface, multiple small fenestrations were made in the cartilage (Fig. 3). A postauricular flap was elevated, so that the anterolateral auricular skin was nourished through the cartilage fenestrations by means of a direct contact with a vascular bed (Fig. 4). The anterior skin of the graft was sutured in layers to the amputated stump of the ear, and the skin of the helical rim was sutured to the elevated postauricular flap (Fig. 5). Two Vicryl 3-0 sutures were used for fixation of the graft to the tissues of the mastoid bed. A Penrose drain was inserted, and a tied-over dressing was then applied, and a Penrose drain was inserted. The drain was removed 3 days later, and antibiotics were administered for a total period of 12 days (5 days intravenously and 5 days orally). The patient was released from the hospital on the ninth postoperative day, 2 days after tied-over dressing removal (Fig. 5). The ear developed some epidermolysis during the first 3 weeks after surgery but went on to reepithelialize spontaneously. Three months later, the patient underwent a second procedure during which the medial surface of the ear was elevated from the recipient bed, and the postauricular area was advanced and reconstructed with the use of a full-thickness skin graft (Figs. 6 and 7). Despite some helical irregularities, and overall shrinkage of the amputated part with an approximately 10% diminishing in the total size of the auricle compared with the normal side, no complications have been noted.



FIGURE 1. Subtotal ear amputation due to human bite.

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FIGURE 2. Amputated segment.

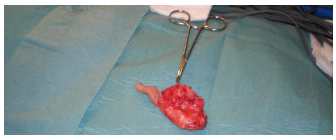


FIGURE 3. Amputated segment: medial view after fenestration of the cartilage.



FIGURE 4. Raising of a retroauricular flap.



FIGURE 5. The amputated ear in place after tied-over dressing removal.



FIGURE 6. Second procedure: separation of the posteromedial surface of the ear.



FIGURE 7. Second procedure: skin grafting of the posteromedial surface.



FIGURE 8. Final result at 2 months after the second procedure.

The patient is happy with the final result and did not request more correction. He is now able again to wear glasses (Fig. 8).

DISCUSSION

Successful microsurgical revascularization of amputated auricle has been reported.[2,3] However, appropriately sized veins are often not available, and if not technically feasible, an effort should be made for primary reconstruction with the amputated segment. The simple reattachment of the ear as a compound graft usually leads to necrosis and total loss of the organ.[4]

In 1971, Mladick et al[5] proposed the principle of the retroauricular pocket, for nonmicrosurgical ear reattachment. This method involved deepithelialization of the amputated part, followed by anatomic reattachment to the amputated stump and then burial in a retroauricular pocket. In this way, a larger area of inset and greater surface of contact with the vascular bed were provided, thus allowing for better composite graft take.

We believe that the Baudet technique is very reliable because it allows a great surface of contact between the graft and the vascular bed, substantially increasing its odds of survival in cases presenting with high risk of infection such as human bite injury. It is also a possible alternative to the technique of Mladick et al because of less flattening of the cartilaginous framework. In addition, by maintaining sufficient dermal connection to the cartilage, the latter is protected from distortion due to scarring. A second procedure is required, and based on our experience,[6] we prefer to wait for 2 to 3 months to enhance the chance of amputated segment to survive. Secondary reconstruction with rib cartilage or use of an ear prosthesis anchored on osseointegrated implants is still possible.[7]

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The Baudet technique has been used successfully in a near-total amputation due to human bite. It is a simple technique and produces excellent aesthetic results, while preserving all neighboring tissues in case of failure with subsequent need for another operation.

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PUBLICATION IV



Evaluation of a Facial Transplant Candidate with a Facegram: A Baseline Analysis

Sir:

Facial transplantation has emerged as the next step on the reconstructive ladder for severe facial disfigurement, but functional recovery and return of facial sensation and motion will vary, be difficult to predict, and may take months or years.[1,2] Motor recovery following composite tissue allotransplantation has been reported to be slower and often less optimal when compared with the sensory recovery outcomes.[3–5]

The facial appearance of the recipient improves gradually along with nerve regrowth, with changes in expression and the appearance of nasolabial folds. A kinematic preoperative evaluation may be important for further analysis of the results.

A 22-year-old man with severe sequelae of thermal burns (55 percent total burn surface area), a candidate for facial transplantation, was analyzed with a novel quantitative method: facegram (Fig. 1).



Fig 1. Male patient, 22 years old, with severe sequelae of thermal burns (55 percent total burn surface area).

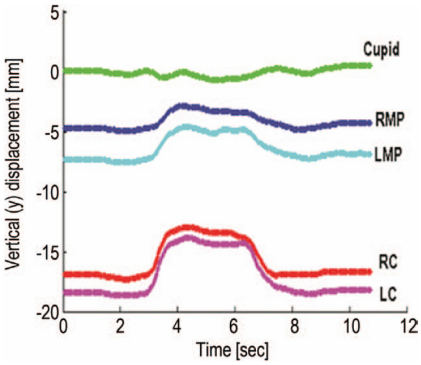


Fig 2. Facegram analysis shows symmetry/balance and temporal consistency. The hold period is not properly maintained (there is a progressive loss of extension). The extension of the commissures is clearly superior to that of the midpoints or Cupid's bow.

In order to reliably capture the dynamics of the smile movements, we developed specialized software capable of simultaneously tracking the position over time of a number of anatomical points (commissures, midpoints, and Cupid's bow), using video recordings of the subject. The programing environment MATLAB (R2011a; MathWorks, Natick, Mass.) was used for computing the facegrams. The software provides a graphic user interface (GUI) to assist the user in different tasks,

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such as drawing a line setting the face's vertical axis of symmetry or pointing and clicking on the colored dots marking the anatomical landmarks.

The main element is the plot, in scale, of the paths followed by each anatomical landmark, as shown in **Figure, Supplemental Digital Content 1, *http://links.lww.com/PRS/A823***. In every pathway, six points mark important times: T1, start of recording; T2, start of contraction; T3, end of contraction; T4, start of relaxation; T5, end of relaxation; and T6, end of recording; as shown in **Figure, Supplemental Digital Content 2, *http://links.lww.com/PRS/A824***. The complete facegram includes four additional elements: the absolute horizontal (and vertical) displacements and the differential horizontal (and vertical) displacements of each landmark as a function of time.

Facegram analysis in this patient revealed symmetry/balance and temporal consistency, despite the reduction in range of motion over time (Fig. 2). The hold period is not properly maintained (there is a progressive loss of extension). Vertical movement appears to be superior in relation to horizontal movement. The extension of the commissures is clearly superior to that of the midpoints or Cupid's bow, which may be explained by cicatricial retraction of the central part of the patient's lips.

Muscles would regain motion through the facial nerve, and if this nerve was being dissected proximally to include all branches, regeneration would take a long time to enable muscular activity within the graft. Mobile facial expression also depends on the depth of scarring before the operation.

There are then two possibilities: (1) the patient has a deformity so obvious that any degree of functional recovery after transplantation means a significant gain on facial expression, or (2) as in this patient, despite scarring caused by burns, it will be difficult to recover motor function that will achieve the same degree of muscle contraction. In this case, the facegram can provide a baseline pattern, which will be important to accompany functional recovery.

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PATIENT CONSENT

The patient provided written consent for the use of his image.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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PUBLICATION V



Facial Disfigurement: Restoration of Facial Dynamics in a Patient with Concomitant Facial Paralysis and Blindness

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Individuals with facial palsy experience physical, psychological, and social disability every single day.

The treatment of unilateral established facial paralysis requires transplantation of new musculature to reach symmetry at rest, and to partially restore facial movement.[1–4]

Effective rehabilitation after muscle transfer requires training and physical therapy to achieve optimal function. The concept of neural plasticity supports that there is central plasticity and reorganization. After a certain training period, patients with gracilis transfers driven by the masseteric branch of the trigeminal nerve are able to achieve movement without initiating clenching of teeth.[5–7]

The rehabilitation in blind patients is one of the greatest challenge that a reconstructive surgeon can face, and to date, there is no previous report of facial reanimation in these particular cases. However, it may have an important functional role in social interaction.

A 37-year-old woman with established facial paralysis as sequelae of surgery for eighth nerve neuroma (►**Fig. 1** [left panel]), undergone right suboccipital craniectomy, removal of the tumor in 2005 and radiosurgery as an adjunct treatment, which was complicated with bilateral blindness secondary to optic atrophy, paralysis of the right oculomotor nerve, right facial palsy, and hydrocephalus managed with ventriculoperitoneal shunt. A year after the removal of the tumor, she was submitted to a cross-face graft with the sural nerve, retaining obvious asymmetry at rest (grade V of the House-Brackmann scale), without frontal function, no function of the orbicularis oculi and minimal excursion of the oral commissure. In 2012, she underwent facial reanimation with gracilis free transfer; microneurovascular anastomosis was performed to the facial vessels, and to the motor nerve of masseter muscle. Time of contraction onset (reinnervation) was 3 months.

The patient then initiated a rehabilitation program that was designed to reinforce the desired facial movement patterns; the first stage of exercises included individualized muscle contractions of the contralateral part of the face only, then with the transferred gracilis contracting. The program consisted of 5 to 20 repetitions of 3 to 5 exercises to be done three times daily. Her mother was used for acoustic feedback during exercise, helping to coordinate facial movements for the construction of different facial expressions. Further, other tasks were added, such as sucking, and saying words containing "f," "p," or "b," which facilitates lip movements. The patient was also educated to evaluate the degree of muscle contraction through the tactile sense, that is, through a sensory feedback.

The patient was further evaluated with a novel quantitative method, called the facegram, which accurately assesses the fundamental aspects of the facial excursion. To reliably capture the dynamics of the smile movements, we developed specialized software capable of tracking simultaneously the position over time of several anatomical points (commissures, midpoints, and Cupid). This is accomplished using video recordings of the subject while controlling the process of smiling. The programing environment MATLAB (R2011a, MathWorks, Natick, MA) was used to develop the tracking software, and for computing the facegrams. The video sequences are not analyzed frame by frame with manual point

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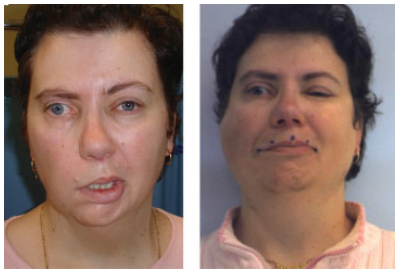


Fig. 1 (Left panel) Established right-side facial paralysis in a blind patient following acoustic neuroma surgery and radiotherapy (preoperatively 6 years from the onset of paralysis). (Right panel) Full contraction with a symmetrical smile.

selection by the user on each frame. The user only identifies the markers' locations in the first frame. The algorithm then tracks automatically the markers independently in (x, y, t) coordinates for the entire video sequence. The process thus takes a few seconds, is reproducible, and reliable, since variability in the point selection of the markers (as long as within its central area) is not translated in variability in the markers trajectories.

The main element in the facegram is the plot, in scale, of the paths followed by each anatomical landmark, and includes four additional elements for analysis: the absolute horizontal (and vertical) displacements and the differential horizontal (and vertical) displacements of each landmark as a function of time. The fact that this plot is on scale also allows direct measurements such as maximal extensions.

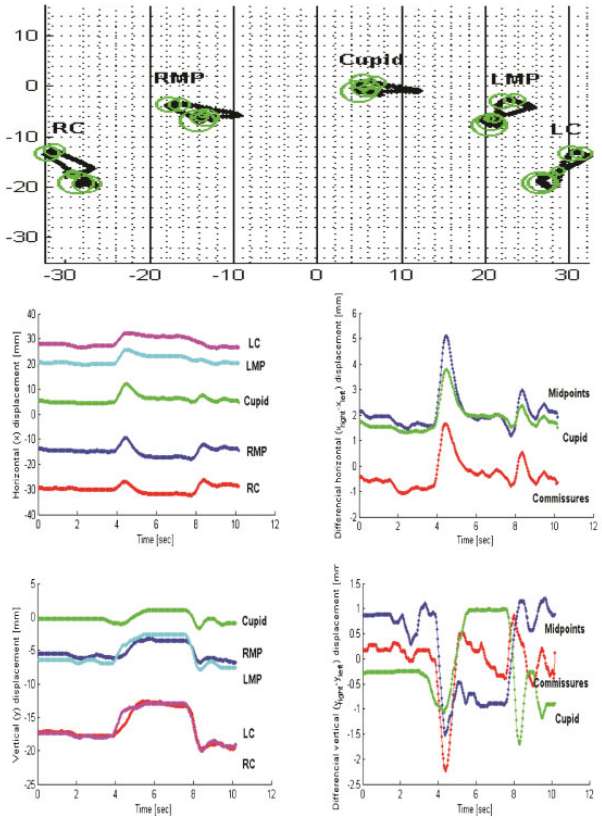


Fig. 2 Some imbalance between contraction and relaxation. However, good vertical excursion of commissure marks is noted (4.8 mm). There is symmetry of the commissures at rest.LC, left commissure; LMP, left midpoint; RC, right commissure; RMP, right midpoint.

In this patient we observe that Cupid mark does not exactly intersects the vertical axis of the face, despite improved symmetry of the face at rest after surgery (►**Fig. 2**).

Some imbalance between contraction and relaxation is observed. Horizontal movements are abrupt at the right side and less coordinated. However, good vertical excursion of the commissure marks is noted (4.8 mm) and there is symmetry of the commissures at rest.

Drooling decreased and speech was improved. Both her self-esteem as well as intellectual performance increased with a more symmetric face at rest and during animation (►**Fig. 1**[right panel]). She could develop social skills to start and carry on conversations, to play games effectively, and to join in and feel part of a group.

The impact of facial disfigurement on social interactions includes psychological and physical fatigue.[8]

Visually-impaired patients suffer from reduced social interaction in part due to reliance upon others to initiate social contact, and they have smaller social circles.[9] The isolation and emotional pain that a blind and visual impaired person experience in association with facial paralysis can be distressing and constrictive in regular public interaction and may also elevate the risk for depression.[10]

In addition to the disfiguring condition that takes away facial expressiveness, facial paralysis is associated to functional problems such as speech impairment, drooling, problems with eating, drinking or rinsing the mouth, and closing or sustaining eye closure for moistening and protection.

Therefore, all efforts should be taken to enhance the recovery of facial expression by means of neuromuscular reeducation, or facial reanimation surgery.

In this article, we describe for the first time the treatment of facial paralysis in a blind patient. The facial reanimation program combined microsurgical facial reanimation, acoustic, and sensorial rehabilitation. A quantitative spatial-temporal analysis (facegram) was performed, and revealed good vertical excursion of the commissure marks (4.8 mm) and symmetry of the commissures at rest.

On the functional aspect, drooling and fluid loss with drinking were eliminated. Speech was significantly improved.

After successful facial reanimation she could develop social skills to start and carry on conversations, to play games effectively, and to join in and feel part of a group. This patient lives in an institution of support/solidarity. The difficult relationship with the children, who do not understand the nature of such deformity, also comes out strongly enhanced, and was one of the great achievements reported by the patient.

Microsurgical muscle-free transplantation in association with acoustic and sensorial feedback rehabilitation achieves good results in blind patients, improving their levels of self-esteem and expectations, and allowing greater social interaction by means of the ability to smile.

Conflict of Interest
The authors of this article have no conflicts of interest to disclose.

Funding
None

Ethical approval
Ethical Approval was given by the Institutional Ethics Committee. This work is included in a research on facial paralysis and transplantation.

Patient consent
Written patient consent has been obtained to publish clinical photographs.

Financial Disclosure
None of the authors has a financial interest in any products, devices, or drugs mentioned in this article.

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PUBLICATION VI



FACIAL ALLOTRANSPLANTATION PROCUREMENT USING A TRANSPAROTID APPROACH: A NEW ANATOMICAL MODEL

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Background: Full face transplantation is a complex procedure and a detailed plan is needed. Coaptation of motor nerve branches at more distal sites instead of the level of the main trunk is highly desirable, but may be difficult to find, are thin, fragile and have limited length for safe and tension-free coaptation. In addition, nerve grafts may be necessary. In this study, the technical feasibility of facial allotransplantation procurement using a transparotid approach was investigated. *Methods:* Three mock cadaver dissections were performed, procuring full face transplants with en bloc facial nerve dissection. The facial nerve (main trunk, temporofacial/cervicofacial divisions, and individual facial branches) was elevated en bloc as part of the allograft, dissected out from the parotid completely, and left as loose attachments to the allograft specimen. *Results:* Full face transplantation with en bloc facial nerve dissection was technically feasible, allowing for more proximal or distal nerve section, and to achieve the desired length and diameter for appropriate matching during nerve coaptation. *Conclusion:* This technique follows principles of targeted nerve reinnervation. It allows to select the level of facial nerve section to the temporofacial and cervicofacial divisions or final branches, with further adaptation to the remaining recipient's anatomic structures, and avoiding the need for nerve grafts; it also excludes the parotid gland (reduces bulk). Despite a small increase in the time required for dissection, this disadvantage may be compensated by an improved functional recovery. © 2013 Wiley Periodicals, Inc. Microsurgery 34:296–300, 2014.

Facial transplantation has emerged as the next step on the reconstructive ladder for severe facial disfigurement which can occur following a variety of events, including ablative surgery, trauma (including burns), and cancer. Full face transplantation is a complex procedure. Adequate perfusion and reinnervation of the allograft are essential, and a detailed plan is needed. In addition, facial anatomies are unique, depending on the extent of the initial injury and previous reconstruction procedures. Pre-clinical research about technical aspects of the facial allotransplantation procedure, including surgical harvesting options, have been investigated in cadaveric models to address different reconstructive needs.[1]

In what concern to functional recovery, return of facial sensation and function will be variable, difficult to predict and may take months/years. The facial appearance of the recipient improves gradually together with nerve regrowth, with the changes in expression and the appearance of nasolabial folds. Coaptation to the facial and infraorbital nerves has been particularly challenging because of incongruence between donors, especially in neurofibromatosis.[2]

Reorganization occurs after face transplantation through neuromuscular pathways and sensory and proprioceptive feedback, and successful coaptation of as many major sensory and motor nerves is a key to optimize functional outcomes.

We report here a new harvesting option for a face allotransplant procurement; a transparotid dissection was not attempted before.

MATERIALS AND METHODS

Three mock cadaver dissections were performed, procuring full face transplants with en bloc facial nerve dissection. The dissection was initially in the caudal-cranial direction, instead of cranio-caudal. Neck dissections were first carried out in the subplastismal plane. Facial vessels were identified by dissection from the carotid arteries and jugular veins distally (Fig. 1). Submandibular glands were excluded. The bilateral facial vessels were dissected as the allotransplant main vascular pedicle.

Facial allografts dissection then followed cranio-caudal and lateral-medial directions as described by Pomahac et al.,[3] procuring allografts that included the fronto-temporo-parietal regions of the scalp to the coronal level, eyelids, nose, muscles of facial animation, lips, motor and sensory nerves, and vessels.

A coronal incision was continued in a cranial direction and in-continuity bilateral preauricular incisions were extended inferiorly to the neck.

Supraorbital dissection was first subgaleal and then subperiosteal 1 cm above the supraorbital rim (Fig. 2). Eyelids were included by performing release along the palpebral conjunctival reflection and canthal ligaments (Fig. 3). Infraorbital dissection was subperiosteal along the anterior maxilla and zygoma (Fig. 4). The nasal bone

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Figure 1. Neck approach to find facial vessels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

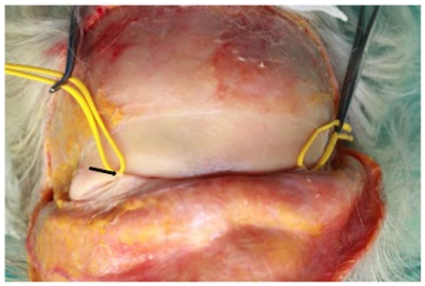


Figure 2. Cranio-caudal dissection was first subgaleal and then subperiosteal until visualization of the supraorbital nerves (black arrow). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

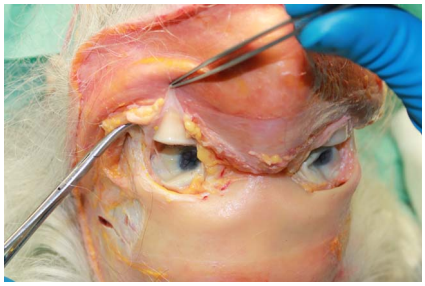


Figure 3. Release along the palpebral conjunctival reflection and desinsertion of the canthal ligaments allowed for eyelids inclusion. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

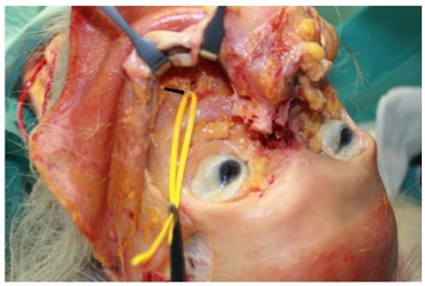


Figure 4. Infraorbital nerve visualization (black arrow). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

pyramid was included and separated from the malar eminence with a osteotome.

Preauricular dissections were performed, and facial nerve main trunk was found at the tragal pointer (Fig. 5, above, left). Transparotideal dissection proceeded with identification of temporofacial and cervicofacial divisions (Fig. 5, above, right), until final division in temporal (frontal), zygomatic, buccal, marginal mandibular, and cervical branches (Fig. 5, below, left). The superficial lobe of the parotid was no taken with the graft.

The extratemporal course of the facial nerve (main trunk, temporofacial and cervicofacial divisions, and individual facial branches) was then elevated en bloc as part of the allograft (Fig. 5, below, right). The nerves were dissected out from the parotid completely and left as loose attachments to the allograft specimen.

At the anterior edge of the masseter muscle, perioral tissues were raised in a subperiosteal plane, along the gingivobuccal sulcus and inferiorly to the mandibular border (Fig. 6). The mental nerve was identified at its exit from the mental foramen included in the allotransplant. Neck dissection plane was finally connected with the facial plane and the allograft dissection completed.

RESULTS

We successfully recovered three full face allografts each under 3 hours. We found it easier and safer to connect neck and facial planes by preliminar dissection of the facial vessels, keeping them always protected and their course identified within the elevated tissues.

Full face transplantation with en bloc facial nerve dissection was technically feasible, allowing for more

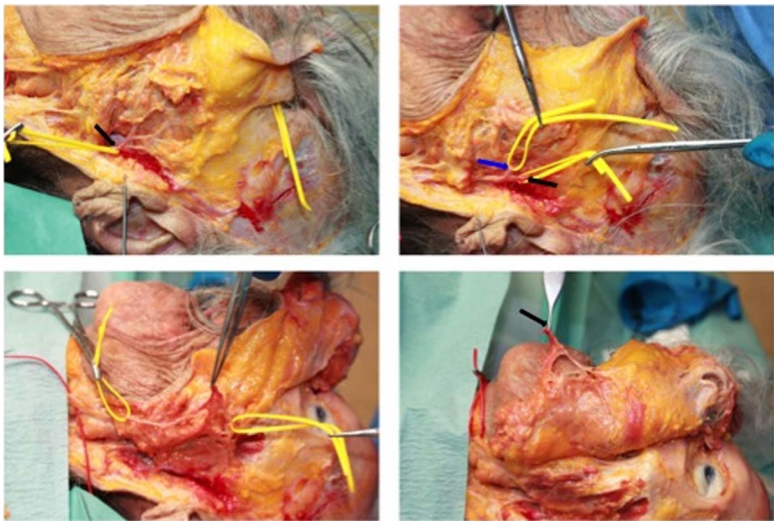


Figure 5. Facial nerve dissection. Above, left: Exposure of the facial nerve trunk (black arrow). Above, right: Identification of the temporofacial (black arrow) and cervicofacial divisions (blue arrow). Below, left: Transparotideal dissection. Below, right: The facial nerve (with all branches included) was elevated en bloc together with the allotransplant; the black arrow is pointing to the facial nerve trunk. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

proximal or distal nerve section, and to achieve the desired length and diameter for appropriate matching during nerve coaptation. It also excludes parotid and submandibular glands, with the potential for best aesthetic outcomes.

DISCUSSION

Since the first face transplantation was successfully completed in November 2005 in Amiens (France),[4] facial transplantation has emerged as the most complex solution to restore a near-normal-appearance, and function on the reconstructive ladder for severe facial disfigurement.

Facial transplantation requires the acquisition of a suitable donor with a good tissue match as well as similar cosmetic features. In addition, the patients need to be placed on immunosuppressant medication to prevent rejection. Connecting just one artery and one vein on each side of the face can provide enough blood flow to the transplanted tissues. In an attempt to restore facial function, the surgical team should also connect all the main available nerves.

Adequate planning requires both complete sensory and motor nerve connection and should be part of each operation. The identification of healthy nerves for neurotization in the recipient is of particular importance for successful nerve regeneration within the allograft. However, due to the severity of the initial injury and resultant scar formation, a lack of healthy nerve stumps in the

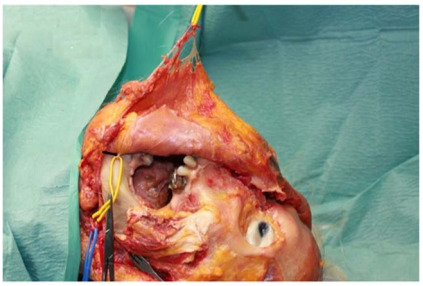


Figure 6. After subperiosteal dissection at the anterior edge of the masseter muscle, the gingival mucosa was cut; the mental nerve (black arrow) was identified and included in the allotransplant. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

recipient is a commonly encountered problem. To reduce time constraints, Cavadas et al.[5] performed an elective surgery 3 months before the transplantation to identify and tag the recipient nerves (including the lower divisions of the facial nerves; this approach can help the facial transplantation team.

The evidence for full neurological recovery following neurorrhaphy of facial nerves is generally poor.[6] Insufficient recovery has been attributed to poor pathfinding of regrowing axons, excessive collateral axonal branching at the lesion site, and polyneuronal innervation of the neuromuscular junctions.[7] Reports of the first seven facial transplants performed, claimed sensory recovery from between 3 and 6 months, with acceptable motor recovery commencing between 9 and 12 months.[8]

Sensory recovery of face composite tissue allotransplatation was reported in all patients as nearly perfect at 3–8 months after transplantation. In fact, nearly normal sensory recovery can be expected following facial transplantation with or without repair of sensory nerves, maybe because of regeneration from the recipient bed and allograft margins, trigeminofacial communications, nervi nervorum of the facial nerve, preservation of normal density of the receptors within the allograft and therapy with tracolimus.[9]

However, sensory function of the face graft is unpredictable in consequence to high-energy trauma and large defects. Rodriguez-Lorenzo et al.[10] performed measurements of the maximum length of dissection for the infraorbitary nerve (IO) and supraorbital nerve (SO) and concluded that SO to IO tension-free nerve transfer is anatomically feasible and may improve the restoration of midfacial sensation by the use of a healthy recipient nerve if IO nerves are not available.

A successful face transplant will also depend on motor recovery. Motor recovery following composite tissue allotransplantation was slower and often less optimal when compared with the sensory recovery outcomes.[11–13] Restoration of motor function has been generally slower than sensory recovery. Active and passive lips movements were obtained between 6 and 12 months but differ between full and partial facial transplants.[14,15]

Muscles would regain motion through the facial nerve and if this nerve was being dissected proximally, regeneration would take a long time to enable muscular activity within the graft. Neurorrhaphy at the trunk of the facial nerve leads to less targeted postoperative reinnervation, and coaptation of motor nerves as close as possible of effector muscles is the best option, as it allows retention of greater native nerve length.[16] Inclusion of the parotid gland and limiting facial nerve coaptation to the level of the main trunk adds complexity, poor aesthetic outcomes with fullness to the cheeks, and synkinesias. Coaptation of motor nerve branches at more distal sites, as recently performed by the Brigham and Womans transplant team, is highly desirable allowing faster reinnervation and decreasing the likelihood of synkinesia. However, distal branches may be difficult to find, are thin, fragile and have limited length for safe, tension-free coaptation. In addition, nerve grafts may be necessary.

Recently, nerve transfers were described as an option that could theoretically be used in face transplantation either as a primary nerve reconstruction when there are no available healthy nerves, or as a secondary procedure for enhancement of functional outcomes.[17] The supraorbital nerve, branches of the cervical plexus, and the masseter nerve are usually located out of the zone of injury and can be selected as neurotizers for the infraorbital nerve, mental nerve, and buccal branch of the facial nerve, respectively.

All surgical team members should participate in a series of mock, fresh-cadaver facial transplants exercises to ensure all details are complete, to define each surgeon's role and for optimizing the team dynamics and effectiveness. This is essential to decrease potential delay, technical problems, and post-operative complications.

Each case is unique and facial transplantation is an original work for each patient. The precise amount of tissue requested, has to be dissected from the donor, including salivary glands, muscle, bone, and even the whole maxilla. It is never the same block of tissue, further adaptation is needed, and a transparotideal approach can be a possibility only when indicated in each particular situation.

In this study, facial vessels were first identified by dissection from the carotid arteries and jugular veins distally. We decided to perform this modification, because we found it easier and safer to connect neck and facial planes by preliminar dissection of the facial vessels. In addition, and according to same clinical observations,[3] in some cases there will be no time for the facial transplant recovery before aortic cross clamping and recovery of live-saving organs. In these situations, visualization of the vascular pedicle facial will be necessary before physiologic perfusion is lost. The bilateral facial vessels were dissected as the allotransplant main vascular pedicle.

The most important modification was introduced, and was related to the facial nerve approach. The transparotid approach can give to the surgeon the option of dissection to the level of temporofacial and cervicofacial divisions or final branches, avoiding section at the level of the main trunk, reducing the likelihood of occurrence of synkinesias (Fig. 7). This technique implies an anterograde dissection from the trunk, which may be easier to perform in some circumstances than a retrograde dissection

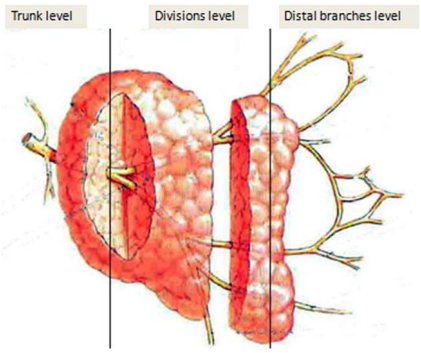


Figure 7. Options for nerve section in a transparotideal approach. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

after finding the distal thin and fragile branches, medial to the parotid gland. It is quite versatile, as it allows to achieve the desired length and diameter for appropriate matching during nerve coaptation and adaptation to the preserved and remaining recipient's anatomic structures, so it can avoids the need for interposition nerve grafts (thoracodorsal, great auricular) that were required in previous cases of full face transplantation. It also excludes the parotid gland from the allograft (reduces bulk).

CONCLUSIONS

This technique follows principles of targeted nerve reinnervation. It allows to select the level of facial nerve section to the temporofacial and cervicofacial divisions or final branches, with further adaptation to the remaining recipient's anatomic structures, and avoiding the need for nerve grafts; it also excludes the parotid gland (reduces bulk). Despite a small increase in the time required for dissection, this approach may increase harvesting options for reconstructive surgeons who are interested on performing facial transplantation, or have already done but were not satisfied with their functional results.

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PUBLICATION VII



LETTER TO THE EDITOR

MICROSURGERY 34:498–499 (2014)

FULL FACE ALLOTRANSPLANTATION PROCUREMENT WITH EN BLOCK FACIAL NERVE DISSECTION AS A WAY TO INCREASE NEUROTIZATION POSSIBILITIES FOR TARGETED REINNERVATION

Dear Editor,

Facial transplantation is an original work for each patient, because facial anatomies are unique, depending on the extent of the initial injury and previous reconstructive procedures.

Reorganization after face transplantation occurs through neuromuscular pathways and sensory and proprioceptive feedback. Successful coaptation of as many major sensory and motor nerves is the key to optimize functional outcomes. The identification of healthy nerves for neurotization in the recipient is crucial for successful nerve regeneration within the allograft. However, due to the severity of the initial injury and resultant scar formation, a lack of healthy nerve stumps is a commonly encountered problem. Recently, nerve transfers were described as an option that could theoretically be used in face transplantation, either as a primary nerve reconstruction when there are no available healthy nerves or as a secondary procedure for enhancement of functional outcomes.[1]

Inclusion of the parotid gland and limiting facial nerve coaptation to the level of the main trunk adds complexity, poor aesthetic outcomes with fullness to the cheeks, less targeted postoperative reinnervation, and synkinesias. Coaptation of motor nerve branches at more distal sites (as close as possible of effector muscles) is highly desirable, allowing faster reinnervation[2]; however, distal branches may be difficult to find, are thin, fragile and have limited length for safe, tension-free coaptation. In addition, nerve grafts may be necessary.

We have investigated the technical feasibility of facial allotransplantation procurement using a transparotid approach in a cadaveric study.The extratemporal course of the facial nerve (main trunk, temporofacial/cervicofacial divisions, and individual facial branches) was elevated en bloc as part of the allograft. The nerves were dissected out from the parotid completely and left as loose attachments to the allograft specimen. Lengthening of all branches (up to 20 mm) was attained just by dissection and mobilization of the parotid gland.

Full face transplantation with en bloc facial nerve dissection was technically feasible and follows principles of targeted nerve reinnervation. It allows to select the level of facial nerve section to the temporofacial and cervicofacial divisions or final branches, avoiding section at the level of the main trunk, reducing the likelihood of occurrence of synkinesias. This technique implies an anterograde dissection from the trunk, which may be easier to perform in some circumstances than a retrograde dissection after finding the distal thin and fragile branches, medial to the parotid gland.

It gives various neurotization possibilities (Fig. 1): direct division to division or branch to branch neurorrhaphy; cross-division neurotization; division to proximal branches coaptation; or division to distal branches with interpositional grafts (e.g., thoracodorsal, great auricular). It also excludes the parotid gland from the allograft (reduces bulk). To reduce time constraints, an elective surgery 3 months before the transplantation as performed by Cavadas et al.[3] to identify and tag the recipient nerves, may be useful.

The transparotideal approach[4] can be a possibility only when indicated in each particular situation, depending on

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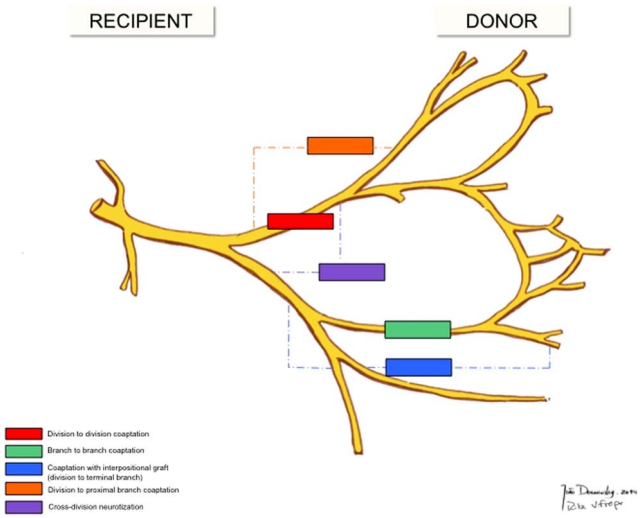


Figure 1. Neurotization possibilities in a transparotideal approach. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the precise amount of tissue requested, and may increase harvesting options for facial allotransplantation.

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PUBLICATION VIII



Journal of Cranio-Maxillo-Facial Surgery 42 (2014) 1250–1259

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A facegram for spatial–temporal analysis of facial excursion: Applicability in the microsurgical reanimation of long-standing paralysis and pretransplantation

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ABSTRACT

Background: There are several techniques available for facial reanimation, but clinicians do not have a simple tool to provide an objective and quantitative spatial–temporal analysis of facial movement in order to compare medical, surgical and physical therapy.
Methods: We developed specialized software capable of simultaneously tracking the position over time of a number of anatomical points. This method was tested in 5 different clinical situations: one normal subject, and 4 patients with facial disfigurement.
Results: A large amount of quantitative information can be extracted directly, such as symmetry assessment in the contraction and relaxation trajectories. The fact that this plot is on scale allows also direct measurements such as maximal extensions. Even smiles that at the macro-scale are essentially symmetrical show at the micro-scale small asymmetries/variability.
Conclusion: In this paper, we describe a novel quantitative, reliable method, which accurately assesses the fundamental aspects of the facial excursion, incorporating spatial and temporal components.
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1. Introduction

The goal of facial reanimation is restoration of both a symmetric face at rest and a spontaneous smile. There are several techniques available for facial reanimation. These include reinnervation techniques, muscle transfers, and static procedures.

An essential element to support and, more importantly, assess the reanimation techniques is the precise measurement of static and dynamic facial features. There are simple methods to assess oral excursion, but they lack some objectivity and standardization (Manktelow et al., 2008). Quantitative methods have been developed but require equipment that usually includes video cameras, a complex calibration device, computer customized software, IR lightings to illuminate the face and minimise the effect of varying lighting conditions (Sjögreen et al., 2011; Frey et al., 1999). Although three-dimensional tracking can provide enhanced information, analysis is time-consuming, expensive, requires complex equipment such as special lighting, the use of reflective markers a dense array of cameras, and the person operating the system has to have thorough education and experience, which may reduce the utility of these methods for clinical assessment.

Clinicians do not have a simple tool providing an objective and quantitative analysis of facial movement in order to compare medical, surgical and physical therapy. Such a tool necessarily involves the acquisition of two-dimensional (2D) or three-dimensional (3D) recordings of patients while carrying out a standard set of facial expressions, and the processing of these spatial–temporal data in order to facilitate analysis and interpretation.

A new method for precise quantification of the characteristics of facial excursion pre- and post-operative is presented here, with emphasis on smile analysis. This method focuses on the assessment of the trajectories of specific anatomical landmarks during rest and facial expressions. Measures based on the trajectories (position

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over time) of the anatomical landmarks cannot only evaluate abnormalities of spatial nature/topological, but can also assess temporal characteristics.

2. Material and methods

A group of 20 normal patients (without paralysis), 10 men aged between 14 and 50 years and 10 women aged between 18 and 57 years, was used as control group to set up the canonical trajectories for specific anatomical landmarks.

This method is applied and tested in different clinical situations: one normal subject, 3 patients with facial palsy and one patient with severe burns sequels (Table 1).

2.1. Video tracking of anatomical landmarks and the construction of facegrams

In order to reliably capture the dynamics of the smile movements, we developed specialized software capable of simultaneously tracking the position over time of a number of anatomical points. This is accomplished using video recordings of the subject while controlling the process of smiling. Detailed quantifications of the spatial–temporal properties of the muscular dynamics are presented using our newly proposed facegrams. The programming environment MATLAB (R2011a, MathWorks, Natick, Massachusetts, U.S.A.) was used to develop the tracking software, and for computing the facegrams.

2.1.1. Video recordings

In the video recording sessions, the subject is placed with his/her face centered in the camera frame, and with the camera's optical axis perpendicular to the face plane. Using a colour pen, a number of small dots are marked on specific anatomical landmarks. In this work five points were marked: commissures, midpoints and Cupid (Figs. 1 and 2).

The lighting conditions and the pen colour are chosen in order to provide a high contrast between the markers and the subject's skin. During the video recording, the subject is asked to smile, while keeping his/her head still, in a series of 5 stages: rest, contract, hold, relax, rest. This is done over a period of roughly 10 s, with the rest and hold stages lasting 3 s each. It is important to notice that the speeds of the contraction and relaxation stages are not affected by the observer: once the recording session starts, only two voice commands are given – "contract" and "relax". During the recording session, a picture is taken of the subject holding a ruler horizontally in front on his mouth. This picture is later used by the tracking software for space calibration purposes.

Table 1
The facegram was applied and tested in different clinical situations.

Patients/ subjects	Sex	Age	Aetiology	Side	Surgery performed
1[a]	Female	18	–	–	–
2	Female	71	Facial palsy (idiopathic)	Left	Fascia lata suspension (S)
3	Female	37	Facial palsy (acoustic neuroma)	Right	Gracilis transplantation (D)
8	Male	33	Facial palsy (cholesteatoma)	Right	Gracilis transplantation (D)
5	Male	68	Burns (55% TBSA)	Bilateral	–

D: Dynamic procedure; S: Static procedure; TBSA: Total burn surface area.
[a] Standard subject.

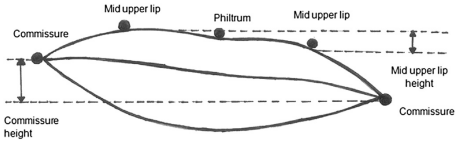


Fig. 1. The selected points (commissures, philtrum, mid upper lip), are placed symmetrical on the vermilion margin; measurements of commissure height and mid upper lip height differences are also performed.

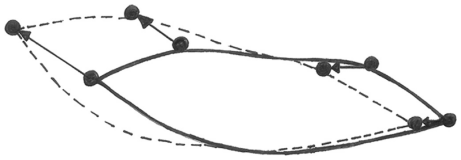


Fig. 2. Movement of the commissures and mid upper lip in a patient with facial paralysis.

2.1.2. Tracking software

Our tracking software is used to convert the video recordings of the subject, acquired under the above mentioned constraints, into lists of (x, y, t) points capturing the movement of the markers associated with the subject's smiling dynamics. The movement is captured in 2D, in the projection of the face's surface into the camera's place. Even using standard, non-expensive HD webcams (50 USD), it is possible to have high resolution in both time (close to 0.03 s, from 30 frames-per-second) and space (close to 0.25 mm). The facial landmark points can have a diameter of 1–2 mm and the spatial precision still be sub-millimetre. This is possible because the tracking algorithm locks on the area of the coloured spot and tracks its centre.

The spatial resolution is therefore largely determined by the resolution of the camera (px/mm) and by the contrast between marker colour and skin colour, not by the area of the spot itself. In high contrast conditions the algorithm is capable of clearly identifying the boundary of the spot/marker and obtaining precise measurements bellow 1 mm.

The tracking system starts by first presenting the initial frame of the video sequence. Here the user is asked to use the mouse to:

1) draw a line setting the face's vertical axis of symmetry and
2) point and click on the coloured dots marking the anatomical landmarks.

The software provides a graphical user interface (GUI) to assist the user in this task. The GUI provides tools such as zooming, and the line axis, together with the marker points, can be edited and visualized over the subject's face. The facial vertical axis is usually defined as the line connecting the mid-glabellar area to the menton. Once line axis and points have been set, an automatic tracking algorithm analyses the video stream, frame-by-frame, extracting the positions of each marker as a function of time. The algorithm uses the "block matching" strategy to track the position of each marker in the sequence of frames. The positions in pixel-space are converted to real-space (in millimeters) using the calibration picture. The scaling factor px/mm is obtained from the length of several centimetres in the ruler. It is therefore possible to estimate the scaling factor with an error which allows sub-millimetre resolution. Despite this we impose a lower bound for this error and

have set the spatial error at 0.25 mm. The positions also suffer a coordinate transformation where the new axes are the face's vertical axis and its perpendicular axis which passes through the central marker (Cupid). This new coordinate system provides immediate evidence for possible asymmetries in the mouth anatomical landmarks with respect to the facial vertical axis.

2.1.3. Facegram

A precise assessment of the muscular dynamics associated with the control of smiling requires inevitably analysis in both spatial and temporal domains; the complexity and dynamical nature of the smile control simply cannot be captured using static examination. In order to deal with the challenge of quantifying spatial–temporal properties of smile control, we developed novel strategies to present/visualize the dynamics data. Using the positions time-series of all anatomical markers we compute several traces, each emphasizing different aspects of dynamics. Collectively we call these traces *facegram*, as they are an invaluable tool for assessing quantitatively, the normal and pathological behaviour on the dynamics of the system. The main element in the facegram is the plot, in scale, of the paths followed by each anatomical landmark. In every pathway, 6 points mark important times:

1) start of recording (T1);
2) start of contraction (T2);
3) end of contraction (T3);
4) start of relaxation (T4);
5) end of relaxation (T5); and
6) end of recording (T6).

A large amount of quantitative information can be extracted directly from these plots such as symmetry assessment in the contraction and relaxation trajectories. The fact that this plot is on scale allows also direct measurements such as maximal extensions. The facegram also contains other elements which help to highlight more subtle properties of the dynamics:

- The horizontal (and the vertical) displacement of each point as a function of time – these traces provide information regarding the temporal coordination/consistency between each anatomical point, and are useful in some forms of paralysis where horizontal or vertical components of the movement are affected.
- The differential horizontal (and the vertical) displacement of each point as a function of time – these traces correspond to the difference between the position of (supposedly) symmetrical anatomical points, and are useful for detecting asymmetries on both spatial and temporal domains.

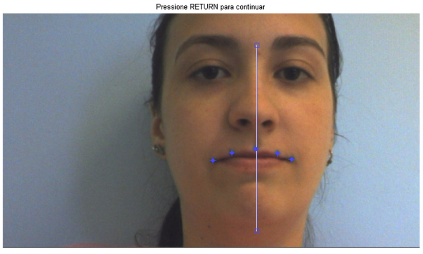


Fig. 3. Facegram analysis in a normal subject.

The facegram implies a projection from a 3-Dimensional object (face) to a 2-Dimensional space (camera plane). The anatomical landmark locations which can be more affected by this projection are the commissure positions, as a result of the face curvature. In order to estimate the error associated with this projection the following procedure was followed. In a group of 5 individuals, the distance between Cupid and left/right commissure was measured at the maximum extension of a smiling expression, using a flexible ruler placed over the face curvature. These maximal extensions were compared with the equivalent measurements on the facegram (therefore measured in 2D). The difference between the maximal extensions in 3D and in 2D was 0.7 ± 0.5 mm (STD); this value can be used as the projection error and it should be taken into account that it was calculated for the worst-case scenario.

3. Results

3.1. Facegram analysis

3.1.1. Standard subject

A normal facegram should reveal symmetrical movement of the face. The vertical axis of the face is assessed drawing a line from mid-glabellar area to the menton. This line should bisect nasal ridge, upper lip, Cupid's bow and central two incisors if there is no deviation (Fig. 3). Coordination between the movement of the five standard landmarks is seen in these subjects and relaxation movement overlaps well with contraction movement (Fig. 4). Temporal symmetry is also observed. Note that even a 0.5 mm of horizontal displacement (x) can be revealed in a facegram analysis of a normal subject with an essentially symmetrical smile. Vertical movement (y) shows good amplitude and is consistent through the time (seconds). Commissure movement length was close to 2.5 mm. These lengths may be determined by examining points on the curve corresponding to a rest situation and maximal contraction and calculating the differences between the coordinates x, y (Fig. 5). Commissure points can also show small differences in vertical assessment.

Using this method even smiles that at the macro-scale are essentially symmetrical, show small asymmetries and a large degree of variability at the micro-scale. The precise quantifications of the landmark trajectories provided by this method allow the establishment of spatial and temporal boundaries for the magnitude of the asymmetries that define a "symmetrical" smile in the macro-scale.

The software also allows the enlargement of each landmark separately and with great detail (Fig. 6). Start and end points (T1 and T6; rest position) can also show a difference in both horizontal (x) and vertical (y) assessment (0.6 mm in this facegram).

A normal excursion should be recorded in a smooth line through the time.

3.1.2. Static reanimation (suspension)

In this patient we can see a Cupid deviation to the right in relation to the vertical axis (Figs. 7 and 8) and significant horizontal and vertical asymmetry between the points at rest. Minimum movement of the midpoints and commissures is detected. Unbalanced distension, almost unilateral (with maximal extension above the normal) or exaggerated compensatory contralateral contraction is noted. We can conclude that this result is very unsatisfactory and a dynamic procedure should be proposed.

3.1.3. Dynamic reanimation (gracilis transplantation)

The movement is almost exclusively horizontal (Figs. 9 and 10). There is symmetry of midpoints at rest, but the right commissure remains in a lower position than the contralateral. The amplitude of

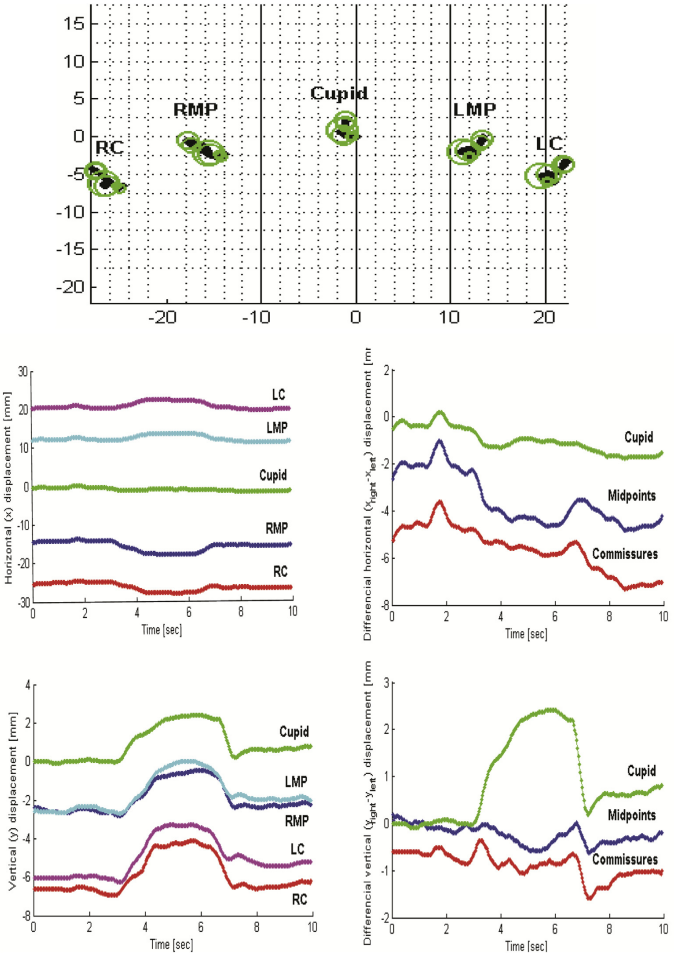


Fig. 4. Coordination between the movement of five points; relaxation movement overlaps well with contraction movement. Note that even a 0.6 mm of horizontal displacement can be revealed in a facegram analysis of a normal subject with a symmetrical smile. RC: right commissure; LC: left commissure; RMP: right midpoint; LMP: left midpoint.

excursion is greater at the right side and predominantly horizontal. This probably reflects the patient's concern on initiating the gracilis muscle contraction (cerebral adaptation) and some incoordination.

This patient will need a revision of the tension and commissure insertion of the flap.

3.1.4. Blind patient submitted to dynamic reanimation (gracilis transplantation)

Cupid mark does not exactly intersect the vertical axis of the face, despite improved symmetry of the face at rest after surgery (Figs. 11 and 12).

Some imbalance between contraction and relaxation is seen: the movement is not very consistent. Horizontal movements are abrupt at the right side and less coordinated. However, good vertical excursion of commissure marks is noted (4.8 mm). There is symmetry of the commissures at rest.

This should be considered as a good result in a blind patient after facial reanimation associated with acoustic and sensorial feedback rehabilitation.

3.1.5. Burn patient candidate to facial transplantation

Facegram shows symmetry/balance and temporal consistency (Figs. 13 and 14). Hold period is not properly maintained (there is a

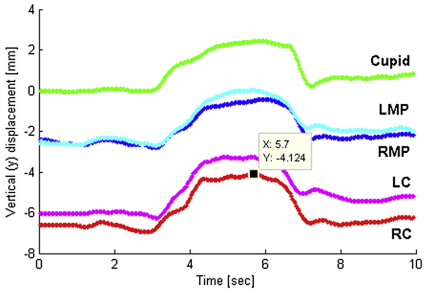


Fig. 5. Differences in facial excursion may be determined by examining on the curve at points corresponding to a rest situation and maximal contraction and calculating the differences between the coordinates (x, y).

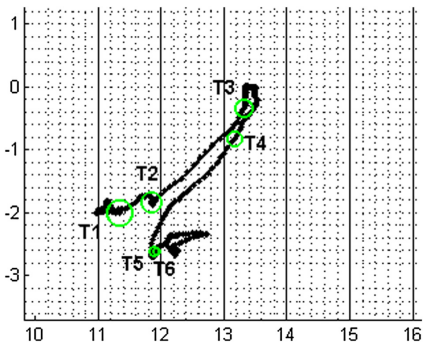


Fig. 6. In every pathway, 6 points mark important times: T1-start of recording; T2-start of contraction; T3-end of contraction; T4-start of relaxation; T5-end of relaxation; and T6-end of recording.

progressive loss of extension). The extent of horizontal movement is very similar to the normal individual, with consistent and coordinated movements over time. Vertical movement appears to be superior in relation to horizontal movement. The extension of the commissures is clearly superior to that of midpoints or Cupid's bow

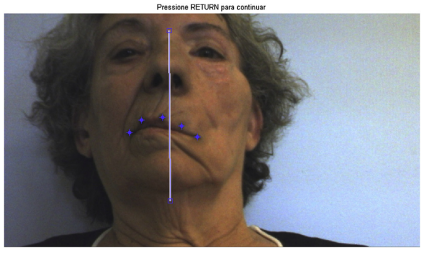


Fig. 7. Facegram analysis in a patient submitted to static reanimation.

compared to a normal individual, which may be explained by cicatricial retraction of the central part of patient's lips. Despite the reduction in range of motion over time this patient has acceptable muscle function and innervation, even in the presence of severe scarring, and facial movement approaches the normal compared to a standard population. After facial transplantation, it will be difficult to recover motor function that will achieve the same degree of muscle contraction. In this case the facegram can be useful to provide a baseline pattern, which will be important to accompany functional recovery.

4. Discussion

The objectives of facial reanimation are a symmetric face at rest and with voluntary motion, corneal protection, restoration of oral, nasal and ocular sphincter control, and controlled balance when expressing emotion with no loss of other significant functions.

Early repair of facial nerve paralysis when cortical neural input cannot be provided by the facial nerve nucleus, may be achieved by anastomosing the extracranial stump of the facial nerve to a motor donor nerve, such as the hypoglossus, or the masseteric nerve (Biglioli et al., 2012; Sforza et al., 2012).

When facial nerve dysfunction has exceeded 18 months, neurofibrosis and myofibrosis in the distal neuromuscular unit preclude successful reinnervation, or in patients with congenital facial paralysis where neuromuscular units never developed, regional muscle transposition and free-muscle transfer are the 2 best modalities to reanimate the face.

Many clinicians and researchers working in the field of mimic muscle evaluation have underlined the need for objective, quantitative ways to evaluate facial excursion as a supplement to subjective assessments. In addition, there is a strong relation between lip contraction, lip force, eating ability, speech and saliva control (Sjögreen et al., 2011).

Numerous subjective facial grading scales have been proposed (Kang et al., 2002; Alicandri-Ciufelli et al., 2013). These include House–Brackmann Scale, Sunnybrook system, Yanagihara system, Burres-Fisch, Nottingham system, Terzis and Noah classification, 'Rough' Grading System.

Rating scales provide a measure of severity, progression of deformity and recovery of normal function. However, they are subjective, lack precise description of facial impairment, and are susceptible to drift among raters. There are differences between individuals, genders and age groups. It is also difficult to find a balance between exact descriptions and minimizing the number of groups in which patients are classified (Peitersen, 2002).

There are no standard measurement techniques for the assessment of facial symmetry at rest and with movement.

The Maximal Static Response Assay (Johnson et al., 1994) is a static assay, in which physical markers are place on facial landmarks and the coordinates of the centre of each marker are manually recorded in the initial and final digitized frames (repose and maximal facial response) of a video sequence of facial expressions. The linear x, y displacement of each marker between repose and maximal response provides a quantitative measure of motion, but no information is given between repose and maximal response and nonlinear motion is ignored. It is time consuming for the operator and the patient.

In the automated face analysis (AFA) (Wachtman et al., 2001), motion of facial features is tracked automatically by a computer vision using dense flow extraction (for motion detection of the overlying skin produced by muscle contractions), feature-based tracking and high-gradient component detection to detect wrinkles and furrow features. AFA automatically extracts and represents nonlinear motion across the image sequence.

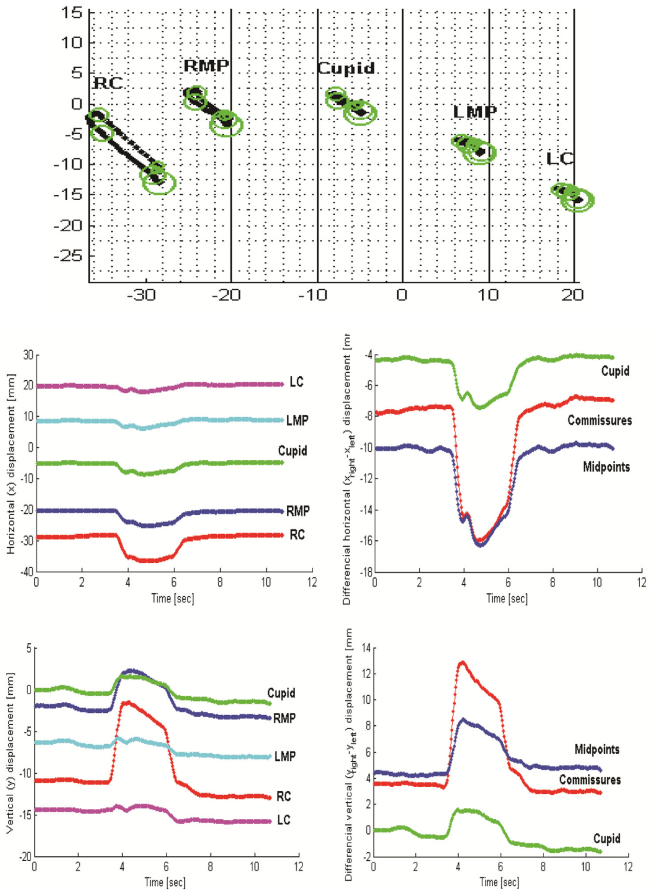


Fig. 8. Unbalanced distension, almost unilateral (with maximal extension above the normal).

Tessa Hadlock introduced the Facial Clinimetric Evaluation (FaCE) instrument (Hadlock et al., 2011). Preoperatively and postoperatively, a resting still photograph and a photograph with the largest smiling effort are compared for the change in position of the oral commissure, related to smiling effort. The smile improvement (Δz) is calculated as a ratio of preoperative to postoperative commissure excursion with smiling effort (Δ denotes the change in position, and z denotes the distance from oral commissure to midline of the lower lip).

Previously described methods (Johnson et al., 1994; Wachtman et al., 2001; Hadlock et al., 2011; He et al., 2008) do not provide information between repose and maximal response, nonlinear motion and temporal components are ignored, or graphic analysis is not the most accurate.

A more practical system was described by Manktelow et al., 2008, for the evaluation of facial paralysis reconstructions, with a handheld ruler being applied to landmarks about the mouth, and quantitative assessment of their positions at rest and when smiling (static measurements). Despite being a simple, reliable and accurate technique, one of the limitations of this method is that it does not account for the direction of the measured movement, and does not provide temporal information.

Some authors suggest that three-dimensional analyses are more accurate (Giovanoli et al., 2003; Gross et al., 1996), and motion systems were developed (Frey et al., 1994; Trotman et al., 1998; Trotman and Faraway, 1998). An interesting 3D capture system was developed by Hontanilla and Aubá, 2008, providing not only distances but also velocities and areas. The FACIAL CLIMA involves placing special reflecting dots on the subject's face and video recording with the subject performing face movements three infrared-light cameras. The lateral cameras are rotated 30° converging on the central camera (placed 20 cm higher).

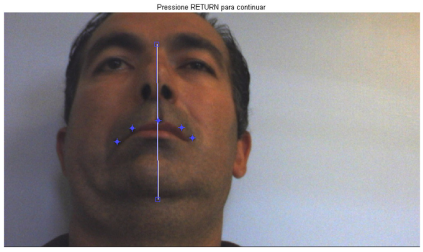


Fig. 9. Facegram analysis in a patient submitted to dynamic reanimation (gracilis muscle free transplantation).

Indeed, with multiple cameras (2 or more, with different view angles) the tracking of the anatomical landmarks would be more precise with respect to the problem of facial convexity. A single camera provides tracking in 2D while two cameras can achieve reasonable tracking in 3D. However, tracking with multiple cameras imposes an important constraint: the relative position and orientation of the cameras need to be precisely known to be able to triangulate the movement of the points in space. This means that the system would require a complicated set up and calibration. A hallmark of our method is the ability to very easily acquire the videos and calculate the facegrams, using an inexpensive webcam. That is, we chose to sacrifice precision in anatomical points distal to the central axis of the face in order to provide a portable system that every clinician can use at the cost of a standard webcam.

An ideal facial grading system should be simple, inexpensive, reliable, require minimal time and equipment, measure both static

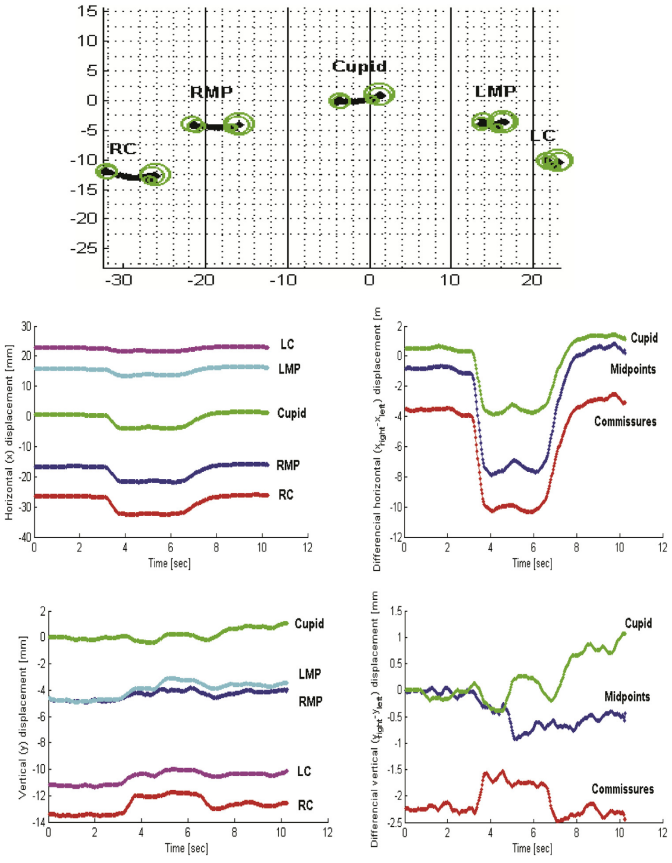


Fig. 10. The movement is almost exclusively horizontal.

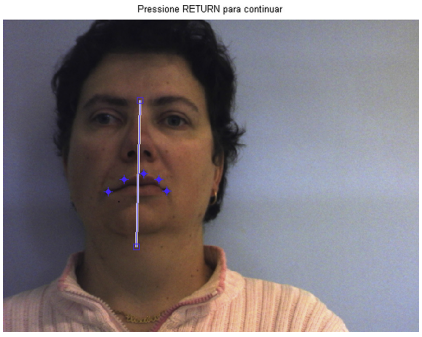


Fig. 11. Facegram analysis in a blind patient submitted to dynamic reanimation (gracilis muscle free transplantation).

and dynamic components, and sensitive to changes over time or following medical therapy or surgical reconstruction.

In this paper, we describe a novel quantitative, reliable method which accurately assesses the fundamental aspects of the facial excursion, incorporating spatial and temporal components. This method allows the construction of what we call a facegram, likewise an audiogram which records auditory frequencies or an electrocardiogram records cardiac electrical potentials.

This system is unique because it allows visualisation in scale the paths followed by each anatomical landmark. It includes the horizontal (and the vertical) displacement, and the differential horizontal (and the vertical) displacement of each point as a function of time .The software also allows the enlargement of each landmark separately and with great detail.

The video sequences are not analysed frame by frame with manual point selection by the user on each frame. The user only identifies the markers' locations in the first frame. The algorithm then automatically tracks the markers independently in (x, y, t) coordinates for the entire video sequence. The process thus takes a

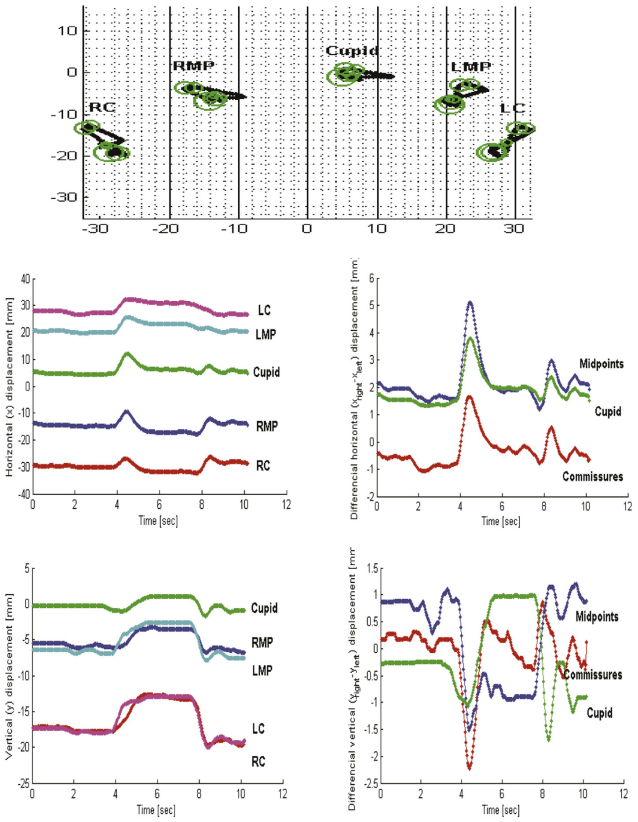


Fig. 12. Some imbalance between contraction and relaxation. However, good vertical excursion of commisure marks is noted (4.8 mm). There is symmetry of the commissures at rest.

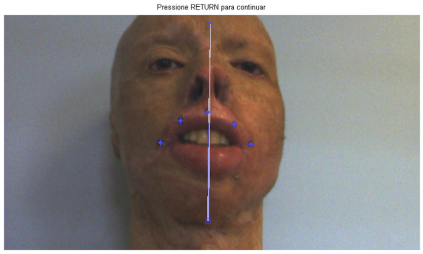


Fig. 13. Facegram analysis in a burn patient candidate to facial transplantation.

few seconds, is reproducible, and reliable, since variability in the point selection of the markers (as long as within its central area) is not translated in variability in the markers trajectories. It is a simple tool, rather than a complex system which would be impractical in the clinical setting.

This study provided an objective analysis of facial movement, allowing in the first instance evaluation of patients with facial paralysis in the perspective of disability, and postoperatively to assess the effectiveness of the reconstructive procedure (nerve grafts/transfers, static and dynamic reanimation). It may also be important for progress in the field of physical therapy and rehabilitation, following the outcome of patients with Bell's palsy in order to assess spontaneous regeneration over time, recovery from acoustic neuroma surgery or some other surgery complicated with facial weakness/paralysis.

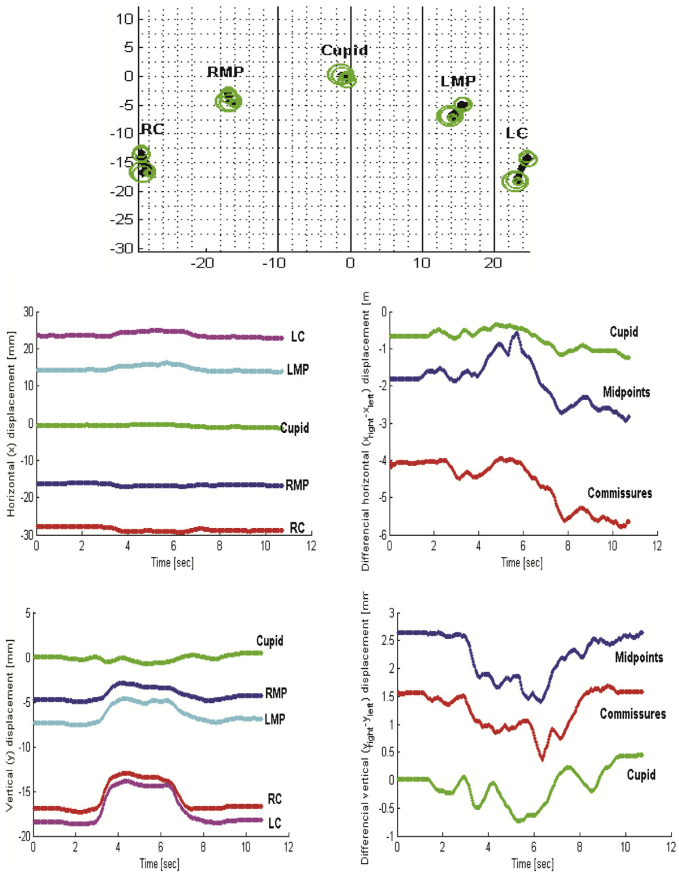


Fig. 14. Facegram with symmetry/balance and temporal consistency. Hold period is not properly maintained (there is a progressive loss of extension).

This facegram was initially developed for analysing facial paralysis, however it has an enormous application potential in all types of reconstructive surgery of the face, particularly in oncologic defects or traumatic aetiology, burned patients, or even in the field of cosmetic surgery.

The case studies presented in this paper focus on smile dynamics but our facegram method can be applied equally to different constellations of anatomical points. In other words, instead of the five landmarks used to track the smile movement, a different number of points associated with other anatomical references could be used in order to produce a facegram such as the nose, palpebral aperture and for dynamic measurements of the eyebrows or eyelids.

As we have recently described (Horta et al., 2013), it may also be an important contribution to the facial transplantation assessment and for comparison of results from centre to centre, since the facial appearance of the recipient will have a direct relationship with the motor reinnervation and simultaneous development of alterations in the expression and nasolabial folds.

5. Conclusion

In this paper, we describe a novel quantitative, reliable method, which accurately assesses the fundamental aspects of the facial excursion, incorporating spatial and temporal components.

Financial disclosure

None of the authors has a financial interest in any products, devices, or drugs mentioned in this manuscript.

Conflict of interest statement

There is no conflict of interests to declare. None of the authors has a financial interest in any products, devices, or drugs mentioned in this manuscript.

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ALT chimeric flap associated to a dura mater biomatrix substitute for severe desfigurative mandible osteoradionecrosis and deficient bone consolidation after a free fibula flap

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Keywords: Severe osteoradionecrosis; ALT chimeric flap; Dura mater biomatrix substitute; Free fibula flap

Although radiotherapy can increase cure rates after head and neck cancer it often comes with secondary effects, one of the worst of which is osteoradionecrosis. Obliterative endarteritis, hyperaemia, hyalinisation, cellular loss, hypovascularisation, thrombosis, and fibrosis are common histological findings. Bone cells are damaged as a result of acute inflammation, free radicals, and the chronic activation of fibroblasts.[1]

In extreme cases, even free transfer may be not enough for adequate reconstruction, and alternative plans should be considered. The persistence of poor coverage in an extensively irradiated area, and an inadequate barrier around the bone, were identified as the two main problems that prevented adequate healing of bone in a 41-year-old woman with severe osteoradionecrosis and deficient bony consolidation after a fibular free flap. Despite the flap being viable with patent microvasular anastomoses and normal radiological bone density, there was no effective consolidation (Fig. 1), and subsequently the mandibular reconstruction plate extruded and a persistent orocutaneous fistula developed (Fig. 2).

To solve the problem, a chimeric anterolateral thigh flap was used, which incorporated two independent fasciocutaneous and muscular components. The skin paddle was placed for external coverage and contour, while the muscular segment was used to obliterate dead space and cover the reconstruction plate. A collagen biomatrix dura mater substitute (TissuDura®; Baxter, Vienna-Austria) membrane was then used to act as a barrier to prevent invasion of soft tissue into the fibula by forming a chamber to guide bony regeneration. The material is composed of colloidal collagen from equine Achilles tendon, and has recently been used in neurosurgical procedures with no local or systemic toxicity, and little inflammation. It has elastic qualities and good anatomical adaptability. [2] A bone substitute was also added in rebuilding mandibular bone stock (Repros ® granules, JRI Orthopaedics Ltd, Sheffield-UK), as a temporary scaffold to fill the gaps made by the osteotomy and to provide biomechanical stability.

According to preliminary clinical reports, the time period for complete bony regeneration of the mandible is 3 months, whereas long bones require more than twice that,[3,4] probably because of the greater vascularity of the mandible and the surrounding soft tissues, the different mechanical environment, and the fact that there is less stress shielding of the fixation. It is also influenced by the distinct pathways of formation of bone in that the mandible has a different embryological origin

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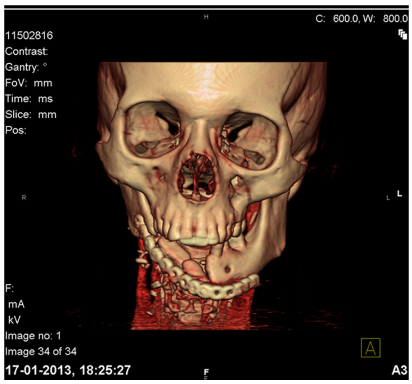


Fig. 1. Severe osteoradionecrosis of the mandible and deficient bony consolidation after a free fibular flap.



Fig. 2. Persistent orocutaneous fistula.

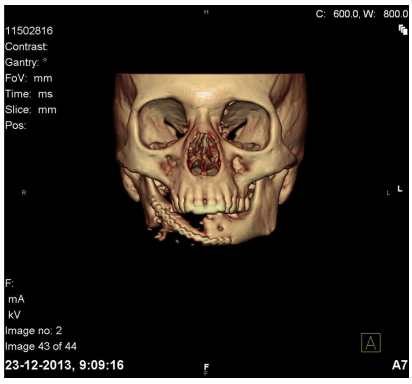


Fig. 3. Initial bony consolidation after 3 months.



Fig. 4. Postoperative appearance after 3 months; good contour and absence of the orocutaneous fistula (published with the patient' consent).

(intramembranous ossification) from the long bones (endochondral ossification). However, complete bony regeneration can be delayed in irradiated tissues.

Initial bony consolidation was seen after 3 months, and closure of the orocutaneous fistula was achieved after reconstruction with a chimeric anterolateral thigh flap and a dural substitute membrane, after failed reconstruction with a fibular free transfer (Fig. 3). The chimeric flap improved the vascularisation of local tissue, and allowed coverage of both a reconstruction plate and the external and internal soft tissues (Fig. 4). The dura mater biomatrix substitute prevented invasion by the soft tissue, and has osteoinductive, osteogenic, and angiogenic properties that guide a vascularised bone transfer for effective consolidation, and posterior rehabilitation with dental implants. [5] However, further data are necessary.

Financial disclosure

None of the authors has a financial interest in any products, devices, or drugs mentioned in this manuscript.

Conflict of interest

The authors have no conflict of interests.

Ethics statement/confirmation of patient permission

The patient gave full written permission for the case to be presented for publication and used for research and teaching purposes.

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PUBLICATION X



CLINICAL STUDY

Microsurgical Reconstruction for Radiation- and Bisphosphonate-Induced Mandible Osteonecrosis Based on Patient-Specific Physiopathologic Mechanisms

Ricardo Horta, MD, Diana Monteiro, MD, Tiago Neto, MD, Rui Balhau, MD, Ligia Coelho, MD, Alvaro Silva, MD, and José Manuel Amarante, MD, PhD

Background: Radiation- and bisphosphonate-induced mandible osteonecrosis have distinct underlying physiopathologic mechanisms, but both can constitute a serious problem and lead to functional impairment and facial disfigurement.

Methods and Results: We describe different clinical situations related to several grades of osteonecrosis, where different options of free transfer should be considered based on case-specific physiopathologic mechanisms. We propose a simple clinical grading system to predict the best treatment option.

Conclusions: For patients with advanced refractory disease, pathologic fracture, orocutaneous fistula, and severe osteolysis, resection associated with microvascular reconstruction seems to be a valid option that stops the underlying pathophysiology of overinfected avascular bone necrosis. Physicians who understand the specific physiopathologic mechanisms of each case can incorporate them into the assessment of the required reconstruction and treatment plans.

Key Words: Osteonecrosis, mandible, radiation, bisphosphonates, microsurgical reconstruction, physiopathologic mechanisms

(*J Craniofac Surg* 2014;25: 1793–1796)

Radiation- and bisphosphonate-induced mandible osteonecrosis can constitute a serious problem and lead to functional impairment and facial disfigurement.

Radiotherapy can increase cure rates after head and neck cancer, but it often comes with secondary effects, and one of the worst complications is the osteoradionecrosis (ORN). Obliterative endarteritis, hyperemia, hyalinization, cellular loss, hypovascularization, thrombosis, and fibrosis are the most common histologic findings in ORN, which may result in metabolic and tissue homeostatic disturbances that decrease the diffusion of oxygen into the tissues. It should be emphasized that ORN is not only a disease of the bone but also affects the surrounding soft tissue. Sometimes, after radical ORN resection, composite through-and-through defects exist, which require a second free flap for reconstruction of the external skin defect of the lower face or neck.

Osteonecrosis of the jaws was also more recently described as an adverse effect of bisphosphonate therapy. Bisphosphonates are inhibitors of bone resorption by osteoclasts, and patients with multiple myeloma and osseous metastasis from carcinomas, who are receiving nitrogen-containing bisphosphonates, are at greatest risk for osteonecrosis.

In both clinical situations, wide radical resection of necrotic bone with immediate replacement with healthy vascularized tissue is often the best option for the treatment of advanced osteonecrosis. Several free flaps such as the scapula bone flap, iliac crest flap, or soft-tissue-only flaps (rectus abdominis and latissimus dorsi myocutaneous flaps) have been used, but the fibula osteoseptocutaneous free flap is usually preferred, because it allows 2 surgical teams to work simultaneously, to perform multiple osteotomies, and to obtain adequate length of bone up to 25 to 27 cm and a vascular pedicle of up to 12 to 15 cm. This is important because identification of adequate recipient vessels may be difficult in the presence of an irradiated neck[1] and may have to be selected outside the irradiated field or in the opposite neck.[2,3]

For patients with advanced refractory disease, pathologic fracture, orocutaneous fistula, and severe osteolysis, resection associated with microvascular reconstruction seems to be a valid option that stops the underlying pathophysiology of overinfected avascular bone necrosis.

METHODS AND RESULTS

We describe different clinical situations related to several grades of osteonecrosis, where different options of free transfer should be considered based on case-specific physiopathologic mechanisms. We propose a simple clinical grading system to predict the best treatment option.

Grade 1

Description: No clinical evidence of necrotic bone, but with early nonspecific or radiographic findings or with exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection (Fig. 1).
Required reconstruction: No specific reconstruction is required.
Treatment plan: Oral hygiene measures, mouthwashes of 0.12% of chlorhexidine, treatment of pain, frequent clinical evaluations (6/6 months), and consideration of suspension of oral bisphosphonates.

Grade 2

Description: Mandible osteonecrosis with or without pathologic fracture.
Required reconstruction: Bone.
Treatment plan: Free fibula transfer (Figs. 2, 3).

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FIGURE 1. Early exposure of necrotic bone in an asymptomatic patient without evidence of infection; conservative treatment is often the best option.

Example

A 54 year-old-male patient was diagnosed with squamous nonsmall cell lung cancer with bone metastasis (left hip). He was submitted to surgery, radiotherapy, and chemotherapy, followed by a 3-year treatment with intravenous bisphosphonate (Zollendronic acid). One year later, he presented with painful bone exposure at the level of the alveolar ridge of the right body of the mandible, associated with pathologic fracture and without history of tooth extraction. He underwent previous treatment with antibiotics, antiseptics, and conservative surgical debridement. A maxillofacial computed tomography (CT) showed a complex lytic lesion in the right body of the mandible, with 42 × 11 mm, bone sequestrum, and pathologic fracture. The patient was submitted to a right segmental mandibulectomy (symphysis to the right angle) including 1-cm margin of macroscopically healthy bone, through a transcervival approach. The defect was reconstructed using a free fibula flap, and the microvascular anastomosis was completed with an end-to-end technique to the right facial vessels. The fibula flap was divided into 2 segments in an attempt to reestablish the mandibular contour, and each segment was fixed with 3 locking screws to the mandibular reconstruction plate. Because there were no significant skin or mucosal defects, no skin paddle was used. The oral mucosa was closed in a watertight manner over the fibula flap. No infection, delayed healing, or compromise to the vascularity of the flap was noted. The patient had complete resolution of symptoms and complications (including pain, fistula, infection, and pathologic fracture) and was satisfied with the esthetic and functional results. An orthopantomography showed proper conformation of the flap and reconstruction plate and no recurrence of osteonecrosis in the resection margins after 12 months.

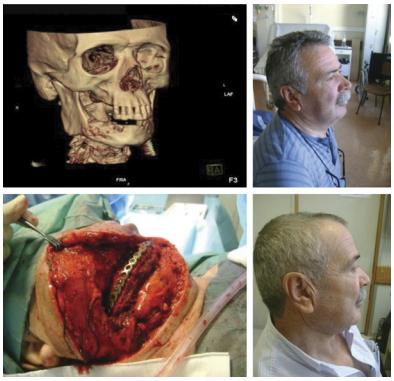


FIGURE 2. Top left, BRONJ. Top right, Preoperative: absence of orocutaneous fistula. Bottom left, The fibula flap was divided into 2 segments in an attempt to reestablish the mandibular contour and was fixed to the mandibular reconstruction plate. Bottom right, Postoperative appearance after 12 months; good contour.

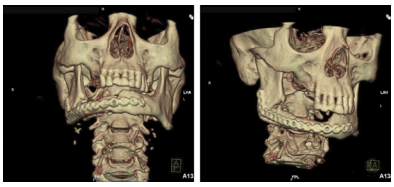


FIGURE 3. Bone consolidation was successfully achieved.

Grade 3

Description: Mandible osteonecrosis + orocutaneous fistula.
Required reconstruction: Bone + internal/external coverage.
Treatment plan: Fibula osteoseptocutaneous free flap (Fig. 4).

Example

A 57 year-old-male patient was diagnosed with squamous cell carcinoma of the hypopharynx (clinical staging, T2 N0 M0). He underwent radiotherapy (2 Gy in 36 fractions with 6-MV energy) with concurrent radio-sensitizing chemotherapy (cisplatin of 100 mg/m^2, 3/3 weeks, for a total of 3 cycles), with clinical remission and no signs of locoregional recurrence. Later, he reported progressive burning-like pain radiating to the ear and making it difficult to open his mouth. The pain was controlled with gabapentin of 300 mg for 8-8 hours, Tradorec XL of 100 mg (tramadol) at night, and Zamadol (tramadol hydrochloride) for 6–6 hours in SOS, but despite conservative treatment, he had great difficulty in opening the mouth and chewing, with impaired quality of life. During his radiation treatment, he developed an orocutaneous fistula on the left angle. A CT scan was performed and showed abnormal trabeculation of the mandible consistent with osteonecrosis (angle and left body). He was submitted to segmental mandibulectomy and reconstruction with a fibula osteoseptocutaneous free flap. Despite good coverage and healing, concomitant with pain relief and improvement of mouth opening, the patient died later as a consequence of cardiorespiratory arrest.

Grade 4

Description: Mandible osteonecrosis + orocutaneous fistula + irradiated external soft tissue.
Required reconstruction: Bone + external soft tissue replacement + separation of bone and soft tissue (guided bone regeneration).



FIGURE 4. Top left, Mandible ORN. Top right, Associated orocutaneous fistula. Bottom left, Fibula osteoseptocutaneous free flap. Bottom right, Immediate postoperative appearance; good contour and coverage.

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FIGURE 5. Top left, Severe mandible ORN and deficient bone consolidation after a free fibula flap. Top right, Persistent orocutaneous fistula. Bottom left, ALT chimeric flap: the skin paddle is independent of the muscle component, the skin paddle was inserted extraorally, and the muscle was used for coverage of the mandibular plate. Bottom right, Postoperative appearance after 3 months; good contour and absence of orocutaneous fistula.

Treatment plan: Fibula + anterolateral thigh flap (ALT) chimeric flaps (Figs. 5 and 6).

Example

Persistence of poor coverage in the context of an extensive irradiated area and inadequate barrier surrounding the bone were identified as the 2 main problems preventing adequate bone healing in a 41-year-old female patient with severe ORN and deficient bone consolidation after a fibula free flap. Despite flap viability with patent microvasular anastomosis and normal radiologic bone density, there was no effective consolidation. Extrusion of mandibular reconstruction plate and persistent fistula orocutaneous were subsequently seen. A modified ALT flap was used incorporating 2 different fasciocutaneous and muscular components. The skin paddle was placed for external coverage and contour, whereas the muscular segment was used for coverage of the reconstruction plate. A collagen biomatrix dura mater substitute (TissuDura; Baxter, Vienna, Austria) membrane was used to act as a barrier to prevent soft-tissue invasion into the fibula and to form a "chamber" to guide the bone regeneration. A bone substitute was also added in rebuilding mandible bonestock (Repros granules; JRI Orthopaedics Ltd, Sheffield, United Kingdom), as a temporary scaffold to fill the osteotomy gaps and provide biomechanical stability.

Initial bone consolidation was seen after 3 months, and closure of orocutaneous fistula was achieved.

DISCUSSION

The incidence of ORN varies widely in the literature ranging from 1% to 37%.[4] The definition of ORN is generally accepted as the presence of exposed bone in an irradiated field, which fails to heal within a 3-month period.[5] Early presentation, within 2 years, is thought to be related to high doses of radiotherapy (>70 Gy), whereas late presentation is usually secondary to trauma and delayed wound healing within compromised tissue.

In an irradiated field, even a minor insult such as a dental procedure can result in delayed healing, and some cases develop into ORN. Signs of radiation may include pigmentary changes, lack of hair, and telangiectasis. Intraorally, the mucosa may be dry with frothy sputum in the acute phase. The patient may have a nonresolving painful mucosal ulcer, inability to open the mouth (trismus), usually 3 to 6 months after radiotherapy. The initial effects of radiotherapy to the oral tissues such as mucositis and loss of taste are troublesome but usually resolve within a few weeks. Xerostomia may be long standing but can be managed with supportive therapy such as sialogues and artificial saliva.[4] Exposed bone inside the mouth can be seen (sequestrum) usually in the posterior mandibular region. There may be exposed bone seen through the skin, in the form of an orocutaneous fistula, or the patient may present with a pathologic fracture,[6] and transfer of microvascularized bone, eventually associating a skin paddle, is often the best reconstructive option.

As previously mentioned, ORN affects surrounding the soft tissue and is not only a disease of the bone. A modified ALT flap can also improve local tissue vascularization, allowing for coverage of both a reconstruction plate and external/internal soft tissue and closure of an orocutaneous fistula in the presence of severe osteoradionecrosis. It can also been used as a salvage procedure after deficient bone consolidation with a fibula free flap, in addition to a collagen biomatrix substitute, to act as a barrier to prevent soft-tissue invasion into the fibula and to guide the vascularized bone transfer for effective consolidation.

Bisphosphonates such as alendronate (Fosamax), pamidronate (Aredia), and zoledronate (Zometa) are commonly used to manage the hypercalcemia associated with malignancies such as multiple myeloma or metastatic breast cancer and, more recently, to prevent osteoporosis. They are analogs of endogenous pyrophosphates with substitution of 1 atom of oxygen for 1 atom of carbon, and they have high affinity to the bone, being accumulated for long periods. Bisphosphonates are inhibitors of bone resorption by osteoclasts, which help reduce calcium levels and preserve bone and also have antiangiogenic properties. They can lead to decreased bone turnover, hypermineralization (target of the therapeutic use), and bone hypovascularization. This results in a combination of a compact and avascular bone and osteoporosis by a mechanism of ischemia and secondary infection.

Like ORN, bisphosphonate-induced osteonecrosis of the jaws (BRONJ) presents as painful exposed bone in the maxillary or mandibular alveolus with intraoral or extraoral drainage and is usually refractory to conventional nonoperative and operative surgical treatment.

The current literature advocates a conservative treatment of BRONJ, using antibiotics and limited surgical debridment. Antibiotics, conservative debridements, irrigations, and topical application of antiinfectives are seldom curative but may be useful in the first stages and permit the patient to live with their disease. Hyperbaric oxygen does not seem to be effective. Patients who have responded poorly to conservative treatment may require segmental mandibulectomy or maxilectomy. Several authors[7,8] have argued against bone reconstruction of segmental defects among patients with BRONJ, owing to the perceived high risk of perioperative complications, risk of transferring malignant cells from the donor site, recurrence of BRONJ at resection margins, and nonunion. Patients often have poor survival and health status. "Skeptics" of microvascular reconstruction report good results with segmental resection without reconstruction.

"Defenders" of microvascular reconstruction[9–13] state that microvascular reconstruction allows for the restitution of bone continuity with vascularized tissue with functional and esthetic advantages. There is a reduced risk of exposure of the reconstructed plate and minor recurrence of osteonecrosis. In addition, fibula is rarely involved

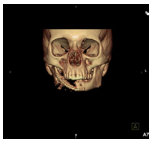


FIGURE 6. The previous fibula flap was finally integrated into the remaining mandible.

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by bone metastasis or multiple myeloma, and the use of autologous fibula bone transfer in patients with a history of cancer poses a minimal risk of transfer of metastatic lesions from the fibula to the mandible. Bisphosphonate-induced osteonecrosis primarily affects the jaw bones and usually follows dental trauma with exposure of bone to oral secretions. Therefore, transferring the fibula does not likely transfer bone adversely affected by systemic bisphosphonate therapy.

In fact, most cases reported of vascularized bone reconstruction of segmental mandibulectomy defects showed minimal perioperative complications, no transfer of malignant cells to the recipient site, improved cosmesis and oral function, decreased complications related to plate exposure, and benefit from the establishment of union of the native mandible with the fibula flap.

We believe that segmental resection and microvascular reconstruction may be a valid option in specific advanced cases of ORN and BRONJ, interrupting the underlying pathophysiology of overinfected avascular bone necrosis.

Physicians who understand the specific physiopathologic mechanisms of each case can incorporate them into the assessment of the required reconstruction and treatment plans.

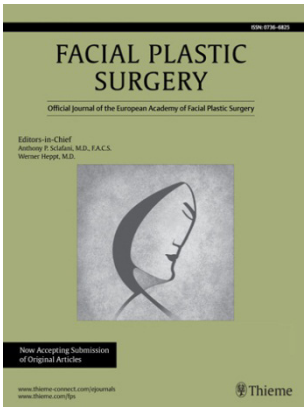
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PUBLICATION XI



Chimeric Flaps and "Their Variations": Different Options for Immediate Reconstruction of Massive Facial Defects

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Abstract

The reconstruction of massive head and neck defects is a difficult challenge, requiring restoration of bone, skin, and oral lining. Their complex three-dimensional nature often dictates the need of more than a single osteocutaneous flap for intra- and extra-oral reconstruction.

Conventional reconstructive options can be considered, but there is no single ideal osteocutaneous free or pedicled flap providing an unlimited length of bone and skin paddle, or that could orient the skin paddle independently of the vascularized bone. The surgeon should then be aware of more complex options for reconstruction of extensive three-dimensional defects, namely chimeric free flaps and "their variations." They can be stratified in three types, either based on their intrinsic vasculature—perforated-based, branch-based, or whether they are prefabricated (surgical junction by microanastomosis). Despite morbidity and not perfect matching in terms of skin texture and pliability, these techniques are a good alternative in the presence of partial defects, especially in the context of immediate oncological reconstruction, where facial transplantation is not considered.

Keywords
- massive defects
- facial reconstruction
- chimeric flaps
- flow-through free flaps

The reconstruction of massive head and neck defects is a difficult challenge, requiring restoration of bone, skin, and oral lining. Their complex three-dimensional (3D) nature often dictates the need of more than a single osteocutaneous flap for intra- and extraoral reconstruction.

Conventional reconstructive options can be considered, but there is no single ideal osteocutaneous free or pedicled flap providing an unlimited length of bone and skin paddle, or that could orient three-dimensionally the skin paddle independently of the vascularized bone. The surgeon should then be aware of more complex options for reconstruction of extensive 3D defects, namely, chimeric free flaps and "their variations" in the context of limited vasculature and immediate oncological reconstruction, where facial transplantation is not applicable.

According to the most recent classification of compound flaps proposed by Hallock, chimeric flaps, also called poly-flaps, refer to multiple otherwise independent flaps that have an independent vascular supply, but in turn all pedicles are linked to a common large vessel. They can be stratified in three types, either based on their intrinsic vasculature—perforated-based, branch-based, or whether they are prefabricated (surgical junction by microanastomosis). The last type can also be subdivided according to the fabricated component as a sequential type (anteriorly known as "flow-through sequentially linked flap") or internal type, when the prefabricated component is attached to an indigenous branch within the flap (►**Fig. 1**).

Concerning "branch-based" chimeric flaps, the classical type, they allow inclusion of multiple skin paddles for intra/extraoral coverage and a muscle or osseous component, for obliteration of dead space/plate or bone coverage, based on individual septocutaneous and musculocutaneous

Issue Theme Reconstruction of the Orbit; Guest Editor, Rainer Schmelzeisen, MD, DDS, PhD, FRCS

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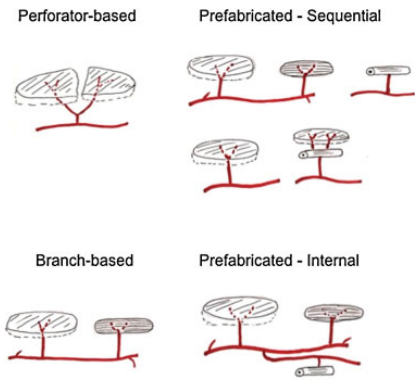


Fig. 1 The anatomical and dynamic concept of chimeric flaps. They can be perforator- or branch-based (depending on their intrinsic vasculature), or prefabricated (i.e., surgically joined together by means of a microanastomosis). The fabricated component can be attached to the terminus of the source vessel to the combination (sequential type) or to a branch indigenous within the flap (internal type).

perforators. A fibula flap can be harvested with dissection of the osteoseptocutaneous component and inclusion of a lateral segment of soleus muscle, as two separate components (►**Figs. 2** and **3**). A chimeric anterolateral thigh (ALT) flap can also be a good option for massive defects, incorporating two different fasciocutaneous and muscular components without bone reconstruction (►**Fig. 4**). The parascapular/scapular/latissimus dorsi muscle/serratus anterior muscle (thoracodorsal vessels-based) chimeric flaps may also be considered for these reconstructions. These types of chimeric flaps have advantages in reconstruction of large and compound defects, allowing easier 3D insertion and require only one pair of recipient vessels, not affecting major vessels. They also present low morbidity, decreased operative time, and acceptable aesthetic results. However, despite their advantages, a learning curve is necessary and variation of the anatomy can be present.

The concept of an uninterrupted arterial flow-through flap was developed by several authors, when vascular reconstruction is required in addition to soft-tissue replacement. Frequently, the "prefabricated type" is a combination of an ALT or radial forearm flap sequentially linked to a free osteocutaneous flap (fibula/iliac crest) for reconstruction. Their great advantage is the possibility of inclusion of two different skin paddles repositioned three-dimensionally independently of the vascularized bone component provided by the osteocutaneous free flap. The long proximal stumps of the radial artery and cephalic vein (or the ALT pedicle), are anastomosed inside the neck, without the need of interpositional vein grafting, overcoming the limited vasculature in the multioperated, and scarred necks. As disadvantages, both free flaps may be lost, in consequence of proximal thrombosis, requiring strict postoperative monitoring. It may be time-consuming (average 8 hours), unless two to three teams are involved.

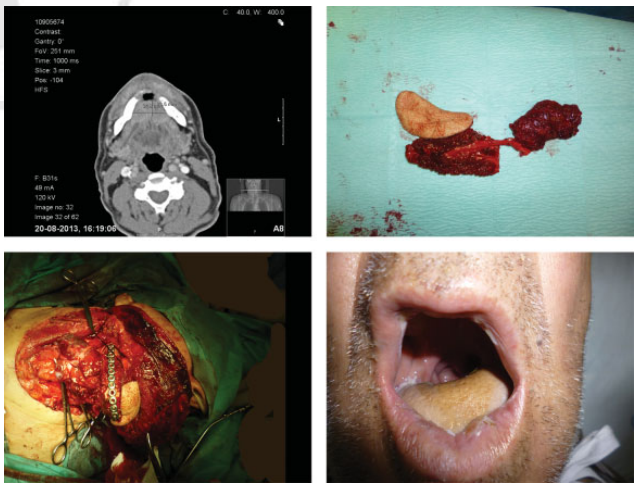


Fig. 2 *Above, left:* Extensive squamous cell carcinoma of tongue with mandibular bone invasion and destruction. *Above, right:* The fibula free flap incorporating soleus muscle as a chimeric flap. *Below, right:* The bone was adapted to a reconstruction plate; the muscle was used for coverage of the mandibular plate and the fasciocutaneous flap for reconstruction of the tongue and floor of the mouth. *Below, right:* Good intraoral coverage and external contour after 2 months.



Fig. 3 *Above, left:* Extraoral recurrence of squamous cell cancer with mandibular invasion (previous pelviglossectomy and reconstruction with a radial forearm free flap). *Above, right:* The fibula free flap incorporating soleus muscle as a chimeric flap. *Below, right:* The bone was shaped to a reconstruction plate; the muscle was used for dead space obliteration. *Below, right:* Immediate postoperative period.

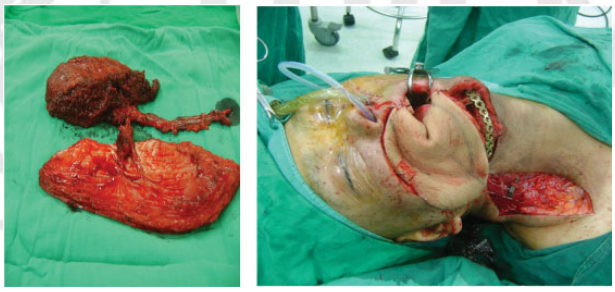


Fig. 4 ALT branch-based chimeric flap: The skin paddle is independent of the muscle component. The skin paddle can be inserted extra and/or intraorally. The muscle is a good option for coverage of a reconstruction plate and for dead-space obliteration. ALT, anterolateral thigh.

Another important consideration of the "prefabricated type" for dealing with such massive defects and to overcome the limited neck vasculature, is the reconstruction using end-to-side anastomosis of one free flap pedicle into the other free flap proximally, or end-to-end anastomosis of one free flap pedicle into a side branch of another free flap. This technique "chain-link flaps" has the advantage of utilizing only one set of recipient blood vessels, while being technically easier than anastomosis of the distal pedicle in flow-through flaps, where the caliber of the distal blood vessels (especially the veins) can be small. In some cases, this strategy also allows a greater degree of insetting freedom, avoiding the need to bend a flap pedicle 180 degrees.

In conclusion, despite morbidity and not perfect matching in terms of skin texture and pliability, these techniques are a good alternative in the presence of partial defects, especially in the context of immediate oncological reconstruction, where facial transplantation is not considered.

Acknowledgment

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Note

Ricardo Horta and Rita Valença-Filipe have contributed equally to this work and should be considered as cofirst authors.

PUBLICATION XII



Severe Traumatic Facial Injury: Avatars and Thermographic Damage Evaluation

Sir:

An ideal method for evaluating facially disfigured patients should combine morphologic analysis and dynamic evaluation. We analyzed a 17-year-old male patient with sequelae of facial trauma caused by a motorcycle accident (Fig. 1). He underwent multiple reconstructive procedures, but a disfigured face remains and further operations are needed.

First, we conceived three-dimensional facial avatars using two different approaches: (1) a moving low-cost RGB-D device for low-resolution results (Kinect; Microsoft Corp., Redmond, Wash.), and (2) a single-shot method taken from multiple high-resolution cameras synchronized and configured in stereoscopic pairs. This system creates an animatable three-dimensional facial model that resembles a real person. The process is divided into three steps: (1) acquisition, (2) re-topology, and (3) texture transfer. [**See Figure, Supplemental Digital Content 1,** which shows an overview of the pipeline. (*Left*) Input RGB and depth maps. (*Second from left*) Three-dimensional mesh reconstruction. (*Second from right*) Alignment of the scanned mesh with our template. (*Right*) Texture computation, ***http://links.lww.com/PRS/B283***.]

The first deals with the three-dimensional data gathering, which allowed us to create the subject virtual face model. The second (re-topology) is the conversion process to a "ready-to-animate" model, fitting the template of a generic mesh to the acquired three-dimensional mesh. Last, the texture transfer method computes the new texture, which is adjusted to the avatar's mesh.

Thermographic measurements were taken posteriorly. The thermography camera used was a FLIR SC7000 (FLIR Systems, Wilsonville, Ore.) with a hot metal colored lens filter that was previous configured to a 30° to 40°C temperature range. The subject sat on a chair at a distance of 1.5 m from the camera. He was asked to perform four facial expressions: facial expression at rest, with eyes closed, with eyes wide open, and while smiling.

Data management was performed with Altair 5.91.010 software (FLIR Systems). An analysis mask was established over the facial areas of interest: (1) right forehead, (2) left forehead, (3) right orbit, (4) left orbit, (5) nose, (6) right labial commissure, (7) left labial commissure, and (8) mouth. For each area, the mean temperature and its standard deviation were calculated, as were the maximum and minimum values (Table 1).

In addition to a detailed analysis of the facial dynamics, three-dimensional models analyzed with MeshLab ("Alessandro Faedo" Institute of Information, National Research Council, Pisa, Italy) allowed for a morphologic study and direct measurements. This avatar showed persistent ectropium and a significant change in vertical height of the palpebral fissure

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Fig. 1. Severe facial trauma in the context of a motorcycle accident without a helmet. Severe disfiguration in the scalp, frontal area, brow, eyelids and middle third of the face was present.

on the left side (Fig. 2). In the frontalis muscle contraction exercise, we have observed asymmetry and gross brow hairline distortion. (**See Figure, Supplemental Digital Content 2,** which shows frontalis muscle contraction, ***http://links.lww.com/PRS/B284***.) When ordering palpebral voluntary closure, the patient could not completely close his left eyelid. The problems seem to affect mainly the upper and middle thirds of the face, as good excursion of the oral commissures was seen.

Concerning thermographic analysis, when comparing the measures to a control group (28 normal subjects), he showed a persistent tendency for contralateral thermal asymmetries, with the highest values of surface temperature on the right side, and the highest values on the right forehead area. [**See Figure, Supplemental Digital Content 3,** which shows average temperature and standard deviation (area 1) and left (area 2) forehead areas during the four facial expressions (patient 1). The *hatched bars* represent the mean values and standard deviations of the control group for the same task, ***http://links.lww.com/PRS/B285***.] Surface temperature reduction on the left labial commissure was also seen. (**See Figure, Supplemental Digital Content 4,** which shows smiling analysis, ***http://links.lww.com/PRS/B286***.) These findings were probably a consequence of muscular

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Table 1. Values Recorded in Each Area Represented by Its Order Number during the Facial Expressions*

	1	2	3	4	5	6	7	8
At rest								
Average	36.84	36.77	37.34	37.20	35.45	37.00	36.80	36.60
Minimum	33.64	34.02	34.91	34.80	33.40	35.66	35.59	34.89
Maximum	37.79	37.74	38.73	38.67	37.90	37.94	37.78	37.94
SD	0.67	0.62	0.72	0.73	1.03	0.49	0.51	0.57
Eyes closed								
Average	36.93	37.06	36.92	36.89	35.48	36.95	36.82	36.56
Minimum	33.79	34.53	34.59	34.66	33.42	35.50	35.57	34.63
Maximum	37.99	37.96	38.57	38.57	37.98	37.92	37.79	37.92
SD	0.76	0.54	0.85	0.82	1.10	0.53	0.52	0.60
Eyes wide open								
Average	36.60	36.66	37.52	37.39	35.36	37.02	36.83	36.67
Minimum	32.56	33.85	35.45	35.36	33.33	35.54	35.53	34.85
Maximum	37.81	37.78	38.76	38.72	37.98	38.03	37.86	38.04
SD	0.88	0.69	0.65	0.68	1.03	0.52	0.54	0.58
Smile								
Average	36.69	36.70	37.29	37.22	35.40	37.16	36.93	36.88
Minimum	33.55	33.95	34.81	35.04	33.41	35.63	35.57	34.62
Maximum	37.71	37.68	38.70	38.67	37.97	38.68	38.33	39.06
SD	0.68	0.64	0.74	0.80	0.93	0.60	0.65	0.81

*All values are shown in degrees Celsius.



Fig. 2. Creation of a three-dimensional face avatar and analysis with MeshLab v.1.3.2. Direct measurements such as maximal eyelid aperture are possible.

damage, fibrosis, facial nerve paralysis, and decrease of the regional blood flow. These technologies could have a place in the management of facially disfigured patients, and further studies are needed.

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PATIENT CONSENT

The patient provided written consent for the use of his images.

DISCLOSURE

None of the authors has a financial interest in any of the products or devices mentioned in this article.

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