Achievements and Challenges in Facial Transplantation

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The first facial transplantation in 2005 ushered in a new era in reconstructive surgery, offering new possibilities for the repair of severe disfigurements previously limited by conventional techniques. Advances in allograft design, computerized preoperative planning, surgical technique, and postoperative revisions have helped push the boundaries in this new frontier of vascularized composite allotransplantation. Over the past 12 years, 40 of these procedures have been performed across the world, offering the field the opportunity to reflect on current outcomes. Successes achieved in the brief history of facial transplantation have resulted in a new set of obstacles the field must now overcome. In this review, we aim to highlight the achievements, major challenges, and future directions of this rapidly evolving field.

Keywords: face transplant, facial reconstruction, vascularized composite allotransplantation

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Vascularized composite tissue allotransplantation (VCA) has emerged as a viable reconstructive option for a wide array of disfigurements and amputations. Modern success in hand transplantation[1] led to the introduction of other types of VCA with promising results. However, the transplantation of a functional face remained a formidable challenge given the complex 3-dimensional architecture involved. The first facial transplantation (FT) in 2005[2] ushered in a new reconstructive era, offering new possibilities for the repair of severe disfigurements previously limited by conventional techniques. This was made possible by combining the unique expertise of transplant immunology with the principles of craniomaxillofacial surgery and microsurgical free tissue transfer. As with every innovative field, the successes achieved in the brief history of FT have resulted in a new set of challenges and hurdles the field must now overcome. In this brief review, we aim to summarize these achievements and identify major challenges that will determine the future of this burgeoning field.

SURGICAL TECHNIQUE

Tissue Transplanted

Much has been accomplished in FT from the perspective of surgical technique, and the design of each new facial allograft has built on previous achievements. Although the first face transplant contained exclusively soft tissue components, teams began including segments of vascularized bone in transplanted allografts as early as 2006.[3] Teams around the world performed extensive cadaveric dissections[4–7] before attempting more complex FT designs, which also served to expedite allograft procurement[8,9] and improve intraoperative dynamics.[10,11] Subsequent procedures successfully transplanted varying amounts of maxilla, mandible, inferior orbital wall, and zygoma, which helped establish FT as a truly custom, recipient-centered reconstruction.[12] Of the 40 procedures performed to date, 25 are reported to have contained bone.[3,13–15] Of these, varying amounts of maxilla were included in 19 allografts, mandible in 16, zygoma in 9, and components of the orbit in 5 cases.

Having established the safety and feasibility of FT, centers went on to refine aspects of allograft design; particularly, the need to reestablish proper cephalometric relationships among donor craniomaxillofacial structures and the recipient skull base became apparent.[16] Thus, modern FT procedures requiring skeletal components began to include computerized surgical planning (CSP) techniques to ensure functional occlusion and adequate cephalometric proportions.[17,18] The incorporation of CSP into FT has resulted in streamlined planning and execution of complex operations, in addition to more predictable intraoperative scenarios and postoperative outcomes (Figs. 1 and 2). However, although CSP provides a guide, there are certain limitations to its use in FT, such as its inability to take into account functional movement from muscles of mastication or elements such as the tongue. In the future, we anticipate widespread use, evolving applications, and continued integration of this technology in FT.

From 2005 to early 2010, 11 FTs were performed containing varying amounts of soft tissue and bone, yet all were partial transplants. The idea of a *full*-face transplant supplied by a single artery remained theoretical. In March 2010, the first full face transplant was performed, involving multiple facial units that included soft tissue, intraoral structures, and skeletal components.[19] Numerous full-face transplants were subsequently performed in quick succession,[20] elevating the quality of the aesthetic outcome while maintaining return of function as the top priority. As a testament to the cautious approach and dedication to excellence characteristic of FT centers, cadaveric dissections have been performed in an effort to minimize ischemic complications[21] and before attempting novel allograft designs.[22] A representative example is the inclusion of vascularized bone not just to replace missing structures, but for the purpose of reestablishing maxillofacial contour and maintaining the soft-tissue suspensory ligaments that may avoid the generalized facial ptosis seen in some FT patients.[23] There was initially much debate on the inclusion of parotid and other salivary glands, but recent reports have shown that most groups exclude salivary glands due to the risk of complications, such as the formation of a sialocele. Combined face and upper extremity transplantation has been also the subject of much debate, with perioperative infections leading to sepsis resulting in recipient death[24] and bilateral upper extremity allograft necrosis and amputation[25] in the 2 patients to date. Although numerous factors have been explored as possible causes of these devastating complications, the concurrent transplantation of different anatomical structures remains a challenge to VCA teams, and a cautious approach is warranted.[26]

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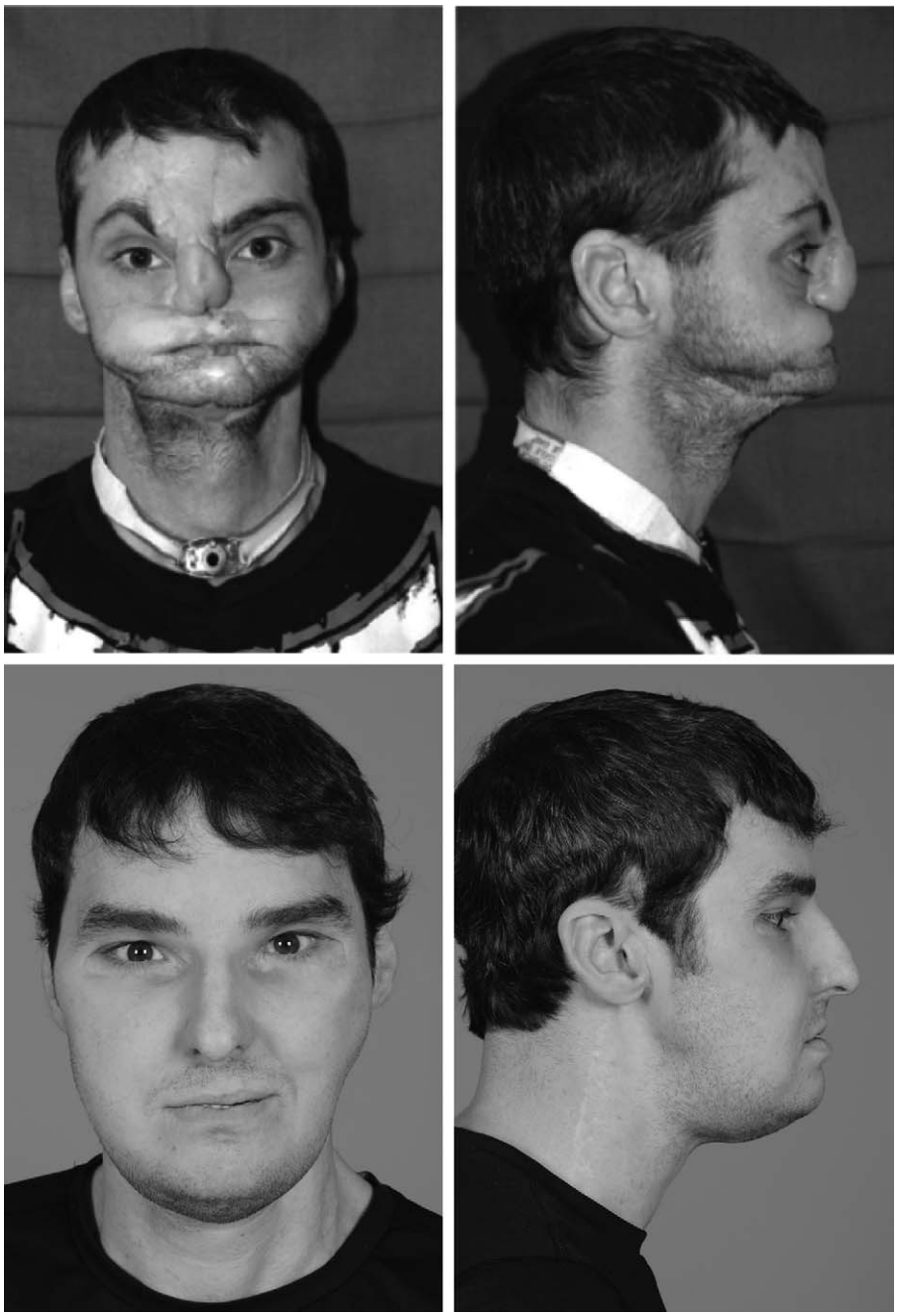

FIGURE 1. Face transplant recipient 23. (Top) Pre-transplant. Frontal and lateral views of the patient following osteocutaneous free tissue transfers to the maxilla and mandible, 2 forehead flaps, and multiple tissue rearrangement procedures. Notice the loss of mid-face projection, extensive forehead and neck scarring, and inadequate nasal reconstructions. (Bottom) Post-transplant, including revisions. Frontal and lateral views of the patient 4 years and 2 months after facial transplantation. (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS).

Allograft Vascularity

Unique facial allograft designs tailored to meet specific patient needs require strategic deliberation on optimal vascularity to said allograft and available recipient vessels for anastomosis. On the basis of cadaveric understanding of vascular territories, most FTs have been based on the facial artery, with some teams conservatively basing allograft blood supply on the external carotid artery. To our knowledge, all reported FTs performed to date have established bilateral outflow with veins that correspond to arterial supply, with the one exception being the FT that transplanted tissue exclusively to a single side.[3] Early investigations suggested that, in contrast to FTs involving only soft tissue, zygomatic or maxillary bone-containing allografts may require bilateral arterial perfusion based on the internal maxillary arteries for success.[27] However, more recent FT outcome analyses have demonstrated that bilateral[6] and even unilateral[28] perfusion by the facial artery can be sufficient for facial allografts containing midface bone. Although preoperative planning details have not been described, the team performing the first full FT also decided on unilateral arterial perfusion to a bone-containing allograft, anastomosing only the right external carotid artery.[19] Another unique vascular pattern was performed for a FT of the lower third of the face whereby the allograft was perfused by both external carotid arteries; however, both of these vessels were fed only

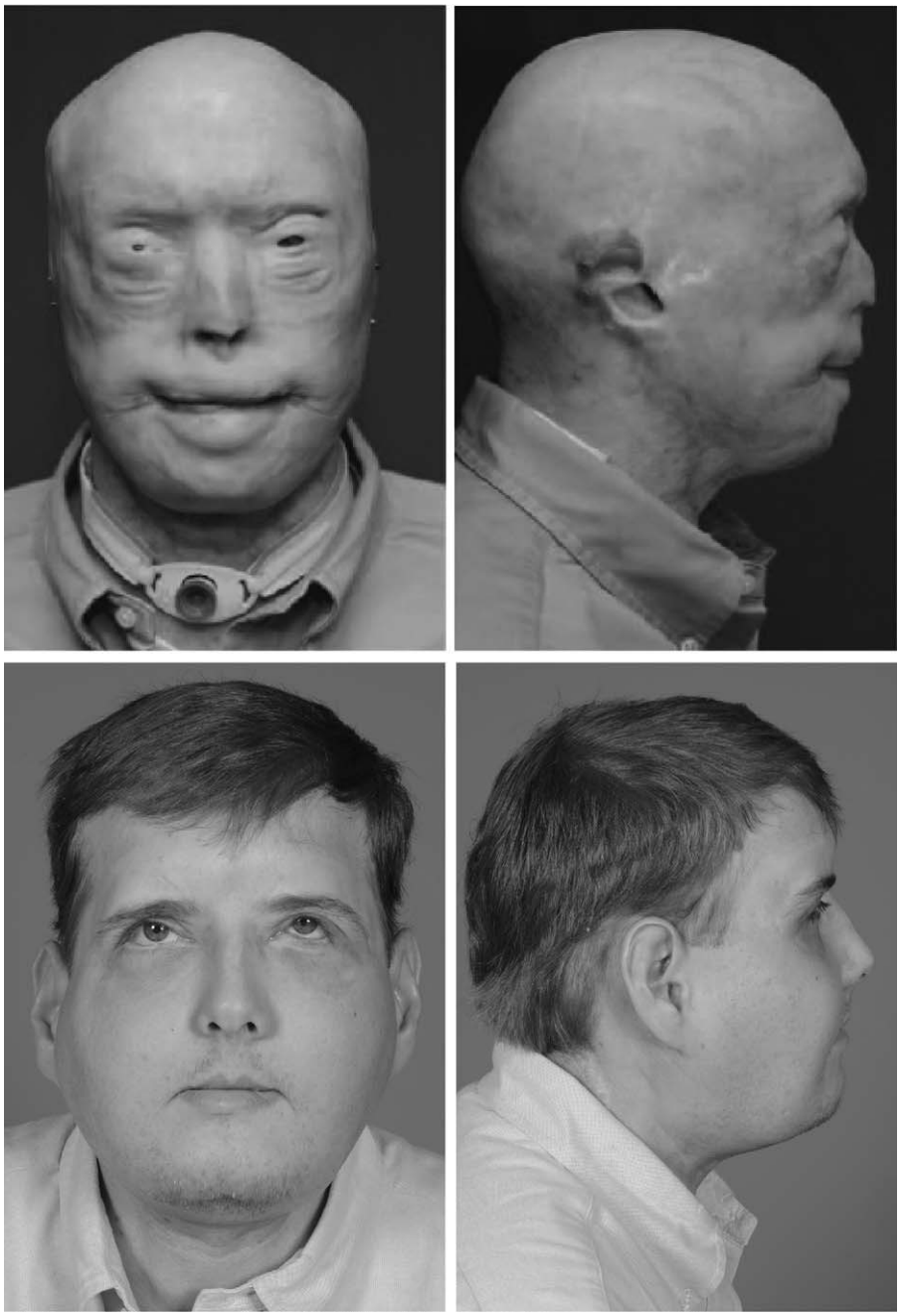

FIGURE 2. Face transplant recipient 37. (Top) Pre-transplant. Frontal and lateral preoperative images of the recipient who sustained a full face and total scalp burn before receiving a face transplant. (Bottom) Post-transplant. Frontal and lateral views of the patient 454 days after facial transplantation. (Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS).

by the recipient's right subclavian artery, near the aortic arch.[29] In any case, bilateral perfusion by the external carotid arteries may be the safest and most conservative approach for this challenging procedure regardless of which facial structures are included, as it increases the length of the pedicle and size of flap vessels. It is the senior author's (E.D.R) preference to perform all anastomoses using an operating microscope, even with the large caliber of the external carotid vessels, in order to optimize anastomotic technique. Of the 40 transplants performed to date, published reports provide information on the vascular design of 24 allografts. Of these, 7 allografts relied on perfusion through donor bilateral external carotids and bilateral thyro-lingual trunks,[24] 4 through bilateral facial arteries,[12,30–32] 5 through contralateral external carotid and facial artery,[20,33,34] 3 through bilateral external carotid,[18,23,35] 1 through bilateral linguofacial trunk,[20] 1 through unilateral external maxillary,[3] 1 through unilateral common carotid,[29] 1 through unilateral external carotid,[19] and 1 through unilateral facial artery.[28]

Recipient vessel choice can also be challenging, as candidates' vascular anatomy can be altered from their initial injury or secondary to previous reconstructive attempts, decreasing available options for anastomotic sites. In these scenarios, vascular supply should be optimized and careful preoperative planning should be performed to provide reliable vascular mapping and avoid unexpected intraoperative findings; conventional angiography (CA)

supplemented by computerized tomographic angiography (CTA) is the senior author's (E.D.R.) preferred imaging protocol.[23] CTA can illustrate vessel patency, but it cannot distinguish anterograde versus retrograde flow. In contrast, CA provides the added benefit of real-time vascular flow dynamics and trajectory data that can alter the surgical approach with sufficient planning time.[18]

Vascular complications were initially anticipated to result from the technically difficult anastomosis of donor and recipient vessels, but no technical complications have been described as of yet.[13] Report of the first full FT described venous thrombosis at 2 anastomotic sites; however, the surgical team has stated that the thrombi were likely due to expanding facial edema compressing the vessels, rather than technical failure during microvascular anastomosis.[19] Early reports discussed difficulties with extensive blood loss during dissection of the recipient parotid glands and, in 1 case, resection of a plexiform neurofibroma, during which substantial hemorrhage was anticipated and ultimately required massive blood transfusion.[36] Continued refinement in surgical techniques has minimized blood loss during these lengthy procedures, and hemodynamic stability for donor solid organ procurement has remained the highest priority. A commonly reported complication of maxilla-containing FTs has been the development of a palatal fistula at the junction of the hard and soft palate. The precise etiology of these complications may be debated, can vary from case to case, and may be multifactorial in nature with elements including tension and donor-recipient bone mismatch playing a role in their development. However, multiple teams report that they believe some to be vascular in nature, as they occur at a known site of collateral circulation.[21,37] Although this is precisely the osteotomy site for the LeFort III technique employed during allograft procurement, 1 team believes that it is likely that the soft tissue incision (that ultimately separates the allograft from the donor at the level of the soft palate) is responsible for disrupting this established vascular network, and has resulted in ischemic fistulas requiring revision.[37]

Post-Transplant Revisions

As the defects treated with FT are severe, complete reconstruction is generally not accomplished with a single transplant procedure, and numerous patients have received revisions. Some groups reserve revision surgery for complications, while others plan ahead during the pre-transplant phase. For example, in a recent full face transplant, the decision was made to leave a portion of the recipient's posterior scalp intact to prevent potential pressure necrosis while the patient recovered in the supine position, with a plan to excise the remaining posterior scalp and advance the allograft once he had recovered mobility.[23]

Ultimately, secondary revision operations following transplantation are commonly utilized to achieve desired function and appearance in the long term, although this is difficult to quantify due to the lack of long-term reports.[38] However, the majority of revisions can be performed in the outpatient setting and address FT complications, including malocclusion, ptosis, ectropion, palatal fistulas, hematoma, skin flap loss or necrosis, muscle contraction, and contour abnormalities.[21,23,38,39] To avoid severe eyelid complications, including lid retraction, ectropion, and loss of blink reflex, careful dissection of motor nerves and functional periorbital structures must be emphasized to preserve function.[19] It is also imperative to avoid disruption of the osteocutaneous retaining ligaments and procure the periorbital regions with bony attachment to prevent ptosis.[39,40]

Of note, there have been only 2 published reports specifically describing revision procedures, in 8 total recipients.[38,39] The first, a series of 7 patients, reports an average of 2.6 revision procedures per patient and consisted mainly of allograft debulking, tissue plication and suspension, and local tissue rearrangement. One patient presented with a persistent palatal fistula and had incomplete resolution after repair, however with limited functional significance. There was a complication after revision in only 1 patient, consisting of acute rejection after autologous fat grafting, which resolved with pulse steroids.[39] The second publication is a single patient case report, which describes 2 surgical revision procedures. The first consisted of a Lefort III osteotomy to correct malocclusion, tissue resuspension, and submental lipectomy. The subsequent operation included bilateral blepharoplasty and scar revision. Separate reports by additional groups mention other common complications, such as palatal fistulas,[21] that required revision surgery, but there are no specific reports or descriptions on the procedures performed, which limits more robust quantitative analysis. Nevertheless, despite concerns for poor wound healing and infection in an immunosuppressed patient, as well as possibly triggering acute rejection or vascular compromise, revision procedures appear to be safe when closely managed by the multidisciplinary FT team.[39]

OUTCOMES

Functional Outcomes

While the technical feasibility of FT may have been anticipated based on the success of autologous free tissue transfer, short-term outcomes have exceeded expectations on many fronts. However, outcome measurement is neither standardized, nor specific to FT. Thus, as with other outcomes, comparison of motor and sensory results from different groups has proven challenging. However, the satisfactory return of facial sensation in FT recipients has been consistently reported by groups that perform sensory nerve repair,[2,33] and even those that do not, as early as 3 months for the mental nerve[36] and 6 months for the trigeminal nerve.[12,18] Return of sensation has been observed as early as post-transplant week 12,[25,36] and recovery of thermal sensation, light touch, 2-point discrimination, and pain response is typically seen by post-transplant month 8.[41] Motor recovery occurs reportedly as early as post-transplant month 2 or 3, with gradual but continued improvement. Long-term outcome reports are necessary to determine whether motor recovery eventually reaches a plateau.

The coaptation of motor nerves has been the subject of much debate, and while all centers report performing intraoperative motor nerve repair, different teams have utilized contrasting neurorrhaphy approaches. Some teams have advocated for proximal facial trunk coaptation in order to reduce operative times.[12] These groups have reported excellent control of the facial musculature over time.[12] However, early reports of facial musculature synkinesis resulted in the choice by other centers to repair facial nerve branches at a location distal to the parotid gland, thus reducing the distance to the target tissues to mitigate that risk.[2,20] Therefore, risks of increased operative time appear to have been offset by decreased synkinesis and adequate return of nerve function. The use of nerve grafts to ensure reinnervation of the facial allograft musculature has also been described.[3,12,18] In specific cases where the existing facial musculature was determined to be sufficient for adequate facial function and expression, nerve coaptation was not performed.[23] Overall, published reports describe excellent return of oral competence, speech and swallow functions, and varying degrees of facial expression.[2,3,25] Long-term outcomes will likely determine the role of physical and occupational therapy in FT functional recovery, regardless of neurorrhaphy location. Despite these positive outcomes, the challenge is set for the VCA community to contribute to current knowledge on nerve healing and regeneration, as it remains one of the major hurdles keeping FT outcomes at ''near-normal,'' and not the ''normal'' results the field aspires to achieve.

Psychosocial Outcomes

Research efforts have yielded data suggesting early FT psychosocial concerns, like the transfer of facial appearance from donor to recipient, may have been overstated.[42] However, the psychological wellbeing of FT recipients continues to be an area of limited understanding. Reports of psychiatric outcomes of FT are scarce, but knowledge in this area is mostly subjective and long-term reports are necessary to draw evidence-based conclusions.[43] Early hand transplantation experience exposed the VCA community to the importance of psychosocial evaluations during the candidate selection phase, particularly when attempting to predict therapeutic and pharmacologic noncompliance.[44] Nonetheless, the dreaded consequences of noncompliance were observed shortly after encouraging outcomes of the second FT recipient were reported.[3] This led to the use of more stringent criteria by FT teams when evaluating possible candidates' mental health. The psychiatric testing and screening performed follows solid organ transplantation guidelines, with the main difference being that the ''fame'' often associated with media coverage of the operation imposing a greater psychological burden in FT recipients. Limited reports are available,[43] but it is likely that the methods used to evaluate the psychosocial state of face transplant candidates vary considerably among groups. Ultimately, the goal is to be able to predict noncompliance, confirm that the patient is not actively psychotic or depressed, and ensure a strong support system is in place and that good follow-up has been demonstrated.

Furthermore, the FT community understood that a grounded support network is imperative to assist the recipient during all stages of the transplantation process, as they face challenges related to identity, a heavy therapeutic burden, a constant risk of rejection, unforeseen media exposure, and the uncertainty inherent to undergoing a procedure still considered experimental. Despite considerable debate, numerous FTs have been performed on candidates with a history of suicide attempts (often the mechanism of their facial injury). Although excellent results have been reported and attributed to constant psychosocial support, the importance of long-term follow-up and monitoring by all members of the FT team was reinforced with news of a recipient's suicide.[24] Collaborative efforts such as the Chauvet Workgroup—which aims to create common protocols for evaluation, follow-up, and supportive treatment in VCA patients—are important and worthwhile endeavors, but ultimately, consistent and objective reporting of long-term psychosocial results is paramount to advancing this aspect of the field.

Immunologic Outcomes

The health risks associated with lifelong immunosuppressive therapy undoubtedly pose the greatest difficulty in FT and other forms of skin-containing VCA. The vast majority of FT recipients have experienced one or more episodes of acute rejection (Table 1), with varying levels of clinical and histopathological severity, despite wide variation in induction and maintenance protocols.[2,3,13,18,23,40,45,47] Many groups utilize an induction regimen consisting of tacrolimus, mycophenolate mofetil (MMF), and steroids, with the addition of either humanized IL-2 antibody or antithymocyte globulin (ATG).[2,3] However, induction regimens utilized by other groups include steroids and alemtuzumab (anti-CD52)[18]; steroids and ATG; steroids, ATG, and rituximab (anti-CD20)[23]; and steroids, ATG, and MMF.[25] Maintenance therapy regimens have been relatively more standardized, with most teams opting for triple therapy consisting of tacrolimus, MMF, and a steroid taper; however, dosages and schedules have varied. Blood concentration ranges of tacrolimus have been maintained anywhere from 3[25] to 25 ng/mL,[3] and the administered doses of MMF range from 0.18 g twice daily[25] to 3 g daily,[30] while 1 group tapered off completely.[12] Similarly, maintenance glucocorticoid administration has varied in the choice of agent (methylprednisolone followed by prednisone, solumedrol followed by methylprednisolone, or prednisolone alone), dosage, and end point (1 week to 22 months).[3,12,25,30]

With few exceptions, acute rejection episodes are successfully treated with pulse dose corticosteroids, with or without increased maintenance doses or topical agents.[41] Due to the well-described complications associated with long-term immunosuppression—including renal toxicity, metabolic complications, opportunistic infections, and increased risk of malignancy[48]—some teams have attempted immunosuppression minimization and/or incorporated alternative immunosuppressive agents. Efforts to minimize FT maintenance immunosuppression include dual therapy with tacrolimus and corticosteroids,[12] or with tacrolimus and MMF.[23,24,41,49] Immunomodulation strategies consisting of tacrolimus monotherapy and donor bone marrow transplantation have resulted in mixed outcomes in upper extremity transplantation, but do show promise.[50] To minimize renal toxicity, some groups have incorporated alternative maintenance immunosuppressive agents, such as sirolimus[51,52] and belatacept,[52] both of which are non-nephrotoxic T-cell inhibitors. One recipient was converted from tacrolimus to sirolimus due to progressive nephrotoxicity and refractory CMV viremia.[52] These resolved temporarily after conversion, but significant lower extremity swelling, worsening renal function with proteinuria, and 2 episodes of cellular rejection led the team to convert the patient to belatacept 14 months post-transplant.[52] Four months after conversion, the recipient experienced an episode of grade II/III rejection, and was restarted on low-dose tacrolimus in combination with belatacept.[52] Another group introduced sirolimus 11 months post-transplant to reduce tacrolimus levels in response to a progressive decrease in renal function.[51] Short- and long-term reports also document the development of post-transplant diabetes, hypertension, and hyperlipidemia as consequences of maintenance immunosuppression regimens, however, these are generally managed successfully with medication and/or lifestyle changes.[24,53] Other maintenance strategies have been reported in the specific setting of FT in a highly sensitized recipient.[54]

Although the components of chronic rejection in the setting of VCA are yet to be fully defined, clinical and pathological findings of graft vasculopathy manifested by intimal hyperplasia have been observed and reported in 2 FT recipients.[45,55] In 1 case, chronic rejection resulted in partial allograft loss, and required resection of necrotic tissue and autologous reconstruction.[55] Close immune monitoring is particularly important now that follow-up times are increasing, and long-term data can finally be obtained. Furthermore, there is currently no consensus on the best method to monitor facial allograft rejection,[13] and institutions currently disagree on the value of sentinel flaps,[56,57] and full-thickness skin and mucosal biopsies.[58] However, histology is currently the standard for diagnosis of rejection in VCA and is assessed and categorized based on the Banff classification system, which defines 5 grades of acute rejection based on several defining features, including inflammatory cell infiltration and epithelial involvement.[59] Noninvasive methods of monitoring FT rejection using modalities such as ultrasound biomicroscopy[60] and vascular magnetic resonance imaging (MRI)[61] have also been reported. There have been no reports of hyperacute rejection, graft-versus-host disease, or donor-derived macro-chimerism. However, centers must remain vigilant, as these complications are theoretically possible based on preclinical VCA studies, and solid organ transplantation.[62]

Infectious complications secondary to immunosuppression have been common.[63] Published reports document infection in 15 of the 40 recipients to date, and 6 of these patients developed multiple infections.[64] Infections observed include 3 patients with HSV, 5 with CMV (1 ganciclovir-resistant), 4 with pneumonia (2 pseudomonas, 1

TABLE 1. Facial Transplantations Worldwide as of January 2018

Patient	Date	Surgical Team	Location	Recipient Details	Indication	Extent of Defect	Allograft Type	Status (COD, TFT)	Acute Rejection	Chronic Rejection
1	November, 2005	Devuchelle and Dubernard	Amiens, France	Female, age 38	Dog bite	Cheek, nose, lips, chin	Partial	Death (malignancy, 11 yrs)[45]	Yes	Yes[45]
2	April, 2006	Guo	Xi'an, China	Male, age 30	Bear bite	Cheek, nose, upper lip, maxilla, orbital wall, zygoma	Partial	Death (noncompliance, —)	Yes	No
3	January, 2007	Lantieri	Paris, France	Male, age 29	Neurofibromatosis	Forehead, brows, eyelids, nose, lips, cheeks	Partial	Alive	Yes	No
4	December 2008	Siemionow	Cleveland, OH	Female, age 45	Ballistic trauma	Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla	Partial	Alive	Yes	No
5	March, 2009	Lantieri	Paris, France	Male, age 27	Ballistic trauma	Nose, lips, maxilla, mandible	Partial	Alive	Yes	No
6	April, 2009	Lantieri	Paris, France	Male, age 37	Third-degree burn	Forehead, nose, eyelids, ears, cheek	Partial	Death (sepsis, 2 mo)	No	No
7	April, 2009	Pomahac	Boston, MA	Male, age 60	Electrical burn	Lower eyelid, cheek, nose, lips, maxilla, zygoma	Partial	Alive	Yes	No
8	August, 2009	Lantieri	Paris, France	Male, age 33	Ballistic trauma	Cheek, nose, lips, maxilla, mandible	Partial	Alive	Yes	No
9	August, 2009	Cavadas	Valencia, Spain	Male, age 42	Cancer/radiation therapy	Lower lip, tongue, floor of mouth, mandible	Partial	Death (malignancy, —)	Yes	No
10	November, 2009	Devauchelle and Dubernard	Amiens, France	Male, age 27	Ballistic trauma	Nose, lips, mandible	Partial	Alive	Yes	Yes
11	January, 2010	Gomez-Cia	Seville, Spain	Male, age 35	Neurofibromatosis	Cheek, lips, chin, mandible	Partial	Alive	Yes	No
12	March, 2010	Barret	Barcelona, Spain	Male, age 30	Ballistic trauma	Eyelids, nose, lips, lacrimal apparatus, zygoma, maxilla, mandible	Full	Alive	Yes	No
13	June, 2010	Lantieri	Paris, France	Male, age 35	Neurofibromatosis	Eyelids, ears, nose, lips, oral mucosa	Full	Alive	Yes	No
14	March, 2011	Pomahac	Boston, MA	Male, age 25	Electrical burn	Forehead, eyelids, left eye, nose, cheek, lips	Full	Alive	Yes	No
15	April, 2011	Lantieri	Paris, France	Male, age 45	Ballistic trauma	Nose, mandible, maxilla	Partial	—	—	No
16	April, 2011	Lantieri	Paris, France	Male, age 41	Ballistic trauma	Nose, mandible, maxilla	Partial	Death (suicide, 36 mo)	—	No
17	April, 2011	Pomahac	Boston, MA	Male, age 30	Electrical burn	Forehead, eyelids, nose, cheek, lips	Full	Alive	Yes	No
18	May, 2011	Pomahac	Boston, MA	Female, age 57	Animal attack	Forehead, eyelids, eyes, nose, lips, maxilla, mandible	Full	Alive	Yes	No
19	December, 2011	Blondeel	Ghent, Belgium	Male, age 54	Ballistic trauma	Eyes, eyelid, cheek, nose, maxillae, mandible, lip	Partial	Alive	Yes	No
20	January, 2012	Ozkan	Antalya, Turkey	Male, age 19	Burn	Forehead, nose, cheeks, lips	Full	Alive	Yes	No
21	February, 2012	Nasir	Ankara, Turkey	Male, age 25	Burn	—	Full	Alive	—	No
22	March, 2012	Ozmen	Ankara, Turkey	Female, age 20	Ballistic trauma	Nose, upper lip, maxilla, mandible	Partial	Alive	—	No
23	March, 2012	Rodriguez	Baltimore, MD	Male, age 37	Ballistic trauma	Forehead, eyelids, nose, cheek, lips, zygoma, maxilla, mandible	Full	Alive	Yes	No
24	May, 2012	Ozkan	Antalya, Turkey	Male, age 34	Thermal burn	Forehead, eyelids, nose, cheeks, lips	Full	Alive	Yes	No
25	September, 2012	Devauchelle and Dubernard	Amiens, France	Female, —	Vascular tumor	Lower eyelid, maxilla, tongue	Partial	Alive	Yes	No
26	February, 2013	Pomahac	Boston, MA	Female, age 44	Chemical burn	Nose, lips, eyelids, forehead, cheek, ears, eyes, neck	Full	Alive	Yes	No
27	May, 2013	Maciejewski	Gliwice, Poland	Male, age 32	Blunt trauma	Nose, lips, eyelid, cheek, maxilla	Partial	Alive	Yes	No
28	July, 2013	Ozkan	Antalya, Turkey	Male, age 27	Ballistic trauma	Forehead, eyelids, left eye, nose, cheek, mandible	Full	Alive	Yes	No

TABLE 1. (*Continued*)

Patient	Date	Surgical Team	Location	Recipient Details	Indication	Extent of Defect	Allograft Type	Status (COD, TFT)	Acute Rejection	Chronic Rejection
29	August, 2013	Ozkan	Antalya, Turkey	Male, age 54	Ballistic trauma	Scalp, forehead, eyelids, nose, left eye, maxilla, mandible, tongue	Full	Death (lymphoma and respiratory failure, 12 mo)	Yes	No
30	December, 2013	Maciejewski	Gliwice, Poland	Female, age 26	Neurofibromatosis	Forehead, eyelids, nose, maxilla, lips, mandible	Full	Alive	Yes	No
31	December, 2013	Ozkan	Antalya, Turkey	Male, age 22	Ballistic trauma	Forehead, lips, nose, maxilla, mandible	Partial	Alive	Yes	No
32	March, 2014	Pomahac	Boston, MA	Male, —	Ballistic trauma	Forehead, nose, lips, lower face	Full	Alive	Yes	No
33	September, 2014	Papay	Cleveland, OH	Male, —	Blunt trauma	Scalp, forehead, eyelids, nose, eye, maxilla, cheeks	Partial	Alive	Yes	No
34	October, 2014	Pomahac	Boston, MA	Male, age 31	Ballistic trauma	—	Full	Alive	Yes	No
35	February, 2015	Barret	Barcelona, Spain	Male, age 45	Arteriovenous malformation	Lower face, neck, lips, tongue, pharynx	Full	Alive	—	No
36	May, 2015	—	St. Petersburg, Russia	Male, —	Electrical burn	Forehead, nose, lips	Partial	Alive	—	—
37	August, 2015	Rodriguez	New York, NY	Male, age 41	Thermal burn	Scalp, forehead, eyelids, nose, cheeks, lower face, ears, lips, neck	Full	Alive	No	No
38[15]	January, 2016	Törnwall	Helsinki, Finland	Male, age 34	Ballistic trauma	Nose, maxilla, central mandible	Partial	Alive	No	No
39[46]	Summer, 2016	Mardini	Rochester, MN	Male, age 32	Ballistic trauma	Nose, upper and lower jaw, cheeks, salivary glands, lower face	Partial	Alive	No	No
40[14]	May, 2017	Papay	Cleveland, OH	Female, age 21	Ballistic trauma	Scalp, forehead, eyelids, orbit, nose, cheeks, maxilla, mandible	Full	Alive	No	No

COD indicates cause of death (where applicable); TFT, time from transplantation.
Sources: [13,41].

aspiration leading to septic shock and resection of concomitant upper extremity allografts), 4 with pseudomonas (2 pneumonia, 1 multi-resistant), 2 with candida, 1 with staph aureus, 1 with an aspergilloma, 1 with polymicrobial bacteremia, and 1 with molloscum contagiosum.[64] Adequate antibiotic and antiviral prophylaxis should be planned for FT recipients, and close follow-up with transplant infectious disease physicians is paramount.

Recent examples of the malignancy-related death of several FT recipients have shed light on the applicability of FT after postoncologic resection.[13] The risk of malignancy attributed to immunosuppressive medications deems a history of malignancy a relative contraindication to FT, while active malignancy is an absolute contraindication. The length of the post-malignancy remission period is also undetermined. It is also reasonable to extrapolate the risk of de novo malignancy observed in solid organ transplantation to FT and other forms of VCA. Moreover, despite the reduction in maintenance immunosuppression dose that follows the diagnosis of malignancy in a FT recipient, the addition of chemotherapeutic agents will most likely result in further immune compromise, promoting oncologic spread. In 1 case, this inevitably led to graft loss, resection, and autologous reconstruction with an anterior thigh flap. This has reignited the debate of back-up plans and autologous reconstruction options after allograft loss and resection.[65] At present, none of the FT recipients who have presented with allograft failure have survived in the long term. In the case of the world's first partial face recipient, graft failure was treated with resection and autologous reconstruction in the form of a radial forearm free flap,[55] and the recent loss and resection of a full face transplant was treated using an anterolateral thigh flap.[66] Few teams have published detailed descriptions of patient-specific back-up plans as part of their preoperative planning process,[54,67] but most agree that autologous tissue contingencies should be designed before listing the patient for transplant. This issue also raises questions as to what extent tissue defects should be covered by the FT procedure. For example, while including larger amounts of tissue as part of the allograft may lead to better aesthetic outcomes, this must be weighed against potentially more limited salvage options in the case of allograft failure. Currently, there is not a clear consensus in the FT community on this issue, and preferences are both center- and patient-specific.

Data Reporting

The challenges inherent to reporting FT outcomes have become increasingly apparent as follow-up times have increased.[13] The low number of procedures performed makes the development of a validated outcomes measure specific to FT recipients especially complicated. Moreover, those centers prospectively following their patients as part of a clinical study have encountered difficulty in adapting existing instruments validated for other conditions, such as facial paralysis, to the subtleties of FT. Although this precludes straightforward comparison of outcomes reported by different centers, it is important to understand that early standardization of technique, treatment, and outcomes measurement is unlikely precisely because of the field's limited experience. Furthermore, the validation of any new instrument is also logistically complex and will require a considerably larger sample size than the currently available FT patient cohort. However, frequent and transparent reporting of each FT center's outcomes remains a pre-requisite for progress. Important functional outcomes, such as speech and swallow trends, achievement of oral occlusion, and decannulation rates for previously tracheostomy-dependent patients, cannot be assessed properly without consistent and detailed long-term longitudinal reports from multiple teams. However, 1 center has reported improvement in speech-related function over time following FT.[68] Preliminary reports have also shown improvements in lip strength and mobility, as well as speech and facial expression, in a FT recipient after a strengthening exercise program,[47] underscoring the need for additional research on the efficacy and role of rehabilitation programs following transplantation. The current disparity between reports in the general media and peer-reviewed scientific journals is concerning.[13] The value of press coverage is well understood,[69] but it is the responsibility of FT providers to openly disclose their successes and setbacks during the infancy of this innovative endeavor. Although most would agree that the ultimate goal is an international community of teams working in collaboration rather than competition, this begins with frequent and transparent reporting of outcomes by individual teams in order to advance the field with common protocols for immunosuppression, patient screening, and determination of outcomes.

PATIENT SELECTION, EVOLVING INDICATIONS, AND COST CONSIDERATIONS

At present, 40 FTs have been performed worldwide by various multidisciplinary centers, each employing a patient-centered approach.[13,46] Selection criteria for FT can be multifaceted,[70] extending beyond surgical needs onto the psychosocial consequences of major facial disfigurement. Thus, candidates require an extensive evaluation by specialized experts in diverse FT teams. During what can be a lengthy evaluation process, FT candidate suitability is determined by a consensus between reconstructive surgeons, transplant specialists, psychologists, dentists, speech therapists, and other medical specialists. A solid support network is crucial for FT success, and it is a critical requirement when attempting to predict adherence to lifelong immunosuppression and acceptance of the psychological implications that result from such an extensive reconstructive procedure.

Surgical indications have remained broad, with facial allografts comprising of all tissue types transplanted as early as 2006. Loss of central facial structures critical to facial function and appearance (eg, nose, eyelids, lips) can be challenging to reconstruct through conventional techniques and is the most definitive surgical indication for FT. Most patients present with acquired facial disfigurement secondary to traumatic injury of diverse etiology, including ballistic injuries, animal attacks, and thermal, chemical, or electrical burns. Although initially considered beyond its scope due to immunosuppression-related risk of malignant transformation or recurrence, FT has been performed to treat disfiguring congenital tumors, such as plexiform neurofibromas,[35,36] as well as large defects following malignant tumor resection.[13,29,71] Similarly, patients with high-risk immunological and infectious states have undergone FT, including patients sensitized with donor-specific antibodies,[54] and an HIV-positive recipient[29]; surgical success was achieved but much has been learned from the ensuing challenges faced by both teams when managing antibody-mediated rejection[54] and oncologic complications.[71] There has also been much debate on the inclusion of facially disfigured blind patients.[72] Detractors argue that such a procedure should not be performed in a patient population that is unable to visually perceive the benefits of the surgery, or monitor acute rejection. However, proponents argue that these patients should be included based on functional and ethical grounds.[72] Although some teams prefer not to perform FT on the blind, other teams are in favor, and ultimately, there are ethical arguments that support offering this or other treatments in blind patients. Currently, blindness remains a VCA-center specific criterion for inclusion or exclusion, and long-term outcomes will lead the way in the future. Similarly, the inclusion of patients with a history of suicidality remains controversial. There have been 4 patients who underwent FT for intentional, self-inflicted gunshot wounds, and for whom outcomes have been published.[73] Of these, 1 patient committed suicide after transplantation, while the

other 3 remain alive with viable allografts.[24] These cases highlight the importance of patient selection and evaluation, but the consensus appears to be that as long as mental health is thoroughly evaluated and considered in these patients, FT can be an option. There has also been discussion on whether FT should be used as primary reconstruction. To date, there has been only 1 primary FT, with encouraging outcomes.[34] However, the logistics and timing of donor matching, as well as the preference to exhaust autologous options before consideration for FT, make this unlikely to become widespread. This ongoing evolution of indications is owed in large part to increased experience and greater confidence, as well as more advanced and coordinated planning by multidisciplinary teams.[44]

Expanding the indications of FT has also highlighted the difficulties that may arise with certain patient subsets, in addition to establishing the current limitations of FT for treating these individuals. The immunosuppression-related risk of de novo malignancy or recurrence, for example, remains a concern; the deaths of postoncological FT recipients have discouraged teams from considering this patient population until less oncogenic immunosuppression strategies are developed.[29]

VCA experience with the pediatric population has ignited debate on extending the indications of FT to this group, for which a more stringent risk-benefit analysis should be considered, particularly concerning lifelong immunosuppression.[74] Although 2 pediatric VCA cases did not require immunosuppression due to immune compatibility between identical[74] and ischiopagus twins,[75] a recent bilateral hand transplant in a previously immunosuppressed pediatric kidney recipient may be a game-changer.[76] As these patients already require immunosuppression, the risk-benefit balance is shifted in favor of VCA transplant. However, there are implications of adding a VCA to a solid organ transplant, including the requirement of another induction regimen as well as a theoretical increase in immunosuppression dosage. In addition, FT imposes far greater psychological and identity-related burdens than limb transplantation, and additional concerns beyond immunosuppressive requirements, such as patient autonomy and issues of consent and assent, must be addressed.

Another challenge that remains unresolved is the criteria for donor selection in FT, which is already limited by a restricted solid organ donor pool and higher specifications for donor-recipient matching. Demographic requirements such as skin tone, hair color, and skeletal shape/size, have introduced a level of difficulty in donor-recipient matching that organ procurement organizations had not encountered before FT. In addition, previous reconstructive attempts through skin grafting or blood transfusions required during resuscitation efforts may result in immune sensitization, making immunocompatibility even more unlikely.[16] Despite a low number of candidates currently awaiting FT, widening of indications coupled with potential advances in immunosuppression will likely lead to a larger patient population in the future, which may further exacerbate the current shortage of suitable donors.[77] In an effort to help alleviate these restrictions, the National Organ Transplant Act now considers VCAs equivalent to organs, which may facilitate VCA donor registration in the future.[78] Nevertheless, a unified front toward educating the public about FT is necessary to expand the donor pool and reduce prolonged wait times, which can present serious psychological burdens and have resulted in candidate withdrawal.[24]

The lifetime cost of a FT is another consideration as the field continues to advance. Figures vary in the literature, but FT costs reportedly exceed $250,000 per patient when long-term management and coverage of lifelong immunosuppression is considered. However, several cost analyses have shown FT to be similar in long-term cost to conventional reconstruction, especially when considering the greater defect severity in transplanted patients.[79,80] Furthermore, as costs are lowered through gains in experience and technology, it is reasonable to expect the cost-benefit ratio to shift even further in favor of FT. These high costs are currently funded by institutions, awards, and private or public endowments, but primarily through government grants. Alternative sources of funding must be identified as the patient base expands. The question of whether and how FT would be covered by health insurance moving forward is currently a matter of debate.[77] Despite the commitment of groups such as the OPTN and UNOS in FT regulation, the field is limited by the inability of insurance carriers or the government to fund deserving patients and improve quality of life for those afflicted by devastating facial disfigurement. We recognize this as a major shortcoming in the field currently; however, our team is working closely with third-party payers to increase reimbursement for selective cases where there are no other conventional methods of treatment that yield acceptable results. Although merely a first step, we believe this to be an important one toward combating this barrier moving forward.

CONCLUSION

In just over a decade, the burgeoning field of FT has achieved numerous breakthroughs and battled ongoing challenges, standing at the very top of the reconstructive ladder. Despite early skepticism, FT has become an effective – and for the right patient, preferred – reconstructive option, applicable to a wider pool of candidates than initially estimated, and to defects more extensive than initially imagined. Short- and medium-term outcomes have proven favorable with promising functional and aesthetic results, and a positive psychosocial impact on recipients. Nevertheless, as new milestones are met, a new set of challenges emerges. Immunological hurdles continue to impede even greater success, and issues such as candidate/recipient mental health, cost coverage, and donor shortages require immediate attention. FT was pioneered on collaborative international efforts, and its growth as a field will depend on teams around the world learning from each other's experience. Thus, it is with great anticipation that we await transparent outcome reports from international leaders, which will shape the second decade in FT.

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