Facial transplantation: the first 9 years

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Since the first facial transplantation in 2005, 28 have been done worldwide with encouraging immunological, functional, psychological, and aesthetic outcomes. Unlike solid organ transplantation, which is potentially life-saving, facial transplantation is life-changing. This difference has generated ethical concerns about the exposure of otherwise young and healthy individuals to the sequelae of lifelong, high-dose, multidrug immunosuppression. Nevertheless, advances in immunomodulatory and immunosuppressive protocols, microsurgical techniques, and computer-aided surgical planning have enabled broader clinical application of this procedure to patients. Although episodes of acute skin rejection continue to pose a serious threat to face transplant recipients, all cases have been controlled with conventional immunosuppressive regimens, and no cases of chronic rejection have been reported.

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Introduction

Composite facial defects lead to severe functional impairment and have detrimental effects on an individual's psyche and quality of life. Facial disfigurement significantly affects social interactions and one's perception of body image, predisposing to depression, discrimination, and disability in many patients.[1–7] Normal facial anatomy is also needed for many functions including air humidification, mastication of food, production of intelligible speech, clear vision, and the opportunity for social reintegration.[1,8–10]

Conventional reconstructive techniques can fall short of restoring form and function to patients with complex facial deformity, often requiring numerous staged procedures to provide only suboptimal results. Facial transplantation is a single operation that can restore aesthetic and functional characteristics of the native face by giving ultimate expression to Sir Harold Gillies' principle of "replacing like with like" (figure 1).[11]

Unlike solid organ transplantation, which is potentially life-saving, facial transplantation is life-changing. The possible consequences of lifelong immunosuppression in otherwise healthy individuals—including cancer, metabolic disorders, opportunistic infections, and death—must therefore be carefully balanced to minimise risk and maximise benefit.[10] Yet, surgical innovation has outpaced the scientific community's ability to fully address certain immunological and clinical challenges. Here, we review the immunological, neurological, and anatomical principles gleaned from the 9 years since the first facial transplantation with a discussion of ethical considerations, highlighting lessons learned from clinical experience.

Immunological principles

Immunosuppressive strategies

Of the 28 facial transplants done to date (table 1), details of the immunosuppression strategy and outcomes have been published for 18.[9,10,12–38] Most recipients—but not all[14,23,39]—had no panel-reactive antibodies. One patient who had 98–99% was treated with protein A immunoadsorption to 5% before transplantation.[23] Antithymocyte globulin was used for induction for all but two patients, who instead received humanised anti-interleukin 2 postoperatively on days 0, 15, and 30, and alemtuzumab intraoperatively.[18,23] Steroid bolus and taper was used for all patients, progressing to lower steroid maintenance doses. Steroids were eventually withdrawn for four patients at 7 weeks,[39] 8 weeks,[39] 22 weeks,[23] and 51 weeks.[40] An antimetabolite (mycophenolate mofetil) was used uniformly, and was discontinued per protocol for one patient.[36] All protocols used calcineurin inhibitors consisting of tacrolimus at the outset, a goal of 10–15 ng/mL in an initial period of 1–5 months and in most cases lowering to a maintenance dose of 8–10 ng/mL. The exception to this initial regimen had a tacrolimus target of 20–25 ng/mL for the first 15 months, decreasing to 10–15 ng/mL maintenance.[23]

Additional immunosuppressive strategies included irradiation of the graft in one patient,[23] extracorporeal photopheresis for at least four patients,[19,25] and IgG infusion per protocol for one patient[23] and during discontinuation of tacrolimus and sirolimus for thrombotic microangiopathy in another.[19] Vascularised bone marrow was present in 16 of 24 patients with details available. Donor iliac crest bone marrow cell infusion was additionally used for three patients.[17,27] Sentinel flaps were used for four patients,[17] and bilateral hands transplanted for two.[16]

Immunological outcomes

All face transplantation recipients have had an acute rejection episode of variable severity within the first year of transplantation.[9,41] At least 11 patients had a single grade 1 episode,[14,25] while five others had progressive episodes of acute grades 1–3 rejection.[38] One recipient had presumed grade 4 rejection leading to death.[22] One other recipient with high panel-reactive antibodies had acute antibody-mediated grade 3 rejection in the first week after a positive cross-match.[42] Few descriptions of rejection episodes after 1 year are available, probably because of—at least partly—little follow-up time. They include two patients,[14,23] one of whom was repeatedly non-compliant with immunosuppression.[23] Another recipient was treated for histopathological evidence of grade 3 rejection in the oral mucosa without any evidence of rejection in the skin.[36] Rosacea developed in one graft and mimicked

acute rejection until successful treatment with topical metronidazole.[34,43]

Rejection episodes have generally been readily reversible with pulse dose corticosteroids, augmented in some cases by topical drugs (steroids[17,36] and tacrolimus[17]). Other treatments have included increasing the tacrolimus target trough level,[23] topical drugs alone,[34] and observation[12] for grade 1 rejection; addition of topical drugs for grade 2 rejection; and addition of plasmapheresis, eculizumab, bortezomib,[42] and induction drugs such as anti-thymocyte globulin[12] and alemtuzumab[42] for grade 3 rejection. One patient had to be switched from mycophenolate mofetil to sirolimus (in addition to tacrolimus and steroids) for non-resolving grade 2–3 rejection.[12]

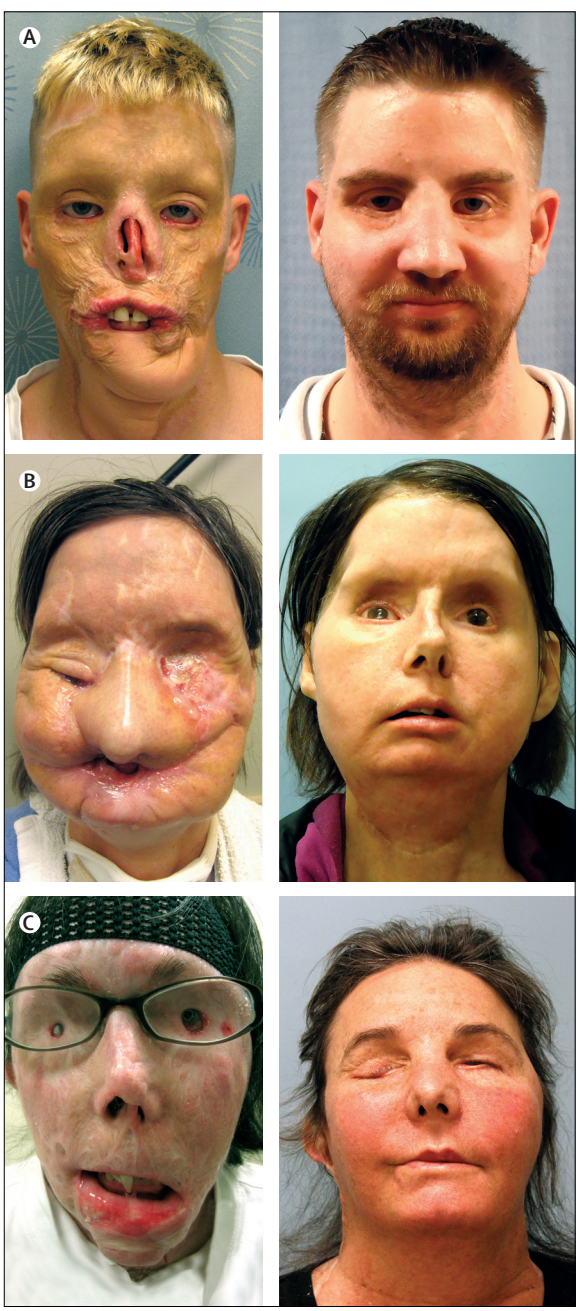


Figure 1: **Outcomes of three facial transplantations**
Preoperative (left) and postoperative images (right) showing the extraordinary restorative capacity of facial transplantation. Postoperative images represent patient outcomes at 18 months (A), 18 months (B), and 9 months (C). Credit: Bohdan Pomahac, Brigham and Women's Hospital.

Chronic rejection or chronic allograft vasculopathy have not been reported; these disorders were previously considered possible and have become evident in human hand transplantation[44] and preclinical studies.[45] Hyperacute rejection from pre-formed antibodies has also not been reported. Donor-derived macrochimerism has not been reported. Microchimerism up to 0·6% was present in peripheral blood and bone marrow samples from one patient who received vascularised and infused bone marrow.[27]

Infectious complications have been common, occurring in at least 11 patients. Cytomegalovirus mismatches in six patients[12,15,21,32,39] led to ganciclovir-resistant and valganciclovir-resistant infection in two patients[21,25] with asymptomatic seropositivity in another.[15] Bacterial infection at the site of operation was reported in three patients (one of whom was co-infected with *Candida*)[39] and systemically in five. Leucopenia was reported in two patients and treated by reduced immunosuppression and filgrastim.[14,36] Both recipients of simultaneous upper extremity transplants developed sepsis:[16] one from aspiration pneumonia, leading to bilateral extremity graft loss with salvage of the face,[39] and one from a pseudomonal graft infection at day 12 after surgery that led to cardiac arrest and death.[25]

Of two recipients who were mismatched for Epstein-Barr virus,[15,29] one developed a monoclonal B-cell lymphoma at 4 months requiring rituximab and reduction of immunosuppression.[29] No graft-versus-host disease has been reported. Chronic renal insufficiency has been reported in two patients,[14,19] one of whom had to be switched from calcineurin inhibitor to sirolimus at 11 months for chronic renal insufficiency, which resolved after treatment for thrombotic microangiopathy that followed treatment conversion.[19] New-onset diabetes developed in two recipients[23,34] (one of whom received prolonged high-dose tacrolimus treatment). A third patient needed to be given insulin.[39] Two recipients had to change from mycophenolate mofetil to mycophenolic acid for gastrointestinal adverse effects.[34,39] Two instances of postoperative delirium were attributed to steroid induction.[14,22] The third confirmed death after face transplantation was the result of tumour recurrence in an HIV-positive patient who had previously undergone cancer resection.[46]

Immunological challenges and future directions

Face transplantation using depletional induction and a standard three-drug immunosuppression regimen results in acceptable immunological outcomes.

	Date	Location	Surgical team	Recipient details	Cause	Extent of defect	Functional deficit	Allograft type
1	November, 2005	Amiens, France	Devauchelle and Dubernard	Female, age 38 years	Dog bite	Cheek, nose, lips, chin	Labial competence, speech	Partial
2	April, 2006	Xi'an, China	Guo	Male, age 30 years	Bear bite	Cheek, nose, upper lip, maxilla, orbital wall, zygoma	..	Partial
3	January, 2007	Paris, France	Lantieri	Male, age 29 years	Neurofibromatosis	Forehead, brows, eyelids, nose, lips, cheeks	Labial competence, speech	Partial
4	December, 2008	Cleveland, OH, USA	Siemionow	Female, age 45 years	Ballistic trauma	Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla	Speech, eating	Partial
5	March, 2009	Paris, France	Lantieri	Male, age 27 years	Ballistic trauma	Nose, lips, maxilla, mandible	Labial competence, speech	Partial
6	April, 2009	Paris, France	Lantieri	Male, age 37 years	Third degree burn	Forehead, nose, eyelids, ears, cheek	Blink	Partial
7	April, 2009	Boston, MA, USA	Pomahac	Male, age 60 years	Electrical burn	Lower eyelid, cheek, nose, lips, maxilla, zygoma	Labial competence, speech	Partial
8	August, 2009	Paris, France	Lantieri	Male, age 33 years	Ballistic trauma	Cheek, nose, lips, maxilla, mandible	Labial competence, speech	Partial
9	August, 2009	Valencia, Spain	Cavadas	Male, age 42 years	Cancer	Lower lip, tongue, floor of mouth, mandible	Labial competence, speech	Partial
10	November, 2009	Amiens, France	Devauchelle and Dubernard	Male, age 27 years	Ballistic trauma	Nose, lips, mandible	Labial competence, speech	Partial
11	January, 2010	Seville, Spain	Gomez-Cia	Male, age 35 years	Neurofibromatosis	Cheek, lips, chin, mandible	Labial competence, speech	Partial
12	March, 2010	Barcelona, Spain	Barrett	Male, age 30 years	Ballistic trauma	Eyelids, nose, lips, lacrimal apparatus, zygoma, maxilla, mandible	Labial competence, speech	Full
13	June, 2010	Paris, France	Lantieri	Male, age 35 years	Neurofibromatosis	Eyelids, ears, nose, lips, oral mucosa	Blink, speech	Full
14	March, 2011	Boston, MA, USA	Pomahac	Male, age 25 years	Electrical burn	Forehead, eyelids, left eye, nose, cheek, lips	Blink, speech	Full
15	April, 2011	Paris, France	Lantieri	Male, age 45 years	Ballistic trauma	Nose, mandible, maxilla	Speech	Partial
16	April, 2011	Paris, France	Lantieri	Male, age 41 years	Ballistic trauma	Nose, mandible, maxilla	Speech	Partial
17	April, 2011	Boston, MA, USA	Pomahac	Male, age 30 years	Electrical burn	Forehead, eyelids, nose, cheek, lips	Labial competence, speech	Full
18	May, 2011	Boston, MA, USA	Pomahac	Female, age 57 years	Animal attack	Forehead, eyelids, eyes, nose, lips, maxilla, mandible	Blink, speech	Full
19	January, 2012	Ghent, Belgium	Blondeel	Male	Industrial accident	..	..	Partial
20	January, 2012	Antalya, Turkey	Ozkan	Male, age 45 years	Burn	..	..	Full
21	February, 2012	Ankara, Turkey	Nasir	Male, age 25 years	Burn	..	..	Full
22	March, 2012	Ankara, Turkey	Ozmen	Female, age 20 years	Ballistic trauma	Nose, upper lip, chin, maxilla	..	Partial
23	March, 2012	Baltimore, MD, USA	Rodriguez	Male, age 37 years	Ballistic trauma	Forehead, eyelids, nose, cheek, lips, zygoma, maxilla mandible	Speech, blink	Full
24	May, 2012	Antalya, Turkey	Ozkan	Male, age 34 years	Burn	..	..	Full
25	September, 2012	Amiens, France	Devauchelle and Dubernard	Female	Vascular tumour	..	..	..
26	February, 2013	Boston, MA, USA	Pomahac	Female, age 44 years	Chemical burn	Nose, lips, eyelids, forehead, cheek, ears, eyes	..	Full
27	May, 2013	Gliwice, Poland	Maciejewski	Male, age 33 years	Blunt trauma	Nose, lips, eyelid, cheek	Speech	Partial
28	July, 2013	Antalya, Turkey	Ozkan	Male, age 27 years	Ballistic trauma	Forehead, eyelids, left eye, nose, cheek, maxilla, mandible	..	Full

Table 1: **Facial transplantations, 2005–14**

Concurrent upper extremity transplantation, recipients with high concentrations of panel-reactive antibodies, and serological matching continue to present challenges. The three patient deaths that have occurred reinforce the importance of patient selection for potential non-compliance and underlying medical comorbidities. As expected from experiences of solid organ transplantation, serological mismatch often leads to infectious and oncological complications and should either be avoided (eg, Epstein-Barr virus) or pre-emptively treated (eg, cytomegalovirus). We believe that it is crucial to avoid giving cytomegalovirus-positive grafts to cytomegalovirus-negative recipients, because it can be life threatening and can trigger acute rejection.[47–50]

Although sentinel flaps might decrease confounding environmental effects on histopathological and clinical analysis, their use for face transplantation is unclear: many patients without sentinel flaps have had successful

immunosuppression. The mucosa—although used in a few cases for pathological diagnosis of rejection—is not addressed by the Banff classification.[51] More importantly, its continuous exposure to low-grade trauma and high antigen loads from food and bacterial flora is likely to cause more confounding than the local graft skin. Nevertheless, episodes of sentinel flap rejection seem to correspond with face transplantation rejection, and sentinel flaps might be useful for patients with little facial skin for biopsies.

Episodes of mild rejection might be more likely to be treated in face transplantation than in solid organ transplantation because of the skin's immediate visibility. This effect could lead to over-treatment of mild rejection and exacerbation of infectious complications; the single reported instance of observation for grade 1 rejection resulted in spontaneous resolution. However, the prompt correction of even mild rejection might be one reason for the absence of chronic rejection in patients who have had face transplantation. Nevertheless, patients are advised to avoid mechanical trauma and environmental injury to the allograft—eg, excessive sun exposure. Such events could precipitate acute rejection episodes, which increase the chances of chronic allograft deterioration and vasculopathy.[32,52]

Because the reporting of outcomes is not standardised, it is impossible to correlate any treatment (including vascularised or infused bone marrow, induction, or maintenance) with the incidence of rejection. Adjunctive cellular treatments, although promising in small animal models, do not seem to promote tolerance or induce chimerism in the absence of depletional preconditioning. A centralised database with standardised reporting intervals, compliant with local and national regulations, and accessible to all contributors, would greatly accelerate the advancement of clinical science in vascularised composite allotransplantation.

Neurological principles

Sensory nerves

Before the first face transplantation in 2005, restoration of normal facial sensation was thought to be unlikely.[41] This assumption has not been borne out by clinical experience over the past decade: rapid restoration of sensory feedback has been reported consistently (table 2). Thermal and mechanical sensation can occur as early as 3 months after surgery,[26,39] with satisfactory sensory restoration often by 8 months (as defined by recovery of heat and cold sensation, discrimination of light touch assessed by static monofilament, well localised two-point touch discrimination, and response to painful stimuli).[19,25,26,39]

The operational strategy used to repair sensory nerves differs between centres. Nevertheless, sensory recovery has occurred independent of nerve repair. An argument has been made for neurorrhaphy of all major sensory nerves after one recipient had anaesthesia at 4 months on the side that did not undergo neurorrhaphy, while the side that did was concurrently sensate.[39] Similarly, direct end-to-end mental and infraorbital neurorrhaphy has resulted in thermal sensation recovery by 2 weeks and response to painful and thermal stimuli throughout the entire allograft by 14 weeks.[17,19] Conversely, simple placement of bilateral donor mental nerves near the mental foramen without neurorrhaphy has produced good sensory outcomes by 3 months.[26] Restoration of sensation can occur without any repair of the trigeminal nerve by 6 months,[14] similar to outcomes from Cleveland and Paris.[25,37] Thus, recovery of satisfactory facial sensation can be obtained in patients with extensive nerve damage without neurorrhaphy; however, further studies are needed to clearly assess the role of neurorrhaphy in affecting the rate, integrity, and topography of facial sensory reinnervation.

Several causes of sensory restoration for patients who have not had trigeminal nerve repair have been suggested. These include recipient and donor characteristics, immunosuppressive side-effects, and various alternative pathways for afferent nerve conduction.[53] The human face has more than 17 000 corpuscles that contribute to various sensory functions, and many of these are probably retained within the allograft.[54] Furthermore, the location of the recipient site affects the outcome of sensory recovery: sensation is recovered better in the orofacial region than in the trunk and lower extremities.[55–57] We suggest that this effect might be partly explained by higher cortical representation of the face.[58]

A beneficial side-effect of immunosuppression with tacrolimus is the dose-dependent acceleration of axonal regeneration, as reported previously for limb allografts.[59] Tacrolimus reduces neuronal recovery time of nerve lesion repair by 50%, increases number of myelinated axons by 40%, doubles the number of regenerating axons after nerve injury, and increases myelin thickness and sprouting of peripheral nerve fibres.[60–62] Pathways for sensory recovery in patients without trigeminal nerve repair include trigeminofacial communications, somatic afferents of the facial nerve, and the adrenergic fibres surrounding the allograft's vascular pedicle.[58] Sensory return paralleled the recovery of the facial nerve in one patient, which could be a result of afferent fibres in the communicating rami between the facial and trigeminal nerves contributing to sensation in the absence of trigeminal nerve signalling.[58]

Motor nerves

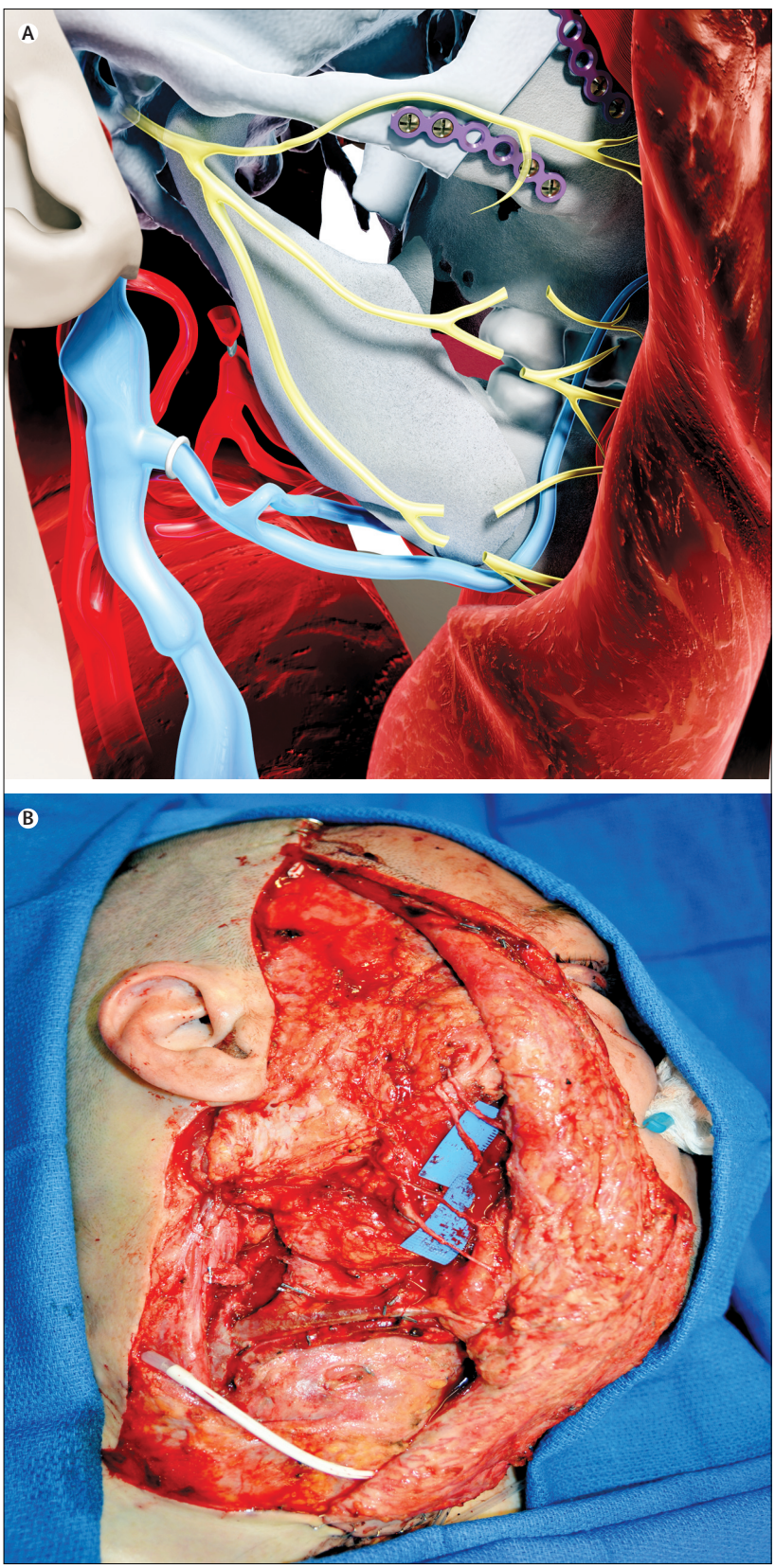
Restoration of motor function is dependent on facial nerve coaptation and has generally been slower than sensory re-innervation. Motor recovery typically occurs by 6–8 months, with ongoing improvements in the subsequent years.[9] With coaptation, lip occlusion can occur by 6 months[19] and complete mouth closure by 8 months,[26] although initial motor recovery was reported even earlier (table 2). In the long term, recovery of the ability to smile has been noted as late as 2 years after transplantation,[63] and continuing improvements have occurred as late as 8 years after

	Sensory recovery	Motor recovery	Functional recovery	Psychological recovery
1	Light touch at 14 weeks, thermal at 6 months	Lip occlusion at 6 months, contractions of chin and nose muscles at 12 months	Mobile food bolus at 6 months, symmetrical smile at 18 months	Social reintegration at 3 months
2	Light touch at 3 months, thermal at 8 months	Poor function of muscles of facial expression	Able to eat, drink, and speak at 2 years, unable to smile symmetrically	Transplant well tolerated, accepted new face easily with improved body image
3	Light touch at 3 months, thermal at 3 months	Motor recovery confirmed by electromyogram at 12 months	Not reported	Objective improvement in quality of life, returned to work at 13 months
4	Light touch at 6 months, thermal not reported	Progressive recovery at 8 months	Able to eat, drink, smell, and speak at 8 months, reduction in chronic pain	Objective improvement in quality of life, body image, and depression
5	Light touch (partial deep pressure) at 8 months, thermal absent at 17 months	Recovery of orbicularis oris at 2 months (left) and 3 months (right)	Complete mouth closure at 8 months	Objective improvement in quality of life and body image, returned to work at 18 months
6	Not reported	Not reported	Not reported	Objective improvement in quality of life and body image
7	Light touch at 6 months, thermal at 6 months	Progressive recovery at 12 months with motor control of lips and symmetrical smile	Able to speak, smell, and breath through nose immediately, able to eat by day 3, unable to pucker lips at 12 months	Early social reintegration by 5 weeks with improved body image, no psychiatric events reported at 3-year follow-up
8	Light touch absent at 12 months, thermal absent at 12 months	Recovery of left zygomatic and orbicularis oris muscles at 5 months, absent on right at 12 months	Complete mouth closure at 12 months	Objective improvement in quality of life and body image
9	Not reported	Mandible excursion 10 mm at 16 months	Swallowing and phonation at 16 months	Not reported
10	Not reported	Not reported	Not reported	Patient satisfied with body image at 20 months
11	Light touch at 6 months, thermal at 6 months	Progressive recovery with satisfactory control of buccinator and levator labii confirmed by electromyogram at 6 months	Able to speak and eat by 6 months	No psychiatric problems reported at 6 months
12	Light touch at 4 months, thermal at 4 months	Satisfactory facial expression at 4 months, reinnervation confirmed by electromyogram	Full masticatory motion at 4 months, limited eye closure at 4 months	Patient satisfied with body image at 4 months, no psychiatric problems reported at 1 year
13	Full sensory recovery after 6 months	Progressive motor recovery, zygomatic muscle contraction (left) at 12 months, absent on right	Complete mouth closure at 12 months	Objective improvement in quality of life and body image, returned to work at 6 months
14	Return of sensation to right side but not left side of face at 4 months	Movement of right side of face at 4 months	Not reported	Objective improvement in quality of life and mental health at 6 months
15	Not reported	Not reported	Not reported	Not reported
16	Not reported	Not reported	Not reported	Not reported
17	Return of sensation to chin and forehead at 3 months	Return of lip motion at 3 months	Not reported	Objective improvement in quality of life and mental health at 6 months
18	Return of sensation to entire allograft at 3 months	No return of motor function at 3 months	Not reported	Objective improvement in quality of life and mental health at 6 months
19	Not reported	Not reported	Able to drink and speak at 6 days	Not reported
20	Not reported	Not reported	Not reported	Not reported
21	Not reported	Not reported	Not reported	Not reported
22	Not reported	Not reported	Not reported	Not reported
23	Light touch at 6 months, thermal at 6 months	Initial motor recovery at 2 months, lip occlusion at 6 months, progressive motor recovery	Able to form food bolus, swallow, and speak at 3 months	Social reintegration by 8 weeks, objective improvement in quality of life, body image, and depression, no psychiatric events at 18 months
24	Not reported	Not reported	Able to speak at 15 days	Not reported
25	Not reported	Not reported	Not reported	Not reported
26	Not reported	Not reported	Not reported	Not reported
27	Not reported	Not reported	Not reported	Not reported
28	Not reported	Not reported	Not reported	Not reported

Table 2: **Sensory, motor, functional, and psychological recovery after face transplantation**

surgery. Initial motor recovery can occur by 3 months, with complete lip occlusion by 6 months,[19] and ongoing improvements at 1 year.[26] We did tongue transplantation without hypoglossal nerve coaptation to the tongue to avoid compromising the patient's baseline tongue function. Nevertheless, the ability to form food boluses, swallow, and produce intelligible speech was restored by 3 months. In such a scenario, end-to-side hypoglossal nerve coaptation might help to accelerate and integrate motor function in donor tissues, although further comparative studies are needed to elucidate how such a procedure might affect functional outcomes. However, unlike sensory nerves, restoration of motor function seems to depend on neurorrhaphy, as evidenced by poor motor function and lack of gradual improvement in a patient with unsatisfactory facial nerve coaptation.[23]

Nerve repair in face transplantation is difficult: neural structures are often damaged, atrophic, or hypertrophic,



either because of the initial injury or scarring from previous reconstruction and salvage attempts.[1] The approach used to repair nerves varies by institution, but one general principle is that facial nerve coaptation should be done as close as possible to target muscles to optimise outcomes and minimise unpredictable re-innervation and synkinesis (figure 2).[64] Although facial nerve coaptation close to the main trunk increases capacity for facial expression and movement as a result of greater control of the target muscles,[25] it risks damaging any intact motor nerve function (eg, blinking). Previous experience shows that motor recovery is accelerated when distal nerve repair is done as opposed to proximal isolation of the main trunk of the facial nerve.[17,19,25,26,35,37,39,41,65]

Functional outcomes

Recovery of facial movements and function has been favourable after face transplantation, with improved ability to eat, drink, speak, smell, and smile in almost all patients.[9,19,26,35,37,39,41] Functional improvements have paralleled motor recovery, with restoration to almost normal functional capacity.[33] Recovery of intelligible speech was reported for four patients within 1 month of transplantation,[25] and significant improvement in swallowing, breathing, and smell immediately after surgery was reported for another.[34] Even without satisfactory facial nerve coaptation, recovery of the ability to speak, drink, and eat normally by 2 years has been noted.[23] The use of interpositional nerve grafts for facial nerve coaptation led to restoration of function by 8 months after transplantation, with a significant reduction of chronic pain caused by scarred and contracted tissues from eight of ten before transplantation to one of ten after transplantation according to patient's self-report.[37] Functional outcomes can be similar, with tracheostomy decannulation at 12 months following 15 years of dependence (unpublished).

The rate of sensory, motor, and functional recovery is contingent on adherence to the immunosuppressive regimen, and some clinicians contend that an early, aggressive rehabilitation programme might help to improve allograft function.[66] At present, the effect of aggressive rehabilitation for improvement of allograft function is unclear: spontaneous use of facial musculature has been reported for some patients shortly after transplantation irrespective of participation in such programmes.[34,39] Nevertheless, rehabilitation often begins as early as 48 h after surgery and includes speech therapy, range-of-motion exercises, and sensory re-education.[66] These measures expedite cortical reorganisation in

Figure 2: **Facial nerve coaptation for motor reanimation**
(A) Three-dimensional modelling of distal facial nerve branches helps to plan the surgery. (B) Intra-operative image showing successful facial nerve coaptation, with distal branches of the patient's facial nerve sutured to the donor's facial nerve stumps. Coaptation is carried out as close as possible to target effector muscles in an effort to prevent dyskinesis.

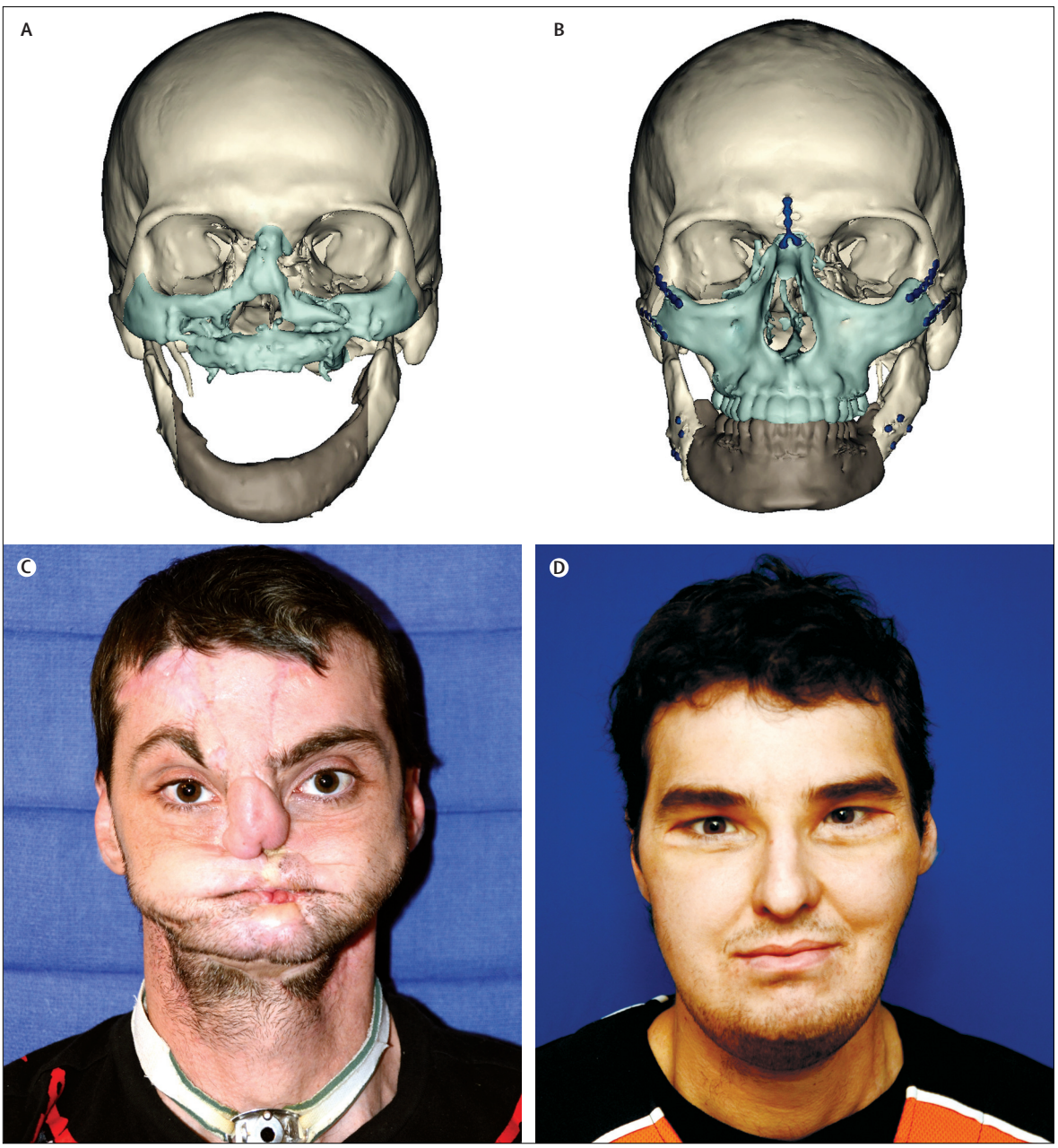


***Figure 3*: Use of computer-aided design and modelling to assist the preoperative planning of facial transplantation**
Three-dimensional craniofacial CT scan reconstruction shows the patient's facial defect before (A) and after (B) facial allotransplantation. The entire midface and mandible—including the donor's teeth and tongue—were transplanted. Corresponding photographs of the patient before the operation (C) and 16 months after (D).

patients, promoting recognition and integration of the newly transplanted muscles into the patient's motor cortex.[67] Such brain plasticity contributes to favourable outcomes after face transplantation.[68] Vision is considered an important determinant of cortical reorganisation, reintegration, and ultimate functional outcome. Blindness has been considered by some to be a contraindication to face transplantation;[69] however, a blind patient given a full face transplantation had promising functional outcomes at 1 year.[39] Thus, the importance of patient motivation, rehabilitation, and adherence to immunosuppression cannot be overstated.

Psychological outcomes

Psychological outcomes for recipients of face transplants have been generally favourable. Initial concerns about feelings of depersonalisation towards the new face and donor identity transfer or split have not been substantiated,

and recipients do not resemble donors according to donor families, recipients, and transplant teams.[39,70] A review of psychological outcomes after face transplantation showed a decreased prevalence of depression and verbal abuse and significantly improved body image, sense of self, and social reintegration.[17,19,22,23,26,36,71] Patients have accepted their new face and describe improved quality of life, with several patients returning to work.[12,17,19,23,25,26,63]

The overwhelmingly positive psychological outcome is probably a result of rigorous preoperative psychiatric and psychological selection of patients deemed to be stable, motivated, and compliant by a multidisciplinary team.[66] The most notable exception is the patient who—displeased with the side-effects of immunosuppressive treatment—came to rely instead on traditional remedies on several occasions, leading to multiple rejection episodes and death.[22] This outcome might have been prevented by more careful preoperative assessment and education, and postoperative psychiatric follow-up.

Anatomical principles

Post-transplantation revision

As the number of face transplantations done has increased, the postoperative focus has expanded to include refining and optimising aesthetic and functional outcomes.[18,72] Functional and aesthetic restoration can be assisted through several secondary procedures, including bone and dental realignment, soft-tissue resuspension and contouring, full-thickness skin grafting, fat injection, and dermabrasion.[73,74] The goals of these revisionary procedures are to optimise functional outcomes, accentuate facial features disguised by bulky tissue, ensure proper colour and texture, and match thickness across the entirety of the face.

Revision of a facial allograft poses additional risks not encountered in conventional reconstructive surgery. Potential complications include increased susceptibility to infection and poor wound healing secondary to immunosuppression,[75,76] complications of anaesthesia in an immunocompromised patient,[77] and increased inflammation as a direct result of the revision, increasing the likelihood of acute rejection.[78] The high cost of a negative outcome leads to an understandable reluctance to revise an otherwise successful allograft.

A face transplantation might not initially fulfil its promise of optimising form and function, tilting the risk-benefit balance in favour of revision despite the potential for complications. Several postoperative revisions have been described, including: excision of redundant skin;[34] rotation, realignment, and re-occlusion of the maxilla;[79] scar revision and tissue resuspension (Mohan R, unpublished data); cartilage grafting for volume restoration;[22] and dental implants to achieve optimal occlusion.[22] Such revisions seem not to cause major complications including rejection[26] and they might further reduce psychological morbidity by alleviating concerns about identity.[80]

Bone and dental occlusion

Correct occlusion of the jaws is a necessary condition for facial transplantation to restore form and function. Of 17 face transplants including either maxilla or mandible, only eight included the full maxilla and mandible. A hybrid occlusion between the jaws of two different individuals is necessary in these cases and an occlusion that is both functional and anatomically accurate is difficult to achieve at the time of transplantation.[81,82] For one patient, the maxilla and partial tooth-bearing mandible were transplanted, resulting in a partial donor and partial hybrid occlusion.[83]

The best hybrid occlusion can only partly recreate the functions of mastication and speech, even after tooth contouring. Use of hybrid occlusion might also further narrow an already small donor pool by imposing additional constraints on jaw morphology or dentition to better fit the opposite recipient jaw. We therefore advocate co-transplantation of the tooth-bearing segments of maxilla and mandible whenever possible, potentially even for defects of a single jaw. Although these additional procedures increase the duration and complexity of surgery, bimaxillary transplantation enables adequate occlusion constrained only by accuracy in placement.

Bimaxillary transplantation might not yield perfect occlusion even with preoperative computer-aided planning (figure 3; unpublished). This failure is probably a result of adjustments of the relation between the mandibular condyle and its fossa while under anaesthesia compared with conscious activity with displacement of the mandible by muscular activity.[84] Refinements in technologies such as computer-assisted design and modelling, intraoperative navigation, and pre-manufactured cutting guides[18] might further improve cutting and positioning of the facial skeleton.

One of the greatest imperatives when planning bony revisions is assessment of the vascular supply of the graft; whether earlier orthodontic management would avoid the need for skeletal revision is unclear, and the best approach to foreseeing or preventing these changes is still a matter of debate. Nevertheless, suboptimal occlusion can safely be corrected by revisionary midfacial osteotomies (unpublished).

Ethical dilemmas

The major ethical concerns about face transplantation are similar to the early ethical debates about hand transplantation.[85] Because of the complexity of the procedure, and the unknown risks and benefits, the most important decision is still the selection of the candidate. The best candidate is one who: fully understands the implications of potentially lifelong immunosuppression and its serious morbidities, including infections, cancer, graft loss, and death; is motivated, committed, and compliant with intense post-operative rehabilitation, psychological treatment, and immunosuppression protocols; and has a strong social support system that

will help them to address the many challenges, including media exposure, body image adaptation, and societal reintegration.[1,10,25,66,85] Because face transplantation is not life-saving, it has been criticised for exposing otherwise healthy people to the risks of immunosuppression.

Fully informed consent is crucial for vascularised composite allotransplantation for the same reasons. Unlike an emergent, life-saving liver transplant, face transplantation should not be done without consent. Furthermore, the question has been raised as to whether consent can be truly informed if the recipient does not live with the defect for some time after an initial, salvage operation.[86] In breast reconstruction, a waiting period can allow steady-state resolution of acute emotional and medical issues, giving the patient the chance of remaining with an acceptable conventional reconstruction, and even increase satisfaction with the eventual results of transplantation.[87,88] These effects might also be true for face transplantation. Severity of disfigurement does not predict psychological outcome and it is not always necessary to pursue an ideal aesthetic outcome to achieve the best possible psychological adjustment. One face transplantation has occurred in which multiple failed salvage attempts and a large exposed defect threatened the patient's life, leading to urgent transplantation with the patient's stated consent.[89] The outcomes from this case might help to clarify the ethical grounds of emergent face transplantation.

Other ethical concerns about the recipient's age and the high costs of face transplantation continue to be debated.[10] The ethical dilemma of paediatric face transplantation involves informed consent, psychological instability during developmental years, lifetime risk of cancer, and complications of lifelong immunosuppression. The high financial cost of this procedure—estimated at US$300 000—together with the cost of lifelong immunosuppressive treatment, precludes its widespread application.[10] Thus, government or insurance funding is essential to the feasibility of face transplantation. This logistical concern became a stark reality in China, where almost all early recipients of hand transplants lost their allografts after authorities stopped supporting immunosuppressive treatment that most patients were unable to afford.[90]

The resolution of many of these ethical dilemmas rests on the minimisation or elimination of conventional immunosuppression. Transplant tolerance is the ultimate ambition of solid organ transplantation and vascularised composite allotransplantation laboratories worldwide, but might not be realised in the near future. Until then, appropriate patient selection by a thorough screening process by a multidisciplinary team with standard immunosuppression treatment serves as the best safeguard against ethical challenges.

Conclusion

In the past 9 years, face transplantation has emerged as a viable and successful option to restore the appearance and function of patients with severe, devastating facial injuries. Depletional induction therapy and a standard three-drug immunosuppression regimen has enabled successful graft survival with highly encouraging functional and immunological outcomes. Tacrolimus has been a cornerstone of nearly all immunosuppression protocols with target trough levels of 10–15 ng/mL for the first 1–5 months with most patients subsequently lowering to a maintenance dose of 8–10 ng/mL. Steroids have been safely tapered after a few months, with complete withdrawal possible within a year in some cases, depending on the immunosuppression regimen. Although acute rejection episodes commonly occur within the first year, all episodes have been controlled with pulse dose corticosteroids, and no cases of chronic rejection or graft-versus-host disease have been reported. The absence of chronic rejection in face transplant recipients might be a result of the prompt treatment of even the most mild acute rejection episodes and the lack of long-term follow-up data. Nevertheless, chronic rejection is possible and thus patients are advised to strictly adhere to their immunosuppression regimen and avoid mechanical trauma and environmental injury to decrease the risk of chronic graft deterioration.

The most important decision determining the success of facial transplantation remains patient selection. Rigorous preoperative psychiatric and psychological selection of patients deemed to be stable, motivated, and compliant by a multidisciplinary team is a crucial determinant of a safe and rapid recovery. The surgical approach and an early, aggressive rehabilitation programme might also dictate the rate of recovery to some extent. Facial sensation can be restored without direct trigeminal neurorrhaphy, although direct neurorrhaphy can accelerate sensory restoration. Conversely, restoration of motor function is critically dependent on facial nerve coaptation and generally takes longer than sensory reinnervation (6–8 months for motor recovery *vs* a few weeks for sensory recovery). A general guiding principle is that facial nerve coaptation should be done as close as possible to target muscles to optimise outcomes and minimise unpredictable reinnervation and synkinesis. Yet irrespective of surgical approach, all patients have regained both motor and sensory function and a high level of independence with significant improvements in quality of life.

Postoperative revisions have also been described, and such revisions seem not to cause major complications. The occlusion of the mandible and maxilla has a substantial effect on functional outcomes and therefore attempts should be made to optimise occlusion either by revisionary procedures (eg, tooth contouring or mid-facial osteotomy) or co-transplantation of tooth-bearing segments of maxilla and mandible whenever possible. Concurrent upper extremity transplantation continues to present challenges, which warrants further discussion as to whether combined hand and face transplantation should be a staged procedure

or avoided altogether. Similarly, serological mismatches often lead to infectious or oncological complications and should be avoided (eg, Epstein-Barr virus) or pre-emptively treated (eg, cytomegalovirus).

At present, research goals are to minimise immunosuppression, and to refine functional and aesthetic outcomes by optimising neurological recovery, craniofacial alignment, and revision. Other future aims include the standardisation of clinical protocols and outcome measures, a multidisciplinary effort to move towards a standard-of-care approach, and coverage by health insurance. Further collaboration and sharing of methods and outcomes is needed to achieve such advances in this small but rapidly expanding specialty.

Contributors

SK, PSB, RM, and EDR planned the Review, searched for and assessed the published work, wrote the first draft, and revised the Review. CS and RNB planned the Review, assessed the published work, and revised the Review. GB assessed the published work and revised the Review.

Declaration of interests

We declare that we have no competing interests.

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