



Evolution of indications for facial transplantation

B. Pomahac*, J.R. Diaz-Siso, E.M. Bueno

Brigham and Women's Hospital, Department of Surgery, 75 Francis St, Boston, MA 02115, USA

Received 22 February 2011; accepted 21 June 2011

KEYWORDS

Face transplantation;
Facial
allotransplantation;
Composite tissue
allotransplantation;
Vascularised Composite
allotransplantation;
Indications for face
transplantation;
Screening for face
transplantation

Summary Face transplantation has the unique potential to restore facial form and function in patients with severe facial defects. Current indications for face transplantation remain limited by unknown long-term outcomes and the requirements for lifelong immunosuppression and substantial plans for reconstruction in case of failure. We initially obtained Institutional Review Board approval for partial face transplantation in patients with defects comprising 25% of the face and/or loss of one or more major facial features. We launched an outcome-oriented face transplantation study and screened 13 potential patients between February 2008 and January 2011. Experience gained during screening motivated the expansion of indications to include full facial defects and the consideration of patient-specific complex issues on a case-by-case basis. Although our programme focuses on restoring absent or severely compromised motor and sensory functions, we recognise aesthetic appearance as a crucial facial function. Patients are extensively educated on the risks and benefits of facial transplantation and then allowed to play the main role in the decision-making process, as long as no absolute exclusion criteria are present. As we learn more about the long-term outcomes of face transplantation and safe reduction of immunosuppression, face-transplant indications may expand from major unreconstructable defects towards potentially minor defects.

© 2011 British Association of Plastic, Reconstructive and Aesthetic Surgeons. Published by Elsevier Ltd. All rights reserved.

Introduction

Facial transplantation (FT) is rapidly gaining widespread acceptance among physicians and the public.^{1,2} FT clearly surpasses conventional reconstruction at restoring complex aesthetic and dynamic facial functions. The face is crucial not only for breathing, speaking, eating, and oral competence, but also for identity perception, social interactions

and facilitating communication of information and emotions. Consequently, facially disfigured patients suffer major bereavement, shame, loss and social isolation^{3,4} which FT could alleviate. Broadly, FT is indicated in adults with a severe facial defect and functional deficits that cannot be helped with conventional reconstruction. Patients must understand the risks and benefits of FT.^{5–7} Risks/benefits must be analysed using an individualised approach.^{6,8,9}

* Corresponding author. Tel.: +617 732 5303; fax: +617 732 6387.
E-mail address: bpomahac@partners.org (B. Pomahac).

Across the world, FT has been performed in 16 patients injured by animal attack, high-voltage burns, gunshot, neurofibromatosis and cancer. Outcomes are reported for only eight. The longest follow-up report covers 2 years.

Several programmes are being developed or are actively recruiting patients. Although each programme may embrace different indications for FT, specific information is limited.^{9,14} Indications are difficult to summarise. The uniqueness of each defect makes the determination of indications for FT highly individualised.⁹ Evolution of indications is constant and may continue until there is adequate experience with the long-term outcomes. Meanwhile, surgeons start by identifying absolute contraindications, then evaluate patient-specific anatomical, functional and psychosocial considerations and finally devise an adequate backup strategy in case of FT failure.⁹ Patients are major participants in the decision-making process.

FT is a complex intervention with significant psychosocial implications and absolute requirement for postoperative lifelong immunosuppression that may introduce significant health risks.^{15–19} Guidelines suggest that FT be used only in patients with severe facial defects that cannot be helped by conventional reconstruction and after case-by-case evaluation of risk/benefit ratios.^{11,20} Therefore, FT candidates must undergo rigorous preoperative screening including psychosocial evaluation focussed on medical compliance, coping skills, expectations, support network and informed consent. In addition, patients must have written confirmation of third-party coverage of post-transplant follow-up and immunosuppression expenses.⁶ General inclusion/exclusion criteria follow standard organ-transplant guidelines. Specific contraindications to FT are the unfeasibility of adequate follow-up, lack of financial support and/or history of poor medical compliance. Psychological issues compromising the patient's ability to understand and cope with FT and/or comply with medical orders are absolute contraindications. Other contraindications remain open to debate. For example, cancer is listed as an absolute contraindication by some,¹³ but many consider it case-by-case and there has been one post-oncological FT recipient.²¹ Blindness and bilateral upper-extremity amputation are absolute contraindications in one programme⁸; others do not report their position. One FT recipient in Spain was human immunodeficiency virus (HIV)-positive,²¹ but most programmes consider HIV an absolute contraindication. Self-induced facial injuries are contraindications in some programmes,⁸ but others have performed transplants in such patients.^{13,22} While most centres are conservative in the preservation of the recipient's healthy facial tissues,^{7,10–13} one recent case performed aggressive resection.²² Only one centre performed FT as the first therapeutic option⁷; in all other patients, conventional reconstruction was exhausted first.^{5,11–13} Most centres performed FT after proper nerve reconnection was deemed possible, as in its absence, functional recovery is poor.¹⁰

Limited knowledge on the indications and long-term outcomes of FT complicates the assessment of indications. Here we provide worthy experience-guided observations during the evaluation of 13 candidates for FT as well as the indications and contraindications stipulated in our Institutional Review Board (IRB)-approved protocol (Table 1). At

Table 1 Inclusion and exclusion criteria for face transplantation according to Brigham and Women's Hospital's IRB protocol (Protocol #2008P000550).

Indications	Contraindications
–Most difficult or impossible to reconstruct facial defects	–Pregnancy
–Defect comprises >25% of the facial area, and/or involves loss of one of the central facial parts such as eyelids, nose, or lips.	–Active psychiatric illnesses are considered individually
–Outcome of an alternative reconstructive method considered unfavourable or unsatisfactory	–Unable to guarantee adequate coverage of follow-up care and immunosuppression

this juncture, it is not possible to summarise indications for FT into a unified recommendation. Rather, case-by-case consideration is encouraged. FT indications will continue to evolve and simplify, as improvements in immunosuppression are achieved.

Materials and methods

In 2008, we gained IRB approval at Brigham and Women's Hospital (BWH) for 'partial' FT (Protocol #2008P000550). Inclusion criteria were adults between 18 and 60 years of age with a defect comprising over 25% of the face and/or loss of one or more major facial features, such as the nose, lip(s) or eyelid(s). Since then, based on experience gained during screening, we expanded the criteria to include full facial defects and patients who, in spite of acceptable appearance, retain significant functional deficits.

We reviewed medical and study records on the screening of 13 candidates for FT surgery at BWH between February 2008 and January 2011. Age, gender and mechanisms of injury were diverse (Table 2). Some candidates motivated the evolution of our indications of FT, and their cases are presented with heightened detail.

Table 2 Patient demographics. ALT: anterolateral, HVB: high voltage burn, MOI: mechanism of injury.

Patient#	Age/Gender	MOI
1	59/M	HVB
2	36/M	Gunshot
3	24/M	HVB
4	57/F	Animal attack
5	30/M	HBV
6	31/F	Burn
7	41/M	Explosive device
8	20/F	Burn
9	42/F	Burn
10	59/M	Cancer
11	39/F	Cancer
12	34/M	Gunshot
13	30/F	Burn



Figure 1 Front view photographs of 8 patients evaluated for facial transplantation. The images were obtained after conventional reconstructive surgical options were exhausted but prior to face transplantation. While all of these patients had aesthetical and functional deficits warranting consideration for facial transplantation, adequate follow up care could not be guaranteed for Patient 8 and Patients 6 and 9 did not enrol owing to personal and health concerns. Patient 1 was transplanted in April of 2009, and Patients 3, 4 and 5 were transplanted in March, May and April of 2011, respectively.

Results and discussion

Patient #1

This 59-year-old male was our first FT patient. He had a complex midfacial bony and soft-tissue defect as a result of high-voltage electrical burn injury (Figure 1). He had undergone conventional reconstruction with unsatisfactory aesthetic and functional results (Table 3). This patient fitted our protocol inclusion criteria perfectly. His 18-month post-transplant outcomes were recently reported.¹³

Conclusion

Strong indication for FT owing to a complex central face defect involving approximately 25% of the facial area including the nose, upper lip and maxilla. FT was expected to restore oral competence, breathing and eating and

provide aesthetic improvement and social reintegration. Expectations were fulfilled.

Patient #2

This 36-year-old male presented with a central face defect, the result of an accidental gunshot wound. He was missing the mandible, nasoethmoid complex, bilateral orbital floors, maxilla and palate, mandible and upper and lower lips (Figure 1). After extensive conventional reconstruction, aesthetic appearance, oral competence and eating and breathing functions remained unsatisfactory (Table 3). After 9 months of screening, the patient was placed in the transplant wait list. Several months after, FT was postponed for personal reasons.

Conclusion

Patient with midfacial defect comprising more than 25% of the facial area and affecting aesthetics, oral competence,

Table 3 Criteria used to evaluate indications for FT in this study's patients. A: No guarantee for adequate post-transplant follow-up. B: patient with significant medical comorbidity. C: Cannot rule out recurrent cancer. D: Patient opted against FT. E: Little or no functional deficit. G: Good. NE: Not fully evaluated. O: Outstanding.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Facial defect focalized in central face	x		x		x			x	x		x	x	
Major functional and aesthetic deficit (e.g. inability to eat, breathe, speak)	x	x	x	x	x	x	x	x	x	x	x	x	x
Conventional reconstruction deemed unsatisfactory	x	x	x	x	x	x	x	x	x	x	x	x	
Significant aesthetic gains	x	x	x	x	x	x		x	x	x	x	x	x
Significant functional gains	x	x	x	x	x	x	x	x	x	x	x	x	
Safe backup plan that leads back to pre-operative state	x	x	x	x	x		x	x	x	x	x	x	x
Strong support network	G	O	O	O	O	O	O	NE	NE	NE	NE	NE	NE
Thorough understanding of FT	G	G	G	G	O	O	O	NE	NE	NE	NE	NE	NE
High Motivation	x	x	x	x	x			NE	NE	NE	NE	NE	NE
Patient has tried prosthesis	x				x					x			
Patient enrolled in study	x	x	x	x	x								
Reason for non-enrolment						D	D	A	B	C	C	D	E

breathing and eating functions. The transplant was expected to restore these.

Patient #3

This 24-year-old male suffered accidental high-voltage electrical burn injuries to the entire face and the left hip 14 months prior to referral. His facial defect comprised the entire area of the face and extended into the scalp (Figure 1). The patient was unfortunately blind as a result of the injury. The left eye had been enucleated and the right eyeball was covered by the muscle flap and had no light perception. All soft tissues of the face were lost to the level of bone. There was no nose, lips, teeth or palatal fistula. There was significant scarring and burn formation on the lower lips. The face was covered with bilateral latissimus dorsi muscles and skin grafts. The mental nerves were intact. Tongue mobility was normal. Maxilla and mandible opening was only approximately 2 cm. There was oral incompetence, yet ability to eat solid foods. The left face had no facial mimetic muscles. There was minimal contraction of platysmal remnants on the right.

Because of absent facial features, the injury had devastating social effects on the patient's life. Just as importantly, there was lack of facial sensitivity and motor function. Speech and sense of smell were affected and facial expression was absent (Table 3). The patient had adapted to blindness and could ambulate aided by a cane.

Full FT was expected to provide remarkable improvement in all of the facial functions. These functional improvements were expected to provide positive quality of life and social implications. The entire co-investigative team agreed that the benefits outweighed the risks of full FT in this case. We obtained IRB approval to expand inclusion criteria to patients in need of full FT. We predicted that challenges associated with the postoperative course would include the lack of visual input to facilitate rehabilitation of the transplanted face, the inability to visually self-monitor for signs of rejection and the need for assistance with the daily medication regime. The patient's support network was scrutinised and found fully committed

to assist with these challenges. The patient was placed in the transplant wait list 11 months after initial consult and received full FT 5 months later with no remarkable complications. Long-term outcomes are not available at this time.

Conclusion

Catastrophic defect of the entire face constituted a strong indication for full FT. Primary goals were to regain sensation and control of facial muscles movement. Restoration of aesthetics was also crucial, as the patient lacked all facial features. Backup strategy consisted of regrafting with essentially no additional morbidity. A strong support network was of heightened importance for assisting this blind patient pre- and postoperatively.

Patient #4

This 57-year-old female was savagely attacked by a large animal 15 months prior to referral. There was massive loss of central facial tissues and extensive scarring of the remaining face, blindness and loss of both hands (except the right thumb). The nose, eyelids, maxilla and both lips were all lost. Both eyes were eviscerated. Basic reconstruction consisted of anterolateral free flap for wound control, nasal reconstruction with rib cartilage and skin grafting (Figure 1).

Although this patient was disabled as a result of blindness and bilateral hand amputation, she was able to perform some activities of daily life with assistance. Oral aperture was 2 cm. The patient could not breathe through the nose (thus requiring tracheostomy), smile or speak clearly and there was minimal facial musculature capable of voluntary control. The tongue protruded midline with normal range of motion. Lack of teeth severely restricted the diet. The face was severely disfigured and the patient wore a veil in public.

This was a very complex combination of multiple composite tissue losses further complicated by blindness.

Indication for FT was strong (Table 3), but blindness and bilateral hand amputation needed special consideration. The postoperative course was expected to be complicated by the same issues described for Patient #3, with the additional complication of lack of tactile input to aid self-care and rehabilitation. Blindness training was strongly incorporated in the pre- and postoperative rehabilitation regime and the patient's support network was found completely committed to assist with visual monitoring and medication compliance. The patient was placed in the transplant wait list for facial and bilateral upper-extremity allotransplantation approximately 22 months after the injury.

Conclusion

Devastating case of multiple composite tissue losses including most of the central face and both hands, further complicated by blindness. As the hands function as the "eyes" of the blind, restoration of tactile function via hand transplantation was extremely important for functional recovery. FT was expected to restore the facial functions and aesthetic appearance. Unfortunately, sight cannot be restored. The patient received full FT 5 months after placement in the waiting list. Long-term outcomes are not available at this time.

Patient #5

This 30-year-old male suffered from high-voltage electrical burn injury 9 years prior to referral, resulting in amputations of the left leg below the knee and two digits on the right hand and severe facial injuries. There was loss of the skin over the forehead, cheeks and eyelids, complete loss of soft tissues of the nose, both lips and remnants of orbicularis in the upper lip and the mandible was exposed in the midline. The patient was unable to close his eyelids due to lower-lid ectropion. Extensive reconstruction had not resolved severe aesthetic and functional deficits (Figure 1). This straightforward case constituted a strong fit with our initial indications for FT (Table 3). The patient was placed in the transplant waiting list 2 months after referral and received full FT 3 months later with no complications. Long-term outcomes are unavailable at this time.

Conclusion

Strong indication for FT owing to massive defect of the midface with loss of the nose and compromised oral competence, breathing and eating functions. The transplant was expected to restore these functions as well as aesthetics.

Patient #6

This 31-year-old female suffered severe and extensive burn injuries, in particular to the entire face and one hand 11 years prior to referral. Appearance and function of the full face were severely damaged. She had received numerous skin grafts and cadaver grafts and a corneal transplant. There was no nose, ears or hair. The entire scalp, forehead, cheek and upper and lower lips had been

grafted (Figure 1). The face and neck were very tight and the patient was unable to open her mouth adequately or smile. The tongue and palate were normal. Of most concern were the grafted upper and lower eyelids which allowed the patient to close her eyes, but there was weakness of the orbicularis muscle and absence of blink reflex, which caused problematic irritation to the eyes. There was some function in the underlying muscles of the face. The patient always wore a hat to hide the disfigurement.

This facial defect was so large and devastating that restoration of aesthetic appearance weighed heavily in the consideration of eligibility (Table 3). The patient was indecisive and eventually chose not to proceed with FT owing to unease about long-term effects of immunosuppression.

Conclusion

Strong indications for full FT to restore the missing and damaged craniofacial features including ears, scalp, hair, nose, eyebrows, eyelashes, peri-oral areas, lips, chin and neck. The transplant would only include soft tissues and in addition to restoring aesthetic appearance, it would alleviate overall tightness and inability to adequately open and close the eyes and mouth.

Patient #7

This 41-year-old male suffered injuries from an explosion 6 years prior to referral. The case was influential to the evolution of our thinking regarding indications for FT. The aesthetics in this patient's case did not weigh heavily (not shown), but functionality did. There was injury to the right cheek, right lower and upper jaw, loss of maxilla with concomitant upper and lower teeth and orbital fractures. There was a through and through defect of the right cheek, including all musculature except of orbicularis oculi and areas supplied by the upper division of the facial nerve. After 22 operations, there was persistent drooling, diffuse tightness of the right cheek and lack of function of the right face due to complete paralysis of the facial nerve except the upper division. There was good symmetrical function of the forehead and upper and lower eyelids bilaterally. The left face had normal appearance, motor and sensory functions except for sensation of the chin in the vicinity of the mental nerve. The upper lip remnant on the left side was approximately 25–30% of the circumference of the upper and lower lip. Remaining parts were substituted by flaps. The patient had multiple dental implants and prosthetic teeth. Fortunately, these injuries did not inflict permanent disability and the patient held a full-time job. His facial appearance was symmetrical and well balanced in proportions and size.

Although the facial appearance of this patient did not warrant FT, he had severe functional deficits that could not be improved with conventional reconstruction (Table 3). The donor would have to be chosen very judiciously so as to maintain the high standard of aesthetic restoration already achieved. This patient was found eligible for FT but decided not to proceed due to personal reasons.

Conclusion

This patient represents a clear evolution of the indications for FT. Despite nice aesthetic reconstruction, there were severe functional deficits that were devastating to the quality of life. There was paralysis of the right face and oral incompetence. A transplant including upper and lower lip with both commissures and soft tissue on the right side of the cheek with the middle and lower division of the facial nerve has great potential of restoring these functions.

Patients #8–#13

An additional six patients were screened (#8–#13). Eight screened patients did not enrol in the study (#6–#13), owing to diverse reasons (Table 3). Three (patients #6, #7 and #12) chose to explore conventional reconstructive options. Two presented high risk of cancer recurrence (patients #10 and #11). One had no significant functional deficits (patient #13). Some of these patients may become eligible in the future, when less toxic immunosuppressive drugs become clinically available. One patient was ineligible because adequate follow-up could not be guaranteed (patient #8 in Figure 1), and another one was otherwise eligible and interested (patient #9) but tested positive for hepatitis C (Figure 1), presenting a significant lifelong risk of cirrhosis and hepatocellular cancer.

Conclusions

Current indications for FT are limited by unknown long-term outcomes and an absolute requirement for lifelong immunosuppression. The first three FTs were partial.^{5,7,10,11} At our institution, FT was initially indicated in adults with partial facial defects resulting from trauma, burns or cancer. The defects were to be larger than 25% of the face and include important central facial unit(s) (e.g., nose, lips and eyelids) or complete loss of orbicularis oris. In 2010, the first full FT was performed in Spain. Also in 2008, FT was performed in a French patient with neurofibromatosis, expanding the indications to congenital disorders.¹² Along with this evolution, we expanded our inclusion criteria to congenital as well as full facial defects, as long as a backup strategy was available. We also strongly emphasised severe functional deficits. Although the term 'facial functions' evokes the concepts of eating, breathing, drinking, expressing or communicating, we also considered aesthetic appearance as one of the crucial functions of the face. Some of our patients' aesthetic defects were so massive and devastating that aesthetics weighed as much as or more than other functions. Patients #3–#5 underwent FT during the first half of the year 2011. Although it is early to report motor and sensory outcomes, significant improvement in appearance was attained immediately for all three patients.

Our patients taught us a few important lessons. As regards our position on contraindications for FT, we consider cancer patients in remission over 5 years; we do not exclude on the basis of blindness, upper-extremity amputation or self-induced injury as long as psychosocial evaluation deems that FT is safe. We consider HIV-positive status as an absolute contraindication. Our approach to native tissue

resection is conservative, and we focus on motor and sensory nerve reconnection to optimise regain of function. Although we have not used FT as the first line of treatment, we suggest FT may be optimally timed after wound coverage and prior to extensive staged conventional reconstruction to prevent surgical fatigue and depletion of donor sites. We will not perform FT without having a solid backup strategy. We consider patient's death an unacceptable outcome of FT. We strongly agree with evaluating indications case by case. Even after deemed eligible, the decision to proceed with FT is only the patient's. Lastly, with evolutions in immunosuppression, post-FT regimes may be significantly reduced or eliminated, opening up FT indications from major unreconstructable defects to potentially minor defects and even facilitating paediatric FT.

Conflict of interest statement

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

Acknowledgements

Infrastructure and patient-related expenses were supported by the United States Department of Defense contract #W911QY-09-C-0216. The sponsor had no involvement in the study design, collection, analysis or interpretation of data, writing this article or submitting it for publication.

References

1. Pomahac B, Aflaki P. Composite tissue transplantation: a new era in transplantation surgery. *Eplasty* 2010;10.
2. Vasilic D, Reynolds CC, Cunningham M, et al. Plastic surgeon's risk acceptance in facial transplantation. *Plast Reconstr Surg* 2008;121:41e–8e.
3. Morris PJ, Bradley JA, Doyal L, et al. Facial transplantation: a working party report from the royal college of surgeons of England. *Transplantation* 2004;77:330–8.
4. Macgregor FC. Facial disfigurement: problems and management of social interaction and implications for mental health. *Aesthetic Plast Surg* 1990;14:249–57.
5. Siemionow MZ, Papay F, Djohan R, et al. First U.S. near-total human face transplantation: a paradigm shift for massive complex injuries. *Plast Reconstr Surg* 2010;125:111–22.
6. Pomahac B, Nowinski D, Diaz-Siso JR, et al. Face transplantation. *Curr Probl Surg* 2011;48:293–357.
7. Devauchelle B, Badet L, Lengele B, et al. First human face allograft: early report. *Lancet* 2006;368:203–9.
8. Siemionow MZ, Gordon CR. Institutional review board-based recommendations for medical institutions pursuing protocol approval for facial transplantation. *Plast Reconstr Surg* 2010;126:1232–9.
9. Hollenbeck ST, Erdmann D, Levin LS. Current indications for hand and face allotransplantation. *Transplant Proc* 2009;41:495–8.
10. Guo S, Han Y, Zhang X, et al. Human facial allotransplantation: a 2-year follow-up study. *Lancet* 2008;372:631–8.
11. Lantieri L, Meningaud JP, Grimbart P, et al. Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study. *Lancet* 2008;372:639–45.

12. Pomahac B, Pribaz J, Eriksson E, et al. Restoration of facial form and function after severe disfigurement from burn injury by a composite facial allograft. *Am J Transplant* 2011;11:386–93.
13. Lantieri L, Hivelin M, Audard V, et al. Feasibility, reproducibility, risks and benefits of face transplantation: a prospective study of outcomes. *Am J Transplant* 2011;11:367–78.
14. Wysong P. Advances in hand and face transplantation: an expert interview with Dr. Jean-Michel Dubernard. *Medscape Plastic Surgery* [serial on the Internet] Available from: <http://www.medscape.com/viewarticle/729305>; 2010.
15. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003;3:178–85.
16. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004;4:905–13.
17. Nalesnik MA. Clinicopathologic features of posttransplant lymphoproliferative disorders. *Ann Transplant* 1997;2:33–40.
18. Splendiani G, Cipriani S, Tisone G, et al. Infectious complications in renal transplant recipients. *Transplant Proc* 2005;37:2497–9.
19. Vicari-Christensen M, Reppe S, Basile S, Young D. Tacrolimus: review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence. *Prog Transplant* 2009;19:277–84.
20. Surgeons ASOP and Microsurgery ASOR. Facial transplantation—asrm/aspa guiding principals 2006: Available from: <http://www.microsurg.org/ftGuidelines.pdf>.
21. Cavadas P, Landin L, Ibanez J, et al. *The Spanish Experience with Face Transplantation*. New York: Springer; 2011.
22. Barret J, Serracanta J, Arno A, et al., editors. Full Face Transplantation: Organization, Development and Results. 10th Meeting of the International Hand and Composite Tissue Allotransplantation Society; 2011 April 8; Atlanta, GA.