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Impact of reconstructive facial transplantation on future of plastic surgery

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- Facial allograft
- Vascularized composite allotransplantatin
- Facial defect
- Computerized surgical navigation
- donor selection

Abstract

Almost two decades after the first face transplant, facial allotransplantation (FAT) had emerged from being considered science fiction to occupy the highest rung **on the reconstructive ladder for patients with extensive facial disfigurement when autologous approaches fail or are inappropriate in restoring optimal facial form and function.** FAT had piqued the interest of the medical community and the general public, as well as strong support from multiple disciplines, as a solution for reconstructing complex facial defects that are unresponsive to conventional methods. The procedure had pushed the boundaries of reconstructive microsurgery, immunology, and transplantation, establishing itself at the crossroads of multiple disciplines. The procedure raised difficult scientific, ethical, and societal issues. Patients and physicians were called upon to deal with a variety of lifelong hurdles, such as immunosuppression management and psychosocial challenges

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Introduction

Facial allotransplantation (FAT) is a procedure through which a patient's extensively destructed face is replaced by a brain-dead donor's facial tissue **achieving optimal aesthetic and functional outcomes**. The type of facial tissue to be harvested is determined by the extent of the defect and whether it involves isolated soft tissue or both soft and hard tissue. It should also be taken into consideration that selecting the recipient is a complex process that needs extensive evaluation of the patient as regard many factors such as psychological evaluation, support network and compliance to postoperative lifelong immunosuppression that must be used to prevent rejection of the allograft, a possible scenario that should be preoperatively discussed with the recipient [1].

Face transplantation became a clinical reality with satisfactory functional outcomes, despite initial debates and ethical concerns. The impact of life-long immunosuppression on otherwise healthy patients, as well as the selection process for face transplant candidates, remain sensitive issues. Supporting technologies aid in the safety and efficacy of this operation at all stages. These include advanced imaging techniques for planning the operation, as well as devices to monitor the flap during the immediate postoperative period [2].

Aim of the work

This essay aims to shed light on facial transplantation as a neglected surgical aspect in Egypt despite of the increasing numbers of extensive facial disfigurement victims over the time because of severe face burns or other injuries hoping that it becomes a clinical routine for such patients.

History and overview

To date, 48 partial and total face transplant have performed worldwide with severe facial burns being the leading indication. The cosmetic outcomes are consistently superior to typical reconstructive methods. **Functional recovery, however being often incomplete, continues to improve even 3 years following the operation.**

In 2005, Dr.Jean-Michel Dubernard and Dr Bernard Devauchelle performed the first face transplant at Amiens Hospital in Amines, France for a 38-year-old woman who was mauled by her pet dog following sleeping tablet overdose. Her distal nose, lips and superficial chin were all amputated because of the facial injuries caused by the attack leaving her with eating, drinking and speech limitations along with other functional disabilities.

Her VCA included anastomosis of the facial arteries and veins, mucosal repair of the mouth and nasal vestibule, sensory and motor neuropathies and facial musculature restoration. The patient had a nearly complete recovery of sensory and motor functions of the face five years after VCA, no signs of chronic rejection, and an outstanding aesthetic outcome.Unfortunately, she died 10 years after VCA because of long-term effects from recurrent malignancies.

In 2009, Dr. Bohdan Pomahac of the Brigham and Women's Hospital in Boston, Massachusetts, led the first facial VCA for a burn damage for a 55-year-old man who had a high-voltage electrical burn to his midface, which left him with a complicated bone and soft tissue deformity. Over the course of four years, he

underwent various reconstructive operations but remained functionally limited. He could not eat, drooled constantly, and his speech was incomprehensive. Three years following the procedure, the patient regained near-normal sensation in the majority of his allograft, as well as enhanced appearance, functional abilities, and social interaction. **(Fig.1**) shows preoperative and postoperative photo of the patient.

In 2010, Dr Joan-Pere Barret performed the first full-face VCA on a 31-year-old man following ballistic trauma at the Vall d'Hebron hospital in Barcelona, Spain. The procedure involved both soft tissue and underlying bone [3].

The most recent recorded face transplant was performed at Brigham and Women's Hospital in Boston in 2019 for 68-year-old Robert Chelsea being the first Black recipient in the USA reflecting the lower rates of organ donation among African-Americans and ethnic minorities in the United States and internationally. In addition, in July 2020 Carmen Tarleton was the first person to receive a second transplant in the USA [4].

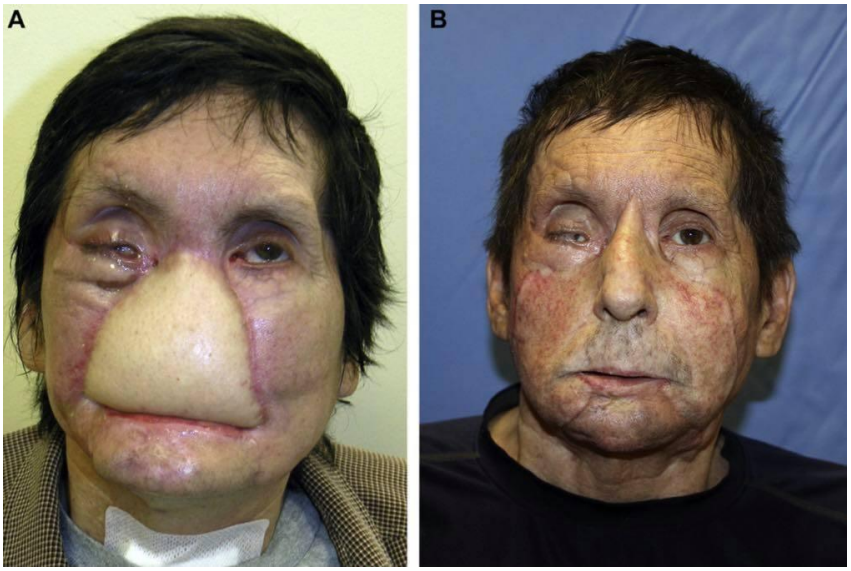

Fig. 1. The patient's midface covered with an anterolateral thigh flap following severe electrical burns (A). Post facial VCA, the patient's appearance has significantly improved along with improvement of mouth opening and nasal breathing (B) [3].

Classification of facial defects

Facial defects are classified according to soft and hard tissue defects. For the soft tissue, one practical method to classify facial transplant defects would be in terms of aesthetic and functional facial components and the Le Fort classification for the hard tissue defects, since they are broadly acknowledged among health-care professionals.

Soft-Tissue Defect

Type 0, is an isolated oral subunit defect without involvement of the nasal subunit, in this type, like any other isolated defect the architecture can be restored with the help of autologous surrounding tissues, with steadfast morphologic results and a satisfactory cosmetic appearance.

Type 1, when the oral subunit defect is associated with a nasal subunit defect including loss of the upper or lower lips, commissure, and for the nasal component structures (soft tissue,

lining or support). It can lead to some functional impairments yielding an elevated or depressed lip or even an oral sphincter providing that not all the structures listed above must be defected.

Type 2, is an oronasal-orbital soft tissue defect including all the components of type 1 as well as **a deficit involving some or all of the soft tissue of the inferior orbital and cheek subunits or even an isolated defect of the inferior orbital and cheek subunit can also be classified as type 2.**

Type 3, the full facial soft-tissue defect, includes the soft-tissue defect of type 2 along with the upper eyelids and forehead with its superior border being the anterior hairline and the lateral border is the preauricular region anterior to the tragus. For a defect to be classified as type 3, it must contain a deficit involving some or all of the soft tissues of the upper eyelid or frontal subunits.

For any patient to be categorized into one of the types mentioned above at least more than 40% of the facial subunit must be involved. All soft tissue defect types are shown in **(Fig.2**)

Le fort classification

Type A, to be classed as type A, a bone defect must be a maxillary alveolus defect that may be partial or total, but would be classified cephalad to the dentition (i.e., the Le Fort I maxillary segment).

Type B involves the nasal bones, portions of the maxilla and zygoma and infero-medial orbital bones, it may also include the vomer, ethmoid, and medial orbits (i.e., the Le Fort III osseous segment).

Type C, must include supraorbital bones and frontal bone defects associated with the segments of a monobloc osteotomy, the defects previously mentioned in type A and B may be also involved in this type (i.e., the monobloc advancement segments).

Type M, if there's mandibular defect affecting the **dental alveolar segment of the mandible, but would be defined at a level caudal to the dentition**, **this designation precedes the bony defect type (i.e., the level of a bilateral sagittal split osteotomy)** [5] all bony defect types are shown in **(Fig.2**).

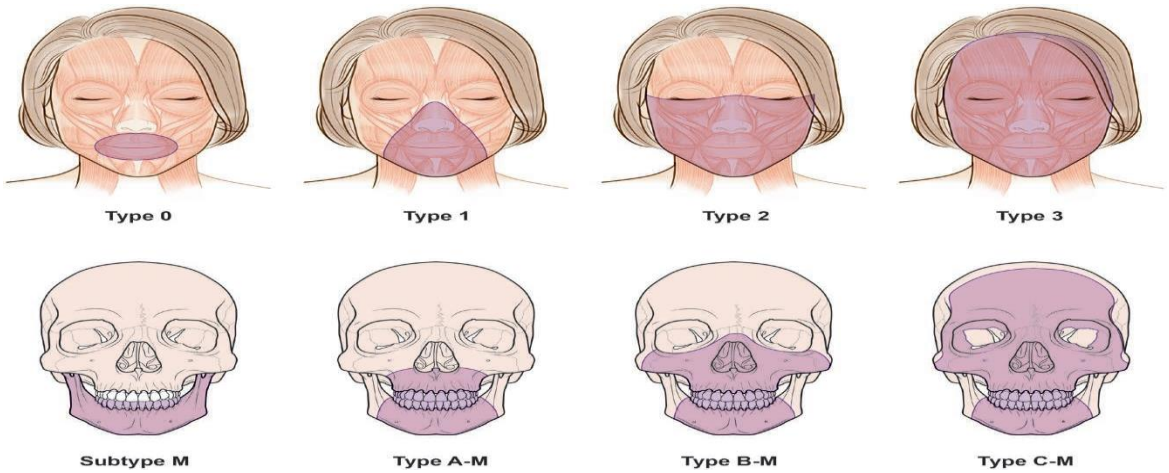

Fig. *2.* Diagram illustrating the extent of each soft-tissue defect (above) and bony defect (below) according to the classification system mentioned previously [6].

Indications and Recipient Selection

The indications for facial VCA are still evolving, although they can be loosely defined as individuals having a significant face deformity that **is challenging to be reconstructed through** autologous procedures **(e.g., the nose, lips, and eyelids)**. High-voltage electrical burns, explosion injuries, chemical burns, and thermal injury are examples of burns that can cause severe facial harm along with other non-burn injuries as animal attacks, facial congenital anomalies, **benign tumors such as neurofibromas, and facial defects resulting from oncologic resections**.

Facial VCA is currently indicated in specific conditions including **Severe disfigurement, affecting more than 25% of facial surface area with soft tissue loss, and/or loss of one of mid-face structures, loss of multiple central facial units including nose, eyelids, and lip, several facial function impairment, including breathing, eating, drinking, expressing or communicating, and even destructive aesthetic defects or multiple failed autologous approaches with inappropriate facial form and function** [3].

Candidate evaluation is a **rigorous process that requires the collaboration of a multi -disciplinary team consisting of plastic surgeons, oral-maxillofacial surgeons, head and neck surgeons, psychiatrists, speech therapists, dentists, transplant surgeons, and transplant medicine physicians.** All potential VCA candidates must undergo preoperative screening, which includes a psychosocial evaluation focused on medical compliance, **adherence to lifelong immunosuppression**, coping abilities, expectations, support network, and informed consent. In the event of allograft failure, a salvage plan must be discussed with the patients[7].Candidates with self-inflicted injuries and a history of substance misuse or suicidality should consider extensive psychosocial evaluation in particular. Although facial transplantation has been found to be successful in these patients, suicidal tendencies and substance abuse must be resolved first [8].

In blind patients, facial transplantation is controversial, with opponents claiming that recipients will be unable to perceive the procedure's results or in case of immunologic rejection, they will not be able to recognize the allograft changes, while supporters argue that excluding blind patients is unethical, especially given the positive reported aesthetic and functional outcomes [9].

With the mandatory use of lifelong immunosuppression, the risk of de novo malignancies should be considered particularly in immunocompromised candidates and patients with facial deformities due to oncologic resections. When considering the risks and advantages of the surgery in potential patients, immunologic risk factors should also be addressed. This is especially important for patients who have had burns or received numerous transfusions, as this can lead to immunosensitization, H.I.V. infection, the presence of donor-specific antibodies, and other immuno- modulatory conditions that can make finding matching donors and recovering from surgery more difficult [10].

Donor selection considerations

Donor selection and matching are more difficult in facial transplantation than in solid organ donation. Blood type and immunologic

criteria, as well as demographic characteristics, hair and skin color, and cephalometric parameters, should be matched for both the donor and recipient. Due to these factors, donor shortages in facial transplantation have become more pronounced, resulting in longer candidate wait times before transplantation.

Donor selection is key to success in such procedures, so all efforts should be made to select the best possible match. The donor must undergo a comprehensive preoperative evaluation involving exchange of lines and facial impressions or three dimensional digital images for donor face restoration, to be illustrated later on, followed by tracheostomy, nasoendoscopy, surveillance cultures, lavage also a three-dimensional craniofacial computed tomographic scan should be obtained for virtual surgical planning, angiography and as well as echocardiography to evaluate for endocarditis [11].

Increasing preoperative vigilance can greatly diminish postoperative complications. In case the investigations yield undesirable results, specially infections, procedure abortion is to be considered as in October 2018 when a planned FAT, for a 28-year-old man with drug-induced anoxic brain injury, was cancelled after microscopic examination of bronchoalveolar specimens showed occasional branching septate hyphae suggestive of *Aspergillus* species for fear of graft failure, and mortality in the recipient. Moreover, in a face and bilateral upper extremity recipient, an untreated preoperative sinus infection is thought to have led to postoperative pneumonia, shock, and bilateral extremities explantation. Similarly, multiple episodes of allograft erythema have previously occurred as a result of donor-to-recipient rosacea transmission, which were first misdiagnosed as rejection before being treated with antibiotics.

After all high risk donors as active cancer, Epstein-Barr virus, Hepatitis C virus or risk factor for any blood-borne disease transmission are excluded and taking all matching criteria into consideration the average wait for a transplant was four months (range, 1 day to 17 months). The majority of disease-related deaths recorded by the United Network for Organ Sharing were Caucasian (63 percent) and male (58 percent). Female donors of African, Hispanic, and Asian ethnicity are underrepresented, accounting for 7, 5, and 1% of all disease-related fatalities, respectively. Seropositivity for Epstein-Barr virus and cytomegalovirus is 95 percent and 65 percent, respectively, among potential donors. Over time, the number of annual hepatitis C–positive donors has increased [12].

Furthermore, organ procurement organizations pay more attention to solid organ donation than vascularized composite allograft. By increasing donor service areas, strong collaborations between face transplant facilities and organ procurement organizations can reduce candidate wait time. Moreover, opt-out donation methods have been demonstrated to dramatically lower candidate wait time. Finally, public education campaigns can provide insight into the procedure's functional and cosmetic effects, as well as dispel misunderstandings, and have been proven to boost the willingness to donate facial tissue by nearly 20% [13].

Types of facial allografts (FAG)

Three primary segmental facial allografts could be obtained from one or more branches of the

network of the external carotid: The lower central facial AG (type I), we harvest the donor's nose, chin and lips from the cutaneous surface to the deep mucosa. It contains all the oral cleft muscles extracted by the elevation of subperiosteom, from the maxillary and the zygomatic bones to the rim of the mandible, and is supplied by the two facial pedicles dissected down to their emergence from the major vessels of the neck and is re-innervated by the zygomatic, mandibular and buccal branches of the facial nerves (VII) dissected as independent segmental rami or traced more proximally up to their shared origin on the trunk of facial nerve. The mental (V3) and infraorbital (V2) nerves are the allograft's sensitive nerves, which are exposed at the corresponding bone foramina and prolonged on their proximal course by intraosseous dissection. Only the soft tissues of the face are involved in this conventional allograft1 (type IA). It can be extended laterally up to the cheeks and pre-auricular areas. It also contains the parotids in the latter condition, and is raised upon the external carotid and jugular axes, as well as the proximal trunks of both facial nerves.

If necessary, this type can extend further to include the mandibular arch in its middle part to gain back the chin's bone support (type IB; B = bone). The periosteal network of the two submental arteries, which are joined in the area of the mental foramina with the inferior alveolar arteries, vascularizes the mandibular bone segment in the latter transplant. The submental vessels must be included and kept unharmed when the type IB graft is obtained. As a result, the latter has an extra skin surface near to the hyoid bone that corresponds to the submandibular region **(Fig. 3)**.

The mid-FAG (type II), the upper lip, cheeks, nose, and muscles elevating the oral cleft make up this graft type, which is similarly elevated on both the left and right facial pedicles. Though it can be made up entirely of soft tissues (type IIA), it frequently contains the zygomatic arches and the maxillae, as well as a different section of the anterior palate (type IIB). The infraorbital nerves (V2) restore its sensitivity, and its motor re-innervation depends on the zygomatic and buccal rami of the facial nerves (VII), as well as the buccal nerves (V3) if tonicity of the buccinator muscles should be restored. The allograft may be very wide and bilateral or unilateral, depending on the degree of the lesion to be rebuilt. It can be more or less extended downwards, towards the lower part of the cheek, in some situations **(Fig. 3)**.

The upper FAG (type III), is made up by root of the nose, eyelids and the superficial planes of the forehead, as well as the deeper planes of the glabellar, orbicularis oculi and frontalis muscles, it is raised on the supraorbital sensitive nerves (V1) and the two superficial temporal pedicles. The preseptal and periosteal anastomotic vascular circle surrounding the orbital rim, as well as the shunts connecting the intracranial and extracranial vascular networks should be part of the deep dissection of the allograft around the palpebral sulci **(Fig. 3)**.

A full FAG (type V) should be conducted as composite transplant or a multisegment, combining types I, II, and III partial allografts in one block of uniform thickness. The complete external carotid axis and the confluent jugular veins would have to be collected on both sides of a donor's head. All of the facial muscles would be included, as well as the three segmental branches

(V1, V2, and V3) of the two trigeminal nerves and the common trunks of both facial nerves. It could comprise soft tissues solely in the deeper planes, including the superficial musculoaponeurotic system, with or without the periosteal plane (complete soft tissue FAG, type VA), If necessary, treatment could also involve the maxillary or mandibular arches (complete hard and soft tissue, type VB, FAG) [14].

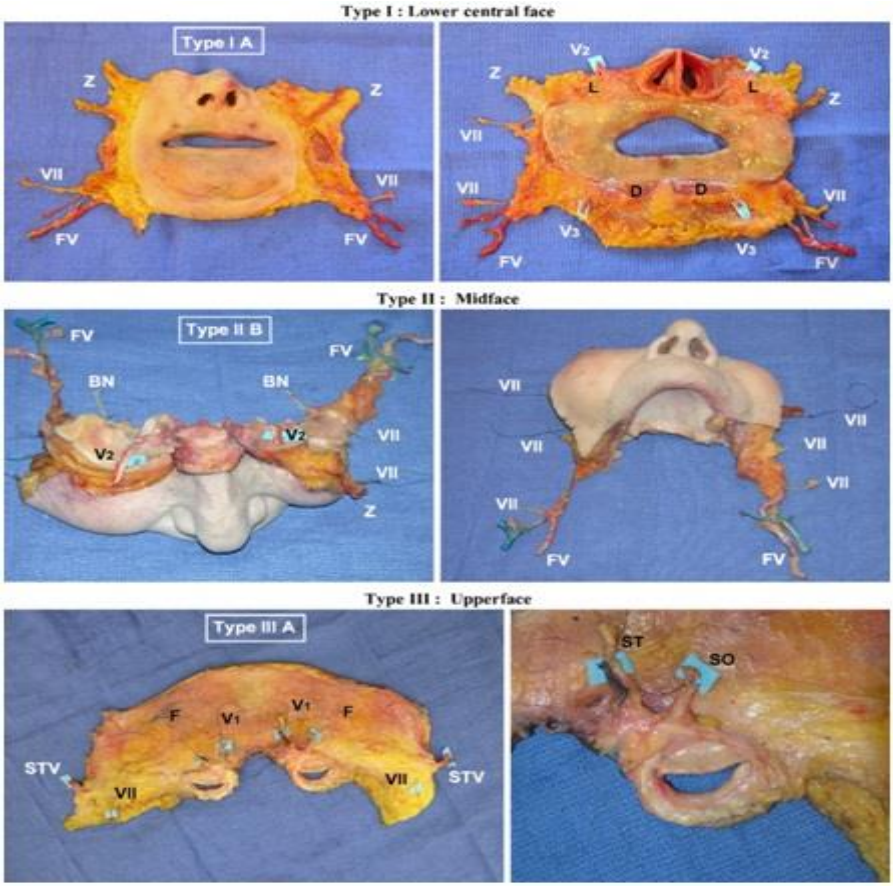

Fig. 3. CTAG segmental facial surgical classification. All tissues from the lower (type I), middle (type II), and upper (type III) regions of the facial architecture are included in partial face allografts, which are functional full-thickness grafts. They can be made up of only soft tissues (type n-A) or both hard and soft tissue (type n-B; B, bone). All of them are made to fit the face defect perfectly, including all muscles, motor and sensitive nerves, and lining, as well as supporting the restoration of any missing functions. **Z, zygomatic muscles; VII, facial nerve branches; FV, facial vessels; V1, V2, and V3, terminal cutaneous branches of ophthalmic, maxillary, and mandibular nerves; D, depressor muscles of the lower lip; L, levator muscles of the upper lip; BN, buccal nerve (V3); F, frontalis muscles; STV, superficial temporal vessels; ST, SO,supratrochlear and supraorbital neurovascular pedicles** [14]**.**

Computerized surgical navigation

Face transplant teams have made great progress in the field as a result of extensive surgical preparations combined with the use of cutting-edge new technologies. Transplant teams can use simulated exercises to get a better understanding of the process and its logistics, as well as troubleshoot any issues that may develop. Practicing on cadaveric donors enables surgical improvement through repetition, objective results evaluation, and real-time high-accuracy simulation of the planned procedure; faster allograft procurement; and reduced operative time and the number of simulated exercises necessary for consecutive transplants. In craniomaxillo-facial surgery, computer-assisted surgical navigation has

recently gained widespread acceptance. Three-dimensional computerized surgical planning and execution, with real-time intraoperative assistance to improve precision, are among the technology's advantages. According to data, available surgical navigation systems appear to be equivalent, with technical accuracy within 1 mm and intraoperative precision between 1 and 2 mm [15].

Furthermore, the utilization of computer-aided design and manufacturing of patient-specific equipment like bone cutting guides has allowed allograft design and surgical technique to be refined even further. This is especially essential for allografts that include skeletal segments, since these technologies allow for more efficient, precise planning and execution of donor and recipient osteotomies **(Fig. 4**) . These benefits may result in enhanced cephalometric and occlusal connections between the craniomaxillofacial segments of both the donor and recipient. Lately, computer-aided surgical navigation has been used intraoperatively, with benefits including the ability to apply the predetermined surgical plan onto the patient's skeletal defect, as well as real-time intraoperative guidance, which can assure more accuracy during donor skeletal segment inset and fixation in the recipient. **(Fig. 5**) Following skeletal fixation and vascular anastomoses, allograft viability and adequate perfusion can be confirmed using indocyanine green fluorescence angiography, which can also be performed prior to final detachment of the allograft from the donor major vessels [16]. **(Fig.6**)

Moreover, computer-aided technologies have been used to restore the donor's face by creating three dimensions printed masks based on digital images of the donor's face acquired prior to surgery. Importantly, because they do not require donor facial impressions, these three-dimensionally printed masks offer a less invasive alternative with a lower risk of iatrogenic injury to the allograft compared to the previously used silicone-based masks. The aim of these masks is **preserving the dignity of the donor, and allows the donor family to perform routine end-of-life rituals [18]. (Fig. 7)**

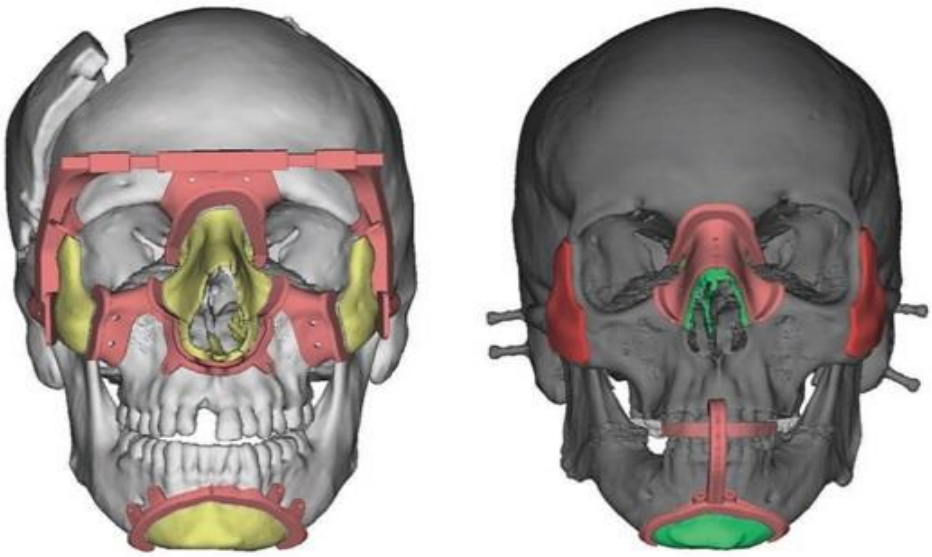

Fig. 4. The figure is showing **the donor (**left**) and recipient (**right**) planned osteotomies** using **computer-aided design and manufacturing of patient-specific skeletal cutting guides** [6].

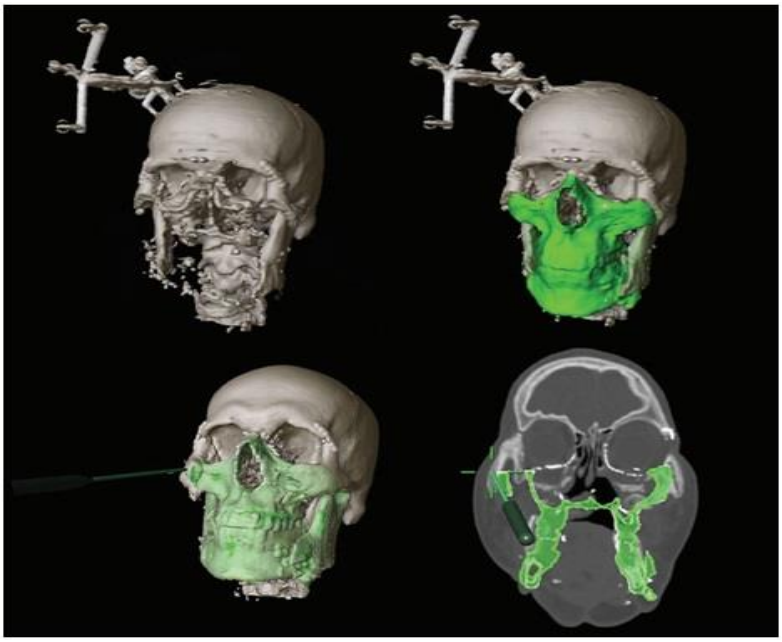

Fig. 5. Using intraoperative surgical navigation to confirm the accuracy of the skeletal allograft positioning and comparing between planned (green) and actual position of the skeletal segments. **Registering the computed tomographic scanned (**above**) verifies an accurate skeletal segment position (**below**)** [6].

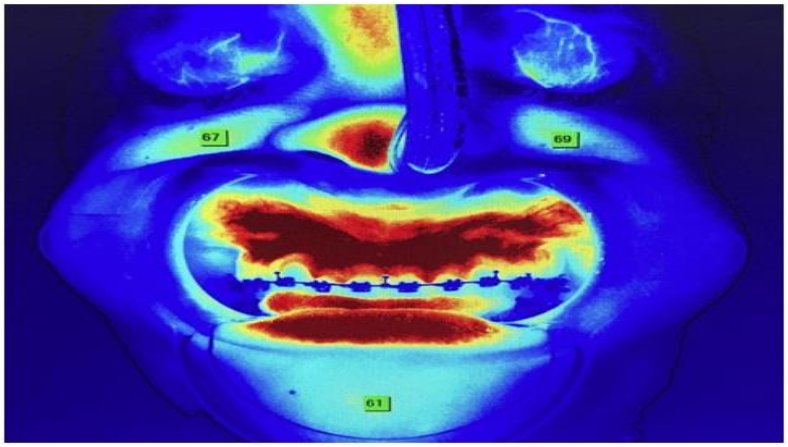

Fig. 6. Indocyanine green fluorescence angiography insuring adequate allograft perfusion and viability prior to graft detachment from donor's blood vessels [17].

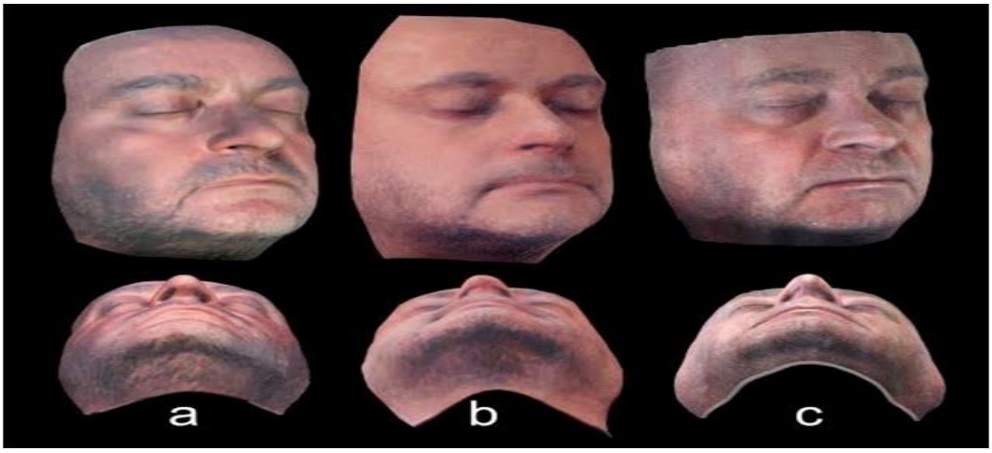

Fig. 7. Three-dimensional printing for restoration of the donor face [18].

Fig. 8. Preoperative and postoperative images of patients underwent facial transplantation showing the aesthetic and functional outcomes of the procedure [3,22].

Table.1. Summary of Cases of Face Transplantations 2005-2020 [4].

Name	Transplant type	Venue	Country	Date	Gender	Age	Cause of facial difference
Dinoire, Isabelle (d. April 2016)	Partial	Centre hospitalier Universitaire Nord, Amiens	France	27 Nov 2005	Female	38	Mauled by pet dog following sleeping tablet overdose
Guoxing, Li (d. July 2008)	Partial	Xijing Military Hospital, Xi'an	China	13 Apr 2006	Male	30	Attacked by bear
Coler, Pascale	Partial	Henri Mondor Hospital, Paris	France	21 Jan 2007	Male	29	Neurofibromatosis type 1
Culp, Connie (d. 29 July 2020)	Partial	Cleveland Clinic, Ohio	USA	9 Dec 2008	Female	45	Third party gunshot injury
(Anonymous)	Partial	Henri Mondor Hospital, Paris	France	24 Mar 2009	Male	27	Accidental gunshot injury
(Anonymous) (d. 8 June 2009)	Partial (& bi-lateral hand)	Henri Mondor Hospital, Paris	France	4 Apr 2009	Male	37	Self-immolation
Maki, James	Partial	Brigham and Woman's Hospital, Boston	USA	Apr 2009	Male	59	Electrical burns from accident
(Anonymous)	Partial	Hospital La Fe, Valencia	Spain	Aug 2009	Male	42	Tongue cancer
(Anonymous)	Partial	Henri Mondor Hospital, Paris	France	19 Aug 2009	Male	33	Self-inflicted gunshot injury
(Anonymous) (d. after 2014)	Partial	Centre hospitalier Universitaire Nord, Amiens	France	27 Nov 2009	Male	27	Pyrotechnic explosion
Rafael	Partial	Virgen del Rocio Hospital, Seville	Spain	26 Jan 2010	Male	35	Neurofibromatosis type 1
Oscar	Full	Vall d'Hebron Hospital, Barcelona	Spain	27 Mar 2010	Male	31	Gunshot injury
Hamon, Jérôme	Full	Henri Mondor Hospital, Paris	France	27 June 2010	Male	35	Neurofibromatosis type 1
Wiens, Dallas	Full	Brigham and Woman's Hospital, Boston	US	March 2011	Male	25	Electrical burns from accident

Wiens, Dallas	Full	Brigham and Woman's Hospital, Boston	US	March 2011	Male	25	Electrical burns from accident
(Anonymous)	Partial	Henri Mondor Hospital, Paris	France	2011	Male	45	Accidental gunshot injury
(Anonymous) (d. 2014)	Partial	Henri Mondor Hospital, Paris	France	April 2011	Male	41	Self-inflicted gunshot injury
Hunter, Mitch	Full	Brigham and Woman's Hospital, Boston	US	April 2011	Male	30	Electrical burns from road traffic accident
Nash, Charla	Full (& failed bilateral hand)	Brigham and Woman's Hospital, Boston	US	May 2011	Female	57	Mauled by a chimpanzee
(Anonymous)	Partial	University Hospital, Ghent	Belgium	2011	Male	54	Gunshot injury
Acar, Ugur	Full	Akdeniz University School of Medicine	Turkey	21 Jan 2012	Male	19	Burns from a domestic fire
Gül, Cengiz	Full	Hacettepe University	Turkey	24 Feb 2012	Male	25	Electrical burns from accident
Nergis, Hatice (d. Nov 2016)	Partial	Gazi University Hospital, Ankara	Turkey	17 Mar 2012	Female	20	Gunshot injury
Norris, Richard	Full	University of Maryland Medical Center, Baltimore	US	19 Mar 2012	Male	37	Accidental gunshot injury
Çolak, Turan	Full	Akdeniz University School of Medicine	Turkey	15 May 2012	Male	35	Burns from domestic accident
(Anonymous)	Partial	Centre hospitalier Universitaire Nord, Amiens	France	June 2012	Female	52	Vascular tumour
Tarleton, Carmen Blandin	Full	Brigham and Woman's Hospital, Boston	US	14 Feb 2013	Female	44	Chemical burns from domestic abuse attack
Galasiński, Grzegorz	Partial	Maria Skłodowska-Curie Institute of Oncology, Gliwice	Poland	15 May 2013	Male	31\33	Industrial accident
Sert, Recep	Full	Akdeniz University School of Medicine	Turkey	18 July 2013	Male	26	Gunshot injury
Üstün, Salih (d. July 2014)	Full	Akdeniz University School of Medicine	Turkey	23 Aug 2013	Male	54	Gunshot injury
Joanna	Partial	Maria Skłodowska-Curie Institute of Oncology, Gliwice	Poland	4 Dec 2013	Female	26\29	Neurofibromatosis type 1
Kaya, Recep	Partial	Akdeniz University School of Medicine	Turkey	28 Dec 2013	Male	22	Gunshot injury
(Anonymous)	Partial	Brigham and Woman's Hospital, Boston	US	March 2014	Male	39	Gunshot injury
Fiddler, Shaun	Partial	Cleveland Clinic, Ohio	US	Sept 2014	Male	46	Road traffic accident
(Anonymous)	Partial	Brigham and Woman's Hospital, Boston	US	October 2014	Male	33	Gunshot injury
(Anonymous)	Full	Vall d'Hebron Hospital, Barcelona	Spain	Jan-Mar 2015	Male	45	Arteriovenous Malformation
(Anonymous)	Partial	S.M.Kirov Military Medical Academy, St Petersburg	Russia	May 2015	Male	21\22	Electrical burns
Hardison, Patrick	Full	NYU Langone Medical Center, New York	US	14-15 Aug 2015	Male	41	Burns received as a firefighter

(Anonymous)	Partial	Helsinki University Hospital	Finland	8 Feb 2016	Male	34	Gunshot injury
Sandness, Andrew	Full	Mayo Clinic, Rochester, Minnesota	US	June 2016	Male	31	Gunshot injury
Stubblefield, Katie	Full	Cleveland Clinic, Ohio	US	4 May 2017	Female	21	Self-inflicted gunshot injury
Underwood, Cameron	Partial	NYU Langone Medical Center, New York	US	5-6 Jan 2018	Male	26	Self-inflicted gunshot injury
(Anonymous)	Full	Helsinki University Hospital	Finland	March 2018	Male	58	Gunshot injury
Hamon, Jérôme	Full (retransplant)	Georges-Pompidou European Hospital, Paris	France	April 2018	Male	43	First transplant failed after rejection
Desjardins, Maurice	Partial	Hopital Maisonneuve Rosemont, Montreal, Quebec	Canada	May 2018	Male	64	Gunshot injury
(Anonymous)	Partial (failed)	Sant' Andrea Hospital, Sapienza University, Rome	Italy	22-23 Sept 2018	Female	49	Neurofibromatosis type 1
Chelsea, Robert	Full	Brigham and Woman's Hospital, Boston	US	July 2019	Male	68	Burns received in a car fire
Tarleton, Carmen Blandin	Full (retransplant)	Brigham and Women's Hospital, Boston	USA	July 2020	Female	52	First transplant failed after chronic rejection

Postoperative Immunosuppression

The postoperative lifelong use of immunosuppressive agents carries high risk of developing many serious side effects including increased incidence of cancer, infections, and end-organ toxicity so it must be weighed with the potential benefits of facial transplantation. The composite FAG must contend with the challenge of long-term survival within the recipient's organism. This survival is immediately conditioned by the ability to biologically control the rejection of all of its tissue components. Because of the extremely high antigenicity of its main component, skin, this immunologic challenge was initially thought to be the main impediment to successful FAT as skin serves as a barrier, with many dendritic cells in the dermis and epidermis. **The main objective is to provide as minimal an immune -suppressive regimen as possible while controlling allograft rejection** [19].

Immunosuppressive regimens, particularly induction regimens, have differed markedly between face transplant teams. Tacrolimus, mycophenolate mofetil, and steroids were used in combination 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. Maintenance immunosuppression regimens reported by different teams are more homogeneous, typically consisting of triple therapy with a steroid taper, tacrolimus, and mycophenolate mofetil, with one team reporting completely discontinuing steroids and another using only tacrolimus and steroids. However, three of the four patients who were tapered off steroids

required therapy reintroduction due to frequent rejection episodes [6].

Immunologic rejection of the allograft is a significant concern after facial transplantation. Clinically, rejection is characterized by allograft erythema, swelling, and redness, and histologically, rejection is graded using the Banff classification system, which is based on inflammatory cell infiltration and epithelial involvement. Recipients should be closely monitored for signs of acute rejection and if positive, rejection episodes are treated by increasing immunosuppression at the time of occurrence, and are frequently treated with pulse-dose corticosteroids or T-cell–specific antibodies. Acute rejection has been reported in up to 85% of face transplant recipients, necessitating hospitalization and treatment. **Chronic immunologic rejection has been reported in two face transplant cases, including the recipient of the first face transplant in 2005 who needed partial resection of the allograft and autologous reconstruction.** End-stage graft failure may necessitate explantation **[20,21].**

Conclusion

Facial VCA provides a new paragon of treatment options for patients who have suffered severe facial injuries. Although there are significant risks associated with the procedure, it can be a powerful reconstructive tool for restoring both facial form and function. Unlike traditional methods, VCA provides a restorative procedure for even the most disfigured and functionally impaired patients. Lessons learnt from two decades of growing experience in this field with innovative technologies, emerging immunologic approaches, and powerful international collaborations will undoubtedly allow face transplant teams to make greater progress in the upcoming years.

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