Facial transplantation.
An update of results and perspectives from tissue engineering

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Facial Transplantation. An update of results and perspectives from tissue engineering

BACKGROUND/AIM: *Facial transplantation is a revolutionary procedure developed recently, which is indicated if autologous transfers fail to restore human appearance. More than 30 patients have undergone facial transplantation in different centers worldwide. Here, we provide an update on its main anatomical, surgical, immunological, ethical, and follow-up aspects. We also provide innovative perspectives of regenerative medicine and tissue engineering that could hold promise for this emerging surgical field.*
METHODS: *Through careful review of the anatomical, surgical, and tissue-engineering literature, we documented the main aspects of this innovative surgical procedure and its potential improvements in regenerative plastic surgery.*
RESULTS: *Compatibility for the major blood groups (ABO) and human leukocyte antigen system between donor and recipient is critical to transplantation success. Major complications are tissue rejection and side effects of immunosuppression. The functional outcomes of facial transplantation are encouraging, with slow recovery of motor and sensory functions. Psychological impact on the family of the donor and recipient is essential for the success of facial transplantation.*
CONCLUSIONS: *Uncertainty of long-term outcomes, immunosuppression-related concerns and ethical debates limit worldwide application of facial allotransplantation. However, in selected patients it is a unique reconstruction method with promising outcomes. Recent developments in regenerative medicine open a new frontier for application of patient-tailored, biocompatible and engineered reproductions of the various anatomical components of the face, and their application to transplant technology. Further research in transplant immunology, survival and conservation of grafts, and regenerative treatments of lesioned and/or transplanted tissues hold the key to advances in this emerging surgical option.*

KEY WORDS: Facial transplantation, Plastic surgery, Reconstructive surgery, , Regenerative medicine, Tssue engineering

Introduction

Facial transplantation (FT) is gaining acceptance among physicians and the general public [1,2]. FT surpasses conventional reconstruction because it can restore complex esthetic and dynamic facial functions. The face is crucial for breathing, speaking, eating, and oral competence, but also for identity perception, social interactions, and communication of information and emotions. Consequently, facially disfigured patients can suffer major shame, loss, and social isolation that could be alleviated by FT [3,4].

In November 2004, based on 20 years of preclinical research, Siemionow *et al.* were granted approval for a FT protocol in humans by their institutional review board [5,6]. That protocol laid the groundwork for clinical testing of a new surgical approach, and resulted in

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TABLE I - *Classification of the facial transplant**

TYPE I	Lower Central (Nose, Lips And Chin)	IA: Soft Tissues Only IB: Bone Included (Mandible)
TYPE II	Mid facial allograft (nose, upper lip, cheeks)	IIA: soft tissues only IIB: bone included (maxilla, zigoma, palate)
TYPE III	Upper facial allograft(forehead, eyelids, root of the nose).	Transplanted only soft tissues.
TYPE IV	Total facial skin allograft transplanted only skin and subcutaneous fat as "carnival mask"	
TYPE V	Full facial allograft (types I + II + III)	VA: soft tissues only VB: bone involved (mandible, maxilla, palate, zigomas, nose)

*ref. 14, modified.

the first partial FT undertaken in November 2005 in Lyon (France) that confirmed its feasibility [7,8].

FT is included in the composite tissue allotransplantation (CTA) concept that combines skin, bone, muscles, tendons, and nerves. To date, tissue transplantations have been described in the hands, abdominal wall, tongue, larynx, face, esophagus, and knees [9]. The first full facial composite tissue allotransplantation (FCTA) was done in March 2010 in Barcelona (Spain) [10]. A full FCTA comprises the entire face with all its esthetic and functional units (forehead, nose, eyelids, cheeks, lips, chin). Since the first FT carried out in France in 2005 [7], the field has expanded considerably and >30 patients have received an FT in different centers worldwide [11,12].

FT differs radically from current methods of facial reconstruction, which involve autologous tissue. The face is taken from an unrelated deceased donor, and transplantation proceeds using a large amount of tissue requiring an arterial input and venous drainage as for an autologous free-flap transfer [13]. In 2009, Lengele et al. proposed a classification for FCTAs based on the amount and type of tissue transplanted [14] (Table I).

The initial success and encouraging early functional outcomes resulted in enthusiastic support of FT by the medical community and general public. However, the first death of a FT recipient in China in 2008, followed by another death in Paris in 2009, opened a debate on the risks, benefits, and alternatives to FT [15-17].

Historical Perspectives

FT is a recent phenomenon and has not yet involved the surgical community in Italy. However, the University of Parma (Parma, Italy) holds an absolutely original preclinical antecedent of this procedure dating back to the end of the 19th century. Lorenzo Tenchini (professor of human anatomy at Parma University between 1881 and 1906) was the first to use the entire facial skin, related hairs, part of subdermal mimic muscles, and anterior scalp to undertake a type of "experimental FT". Tenchini removed these structures *en block* from a cadaver to cover a plaster cast that was a reproduction of his face. Upon adherence to the cast, the transplanted "face" was coated with a blend of wax and pigments to reproduce the finest surface details of the deceased subject. Thus, a "mask" realized by "transplantation" of part of his facial structures onto a corresponding mold mimicking his facial bones was achieved (Fig. 1A). Judging from the records of the cadavers used (which are maintained in the Museum of the Department of Biomedical, Biotechnological and Translational Sciences (S.Bi.Bi.T.) in Parma University), Tenchini probably prepared >150 of these masks, some of which are visible at the S.Bi.Bi.T. Museum, and at the Lombroso Museum in Turin (Turin, Italy). Simultaneously, he mummified the remaining cadaveric portions of the face (facial and skull bones, masticatory and neck muscles, vessels and nerves) to prepare a corresponding anatomical specimen (Fig. 1B) for lectures on human anatomy and research purposes. He also made dehydrated and injected preparations of the brain and other parts of the body to provide a unique and extraordinary anatomical collection of considerable academic, historical, and scientific value that is used by the students and fellows of the University of Parma for medical and surgical training. Tenchini was a follower of the physiognomy ideas of Cesare Lombroso, who believed that the psychological and emotional parts of an individual are reflected in his/her body morphology (including the face). That hypothesis has failed the test of time, but the innovative and exclusive concept of "transplantation" of facial structures to restore an inexpressive face mold could be considered a precursor of the sophisticated surgery of FT that has now become a reality.

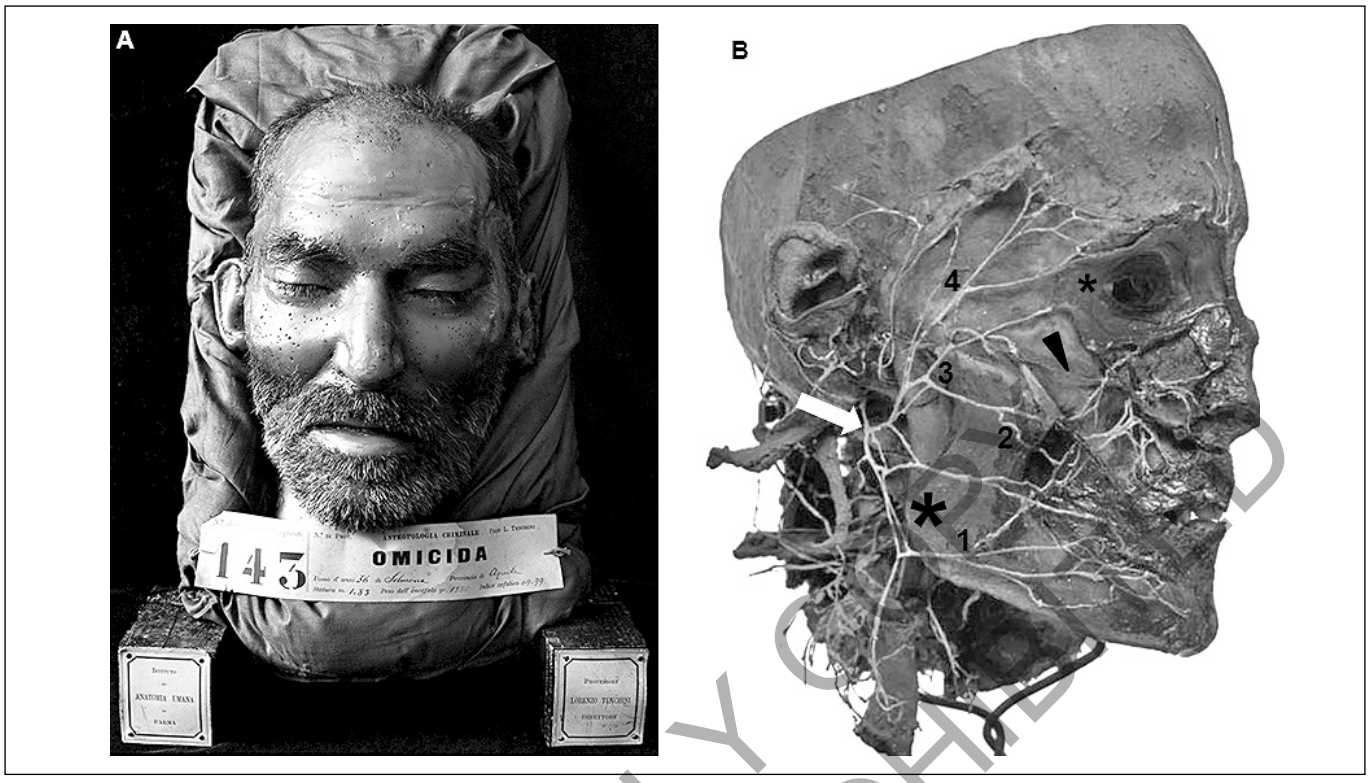

Fig. 1: A) Tenchini's collection (19th century). One of the masks kept in the S.BI.BI.T. Museum in Parma. Note that the facial surface details are obtained layering a pigmented wax onto the skin, hairs, dermal, and subdermal mimic muscles, transplanted "en block" directly onto a face cast. This cast, reproducing the profile of facial bones and cartilages, had been previously obtained by coating the cadaver face with a plaster paste, eventually solidified. The aim was to retrieve as much as possible the facial features of expression at the moment of death; B) Tenchini's collection (19th century). Mummified preparation of the head of one of the cadavers used as donors for the "face". It is possible to recognize some of the anatomical landmarks currently used during FT, including the masseter muscle (large asterisk), the mimic *orbicularis oculi* muscle (small asterisk) the mandible, the facial nerve (arrow) with its 1) mandibular, 2) buccal, 3) zygomatic, and 4) temporal branches, 5) the transverse artery of the face (arrowhead). coursing anteriorly to the parotid space as a branch of the superficial temporal artery.

Indications

In the future, FT could become first-line treatment for patients whose severe facial disfigurements induce considerable functional and social impairment. These disfigurements are usually large (involving ≥25% of the surface area of the face) or the loss or inclusion of one or more esthetic units [18]. The most important criterion when selecting FT candidates is that their facial defect cannot be reconstructed adequately using conventional methods. Severe facial disfigurement may be attributed to different causes. For example, the first two recipients suffered traumatic destruction of facial tissues due to a violent attack by a dog [8] and a bear [19], whereas FT procedures in the USA corrected defects caused by a shotgun blast [20], and high-voltage electrical burns [21]. FT has also been undertaken to correct disfigurement caused by a massive plexiform neurofibroma [22]. The wide variety of indications in these few cases suggest that each patient will present with a unique defect [23] that carries its own particular set of challenges and difficulties.

Patient Selection

Long-term outcomes and risks of FT are not known. The procedure and immunosuppression regimens pose considerable risks to the patient. Patient screening aims to include candidates with appropriately severe facial disfigurements and exclude candidates at an increased risk of complications and side effects. FT leads to a unique combination of physical, emotional, psychosocial, and behavioral consequences. Therefore, to regain function of the allograft, recipients must: (i) withstand the stress of the procedure; (ii) comply with lifelong immunosuppression; (iii) engage in aggressive rehabilitation during the first 2 years after surgery [24].

Donor Selection

A suitable donor should be the same sex as well as have acceptably close skin color and tissue texture to that of the recipient. Results from a computer-simulation study

suggest that the donor's age should lie between 20-years below and 10-years above that of the recipient [25].
Donor and recipient must be compatible for the major (ABO) blood groups. A crossmatch between the recipient and donor must be negative (i.e., the recipient does not have antibodies that recognize the human leucocyte antigen (HLA) system of the donor). Whether tissue matching for HLA (the major histocompatibility complex in humans), as undertaken for kidney transplantation, would confer a significant benefit on graft survival after FT is not known but, on the basis of experimental skin grafting in humans, it probably would be beneficial if it could be achieved [26,27]. Interestingly, the recipient of the partial FT in France had a well-matched graft, with only one HLA-DR mismatch out of a possible six-antigen mismatch [7].

Surgical Planning

The surgical complexity of facial allotransplantation necessitates extensive preoperative evaluation of facial anatomy in preclinical studies, as well as careful evaluation of the recipient, to ensure the optimal surgical approach [28]. Computed tomography (CT) allows for analyses of the deeper structures of the head and neck. Detailed knowledge of the vascular system is critical to guide procurement and dissection of recipient tissue. Assessment of vascular anatomy with CT angiography is particularly important in cases of previous surgery and extensive scarring [29]. Three-dimensional rendering enables assessment of the skeletal anatomy of the recipient, and osteotomies for the donor can be carried out accordingly [28]. There is no evidence that a facial graft can be used after a prolonged period of ischemia. Most FTs have been done in a setting of two adjacent operating rooms where two surgical teams work in parallel to prepare the recipient while the graft is procured [28].

Anatomical Bases and Surgical Method for FT

Anatomical Bases

Survival of transplanted facial tissue is dependent upon adequate arterial input and venous drainage [13]. Essential vessels are the facial artery (arising from the external carotid artery), facial vein, transverse facial artery (arising from the superficial temporal artery) and transverse facial vein [13]. These vessels are relatively constant but,

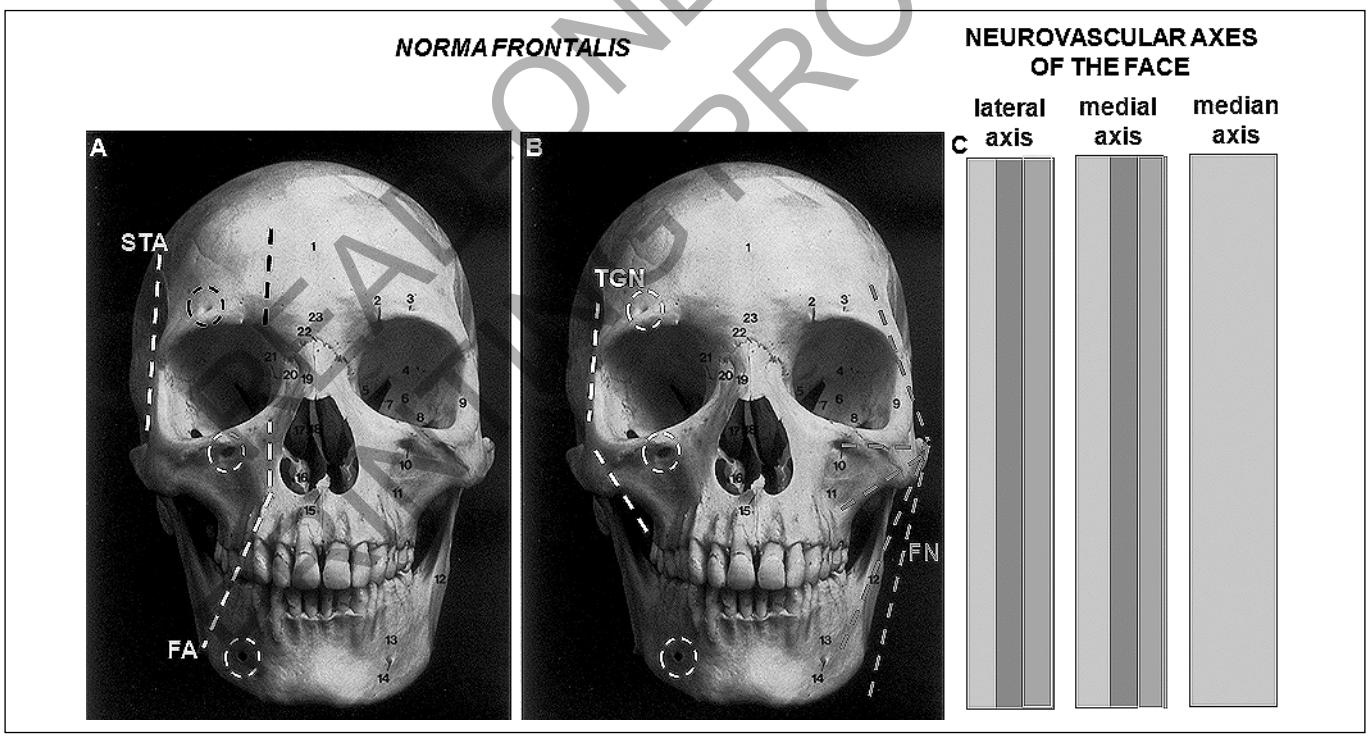

Fig. 2: Topography of major vascular and nervous (motor and sensitive) structures of the face in *norma frontalis*, and their anatomical relations with specific anatomical landmarks of the skull bones. Dotted lines represent the course of the major vascular (light blue) and nervous (yellow and red) axes, dotted circles identify the facial foramina, offering passage to branches of the external (light blue) and internal (black) carotid artery, and to the trigeminal nerve (yellow): A) schematics of the distribution of the superficial temporal artery (STA) and facial artery (FA); B) schematics of the distribution of the trigeminal nerve (TGN) and facial neve (FN); C) schematics of the relations between vessels and nerves in one half of the face. Colors of the stripes refer to those of the dotted lines on the facial bones. Note that each half face can be segmented in three parallel neurovascular territories, whose the lateral and medial exhibit co-localization of both vascular and nervous structures, as opposed to the most median, having only a terminal vascular surface.

in the absence of the facial artery, the transverse facial artery becomes dominant 13 . Consistency of the normal anatomy of facial vessels (Fig. 2) with that of the transplantation setting can be determined routinely using ultrasound [30,31], the reliability of which has been substantiated in preclinical investigations [32,33]. Generous anastomoses between various arterial territories ensure the feasibility of restoring the blood supply of a transplanted face by micro-anastomoses of selected vessels [13]. A micro-anastomosis of the facial artery and facial vein on each side would most probably be sufficient for facial viability, but additional venous anastomoses may render the transplant safer and more likely to be successful [13].

Dissection of the Graft from the Donor's Face

Among the possible procedures, we describe the one used by Barret et al. [34] during the first full-face transplant undertaken on 27 March 2010 at the University Hospital Vall d'Hebron (Barcelona, Spain). This procedure could be considered to be the "prototype" for FT.
The soft tissues and bony structures of the face were harvested from a 41-year-old, multiple-organ donor. They were removed *en block* based on the main vascular and nerve pedicles, taking special care to preserve all retaining ligaments of the face. Vascular pedicles comprised bilateral external carotid arteries, bilateral external and internal jugular veins, the right anterior jugular vein, and the left retromandibular vein (or posterior facial vein, a tributary of the internal jugular vein). Nerves comprised sensory branches of the trigeminal (supraorbital, infraorbital, and mandibular) and the buccal, zygomatic, orbicularis oculi, and frontalis branches of the facial nerve. Each individual vessel and nerve was identified carefully, dissected and cut to preserve as much length as possible to connect with the corresponding vessels and nerves of the recipient. The facial tissue allograft comprised all skin and soft tissues of the face (frontally, from the hairline to the middle of the neck and laterally from the right to the left preauricular creases), facial mimic muscles, lachrymal ducts and cysts, eyelids, mouth floor, lips, upper and lower teeth, hard palate, all cheek mucosa (up to the anterior pharyngeal pillar), the mandible (from the right coronoid to left coronoid process), the maxilla, 2/3 of both zygomatic bones, the nose (including cartilage, nasal bones and septum), turbinates, vomer, ethmoid bone, and maxillary sinuses (Fig. 3). The final part of the procedure consisted of osteotomies and separation of the mouth floor, the anterior pillar of the pharynx, and the nasopharynx . Harvesting the full facial allograft took 4.5 h. When the primary blood supply to the facial allograft was cut, a cannula was placed in the aortic arch (which had been isolated adequately) through which the facial tissues were perfused continuously with cold (4°C) Wisconsin solution for protection during ischemia time. Total time of cold ischemia from when the donor vessels of the allograft were divided until they were reconnected to the counterpart vessels of the recipient was 2.5 h [34].

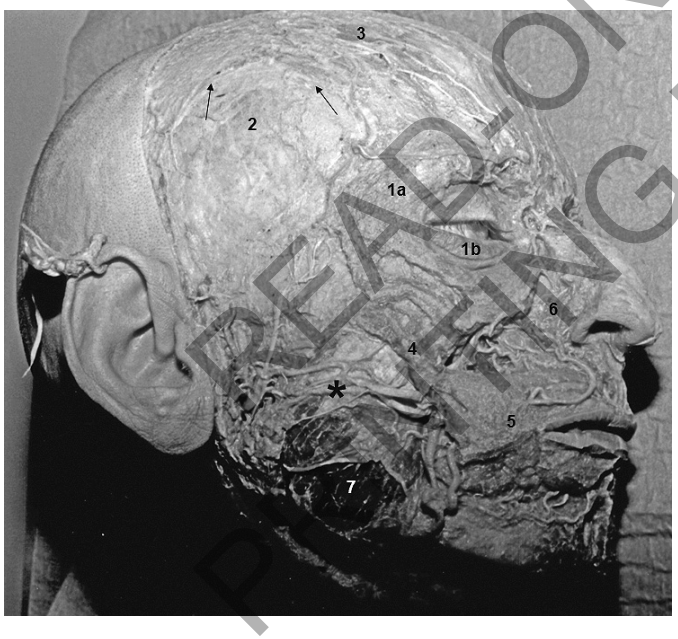

Fig. 3: Cadaveric preparation by the authors, visualizing some of the subcutaneous structures to be preserved in a complex facial flap, like in the case of an FT. Note that the subcutaneous connective layer irregularly adhere to the mimic muscles and masticatory fasciae: 1a, b) *orbicularis oculis* muscle, with its orbital and palpebral parts; 2) *fascia temporalis*, covering the temporal muscle. Arrows point to the semilunar profile of the superior temporal line, at the border with the *galea capitis*; 3) *galea capitis*; 4) part of the zygomatic muscle; 5) area of the *orbicularis* muscle of the mouth; 6) part of the nasal muscle; 7) masseter muscle. The asterisk depicts the Stensen's duct. Branches of the facial nerve and artery are also visible.

Graft to the Recipient's Face

Initially, all scar tissue and bone fragments were removed from the recipient's face. Implantation of the facial allograft began by reattachment of the blood supply. Arterial revascularization was achieved with an end-to-end anastomosis of both external carotid arteries as a backup in case of unexpected thrombosis in one of the vessels [34]. Venous drainage was ensured through end-to-end anastomoses with external jugular veins and end-to-side anastomoses with internal jugular veins, bilaterally. Thus, perfusion of the entire allograft was obtained, and confirmed by profuse bleeding of the flap through unsutured, secondary vascular stumps.
After completion of vascular sutures, facial bones were approximated and rigid fixation undertaken using miniplates and screws made of titanium. Then, the intraoral mucosa and hard and soft palate were sutured together, taking care to achieve a "watertight" closure. Finally, all sensory and motor nerves were reattached using end-to-end anastomoses, and muscles, soft tissues, and skin were

approximated and sutured. Excess skin in the neck and left preauricular regions was preserved to allow for postoperative tissue biopsies to monitor rejection [34].

Complications

The first three recipients of FT (from France and the USA) experienced episodes of acute rejection in the first year after transplantation. All episodes were reversed by adjustment of immunosuppression medications [35,36]. This higher prevalence of acute rejection (as compared with solid-organ transplantation) was probably due to the high antigenicity of the skin [37,38]. In addition, severe postoperative graft edema was observed in most patients [39]. In the intensive care unit, patients encountered complications such as renal insufficiency, acute respiratory distress syndrome, and jugular thrombosis [39].

Of the 27 cases of FT reported up to 2013, vascular complications have been reported in only 2 patients in the immediate postoperative period [12,40] and both were associated with venous thrombosis that resolved eventually [34,41]. This finding is in accordance with most of the vascular complications documented in conventional free-tissue transfer during head-and-neck reconstructions, whereby venous problems are encountered more frequently than arterial occlusion [42]. Clinically apparent opportunistic infections during immunosuppression after facial CTA (*Herpes simplex* [17], *Molloscum contagiosum* [7] and cytomegalovirus [22]) have been documented. Often, these infections have been associated with increased immunosuppression after episodes of acute rejection [28].

Functional Outcomes

All patients subjected to FT have undergone preoperative tracheostomy, and subsequent successful decannulation during the first postoperative week (range: day-3 to day-8) [7,20]. Phonation recovery has been impressive and has allowed patients to talk, smile, chew, swallow, and blow their nose in a normal fashion [43]. Normal mobilization of a food bolus (in part dependent on re-innervation of the buccal nerve in the perioral musculature for establishment of labial contact and oral competence) has, in general, been slower to return (range: 6 months [7,8,20] to still largely incomplete at 2 years [19]). One research team reported stenosis of Stensen's duct at 8 months that necessitated reoperation [8]. Sensory recovery was clinically apparent by the second postoperative month, and returned to objectively normal ranges by 3-6 months [7,8,20,22]. Several research teams have reported hot/cold protective sensations 3–8 months postoperatively [7,22]. Re-innervation of the facial musculature after CTA restores numerous vital functions (e.g., speech and oral competence). However, muscular re-innervation by the facial nerve has been observed to be uniformly slower than the return of trigeminal sensitivity. Most authors have report continued progress with smile and pucker expressions throughout 1.5 years after surgery, with varying degrees of success [7,8], failure [19] and asymmetry [22]. Cases of hyperesthesia or dysesthesia have not been observed [7,20].

Regenerative Medicine/Tissue Engineering For FT

FT is one of the most complex vascular composite allograft (VCA) procedures. It incorporates a single, natural biological "scaffold" made of all the tissue components (skin, muscles, bones, nerves, tendons, ligaments, and vessels) and macroscopic functional units (nose, lips, eyelids and ears) of the donor into the defect that must be reconstructed in the recipient [44]. This strategy is a challenge for regenerative medicine and tissue engineering because it implies integration of different scaffolds seeded with different cell lines (each for any tissue/anatomical facial part) into a final composite [40]. In addition, bioengineered components must function at macro- and micro-scales [44]. Therefore, standard VCA will remain applicable for a long time, primarily for the most severe cases [45].

However, potential advantages of transplantation of facial structures engineered outside the living body seem to be exceedingly high due to the possibility of bypassing the shortage of human donors and avoidance of immunosuppression. Localized modulation of the immune system at the level of facial-tissue implants into the recipient using appropriate cytokine regulators might minimize immunosuppression requirements and improve tissue regeneration [45]. An additional perspective is offered by simultaneous transplantation of facial structures with a bioengineered human thymus gland prepared as a chimera with the medullary lymphocytes of the donor to induce central tolerance of facial tissue antigens into the recipient [46,47].

Engineering of facial parts *in vitro* to be transplanted at a later time has been achieved by implanting grafts of the alar nasal lobule reconstructed using autologous stem cells isolated from the nasal septum of the recipient [48]. Therefore, tissue engineering will probably contribute to the treatment of limited facial defects in the short term. Another option is available for larger injuries involving lesion areas comprising different tissue types: implantation of "bionanoscaffolds" (nanoparticles with controlled local release of tissue- and organ-specific growth factors and chemoattractants for the immune cells involved in the inflammatory processes during repair) into the lesion site [49]. This approach exploits the "facilitated endogenous repair" based on "reawakening" the intrinsic regenerative potential of heterogeneous tissue structures [50]. In the future, this process might develop into reactivation of the regeneration potential lost by higher mammals during phylogenesis, which is still present in invertebrates and amphibians [51].

Conclusions

FT has the unique potential to restore the form and function of the face in patients with severe facial defects. Psychological improvements have been remarkable, and have resulted in reintegration of patients into society and the workplace. It has been reported that psychological distress occurs well above normal levels in family members during the immediate postoperative period, but seems to decline gradually in the long term. However, uncertainty about long-term functional and esthetic outcomes, ethical and immunosuppression-related concerns, and expense limit worldwide application of FT. New perspectives to overcome (at least in part) these issues have been raised by tissue engineering and regenerative medicine applied to vascularized allografts of CTA, which may bypass the need for donors and immunosuppression. Within the next decade, these biotechnologies are expected to introduce new prototypes of multi-tissue scaffolds able to replace or complement the VCA procedures of FT, and could be considered to be a standard of care by insurance companies [40]. However, longer-term reporting of results is necessary, and innovative treatment approaches are eagerly anticipated, to increase understanding of this emerging surgical field.

Riassunto

In questo nostro studio abbiamo riportato in dettaglio gli aspetti anatomici, chirurgici, immunologici ed etici del trapianto di volto. Tale procedura rivoluzionaria si è sviluppata nell'ultimo decennio per il trattamento di quei pazienti con perdita totale o parziale del volto in seguito a traumi per i quali non erano attuabili le tecniche ricostruttive tradizionalmente adottate utilizzando tessuti autologhi.
Nel novembre 2005 a Lione è stato eseguito il primo trapianto di volto parziale, seguito nel 2010 a Barcellona dal primo trapianto totale, ossia comprendente strutture ossee, muscolari, nervose e vascolari.
Dal 2005 ad oggi sono stati eseguiti più di 30 trapianti di volto nel mondo, in Italia ancora nessun trapianto è stato eseguito.
Tuttavia, Lorenzo Tenchini, Professore di Anatomia Umana dell'Università di Medicina di Parma, alla fine del 19° secolo fu il primo a rimuovere in blocco tutte le strutture anatomiche dal volto dei cadaveri per i suoi studi di antropologia criminale. Realizzò più di 150 maschere la maggior parte conservate nel Museo Lombroso di Torino ed alcune di esse sono ancora visibili nel Museo del Dipartimento di Scienze Biomediche, Biotecnologiche e Traslazionali dell'Università di Parma. Ad oggi il ricercatore italiano Prof. Tenchini può essere considerato un precursore dell'odierno trapianto di volto.
Nel nostro lavoro abbiamo riportato in modo dettagliato le varie fasi del trapianto, dalla selezione del paziente a quella del donatore, ponendo l'attenzione sugli aspetti chirurgici, immunologici ed etici che sono stati riscontrati nei vari centri dove è stato effettuato.
La procedura chirurgica adottata prevede un fase di dissezione ed una di impianto, anch'esse accuratamente descritte. Sono state riportate le principali complicanze riscontrate in letteratura a breve ed a lungo termine ed i risultati ottenuti.
Nell' immediato futuro la medicina rigenerativa e l'ingegneria tissutale saranno d'ausilio e permetteranno lo sviluppo del trapianto di volto come procedura consolidata della chirurgia ricostruttiva facciale.

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