CME

Facial Transplantation: Principles and Evolving Concepts

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Learning Objectives: After studying this article, the participant should be able to: 1. Appreciate the evolution and increasing complexity of transplanted facial allografts over the past two decades. 2. Discuss indications and contraindications for facial transplantation, and donor and recipient selection criteria and considerations. 3. Discuss logistical, immunologic, and cost considerations in facial transplantation, in addition to emerging technologies used. 4. Understand surgical approaches and anatomical and technical nuances of the procedure. 5. Describe aesthetic, functional, and psychosocial outcomes of facial transplantation reported to date.

Summary: This CME article highlights principles and evolving concepts in facial transplantation. The field has witnessed significant advances over the past two decades, with more than 40 face transplants reported to date. The procedure now occupies the highest rung on the reconstructive ladder for patients with extensive facial disfigurement who are not amenable to autologous reconstructive approaches, in pursuit of optimal functional and aesthetic outcomes. Indications, contraindications, and donor and recipient considerations for the procedure are discussed. The authors also review logistical, immunologic, and cost considerations of facial transplantation. Surgical approaches to allograft procurement and transplantation, in addition to technical and anatomical nuances of the procedure, are provided. Finally, the authors review aesthetic, functional, and psychosocial outcomes that have been reported to date.

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The first face transplant in 2005 introduced a paradigm shift in craniofacial reconstructive surgery.[1] Since then, facial transplantation has evolved into an effective solution for patients with extensive facial disfigurement when autologous approaches fail or are inappropriate in restoring optimal facial form and function.[2] Growing international experience with the procedure has revealed overall satisfactory results and shifted the focus of the field from demonstrating feasibility, to refining approaches, outcomes, and addressing new challenges.[2,3]

Over the past 15 years, a total of 48 face transplants have been performed in 46 patients.[2,4–6] Moreover, data suggest that the annual incidence rate of individuals aged 20 to 64 years who suffer from preventable nonfatal severe craniofacial injuries in the United States lies between 32.1 and 58.1 per 100,000.[7] These figures, combined with recent encouraging reports of face transplant cost coverage by third-party payers, suggest a high likelihood that an increasing number of patients with extensive facial injuries who are not amenable to conventional reconstruction will seek evaluation and undergo facial transplantation when appropriate.[8]

Facial transplantation is complex, requires extensive preparation, and relies on a multidisciplinary approach to achieve optimal outcomes. Despite the growing number of procedures performed around the world, consensus regarding a number of perioperative considerations is lacking. This is further exacerbated by limited data regarding long-term outcomes given the recent

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advent of the field. With these issues in mind, the goal of this CME article is to provide an overview of current and evolving concepts in facial transplantation, and review important preoperative, intraoperative, and postoperative principles.

SURGICAL INDICATIONS AND RECIPIENT SELECTION

Surgical indications and patient selection criteria in facial transplantation are closely related, and determining the appropriate candidate for the procedure requires rigorous evaluation. Candidate evaluation should be performed through a collaborative and multidisciplinary team-based approach between reconstructive surgeons, psychologists, speech therapists, dentists, transplant specialists, and others.[9] Face transplant teams must also thoroughly assess a candidate's social support system to ensure favorable conditions for the lengthy postoperative recovery, adaptation to psychological repercussions, and adherence to lifelong immunosuppression that accompany the procedure.[2,10] Psychosocial factors are particularly important in candidates who have sustained self-inflicted injuries and have a history of substance abuse or suicidality. Facial transplantation has been reported to be successful in these patients, but resolution of suicidal tendencies and substance abuse must be ensured before performing the procedure.[2] Facial transplantation in blind patients remains controversial, with opponents suggesting that recipients will not be able to perceive the outcomes of the procedure or allograft changes that may indicate immunologic rejection, whereas supporters argue that it is unethical to exclude blind patients, especially in light of favorable reported aesthetic and functional outcomes.[11–15] Immunologic risk factors also need to be considered when weighing the risks and benefits of the procedure in potential candidates. This is particularly relevant for patients with a history of burns and extensive transfusions that can lead to immunosensitization, human immunodeficiency syndrome infection, presence of donor-specific antibodies, and other immunomodulatory conditions that can complicate finding matching donors and postoperative recovery.[16–18] The risk of de novo malignancies associated with the mandatory use of lifelong immunosuppression should also be taken into consideration, especially in immunosuppressed candidates and in patients with facial defects resulting from oncologic resections.[17,19] To date, facial transplantation has been limited to adult patients, with ongoing ethical debates and discussions regarding the appropriateness of performing the procedure in pediatric patients.[20]

Extensive facial disfigurement involving the majority of the surface area of the face in association with significant damage to or loss of central facial structures that are critical to facial function and appearance, and that are challenging to reconstruct through autologous techniques (e.g., the nose, lips, and eyelids), is the most widely accepted indication for facial transplantation.[2,17] The most common mechanism of injury in patients who have undergone facial transplantation is trauma, including ballistic injury, burns, animal attacks, and others.[2] The procedure has also been performed to treat benign tumors such as neurofibromas, and facial defects resulting from oncologic resections.[2,17,19,21–23] Although immediate facial transplantation following injury has been performed successfully with encouraging outcomes, the viability of this approach, especially when considering donor shortages and matching criteria, remains to be determined.[24] Table 1 highlights surgical and nonsurgical indications, and contraindications to facial transplantation based on the experience of the senior author (E.D.R).

DONOR SELECTION AND CONSIDERATIONS

Donor selection and matching in facial transplantation are more challenging than in solid organ transplantation. The donor and recipient must be appropriately matched based on blood type and immunologic criteria in addition to demographic factors, hair and skin color, and cephalometric parameters.[2] These considerations have made donor shortages more pronounced in facial transplantation, and have often resulted in prolonged candidate wait times before transplantation. Moreover, discrepancies exist between organ procurement organization involvement in solid organ and vascularized composite allograft donation, including facial allografts, in favor of solid organ donation.[25] Strong collaborations between face transplant centers and organ procurement organizations can alleviate candidate wait times by expanding donation service areas.[25] Furthermore, opt-out donation systems have been shown to significantly reduce candidate wait time.[24] Lastly, educational initiatives targeting the general public can provide insight into functional and aesthetic outcomes of the procedure and reduce misconceptions, and have been shown to increase the willingness to donate facial tissue by almost 20 percent.[26]

Table 1. Surgical and Nonsurgical Indications and Contraindications to Facial Transplantation Based on the Senior Author's Experience

Considerations	Strong Indications	Strong Contraindications	Relative Contraindications
Surgical	Extensive defects involving the majority of the surface area of the face	Sufficient tissue of the central face subunits (upper/lower eyelids, upper/lower lips, nose) to complete autologous reconstruction	
	Extensive damage to or loss of the central face subunits (upper/lower eyelids, upper/lower lips, nose)	Adequate autologous tissue donor sites	
	Lack of autologous reconstructive options		
Nonsurgical	Adequate support system	Inadequate support system	History of malignancy
	No active psychiatric disorders	History of poor compliance	Blindness
		Active psychiatric disorder	Immunocompromised/immunosensitized
		Active malignancy	
		End-organ dysfunction	

LOGISTIC CONSIDERATIONS

Developing and implementing standardized logistic processes and workflows are critical for patient safety, quality improvement, and obtaining reproducible outcomes in complex surgical procedures such as facial transplantation.[27] Moreover, the efficacy of surgical technologies and tools that will be used in the face transplant such as three-dimensionally–printed cutting guides, intraoperative navigation, masks for donor facial restoration, and indocyanine green fluorescence angiography should be tested before the procedure, and team members should be familiar with their use.[8,28–31] Close collaboration with key stakeholders in transplantation, including local organ procurement organizations, have led to the development of elaborate algorithms for transferring face donors to recipient institutions and concomitant procurement of solid organs and facial allografts.[8,27,32,33] Such algorithms in addition to perioperative workflows ensure team readiness and team dynamics, and uphold optimal performance during a face transplant, especially when the donor facial procurement and recipient procedure are being performed concurrently (Fig. 1).[27,34] Most importantly, face transplant teams need to account for

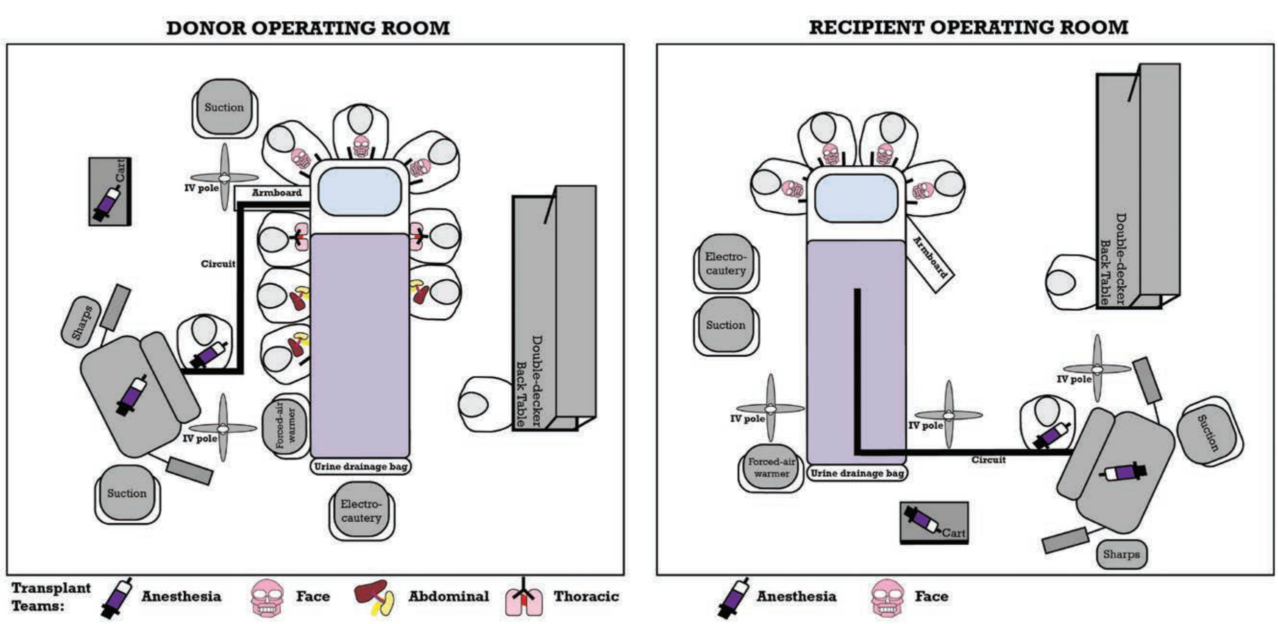

Fig. 1. Setup of face transplant donor and recipient rooms. Schematic of the donor (*left*) and recipient (*right*) operating rooms, with strategic placement of multidisciplinary team members and required equipment. *IV*, intravenous. (From Alfonso AR, Ramly EP, Kantar RS, et al. Anesthetic considerations in facial transplantation: Experience at NYU Langone Health and systematic review. *Plast Reconstr Surg Glob Open* 2020;8:e2955; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

geographic challenges that may arise when transplant candidates need to travel long distances for their procedures and postoperative visits, to ensure close follow-up and prompt treatment of potential complications and rejection episodes.[8,35]

COMPUTERIZED SURGICAL PLANNING AND IMPLEMENTATION

Extensive surgical preparations, combined with the use of cutting-edge emerging technologies, have allowed face transplant teams to make significant strides in the field. Simulated exercises allow face transplant teams to familiarize themselves with the procedure and associated logistics, and troubleshoot potential challenges that may arise.[2,27] Cadaveric rehearsals allow surgical refinement through repetition, objective outcomes assessment, and real-time high-fidelity simulation of the planned procedure; expedited allograft procurement; and decreased operative time and the number of required simulated exercises with subsequent transplants.[2,8,15,30,31,36–39] This can be further supplemented with research procurements in brain-dead donors.[28,29] The application of computerized surgical planning to facial transplantation has perhaps been the most significant advancement in the field, introducing a paradigm shift in allograft design, and allowing face transplant teams to adopt a personalized patient-centered reconstructive approach. Similarly, the use of computer-aided design and manufacturing of patient-specific devices such as skeletal cutting guides has allowed further refinement of allograft design and surgical technique (Fig. 2). This is particularly important for allografts including skeletal segments, where the use of these technologies allows more streamlined, accurate planning and execution of donor and recipient osteotomies.[31] [**See Video 1 (online)**, which shows computerized surgical planning. For allografts including skeletal segments, the use of computerized surgical planning and computer-aided design and manufacturing allows accurate, streamlined planning and execution of donor and recipient osteotomies. (Adapted from Ramly EP, Kantar RS, Diaz-Siso JR, Alfonso AR, Rodriguez ED. Computerized approach to facial transplantation: Evolution and

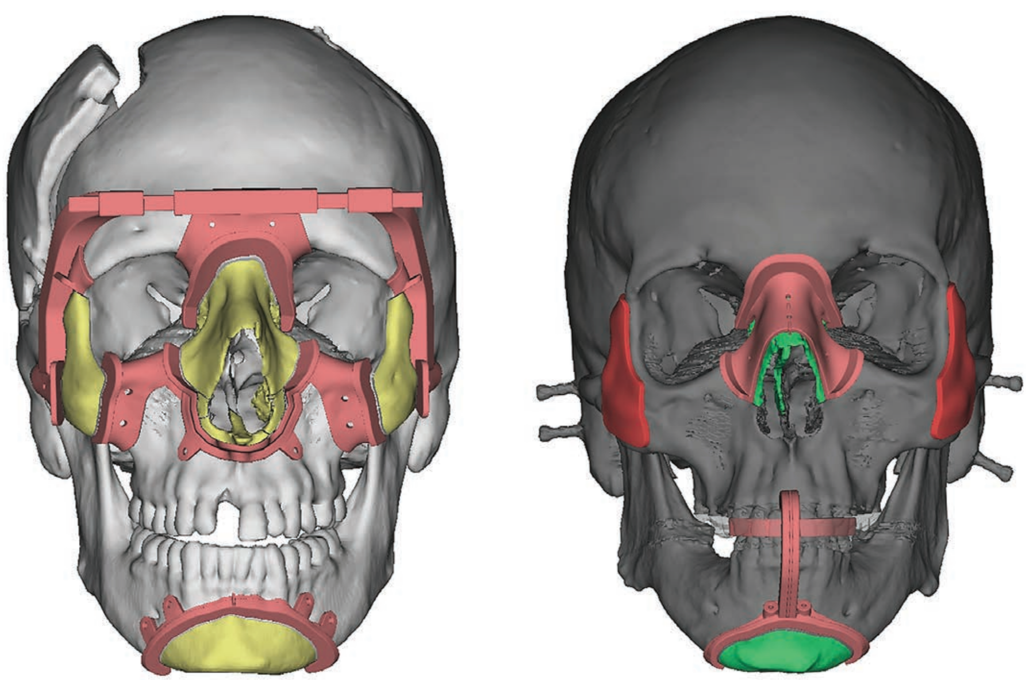

Fig. 2. Computer-aided design and manufacturing of patient-specific skeletal cutting guides. These guides have refined surgical approaches in facial transplantation. Although this recipient's facial defect did not involve skeletal segments, the allograft was designed to include skeletal subunits to augment facial projection while preserving retaining ligaments and muscular insertion sites. Donor (*left*) and recipient (*right*) planned osteotomies and customized cutting guides are shown. (From Sosin M, Ceradini DJ, Levine JP, et al. Total face, eyelids, ears, scalp, and skeletal subunit transplant: A reconstructive solution for the full face and total scalp burn. *Plast Reconstr Surg*. 2016;138:205–219; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

application in 3 consecutive face transplants. *Plast Reconstr Surg Glob Open* 2019;7:e2379; provided with permission from and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

These advantages can translate into improved cephalometric and occlusal relationships between donor craniomaxillofacial segments and the recipient craniofacial skeleton.[31,40] More recently, computer-aided intraoperative surgical navigation has been proposed as an adjunct to these tools, with benefits including the capability to register and overlay the predetermined surgical plan onto the patient skeletal defect and real-time intraoperative guidance, which can translate into improved accuracy during donor skeletal segment inset and fixation in the recipient (Fig. 3).[8,41] Adequate allograft perfusion and viability following skeletal inset and vascular anastomoses can then be verified using indocyanine green fluorescence angiography, which can also be performed before final detachment of the allograft from the donor major vessels (Fig. 4).[8,28,29,36,37,42,43] Lastly, computer-aided technologies can also be used for donor facial restoration, with recent data demonstrating that three-dimensionally–printed masks based on preoperatively acquired donor digital facial images are more accurate than traditional silicone-based masks (Fig. 5).[44] Importantly these three-dimensionally–printed masks offer a less invasive alternative with a lower risk of iatrogenic

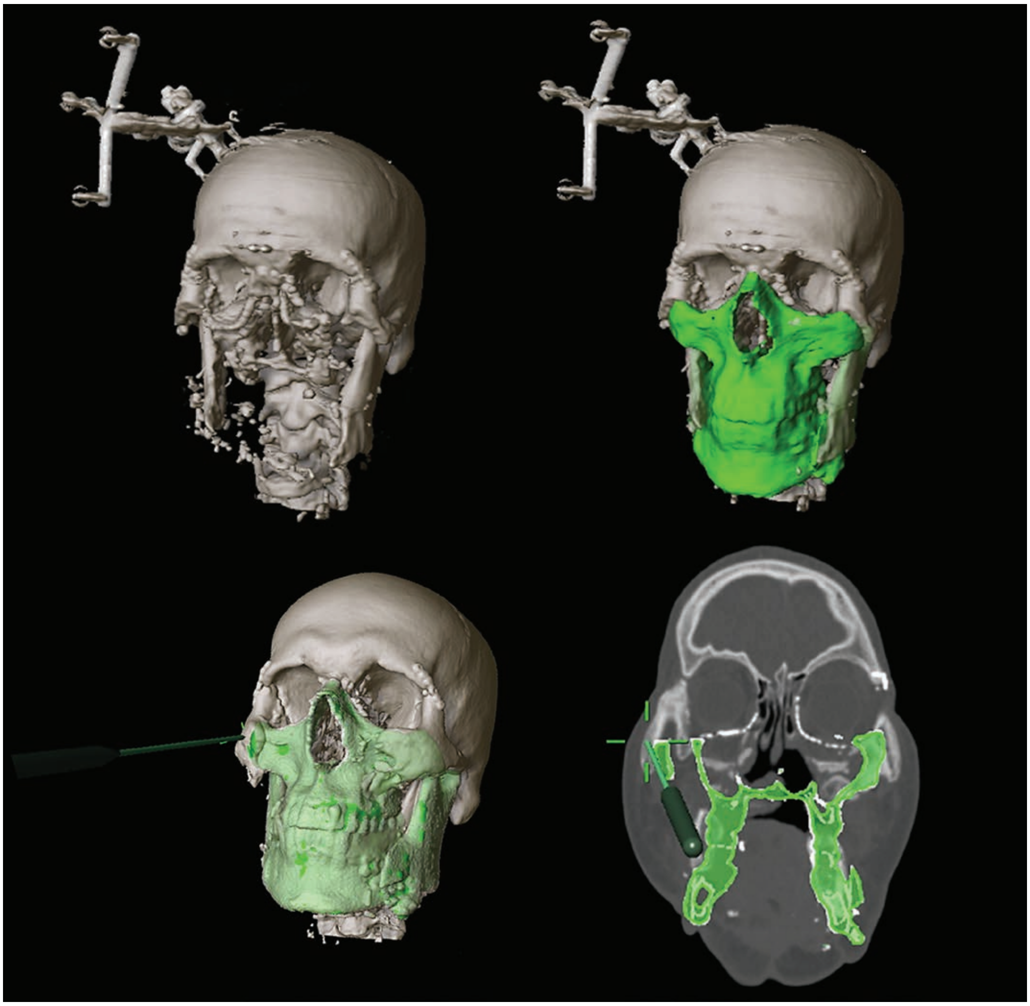

Fig. 3. Intraoperative navigation. Real-time intraoperative surgical navigation can be used to confirm accurate allograft skeletal inset, and compare planned (*green*) versus actual (*gray*) position of the skeletal segments. Intraoperative computed tomographic scanning and registration of scan data using a registration device (*above*, *left and right*) allow real-time surgical navigation and verification of skeletal segment positions (*below*, *left and right*). (From Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg*. 2019;144:264e–283e; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

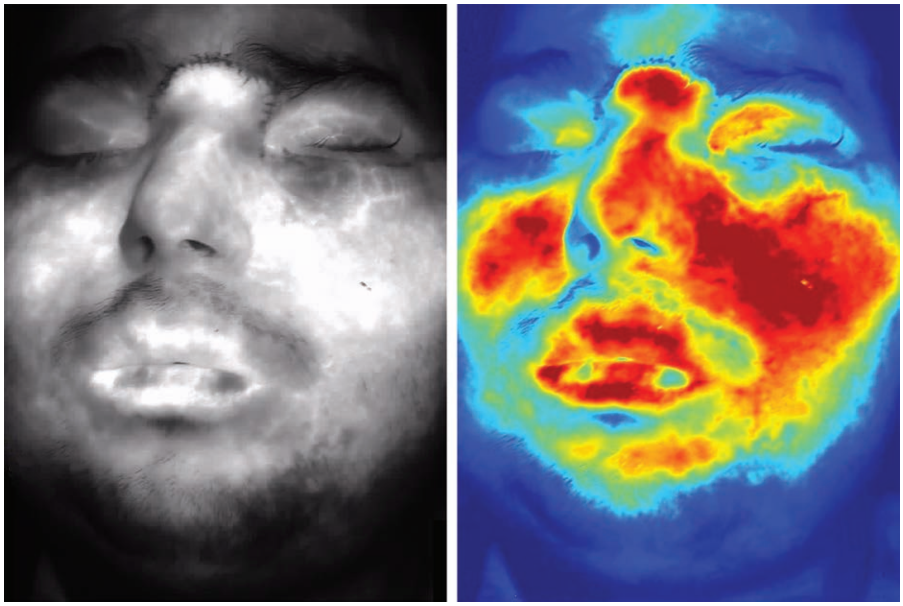

Fig. 4. Indocyanine green fluorescence angiography. The use of indocyanine green fluorescence angiography allows face transplant teams to verify appropriate allograft arterial perfusion and venous outflow before release from the donor major vessels and following transplantation. (From Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg*. 2019;144:264e–283e; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

injury to the allograft compared to silicone-based masks, given that they do not require donor facial impressions.[44] All of these innovations can be thoroughly tested during simulated exercises before implementation during a clinical face transplant, which can streamline the planning and execution of these complex procedures, overcome intraoperative anticipated and unexpected challenges, and translate into more predictable outcomes.

TECHNICAL NUANCES AND CONSIDERATIONS

Growing experience in the field and the technological and logistical improvements listed above have allowed teams to successfully navigate the anatomical complexities inherent in the head and neck, and transplant increasingly complex facial allografts including a large amount of bone (Fig. 6).[2] This has allowed face transplant teams to provide customized patient-specific reconstructive solutions to individuals with extensive facial disfigurement resulting from a myriad of congenital or acquired conditions (Table 2). Although surgical approaches have varied significantly between face transplant teams around the world, the growing popularity of the procedure as a reconstructive solution for patients affected with extensive facial injuries not amenable to autologous approaches mandates developing standardized classification schemes and nomenclature for these injuries to improve communication between transplant teams and strengthen collaborative efforts (Fig. 7).[45]

When designing the facial allograft and planning recipient tissue excision, we recommend taking into consideration functional and aesthetic facial subunits for soft-tissue components, and using Le Fort–type osteotomies for skeletal segments. [**See Video 2 (online)**, which shows Le Fort–type osteotomies. This video shows how Le Fort III–type skeletal osteotomies can be used for donor allograft procurement, using custom-tailored virtually designed cutting guides that are preoperatively planned to match donor and recipient facial skeletons. (Adapted from Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg*. 2019;144:264e–283e; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

Appropriate allograft vascular perfusion is the cornerstone to successful transplantation, and numerous allograft vascular pedicles have been described (Table 2). To ensure optimal perfusion

Fig. 5. Donor mask for facial restoration. A high-fidelity, three-dimensionally–printed mask (*right)* can be created from preoperative facial three-dimensional images for optimal donor likeness. It is used to cover the facial defect following allograft procurement. The three-dimensional printing technique (*right*) provides superior donor likeness compared to the traditional silicone-based technique (*left*), which generates a mask from preoperative facial impressions. The three-dimensionally–printed mask technique is also less invasive and can be initiated as soon as three-dimensional digital images of the donor face are obtained preoperatively; it preserves the dignity of the donor, and allows the donor family to perform routine end-of-life rituals. (From Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg*. 2019;144:264e–283e; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

and vascular pedicle lengths, we recommend establishing bilateral arterial inflow through the external carotid arteries, with corresponding appropriate bilateral venous outflow, which requires meticulous bilateral neck dissections at the time of transplantation. [**See Video 3 (online)**, which demonstrates neck dissection. Neck dissection involves initial elevation of the subplatysmal flap, circumferential exposure of the major vessels, harvesting of lymph nodes, and excision of the submandibular gland. Meticulous dissection results in clear identification of critical head and neck anatomical structures, including the internal jugular vein, facial vein, common carotid artery, external and internal carotid arteries, occipital artery, lingual artery, facial artery, and the hypoglossal nerve. (Adapted from Sosin M, Ceradini DJ, Levine JP, et al. Total face, eyelids, ears, scalp, and skeletal subunit transplant: A reconstructive solution for the full face and total scalp burn. *Plast Reconstr Surg*. 2016;138:205–219; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

It is the senior author's (E.D.R) preference to perform all vascular anastomoses using the operating microscope to optimize anastomotic technique, and to perform allograft skeletal inset and fixation in the recipient before vascular anastomoses to prevent kinking of the vascular pedicles. [**See Video 4 (online)**, which demonstrates vascular anastomoses. This video shows how the vascular pedicles are tailored to limit vessel redundancy and to help prevent kinking, and how the anastomoses are performed using the operating microscope. Here, the right donor external carotid artery was anastomosed to the right recipient external carotid artery end-to-end. Because of a donor vascular variant identified during preoperative imaging, the donor anterior jugular vein was anastomosed end-to-end to the recipient internal jugular vein, as opposed to the more commonly

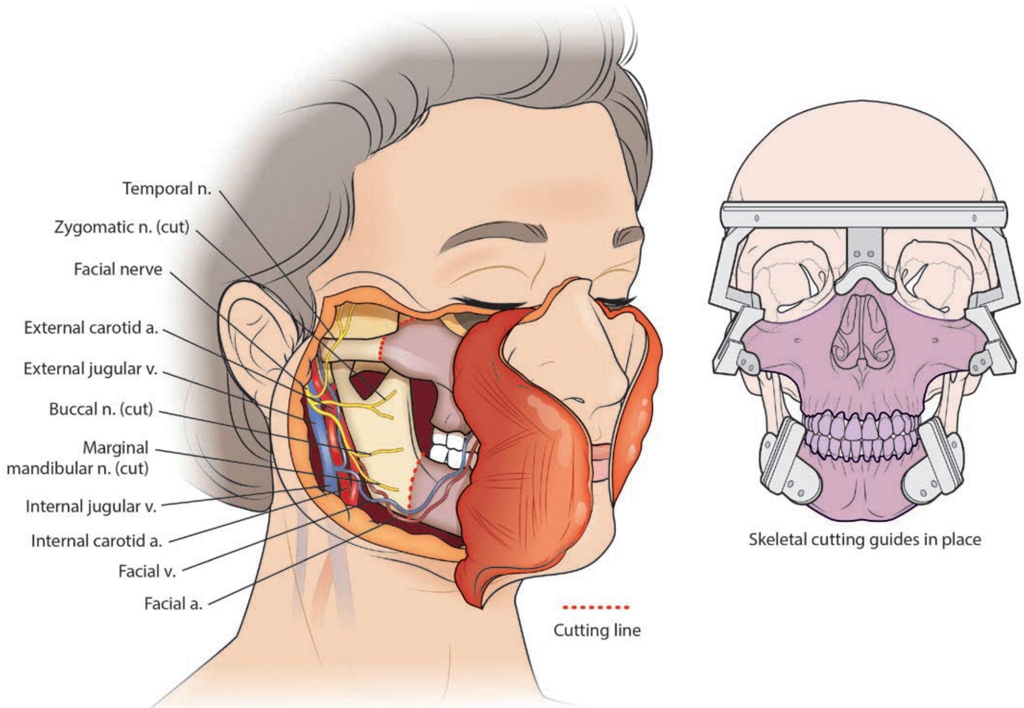

Fig. 6. Face transplant/head and neck anatomy with cutting guides. (Printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

used donor and recipient internal jugular veins anastomosed end-to-side. (Adapted from Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg.* 2019;144:264e–283e; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

Moreover, it is important to mention that our preferred preoperative vascular imaging protocol consists of conventional angiography supplemented by computerized tomographic angiography, to visualize vessel patency and real-time vascular flow dynamics, which can significantly affect surgical planning.[2,46] Despite early debate on the inclusion of salivary glands within the allograft, we recommend excluding the parotid and remaining salivary glands to minimize the formation of sialoceles [**see Video 3 (online)**]. Optimal patient outcomes are highly dependent on restoring appropriate sensory and motor facial functions following transplantation. This relies on identification and meticulous dissection of the facial nerve and corresponding branches, which can be facilitated by the use of intraoperative nerve stimulation. [**See Video 5 (online)**, which demonstrates facial nerve dissection. The approach to facial nerve dissection is similar for both the donor and recipient operations. A skin flap is elevated in the subcutaneous plane and continues deep to the masseteric fascia as the nerve exits the parotid gland. The upper, middle, and lower divisions of the facial nerve are identified using intraoperative nerve stimulation. (Adapted from Dorafshar AH, Bojovic B, Christy MR, et al. Total face, double jaw, and tongue transplantation: An evolutionary concept. *Plast Reconstr Surg.* 2013;131:241–251; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

It is also important to mention that coapting the facial nerve branches distally in proximity to the target muscles has been proposed to reduce the risk of synkinesis.[1,2,47,48] We also recommend coapting sensory nerves when possible. Preventing ocular complications including ectropion, lid retraction, and loss of blink reflex, is also critical in facial transplantation and relies on meticulous dissection and preservation of periorbital structures.[2,48–50] [**See Video 6 (online)**, which demonstrates periorbital dissection. In this video we demonstrate our periorbital approach in one of our face transplant recipients, where the periorbital dissection proceeds in the subcutaneous plane. The orbicularis oculi and underlying structures are preserved in an effort

Table 2. Facial Transplantation Worldwide as of April 2020

Patient	Surgical Team	Location of Transplant	Date of Transplant	Recipient Age (yr)	Sex	Indication	Extent of Defect	Allograft Type	Allograft Vascular Pedicle	Status (COD, TFT)	Acute Rejection	Chronic Rejection
1	Devauchelle, Dubernard	Amiens, France	11/2005	38	F	Animal attack	Cheek, nose, lips, chin	Partial	Facial artery	Death (malignancy, 11 yr)	Yes	Yes
2	Guo	Xi'an, People's Republic of China	04/2006	30	M	Animal attack	Cheek, nose, upper lip, maxilla, orbital wall, zygoma	Partial	Maxillary artery	Death (noncompliance, 27 mo)	Yes	No
3	Lantieri	Paris, France	01/2007	29	M	NF	Forehead, brows, eyelids, nose, lips, cheeks	Partial	ECA	Alive	Yes	No
4	Siemionow	Cleveland, Ohio	12/2008	45	F	Ballistic trauma	Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla	Partial	Facial artery	Alive	Yes	No
5	Lantieri	Paris, France	03/2009	27	M	Ballistic trauma	Nose, lips, maxilla, mandible	Partial	ECA	Alive	Yes	No
6	Lantieri	Paris, France	04/2009	37	M	Third-degree burn	Forehead, nose, eyelids, ears, cheek	Partial	ECA	Death (sepsis, 2 mo)	No	No
7	Pomahac	Boston, Mass.	04/2009	59	M	Electrical burn	Lower eyelid, cheek, nose, lips, maxilla, zygoma	Partial	ECA plus facial artery	Death (HCC, 10 yr)	Yes	Yes
8	Lantieri	Paris, France	08/2009	33	M	Ballistic trauma	Cheek, nose, lips, maxilla, mandible	Partial	ECA	Alive	Yes	No
9	Cavadas	Valencia, Spain	08/2009	42	M	ORN after malignancy	Lower lip, tongue, floor of mouth, mandible	Partial	CCA	Death (malignancy)	Yes	No
10	Devauchelle, Dubernard	Amiens, France	11/2009	27	M	Ballistic trauma	Mandible, upper and lower lips, chin, perioral area	Partial	—	Alive	Yes	Yes
11	Gomez-Cia	Seville, Spain	01/2010	35	M	NF	Cheek, lips, chin, mandible	Partial	CCA	Alive	Yes	No
12	Barret	Barcelona, Spain	03/2010	30	M	Ballistic trauma	Eyelids, nose, lips, lacrimal apparatus, zygoma, maxilla, mandible	Full	ECA	Alive	Yes	No
13	Lantieri	Paris, France	06/2010	35	M	NF	Eyelids, ears, nose, lips, oral mucosa	Full	ECA	Alive	Yes	Yes
14	Pomahac	Boston, Mass.	03/2011	25	M	Electrical burn	Forehead, eyelids, left eye, nasal bone, cheek, lips	Full	Linguofacial trunk	Alive	Yes	Yes
15	Lantieri	Paris, France	04/2011	45	M	Ballistic trauma	Nose, mandible, maxilla	Partial	ECA	Alive	Yes	No
16	Lantieri	Paris, France	04/2011	41	M	Ballistic trauma	Nose, mandible, maxilla	Partial	ECA	Death (suicide, 36 mo)	Yes	No
17	Pomahac	Boston, Mass.	04/2011	30	M	Electrical burn	Forehead, eyelids, nasal bone, cheek, lips	Full	Facial artery plus ECA	Alive	Yes	No
18	Pomahac	Boston, Mass.	05/2011	57	F	Animal attack	Forehead, eyelids, eyes, nasal bone, lips, maxilla, mandible	Full	Facial artery plus ECA	Alive	Yes	No
19	Blondeel	Ghent, Belgium	12/2011	54	M	Ballistic trauma	Eyes, eyelid, cheek, nose, maxilla, mandible, lips	Partial	Facial artery	Alive	Yes	No
20	Ozkan	Ankara, Turkey	01/2012	19	M	Burn	Forehead, nose, cheeks, lips	Full	ECA	Alive	Yes	No
21	Nasir	Ankara, Turkey	02/2012	25	M	Burn	—	Full	—	Alive	—	—
22	Ozmen	Ankara, Turkey	03/2012	20	F	Ballistic trauma	Nose, upper lip, teeth, maxilla, mandible	Partial	—	Alive	—	—
23	Rodriguez	Baltimore, Md.	03/2012	37	M	Ballistic trauma	Forehead, eyelids, nose, cheek, lips, zygoma, maxilla, mandible	Full	ECA	Alive	Yes	No
24	Ozkan	Ankara, Turkey	05/2012	35	M	Thermal burn	Forehead, eyelids, nose, cheeks, lips	Full	ECA	Alive	Yes	No
25	Devauchelle, Dubernard	Amiens, France	09/2012	—	F	Vascular tumor	Lower eyelid, mandible, maxilla, tongue	Partial	—	Alive	Yes	No
26	Pomahac	Boston, Mass.	02/2013	44	F	Chemical burn	Nose, lips, eyelids, forehead, cheek, ears, eyes, neck	Full	—	Alive	Yes	No
27	Maciejewski	Gliwice, Poland	05/2013	32	M	Blunt trauma	Nose, lips, eyelid, cheek, maxilla	Partial	ECA	Alive	Yes	No

(Continued)

Table 2. ***Continued***

Patient	Surgical Team	Location of Transplant	Date of Trans-plant	Recipient Age (yr)	Sex	Indication	Extent of Defect	Allograft Type	Allograft Vascular Pedicle	Status (COD, TFT)	Acute Rejection	Chronic Rejection
28	Ozkan	Ankara, Turkey	07/2013	26	M	Ballistic trauma	Forehead, eyelids, left eye, nose, cheek, mandible	Full	ECA	Alive	Yes	No
29	Ozkan	Ankara, Turkey	08/2013	54	M	Ballistic trauma	Scalp, forehead, eyelids, nose, left eye, maxilla, mandible, tongue	Full	ECA	Death (respiratory failure, 11 mo)	Yes	No
30	Maciejewski	Gliwice, Poland	12/2013	28	F	NF	Forehead, eyelids, nose, maxilla, lips, mandible	Full	ECA	Alive	Yes	No
31	Ozkan	Ankara, Turkey	12/2013	22	M	Ballistic trauma	Forehead, lips, nose, maxilla, mandible	Partial	ECA plus facial artery	Alive	Yes	No
32	Pomahac	Boston, Mass.	03/2014	39	M	Ballistic trauma	Forehead, nose, lips, lower face	Full	—	Alive	Yes	No
33	Papay	Cleveland, Ohio	09/2014	44	M	TINI	Scalp, forehead, eyelids, nose, eye, maxilla, cheeks	Partial	ECA	Alive	Yes	No
34	Pomahac	Boston, Mass.	10/2014	31	M	Ballistic trauma	Forehead, mandible, maxilla, lips and nose	Full	Facial artery	Alive	Yes	No
35	Barret	Barcelona, Spain	02/2015	45	M	AVM	Lower face, neck, lips, tongue, pharynx	Full	—	Alive	No	No
36	Volokh	Saint-Petersburg, Russia	05/2015	22	M	Electrical burn	Forehead, nose, lips	Partial	ECA	Alive	Yes	No
37	Rodriguez	New York, N.Y.	08/2015	41	M	Thermal burn	Scalp, forehead, eyelids, nose, cheeks, lower face, ear, lips, neck	Full	ECA	Alive	Yes	No
38	Tornwall	Helsinki, Finland	02/2016	34	M	Ballistic trauma	Nose, maxilla, central mandible	Partial	ECA plus facial artery	Alive	No	No
39	Mardini	Rochester, Minn.	06/2016	32	M	Ballistic trauma	Nose, maxilla, mandible, cheeks, salivary glands, lower face	Partial	—	Alive	Yes	No
40	Papay	Cleveland, Ohio	05/2017	21	F	Ballistic trauma	Scalp, forehead, eyelids, orbit, nose, cheeks, maxilla, mandible	Full	—	Alive	No	No
41	Rodriguez	New York, N.Y.	01/2018	25	M	Ballistic trauma	Eyelids, nose, cheek, lips, maxilla, mandible, zygoma, right orbital floor	Partial	ECA	Alive	Yes	No
42	Lantieri	Paris, France	01/2018	43	M	CR of previous FT	—	Full	—	Alive	—	—
43	Lassus	Helsinki, Finland	03/2018	58	M	Ballistic trauma	Maxilla, mandible, full face soft tissue	Full	—	Alive	No	No
44	Borsuk	Montreal, Canada	05/2018	64	M	Ballistic trauma	Maxilla, mandible, nose, lower 2/3 of face	Partial	—	Alive	—	—
45	Santanelli, Longo	Rome, Italy	09/2018	49	F	NF	—	—	—	—	—	—
46	Pomahac	Boston, Mass.	07/2019	68	M	Thermal burn	Lips, nose, facial skin	Full	—	Alive	—	—
47	Pomahac	Boston, Mass.	07/2020	52	F	CR of previous FT	—	Full	—	Alive	—	—
48	Rodriguez	New York, N.Y.	08/2020	22	M	Thermal burn	Scalp, forehead, eyelids, nose, cheeks, lower face, lips, ears, neck, also included bilateral hands	Full	ECA	Alive	—	—

COD, cause of death; TFT, time from transplantation; F, female; M, male; NF, neurofibromatosis; ECA, external carotid artery; HCC, hepatocellular carcinoma; ORN, osteoradionecrosis; CCA, common carotid artery; TINI, trauma-induced necrotizing inflammation; HCC, hepatocellular carcinoma; TINI, trauma-induced necrotizing inflammation; AVM, arteriovenous malformation; CR, chronic rejection; FT, face transplant.

to avoid impairment of corneal blink. (Adapted from Dorafshar AH, Bojovic B, Christy MR, et al. Total face, double jaw, and tongue transplantation: An evolutionary concept. *Plast Reconstr Surg.* 2013;131:241–251; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

Although an extensive discussion regarding posttransplant revisions is beyond the scope of this article, it is important to highlight that they are commonly performed to improve functional and aesthetic outcomes and to address postoperative complications and conditions including ptosis, malocclusion, hematomas, palatal fistulae, ectropion, lid retraction, facial muscle retraction, and contour abnormalities.[2,42,48,50–53] In patients receiving allografts that include predominantly soft-tissue components, we believe it is important to preserve and avoid disrupting critical facial osteocutaneous retaining ligaments by including donor skeletal segments to minimize ptosis.[42] The senior author's (E.D.R) surgical approach in three face transplant recipients has previously been described extensively.[8,29,36,37,42,43] In this article, we include two animated overviews highlighting the considerations discussed and representing our approach with a patient who received an allograft containing an extensive amount of bone and a patient who received an allograft containing predominantly soft-tissue elements. [**See Video 7 (online)**, which displays digital animation depicting a partial face and double-jaw transplant. This digital animation depicts a partial face and double-jaw transplant in a patient who sustained a ballistic facial injury. (Adapted from Kantar RS, Ceradini DJ, Gelb BE, et al. Facial transplantation for an irreparable central and lower face injury: A modernized approach to a classic challenge. *Plast Reconstr Surg.* 2019;144:264e–283; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.) **See Video 8 (online)**, which displays digital animation, depicting a face transplant that involved predominantly soft-tissue components. This digital animation depicts a total face, eyelids, ears, scalp, and skeletal subunit transplant in a patient who sustained a full facial and total scalp burn injury. (Adapted from Sosin M, Ceradini DJ, Levine JP, et al. Total face, eyelids, ears, scalp, and skeletal subunit transplant: A reconstructive solution for the full face and total scalp burn. *Plast Reconstr Surg.* 2016;138:205–219; provided with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)]

IMMUNOLOGIC CONSIDERATIONS AND OUTCOMES

Immunosuppressive regimens, especially induction regimens, have varied significantly between face transplant teams. Regimens have included tacrolimus, mycophenolate mofetil, and steroids, with humanized interleukin-2 antibody or antithymocyte globulin; steroids and anti-CD52 antibody; steroids and antithymocyte globulin; steroids, antithymocyte globulin, and anti-CD20 antibody; and steroids, antithymocyte globulin, and mycophenolate mofetil.[42,43,54–57] Maintenance immunosuppression regimens reported by different teams are more homogenous and typically consist of triple therapy with a steroid taper, tacrolimus, and mycophenolate mofetil, with one team reporting tapering steroids off completely, and another team using only tacrolimus and steroids.[55–59] Three of the four patients in whom steroids were tapered off, however, required therapy reintroduction because of frequent rejection episodes.[57]

The side effects and risks associated with lifelong immunosuppression that accompany facial transplantation are the most significant challenges facing the field. Complications associated with long-term immunosuppression include kidney injury, increased risk of malignancy, metabolic abnormalities, and opportunistic infections.[57,60] Kidney injury can progress to end-stage renal failure requiring dialysis and transplantation.[61] In an attempt to minimize renal toxicity, some teams have used sirolimus and belatacept instead of tacrolimus, with limited success.[62,63] Mycophenolate mofetil is typically associated with mild gastrointestinal side effects, and metabolic abnormalities can develop following facial transplantation because of the use of steroids. These include diabetes, hypertension, and dyslipidemia, and are usually managed with lifestyle modification and medications.[38,60,64] Face transplant recipients should also receive appropriate prophylaxis for opportunistic viral and bacterial infections that may arise because of chronic immunosuppression. These infections have been reported frequently, and should be managed swiftly when they occur to minimize the risk of injury to the allograft.[65]

Immunologic rejection of the allograft is a major concern following facial transplantation. Rejection is typically characterized clinically by allograft erythema, swelling, and redness, and is graded using the Banff classification system histologically, based on epithelial involvement and inflammatory cell infiltration.[66] Facial allograft

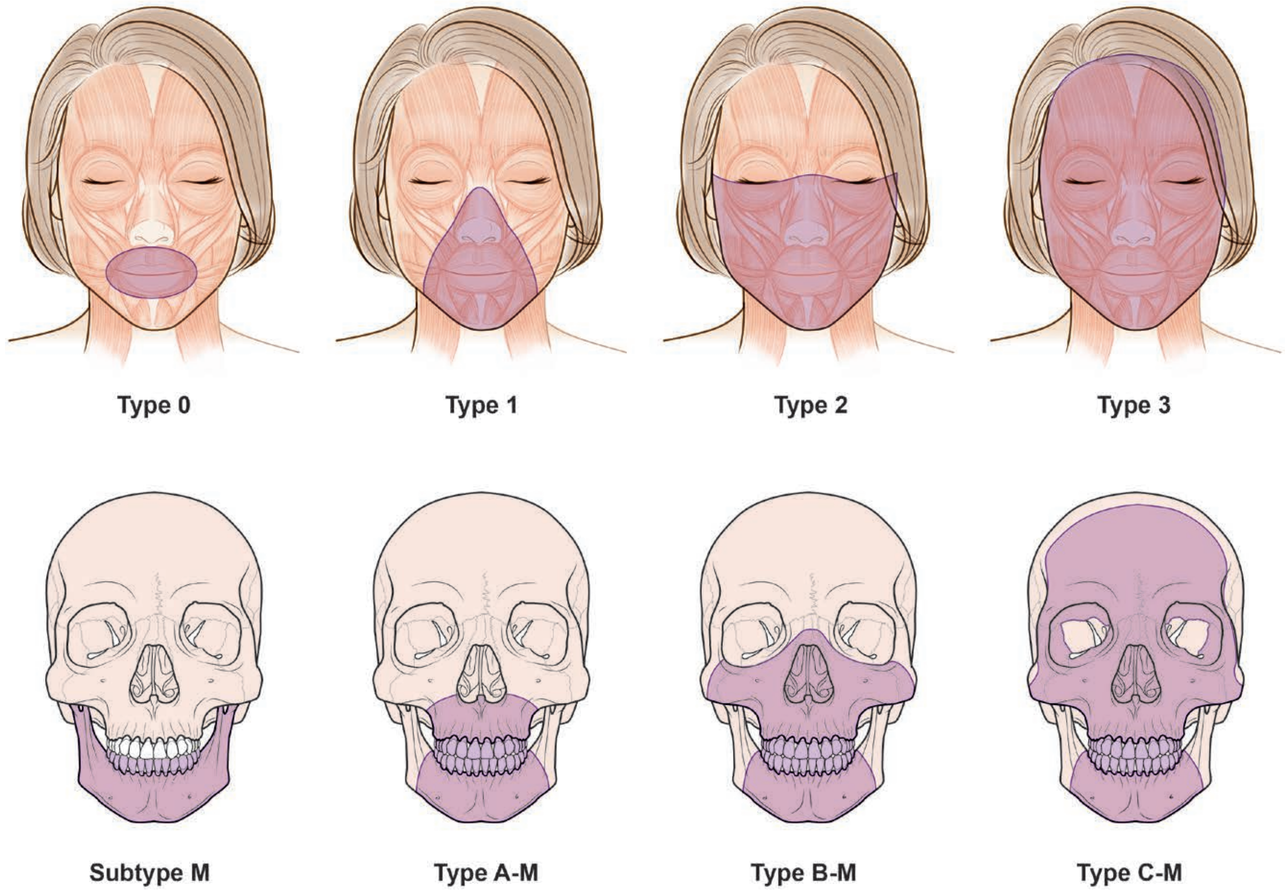

Fig. 7. Soft-tissue and skeletal tissue defect classification system for facial transplantation. Soft-tissue defects (*above*) are classified as type 0, oral (includes the upper lip, lower lip, and oral commissures); type 1, oral-nasal (includes the nasal soft-tissue structures with or without type 0; type 2, oral-nasal-orbital (includes infraorbital and malar regions with or without type 1; type 3, full facial (includes the forehead, supraorbital, and preauricular regions and can include all facial soft tissues. Skeletal tissue defects (*below*) are classified as type A, Le Fort I–type (involves the maxilla partially or completely); type B, Le Fort III–type (includes the maxilla, inferomedial orbital, and zygomatic bones with or without nasal, vomer, and ethmoid bones); type C, monobloc advancement type (includes frontal and supraorbital bones with or without facial bones in the other types of defects); and subtype M, mandibular involvement (includes the mandible partially or completely. (Adapted from Mohan R, Borsuk DE, Dorafshar AH, et al. Aesthetic and functional facial transplantation: A classification system and treatment algorithm. *Plast Reconstr Surg*. 2014;133:386–397; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

recipients should be closely monitored for signs of acute rejection, and treatment of rejection episodes, typically with pulse dose corticosteroids and adjustment of maintenance immunosuppressants if needed, must be initiated early.[48] Some teams have used sentinel flaps to assist with clinical monitoring, but the utility of this approach and the value of routine skin and mucosal surveillance biopsies remain unknown.[67–69] Similarly, noninvasive imaging-based methods to monitor for allograft rejection remain experimental at this stage.[2,70] Chronic immunologic rejection has been reported in two face transplant recipients, including the recipient of the first face transplant in 2005 who required resection of part of the allograft and autologous reconstruction.[71,72] To date, there have been no reports of hyperacute rejection or graft-versus-host disease. Donor-derived macrochimerism has been previously reported in animal models of facial transplantation but has yet to be reported in face transplant recipients.[73]

The majority of reported face transplant recipients have experienced one or several acute rejection episodes (Table 2). Two patients treated by our team with steroids, antithymocyte globulin, and anti-CD20 for induction immunosuppression, and steroids, tacrolimus, and mycophenolate mofetil for maintenance remained free from any acute rejection episodes for more than 5 years and 2 years, respectively, following facial transplantation.[8,42,74]

AESTHETIC, FUNCTIONAL, AND PSYCHOSOCIAL OUTCOMES

Reporting outcomes in facial transplantation is challenging because of the limited number of procedures that have been performed to date, and the recent advent of the field. This has contributed to the lack of standardized and validated assessment tools in facial transplantation, and the paucity of long-term outcome reports.[10] Nevertheless, available data suggest favorable overall aesthetic, functional, and psychosocial outcomes (Fig. 8).[1,2,8,38,48,56,57] Recovery of motor function has been reported to occur as early as 3 months, but typically occurs at 6 to 8 months with progressive improvement.[2,48,57,75] Available outcome reports suggest that facial expression, speech, lip competence, and swallow demonstrate overall satisfactory recovery.[2,48] Although the ideal postoperative rehabilitative strategy remains to be determined, motor recovery is certainly highly dependent on strict patient adherence to therapy.[2,48] Recovery of sensory function

Fig. 8. Preoperative and postoperative images of three face transplant recipients, patient 1 (*left*), patient 2 (*center*), and patient 3 (*right*), before facial transplantation (*above*) and after facial transplantation and all revision procedures (*below*). The postoperative photographs were taken at 5 years and 1 month after transplantation for patient 1, 4 years and 1 month after transplantation for patient 2, and 1 year after transplantation for patient 3. The senior author's experience with these three patients demonstrates the satisfactory long-term aesthetic and functional outcomes that can be achieved through facial transplantation in patients with extensive facial disfigurement, who are not amenable to autologous reconstruction. (Reprinted from Diep GK, Ramly EP, Alfonso AR, Berman ZP, Rodriguez ED. Enhancing face transplant outcomes: Fundamental principles of facial allograft revision. *Plast Reconstr Surg Glob Open* 2020;8:e2949; printed with permission and copyrights retained by Eduardo D. Rodriguez, M.D., D.D.S.)

has been reported to occur earlier than motor function, even when sensory nerve coaptation is not performed.[1,2,48,57,76] Sensory recovery has been reported as early as 3 months, with earlier recovery for the mental nerve compared to the trigeminal nerve.[2,23,43,48,56–58] Light touch, two-point discrimination, pain sensation, and thermal sensation have been reported to recover later around 8 months after facial transplantation.[2,48,57] Both motor and sensory functions have been shown to demonstrate steep significant improvements in the first year after transplantation, with slower progressive recovery afterward.[57]

Psychosocial outcomes following facial transplantation are encouraging, despite early concerns that the procedure may compromise the recipient's sense of identity.[2,10,48,56,57,77–79] Patients receiving facial allografts have demonstrated improved quality of life, sense of self, social integration, and decreased prevalence of depression, with several patients returning to work following the procedure.[2,10,48,57] Satisfactory psychosocial outcomes are heavily dependent on appropriate patient selection and screening before transplantation. Rigorous candidate evaluation can allow face transplant teams to predict noncompliance, detect substance abuse disorders and psychiatric illnesses, and determine whether the candidate's social support system is adequate for the lengthy recovery following transplantation and for the extensive media exposure that these patients usually receive.[2,48] Development of collaborative, multi-institutional protocols for psychosocial screening, evaluation, follow-up, and treatment through initiatives such as the Chauvet Workgroup and the New York University/Johns Hopkins Working group, and transparent reporting of outcomes by face transplant teams, are critical to determine the long-term impact of facial transplantation on recipients.[57,80–82]

ALLOGRAFT FAILURE MANAGEMENT STRATEGIES

Risks of facial allograft failure, including significant morbidity, mortality, and disfigurement, need to be discussed with candidates extensively preoperatively. Surgical teams need to weigh the potential aesthetic benefits of including additional tissue in the transplanted allograft against limiting their autologous reconstructive options. To date, contingency plans in case of allograft failure remain team- and patient-specific, with no clear consensus within the field.[83] Partial allograft failure in the first face transplant recipient was managed with excision of necrotic tissues and reconstruction using a radial forearm free flap, whereas allograft failure in a full face recipient was treated with excision and coverage with an anterolateral thigh flap resulting in significant facial disfigurement.[72,84] Recently, facial retransplantation was performed successfully in a transplant recipient who suffered from chronic rejection of his first allograft, demonstrating the technical feasibility of the procedure in case of allograft failure.[83] Nevertheless, short- and long-term outcomes of this salvage option in addition to the immunologic consequences of using additional induction immunosuppression with facial retransplantation remain unknown.

COST CONSIDERATIONS

Face transplant procedures remain costly, especially in light of the need for lifelong immunosuppression and follow-up. However, previous analyses have demonstrated that the long-term costs associated with conventional autologous reconstruction and face transplantation are comparable.[85,86] To date, the majority of face transplants performed have been supported through institutional or grant-based funding, with significant debate regarding the role of health insurance coverage.[87] Recent experience with third-party coverage of costs associated with face transplantation brings the procedure one step closer to becoming standard of care in the treatment of craniofacial disfigurement.[8] This holds significant promise for patients afflicted with extensive craniomaxillofacial injuries who are not amenable to or have failed conventional autologous reconstruction and for the future of the field, especially when considering the significant number of patients who are estimated to potentially benefit from face transplant evaluation.[7]

CONCLUSIONS

Almost two decades after the first face transplant, the procedure has emerged from the experimental realm to occupy the highest rung on the reconstructive ladder for patients with extensive facial disfigurement who are not amenable to autologous reconstructive approaches, in pursuit of optimal functional and aesthetic outcomes. Combining lessons learned from growing experience in the field over the past two decades with emerging technologies, innovative immunologic approaches, and strong international collaborations will certainly allow face transplant teams to make greater strides in the years to come.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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