Thesis

Beyond Conventional Reconstruction: The Concept of Facial Transplantation.

submitted by

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in partial fulfillment of the requirements for the degree of

Doktorin der gesamten Heilkunde

(Dr.^{in} med. univ.)

at the

Medical University of Graz

executed at the

Department of Surgery
Division of Plastic, Aesthetic and Reconstructive Surgery

under the supervision of

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and

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Graz, 22 January 2026

Declaration of Academic Integrity

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Graz, 22 January 2026 Annalina Messua Meyka m.p.

Acknowledgement

At the conclusion of this work, I would like to express my sincere gratitude to all those who have supported, encouraged and believed in me throughout my medical studies and the preparation of this thesis.

First and foremost, I wish to thank my academic mentors Ao. Univ.- Prof. Dr. med. univ. Stephan Spendel and Dr. med. univ. Christian Smolle for your expertise, valuable guidance and constructive feedback. I sincerely thank you for providing me with the opportunity to undertake this research in the innovative and evolving field of facial transplantation, which allowed me to gain valuable insights and shape my approach to scientific thinking.

I am deeply grateful for my parents and siblings for their unwavering support, patience and belief in me over the years. Their encouragement provided the foundation on which I was able to build and persevere through many challenges of medical education.

I also extend my heartfelt thanks to my friends and fellow students Vanessa and Sophie for the many shared experiences, intellectual exchanges, and mutual support along the way. Facing the challenges of this journey together brought us closer and laid the foundation for a lasting and meaningful friendship that I truly cherish.

Finally I would like to thank my partner Balázs for your understanding, emotional support and strength during the most demanding phases of this process. Your presence was a constant source of balance and resilience.

Zusammenfassung

Hintergrund und Zielsetzung: Die Gesichtstransplantation stellt einen bedeutenden Meilenstein in der Entwicklung der rekonstruktiven Gesichtschirurgie dar und eröffnet neue therapeutische Perspektiven für Patient:innen mit schweren Gesichtsdefekten. Trotz ihrer zunehmenden Etablierung als Behandlungsstandard in ausgewählten Zentren bleibt der Eingriff weiterhin selten. Nicht zuletzt deswegen existieren bis dato kaum Übersichtsarbeiten, die einen umfassenden Einblick in die Thematik bieten.

Material und Methoden: Es wurde eine narrative Literaturübersicht unter Einbeziehung aktueller wissenschaftlicher Quellen durchgeführt, darunter peer-reviewte Publikationen aus der "PubMed"-Datenbank sowie anerkannte Fachbücher zur Gesichtstransplantation und rekonstruktiven Chirurgie. Ziel dieser Arbeit war es, fragmentierte Informationen zusammenzuführen, um einen kohärenten Überblick über den aktuellen Stand der Gesichtstransplantation im Hinblick auf Indikationen, vorbereitende Maßnahmen, operative Verfahren, postoperative Versorgung sowie auftretende Komplikationen und erzielte Ergebnisse zu geben.

Ergebnisse: Fortschritte in der präoperativen Planung, operativen Technik, immunsuppressiven Therapie und interdisziplinären Zusammenarbeit haben die Behandlungsergebnisse deutlich verbessert. Dennoch ist der Eingriff weiterhin mit relevanten Risiken und Komplikationen verbunden.

Schlussfolgerung: Der zukünftige Fortschritt auf diesem Gebiet erfordert die Entwicklung einheitlicher perioperativer Vorgehensweisen. Dazu zählen standardisierte Abläufe zur Patient:innenauswahl, zur operativen Technik und zur immunsuppressiven Therapie. Die Etablierung eines internationalen Datenregisters würde eine umfassende Datenerhebung ermöglichen, die Verfolgung langfristiger Ergebnisse erleichtern und Transparenz sowie eine evidenzbasierte Weiterentwicklung auf diesem Gebiet fördern.

Abstract

Background: Facial Transplantation marks a significant milestone in the evolution of facial reconstructive surgery, offering new therapeutic perspectives for patients with severe facial defects. Despite its increasing adoption in selected centers as a standard of care, the procedure still remains rare, lacking comprehensive, consistent and centralized reporting in peer-review literature.

Methods: A narrative review was conducted using current scientific sources, including peer-reviewed articles from the "PubMed" database and authoritative textbooks covering facial transplantation and reconstructive surgery. The objective of this work was to consolidate fragmented information to provide a coherent overview of the current state of facial transplantation regarding indications, preparatory measures, surgical techniques, postoperative care, as well as complications and outcomes.

Results: Advances in surgical planning and techniques, immunosuppressive therapy and interdisciplinary collaboration have improved outcomes of facial transplantation, yet the procedure remains associated with considerable risks and complications.

Conclusions: Future progress relies on the development of uniform perioperative procedures. This includes standardized protocols for patient assessment, surgical techniques and immunosuppressive therapy. The establishment of an international data registry would support comprehensive data collection, facilitation long-term outcomes, transparency and evidence-based advancement in the field.

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List of Abbreviations

15D	*15 Dimensions of Health-Related Quality of Life Questionnaire*
3D	*Three-dimensional*
BSSO	*Bilateral sagital split osteotomy*
CAD	*Computer-aided design*
CAM	*Computer-aided manufacturing*
CMV	*Cytomegalovirus*
CSP	*Computerized surgical planning*
CT	*Computed tomography*
CTA	*Composite tissue allotransplantation/ composite tissue allograft*
EBV	*Epstein-Barr Virus*
ECA	*External carotid artery*
EORTC QLQ-H&N35	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Head and Neck Module 35*
FAI	*Facial Aesthetic Index*
FDA	*Federal drug administration*
FT	*Facial transplantation*
FYI	*Facial Youthfulness Index (FYI)*
HES	*Hydroxyethyl starch*
HIV	*Human Immunodeficiency Virus*
HLA	*Human Leukocyte Antigen*
HPV	*Human Papillomavirus*
HSV	*Herpes Simplex Virus*
ICGA	*Indocyanine Green Angiography*
IRI	*Ischemia and reperfusion injury*
MMF	*Mycophenolate Mofetil*
MRI	*Magnetic Resonance Imaging*
rATG	*Rabbit Anti-Thymocyte Globulin*
SMAS	*superficial musculoaponeurotic system)*
SQI	*Skin Quality Index*
TMJ	*Temporomandibular joint*
UW	*University of Wisconsin*
VCA	*Vascularized composite allotransplanation/vascularized composite allograft*

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1 Introduction

The evolution of facial reconstructive surgery has followed a gradual course, marked by occasional transformative leaps. The advent of facial transplantation (FT), made possible by groundbreaking pharmaceutical discoveries and the pioneering spirit of surgeons, represents a recent milestone in this progression (1). While it still stands as a novel surgical approach that could redefine facial reconstruction paradigms, it has already been adopted as the standard of care in certain centers (2). Facial transplantation represents a prominent domain within vascular composite allograft (VCA), alongside upper and lower extremity, uterus, abdominal wall and penis transplantation (3).

Since the inaugural facial allograft transplantation in France in 2005, almost 50 procedures have been performed globally, yielding promising outcomes (1). However, like any pioneering procedure, it has raised numerous questions and concerns still existing and relevant to this date. While the number of facial transplantations remains limited today, the cumulative count of allograft recipients, encompassing the aforementioned VCAs has exceeded 300 (3). Moreover, some of these patients have been under observation for over a decade, providing valuable long-term follow-up data. Yet the data available in the peer-reviewed literature is incomplete and inconsistently presented, and in some cases even contradictory, making it difficult to provide a fully comprehensive summary (4). This lack of oversight hinders efforts within the reconstructive transplantation community to gather comprehensive data on global face transplant procedures and their outcomes. Consequently, a substantial gap in statistical data exists, leading to inherent biases in the available information. The objective of this study was to compile the existing data from various sources in order to provide a narrative overview of the current state of facial transplantation as of July 2025.

2 Historical Overview

Over the past 20 years, the field of VCA transplantation has expanded (5). The history of face transplantation begins in 1991, when a congress on VCA, former known as composite tissue allograft (CTA), was held for the first time, though focusing on limb transplantation in the context of war casualties. After various studies, it became apparent that anti-rejection drugs already approved by the federal drug administration (FDA) for kidney and pancreatic transplantation could also be used for limb transplantation. As a result, the first hand transplantation took place in 1998, performed by the surgeons Jean-Michel Dubernard and Earl Owen in Lyon (France) (6). This was a significant event for the introduction of face transplantation due to the positive outcome and solving the existing problem of transplanting allogenic and composite tissues such as muscles, bones, nerves and the strongly immunologically active skin (7).

In the following years, various international plastic and reconstructive surgeons expressed their intentions and ambitions to perform the first face transplantation, but initially addressed only the surgical and immunological complexities. Subsequently, the psychological, ethical and moral difficulty was included in the discussion more intensively (6). High expectations were tempered after a working group in the UK consisting of experts in the fields of immunology, transplantation, reconstructive and plastic surgery, medical ethics and psychology came to the conclusion that face transplantations should not be performed due to missing risk and benefit analysis as well as immunological, psychologic, societal, ethical and legal issues and the “highly experimental character” of the entire procedure. In close temporal relation, the Paris surgeon Laurent Lantieri received a rejection by the Frensh Ethics Committee of his previously submitted application to perform five face transplants. Again, lack of evidence regarding ethical acceptability of the potential serious risks was pointed out (8).

In the early 2000s, working groups were formed internationally at renowned hospitals with the goal of establishing an appropriate protocol for approaching a face transplant. By now, the surgical techniques and immunologic challenges were no longer an issue, as surgeons were confident of clinical feasibility. It was now mainly about psychological and ethical apprehension, as this was an innovative procedure that could significantly improve quality of life, but was still not a life-saving intervention (9). This resulted in a major public debate in which four ethical requirements for medical revolutions were discussed, which were (i) an adequate scientific preparation, (ii) a skilled and experienced team, (iii) an ethical climate in the institution and (iv) a public and professional evaluation prior (6).

The constant progress in medicine lives through innovative procedures. An important point, however, is that there is always a certain degree of uncertainty in advance as to whether an innovation will achieve a justifiable result or whether it may lead to harm. In general, it is difficult to establish something new whose performance carries with it a potential risk to patient safety, especially since surveying the likelihood of complications is almost impossible without ever having performed the procedure in the first place. No further knowledge can be acquired through research in this case, except by actually putting the procedure into practice. Therefore it was emphasized that potential recipients are informed in detail about the experimental character in advance (6).

Barker et al. published a study in which they used standardized questionnaires to determine the individual risk propensity of three defined target groups (healthy individuals, organ transplant recipients, individuals with facial deformities) for different transplants, including facial transplantation. All groups had in common, that they would be willing to take the highest risk for receiving a face transplantation (10).

In 2005 surgeon Bernard Devauchelle performed the first partial face transplant after receiving approval from the Ethics Committee directly for the specific patient case. Various postoperative complications were satisfactorily treated, so that the operation as a whole was hailed as a success and a medical breakthrough. A new era in reconstructive surgery began, opening up new opportunities for the treatment of severe disfigurements that had previously been constrained by traditional methods (6).

From there until now a total of 49 known reported face transplants have been implemented worldwide in different transplant centers (6). Since the first case, FTs have then become more complex, moving from soft tissue exclusively to osteomyocutaneous allografts of different compositions, which may include the mandible, maxilla and palate, tongue and related teeth (11).

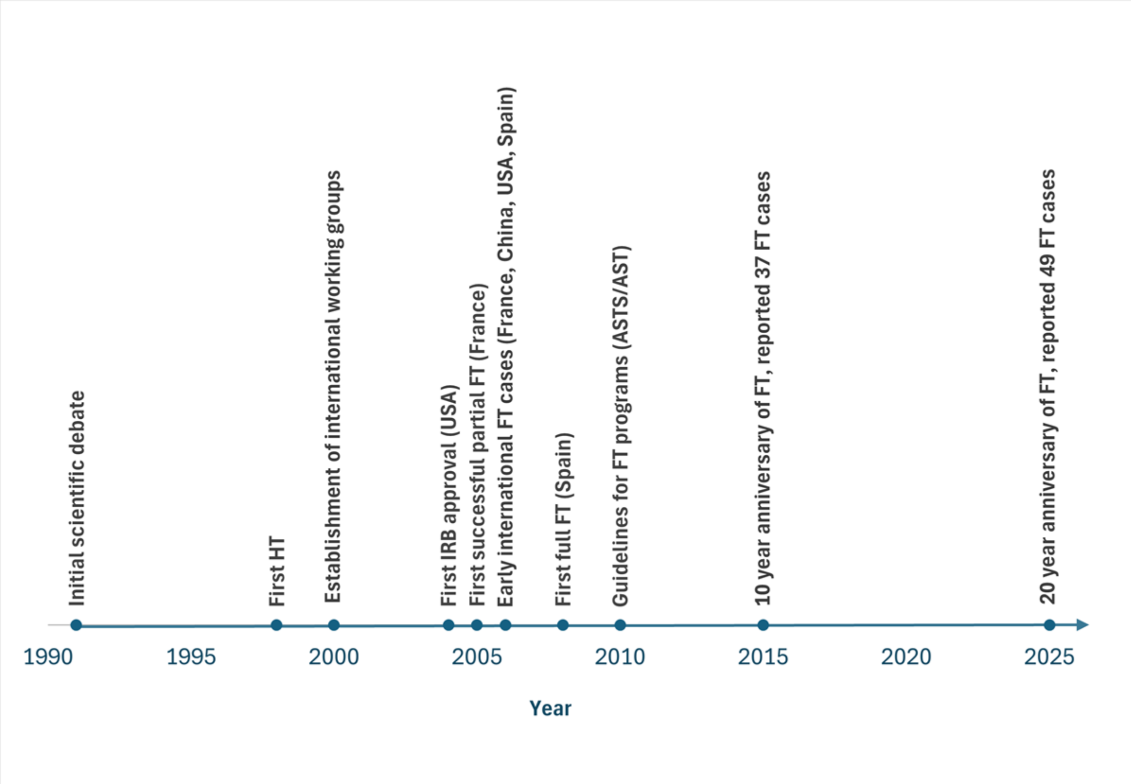

Figure 1. Timeline of major milestones in FT (1991-2025)
Based on references from (6). ***Abbr.:*** HT: Hand transplantation; IRB: Institutional review board; FT: Face Transplantation; ASTS: American Society of Transplant Surgeons; AST: American Society of Transplantation

Table 1. 49 FTs worldwide as of july 2023
Based on references from (2,12,13)

No.	Year	Location	Age	Sex	Indication	Specification	Full FT	Deceased	AR	CR
1	2005	France	38	F	Trauma	Animal attack	No	Yes	Yes	Yes
2	2006	China	30	M	Trauma	Animal attack	No	Yes	Yes	No
3	2007	France	29	M	Tumor	NF	No	No	Yes	No
4	2008	USA	45	F	Trauma	Ballistic	No	Yes	Yes	No
5	2009	France	27	M	Trauma	Ballistic	No	No	Yes	No
6	2009	France	37	M	Burn	Not specified	No	Yes	No	No
7	2009	USA	59	M	Burn	Electrical	No	Yes	Yes	Yes
8	2009	France	33	M	Trauma	Ballistic	No	No	Yes	No
9	2009	Spain	42	M	Others	ORN	No	Yes	Yes	No
10	2009	France	27	M	Trauma	Ballistic	No	No	Yes	Yes
11	2010	Spain	35	M	Tumor	NF	No	No	Yes	No
12	2010	Spain	30	M	Trauma	Ballistic	Yes	Yes	Yes	No
13	2010	France	35	M	Tumor	NF	Yes	No	Yes	Yes
14	2011	USA	25	M	Burn	Electrical	Yes	No	Yes	Yes
15	2011	France	45	M	Trauma	Ballistic	No	No	Yes	No
16	2011	France	41	M	Trauma	Ballistic	No	Yes	Yes	No
17	2011	USA	30	M	Burn	Electrical	Yes	No	Yes	No
18	2011	USA	57	F	Trauma	Animal attack	Yes	No	Yes	No
19	2011	Belgium	54	M	Trauma	Ballistic	No	No	Yes	No

20	2012	Turkey	19	M	Burn	Not specified	Yes	No	Yes	No
21	2012	Turkey	25	M	Burn	Not specified	Yes	No	Yes	Yes
22	2012	Turkey	20	F	Trauma	Ballistic	No	Yes	Unk	Unk
23	2012	USA	37	M	Trauma	Ballistic	Yes	No	Yes	No
24	2012	Turkey	35	M	Burn	Thermal	Yes	No	Yes	No
25	2012	France	52	F	Tumor	AVM	No	No	Yes	No
26	2013	USA	45	F	Burn	Chemical	Yes	No	Yes	Yes
27	2013	Poland	31	M	Trauma	Blunt	No	No	Yes	No
28	2013	Turkey	26	M	Trauma	Ballistic	Yes	No	Yes	No
29	2013	Turkey	54	M	Trauma	Ballistic	Yes	Yes	Yes	No
30	2013	Poland	28	F	Tumor	NF	Yes	No	Yes	No
31	2013	Turkey	22	M	Trauma	Ballistic	No	No	Yes	No
32	2014	USA	39	M	Trauma	Ballistic	No	No	Yes	No
33	2014	USA	44	M	Tumor	GPA	No	No	Yes	No
34	2014	USA	33	M	Trauma	Ballistic	No	No	Yes	No
35	2015	Spain	45	M	Tumor	AVM	Yes	No	No	No
36	2015	Russia	22	M	Burn	Electrical	No	No	Yes	No
37	2015	USA	41	M	Burn	Thermal	Yes	No	Yes	No
38	2016	Finland	34	M	Trauma	Ballistic	No	No	No	No
39	2016	USA	31	M	Trauma	Ballistic	No	No	Yes	No
40	2017	USA	21	F	Trauma	Ballistic	Yes	No	No	No
41	2018	USA	25	M	Trauma	Ballistic	No	No	Yes	No
42	2018	France	44	M	Other	Retransplant (CR)	Yes	No	Unk	Unk
43	2018	Finland	58	M	Trauma	Ballistic	Yes	No	No	No
44	2018	Canada	64	M	Trauma	Ballistic	No	No	Unk	Unk
45	2018	Italy	49	F	Tumor	NF	No	No	Unk	Unk
46	2019	USA	68	M	Burn	Thermal	Yes	No	Unk	Unk
47	2020	USA	52	F	Other	Retransplant (CR)	Yes	No	Unk	Unk
48	2020	USA	22	M	Burn	Thermal	Yes	No	Unk	Unk
49	2023	USA	46	M	Burn	Electrical	Unk	No	Unk	Unk

Abbr.: AR: Acute rejection; CR: Chronic rejection; NF: Neurofibromatosis; ORN: Osteoradionecrosis; AVM: Arteriovenous Malformation; GPA: Granulomatosis with Polyangiitis; Unk: Unknown

3 Conceptual Framework

3.1 Definition of Vascularised Composite Allografts (VCA)

Formerly referred to CTA, VCA describes the transfer of human allogeneic tissue types such as skin, muscle, fat, bone, blood vessels, nerves, lymph nodes, cartilage and ligaments. These composite grafts are transplanted as a single structural unit preserving the integral connection between soft tissue and bone, maintaining their natural harmony and continuity (14). They are used in special cases to reconstruct functional and aesthetic features, where conventional techniques would give poor or insufficient results (15,16). VCAs could be seen as a transition between tissue and organ transplantation (16). In 2014 the *United States Department of Health and Human Services* included VCA as an organ and established 9 criteria to define it, consequently regarding VCA as standard care (5,17).

Table 2. US regulatory criteria for defining VCA
The following criteria are a direct quote from: U.S. Department of Health and Human Services. Organ Procurement and Transplantation Network; Final Rule 42 CFR§121.2 – Definitions. Code of Federal Regulatins, Title 42 – Public Health. 2014 Jul 3;42:§121.2. (18)

1	That is vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation
2	Containing multiple tissue types
3	Recovered from a human donor as an anatomical/structural unit
4	Transplanted into a human recipient as an anatomical/structural unit
5	Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement)
6	For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor)
7	Not combined with another article such as a device
8	Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved
9	Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient

The *Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation* does not explicitly mention VCAs, however it defines organs as follows: "Organ means a differentiated part of the human body, formed by different tissues, that maintains its structure, vascularisation, and capacity to develop physiological functions with a significant level of autonomy. A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularisation." (19) As of now, FT has been carried out in several member states of the European Union, including France, Spain, Belgium, Poland, Finland and Italy (13).

In addition to facial transplantation, as previously mentioned, VCA encompasses a broad spectrum of procedures, such as the transplantation of upper and lower limps, the uterus, the abdominal wall and the male genitalia (3).

3.2 Classification System of Facial Transplantation

Surgical approaches between transplant teams vary widely internationally, yet the development of a standardised classification and nomenclature is necessary. To date, there is no standardized classification of facial transplants (13). In general, the procedure can be classified into partial, near-total, and full facial transplantation, according to the anatomic deficiencies (20).

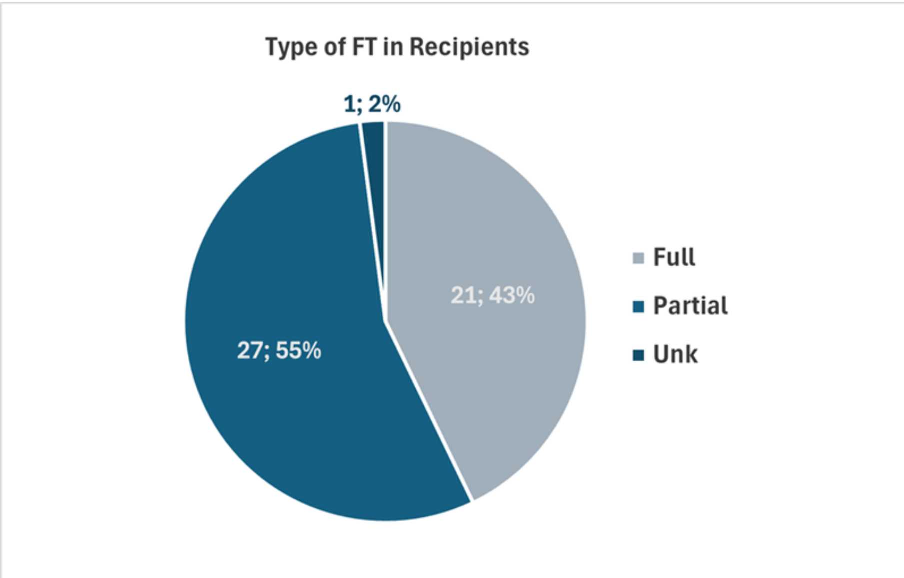

Figure 2. Type of FT in recipients
(n=49) Based on references from (13)

Furthermore Rodriguez et al. introduced a potential classification framework that categorizes VCA procedures based on the tissue types involved. This system broadly differentiates between soft-tissue and skeletal tissue defects (13).

Accordingly, the soft tissue defect is subdivided based on aesthetic and functional considerations into nasal (Type 0), oro-nasal (Type 1), oronasal-orbital (Type 2) and full facial (Type 3) defect. For hard tissue defects, the Le Fort classification was utilized, due to its international recognition, along with the inclusion of mandibular involvement. This resulted in the following groups: Le Fort 1 (A), Le Fort 3 (B), and monobloc (C), as well as mandibular involvement (M) (13,14).

Table 3. Classification system for soft-tissue and skeletal tissue defects
Based on references from (13,14)

Defect	Type	Content
Soft tissue	Type 0: oral	Lips and oral commissures
	Type 1: oral – nasal	Type 0 + Nasal structures *or* Isolated nasal defects
	Type 2: oral – nasal – orbital	Type 1 + inferior eyelid and cheek region *or* isolated orbital defects
	Type 3: full face	Type 2 + upper eyelids, forehead and preauricular region
Hard tissue	Subtype M: mandibular	Partial or entire mandible involvement (level of BSSO)
	Type A: Le Fort I	Partial or entire maxilla involvement, cranially to the dentition
	Type B: Le Fort III	Zygomatic, maxillary, nasal and inferomedial orbital bones *Additional:* vomer and ethmoid bones
	Type C: monobloc advancement	frontal and supraorbital bones additional to previous types

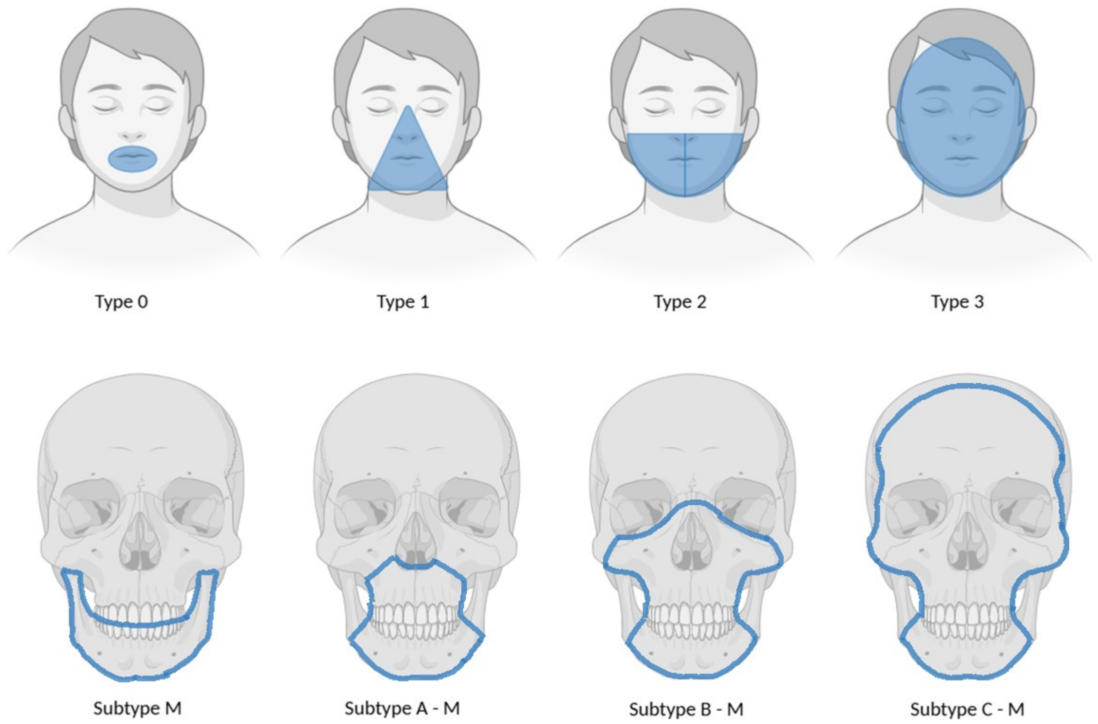

Figure 3. Soft and hard tissue defects
Schematic representation of the tissue classification system. Illustration visualized by the author. Based on references from (13)

Respecting the aestethic subunit concept is essential in facial reconstruction to achieve a more symmetrical and subtle outcome. Beyond aesthetic considerations, selecting flaps that match the soft-tissue subtypes within the classification system is crucial for reliably restoring functional units. Key subunits in this context include the oral and orbital region (14). For isolated orbital or nasal soft tissue defects, it is essential to consider the medial corner of the eye including the lacrimal apparatus, which can be difficult to maintain or reconstruct. To achieve this, a naso-orbito-ethmoidal osteotomy connected to the soft tissues should be performed (14).

A further consideration is whether the salivary glands should be included in the allograft. The parotid glands have initially been frequently incorporated in face allografts as this favors the preservation of the intraparotid plexus of the facial nerve and adds volume if needed (21–23). If inclusion is pursued, efforts should be made to maintain the patency of the ductal orifice (24). Nevertheless, the parotid drainage system is one of the structures that is time consuming and particularly difficult to preserve or reconstruct in FT (14). Regarding the submandibular glands, inclusion may minimize potential harm to the facial artery, as well as facial, lingual and hypoglossal nerves. However, saliva accumulation, excessive volume and undesirable facial fullness often occur if salivary glands are retained (24). Therefore Kantar et al. suggest to remove all salivary glands in their entirety to prevent associated posttransplant complications (13).

The Le Fort classification system is used for categorizing midfacial fractures and consists of three main types. Le Fort I fractures detach the maxilla from the craniofacial skeleton above the tooth roots, with the fracture line traversing horizontally across the hard palate through the maxilla, both maxillary sinuses, and the pterygoid process (25). If performing Le Fort I Osteotomy it is important to pay attention to the neurovascular complex consisting of the greater palatine nerve and the descending palatine artery, which can lead to massive bleeding (26). Le Fort II fractures detach the maxilla and in a pyramidal pattern. The fracture line originates at the nasal root, traverses anteriomedially through the orbital floor, and proceeds downward through the maxillary projection toward the zygomatic bone, ultimately involving the posterior boundary of the maxillary sinus (25). Le Fort III fractures result in complete separation of the viscerocranium, detaching the maxilla and zygomatic bones as a unified segment. The fracture line also originates at the nasofrontal suture, traverses through the lacrimal bone, along the medial and lateral orbital wall to the zygomatic arch and pterygoid plates (27).

For extensive defects involving the tooth-bearing regions, a comprehensive reconstruction using Le Fort or bilateral sagittal split osteotomy (BSSO) should be considered (14). In BSSO the mandible is separated, with the lateral extension of osteotomy lines varying according to anatomical considerations and surgical planning (28). In the context of FT the goal of BSSO is to restore adequate chewing and swallowing functions, as well as proper alignment (14).

For type C defects, the frontal and supraorbital bone segment should be harvested en monobloc, distinct from the Le Fort III segment. This separation of the sinonasal communication helps mitigate the risk of severe ascending intracranial infections (14).

4 Anatomy

To provide an overview of the complex interplay of form and functions on face, the following highlights the basic anatomical features of the head and neck region and aspects that are important for facial transplantation.

4.1 Head

The human head is connected to the torso via the neck. As VCAs comprise multiple distinct tissue components, their key anatomical characteristics are outlined in greater detail below. Particular emphasis is placed on the osseous structures, the facial musculature and innervation, vascular supply, and other anatomically significant regions critical to the success of composite tissue transplantation.

4.1.1 Skull

The skull constitutes the bony foundation of the head and is divided into two distinct regions (26,29). The posterior portion, known as the neurocranium, encloses critical components of the central nervous system, specifically the brain. The anterior portion, or viscerocranium, houses the primary sensory organs, each with distinct functions: the eyes (vision), ears (hearing and balance), nose (olfaction), and the structures of the oral cavity and pharynx (taste). This region also marks the commencement of both the respiratory and digestive tracts and is integral to speech production (29). The viscerocranium, crucial for FT, consists of 14 bones (6 paired, 2 single), which are shown in the following illustration. (30).

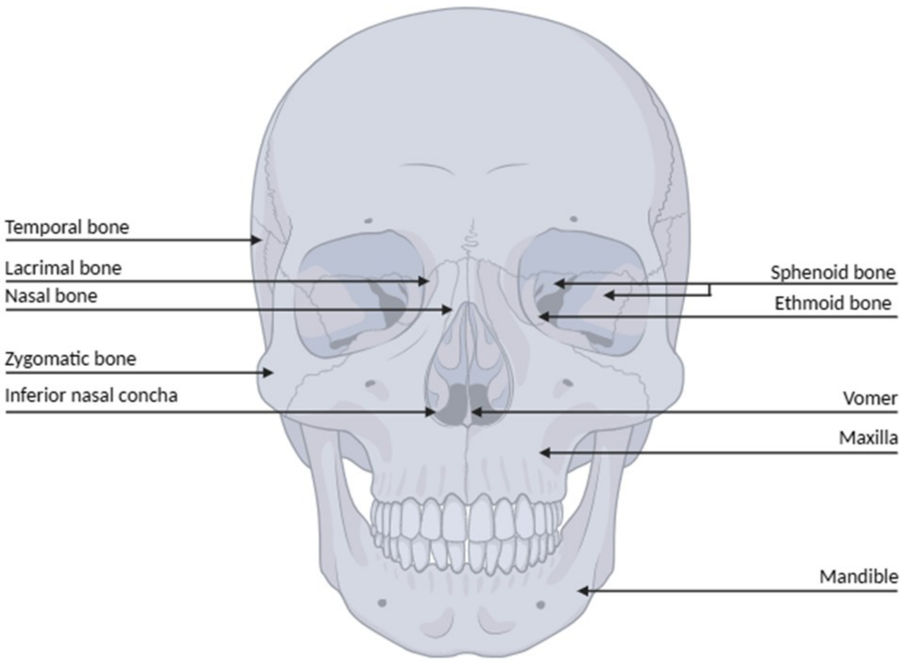

Figure 4. Bones of the viscerocranium
Schematic representation of bones of the viscerocranium. Illustration created by the author with BioRender.com. Note: The hyoid bone and palatine bones are not depicted in this illustration. Based on references from (30)

4.1.2 Muscles of Facial Expression and Mastication

Unique among muscles, the facial muscles lack a fascia and attach directly to the skin of the head, enabling distinctive facial expressions that facilitate non-verbal communication (29). Therefore, the surgeon must exercise exceptional caution when performing dissections in this area. The facial muscles also provide protection, particularly for the eyes, through their sphincter-like actions, and they are active in the ingestion process by enabling mouth closure during swallowing (31). The majority of these muscles originate directly from the periosteum, fibrous structures of the skull or adjacent muscles (30). All facial muscles receive innervation from branches of the facial nerve, whereas the muscles responsible for mastication are supplied by motor fibres from the trigeminal nerve (29,30). In order to better understand the mimic musculature, the systematic subdivision into different areas has proven useful. These regions are as follows: calvarium, palpebral fissure (orbital group), nose (nasal group), mouth (buccolabial group), external ear (auricular group) and neck (30).

In the area of the calvarium runs the epicranial muscle, consisting of the occipitofrontalis muscle with its interposed galea aponeurotica and the tempoparietalis muscle, which is responsible for the frown and the elevation of the eyebrows (32). While its anatomical role includes maintaining a clear visual field, it is equally important in mediating subtle social cues and emotional expression, thereby playing a central role in nonverbal interpersonal communication (32).

The ocular group, innervated by the zygomatic and temporal branches of facial nerve (CN VII), consists of the corrugator and depressor supercilii muscle, as well as the orbicularis oculi muscle. The latter holds significant functional importance as it's sphincter-like and closes the palpebral fissure, acting as a protective reflex against foreign particles as well as supporting the tear drainage (30). The orbicularis oculi muscle encircles the orbit and the surrounding area, and can be divided into three parts: orbital, palpebral and lacrimal part (33). Inactivity of the orbicularis oculi impairs the protective blink reflex and lacrimal pump function, leading to ocular dryness (30).

The nasal group, comprising the nasalis and procerus muscles, plays a key role in facial expressions and also aids in respiration (30). The buccolabial group, or muscles of the mouth, comprises a broad set of muscles that collectively manage the shape and movements of the mouth and lips. This group consists of 11 muscles, which function to elevate, evert, depress and close the lips, as well as compress the cheeks (30). Most of these muscles are anchored by a fibromuscular hub, known as the modiolus, located at the corners of the mouth where their fibers converge (31,34).

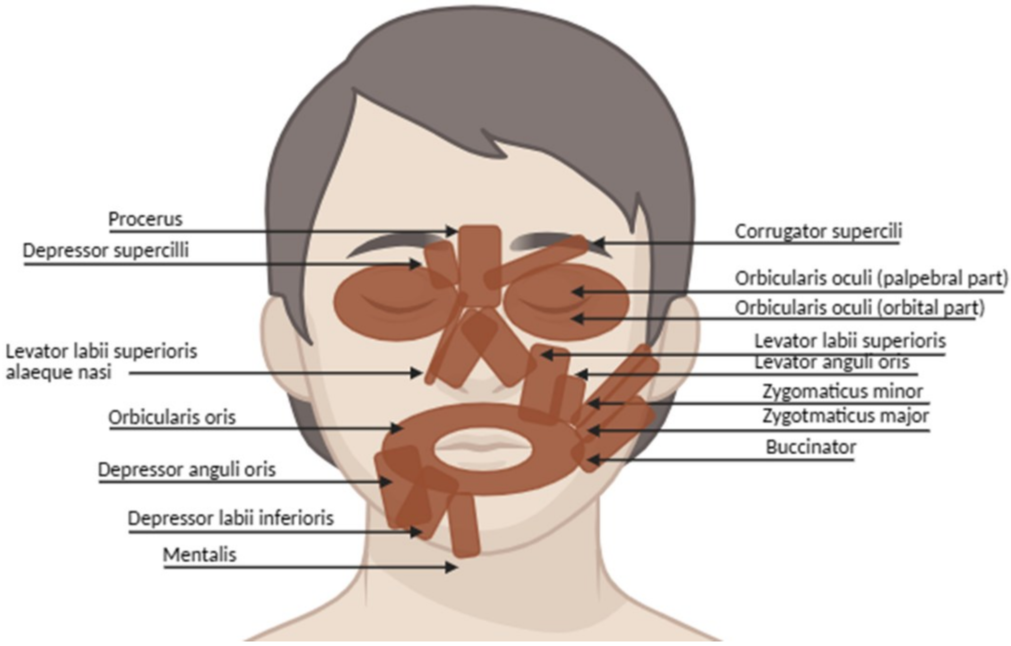

Figure 5. Ocular, nasal and oral muscle groups
Schematic representation of muscles of facial expression. Illustration created by the author with BioRender.com. Based on references from (30)

In a wider context, the auricular muscles can be classified as facial mimic muscles (30). These slender, fan-shaped muscles link the auricle to the scalp and facilitate limited movements of the auricle (35).

The masseter, temporalis and pterygoid muscles belong to the masticatory muscles, with the masseter muscle being the strongest (30). The masticatory muscles attach to the mandible, allowing the lower jaw to move at the temporomandibular joint (TMJ), essential for closing the mouth and align the upper and lower teeth for chewing and grinding (36). In contrast to the mimic muscles, which are innervated by the facial nerve, the masticatory muscles are supplied by branches of the mandibular division of the trigeminal nerve (CN V3) (36).

4.1.3 Blood Supply

The blood supply to the head and neck regions is primarily provided by branches of the external carotid artery (ECA), with additional contributions from branches of the internal carotid artery forming interconnecting anastomoses. Both arteries are encased in a fibrous extension of the cervical fascia (carotid sheath) and originate from the common carotid artery, which bifurcates in the neck after emerging from the aortic arch (37). The cervical segment of the external carotid artery primarily supplies the anterior structures of the neck, including the cervical viscera (30,38). The branches of ECA can be divided into four main groups: anterior, medial, posterior, and terminal (30).

Table 4. Main branches of the ECA and their distribution
Based on references from **(30)**

Main branch	Arteries	Distribution
Anterior	Superior thyroid artery	larynx, thyroid gland
	Lingual artery	oral floor, tongue
	Facial artery	superficial face region
Medial	Ascending pharyngeal artery	plexus to the skull base
Posterior	Occipital artery	occiput
	Posterior auricular artery	ear
Terminal	Maxillary artery	maxillary strucutes, TMJ, mandible, masticatory muscles, nasal cavity, palate
	Superficial temporal artery	temporal region, soft tissues below zygomatic arch, ear, lateral orbital wall

The segmentation of the face into distinct vascular supply regions, known as angiosomes, is a concept frequently invoked in the context of flap surgery. Within each angiosome lies a well-defined source artery that nourishes the three-dimensional composite units comprising skin, subcutaneous tissue, nerves, fascia, muscles, and skeletal structures (39,40). This principle posits the necessity of multiple arteries for the perfusion of facial skin, with the superficial temporal, facial and ophthalmic arteries serving as primary suppliers to most facial regions (26).

The facial artery originates from the ECA, slightly superior to the lingual artery's origin, at the level of the greater horn of the hyoid bone (26). This artery ascends beneath the posterior belly of the digastric and stylohyoid muscles, creating a groove on the submandibular gland and then curves upward over the mandible's body at the anteroinferior angle of the masseter muscle (41). The artery proceeds anteriorly and superiorly across the cheek, reaching the labial commissure, and continues its course along the side of the nose (41). It sequentially emits the ascending palatine, submental, labial, and lateral nasal arteries before terminating at the medial commisure of the eye, where it is known as the angular artery (30).

Furthermore, the maxillary artery generates additional contributions to facial vascularity, including the infraorbital, zygomaticofacial, and mental arteries. These arterial branches travel alongside cutaneous branches of the trigeminal nerve, further contributing to the intricate sensory and vascular innervation of the face (26).

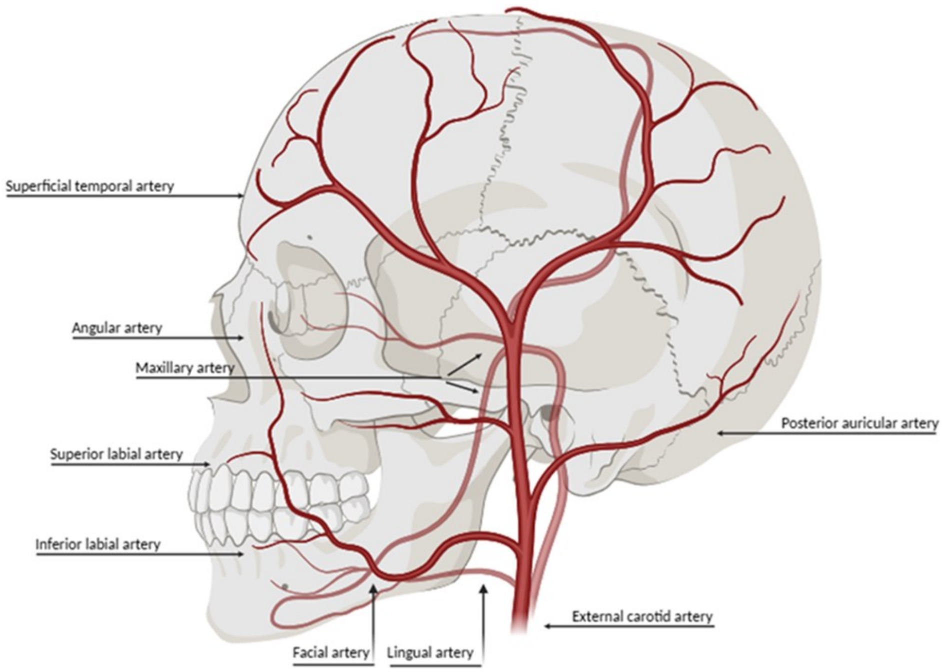

Figure 6. Arteries supplying the head
Schematic representation of the arteries supplying the head. Illustration created by the author with BioRender.com. Based on references from (30)

4.1.4 Venous Drainage

The principle venous drainage route of the face is predominantly the hemiloop-like vein, which encircles the orbit at the center of the face. It primarily receives contributions from the facial vein, but also from the supraorbital and angular vein and is linked to the zygomatico-temporal vein, to the superior ophthalmic vein, to the deep facial vein and the internal jugular vein (26). The latter functions to collect blood from the skull, brain, superficial regions of the face and most parts of the neck, utilizing parts of the facial, retromandibular, lingual, pharyngeal, superior, and middle thyroid veins (26,42).

At the level of the mandibular angle, the external jugular vein originates from the confluence of the posterior auricular vein with the posterior division of the retromandibular vein (26). The external jugular and anterior jugular veins largely drain superficial layers from the scalp and face into the subclavian vein (43).

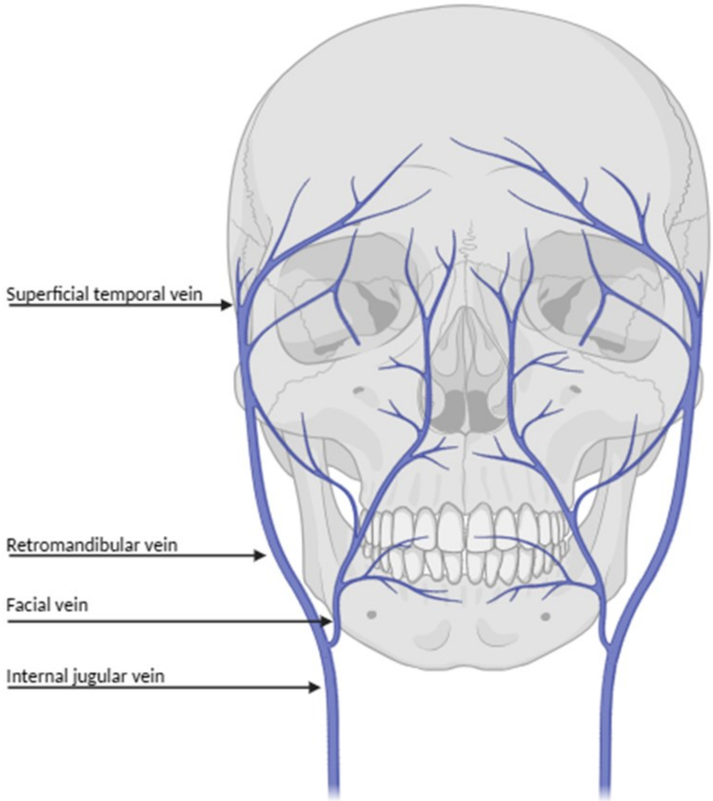

Figure 7. Venous Drainage
Schematic representation of the venous drainage of the head and neck. Illustration created by the author with BioRender.com. Based on references from (30)

4.1.5 Nerves

The trigeminal nerve (CN V) and its three main branches are responsible for the sensory innervation of the face and its skin (44). The mimic muscles receive motor innervation from the facial nerve (CN VII) (26). The hypoglossal nerve (CN XXII) enervates the intricate musculature comprising the tongue and the contiguous floor of the oral cavity

(45). These three cranial nerves are important for facial transplantation and are therefore discussed in more detail below.

4.1.5.1 Trigeminal nerve (CN V)

The trigeminal nerve (CN V) comprises both general somatosensory and specific visceromotor fibres, playing a crucial role in facial sensation and mastication. Intracranially, it bifurcates into three major divisions: the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves (44). Each division exits the middle cranial fossa through distinct foramina, thus facilitating the innervation of their respective anatomical territories (26).

Upon entering the orbit, the ophthalmic nerve (V1) bifurcates into three terminal branches: the frontal nerve, the nasociliar nerve, and the lacrimal nerve, each reflecting their specific anatomical distribution.

The maxillary nerve (V2) traverses the foramen rotundum where it bifurcates into its terminal branches: the zygomatic nerve, the infraorbital nerve, and the ganglionic branches (30). These branches provide innervation to nearly the entire mucous membrane of the nasal cavity, the palate, the upper jaw, including the gingiva and teeth, as well as the cutaneous region between the lower eyelid and the upper lip (46).

The mandibular nerve (V3) traverses the foramen ovale to enter the infratemporal fossa, where it bifurcates into four primary general somatosensory branches: the auriculotemporal nerve, the lingual nerve, the inferior alveolar nerve, and the buccal nerve (30). The auriculotemporal nerve innervates the temporomandibular joint, whereas the lingual nerve in addition to the chorda tympani is involved in the secretomotor innervation of the parotid gland, submandibular gland, and sublingual gland (47). Sensory innervation provided by the mandibular nerve encompasses the skin extending from the chin to the temple, the anterior two-thirds of the tongue, and the lower jaw, including the teeth and gingiva. Uniquely among the branches of the trigeminal nerve, the mandibular nerve contains motor fibers. These motor fibers innervate the muscles of mastication as well as portions of the muscles in the middle ear, floor of the mouth, and palate (48).

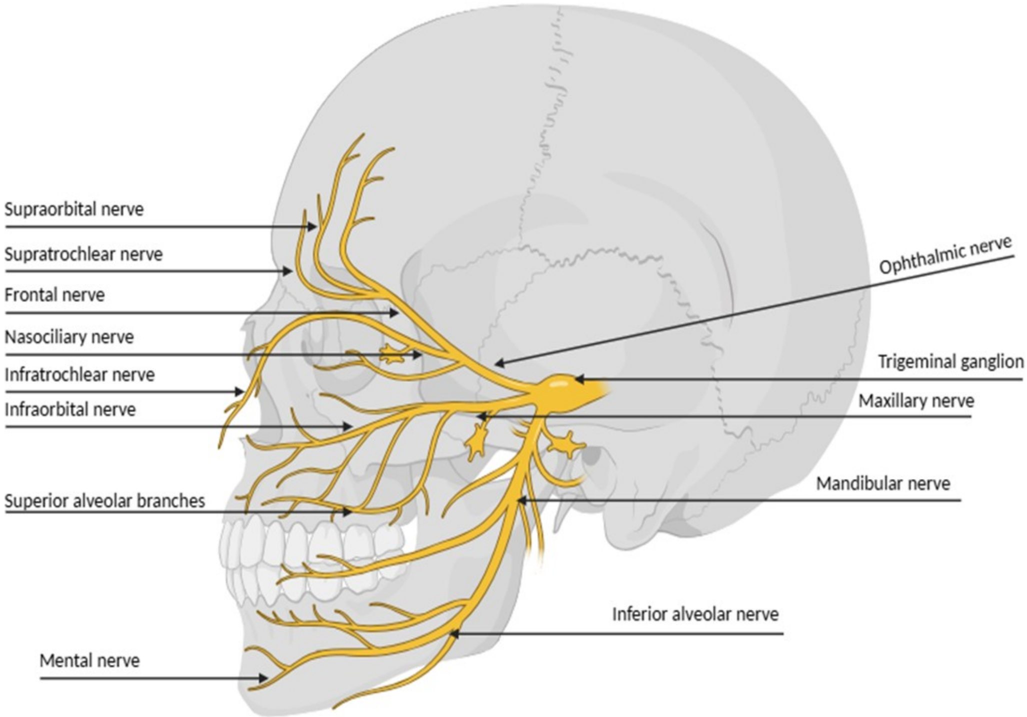

Figure 8. Trigeminal nerve (CN V) and its branches
Schematic representation of the trigeminal nerve and its branches. Illustration created by the author with BioRender.com. Based on references from (30)

4.1.5.2 Facial nerve (CN VII)

The facial nerve conveys fibres that are motor, sensory, and parasympathetic in function. With its special visceromotor fibres, it supplies the mimic musculature and parts of the suprahyoid musculature (30). In the following, only the final extratemporal segment of the facial nerve is described after it emerges from the petrous bone via the stylomastoid foramen, where it divides into its branches (49). The first one is the posterior auricular nerve, followed by smaller branches like the stylohyoid and digastric rami, supplying their corresponding muscles (26). Between the superficial and deep parts of the gland the facial nerve forms the intraparotid plexus, which is giving off two main trunks: the upper pars temporofacialis and the lower pars cervicofacialis. Its successive branches supply the mimic muscles and include the temporal, zygomatic, buccal, mandibular and cervical branch (29,30,38).

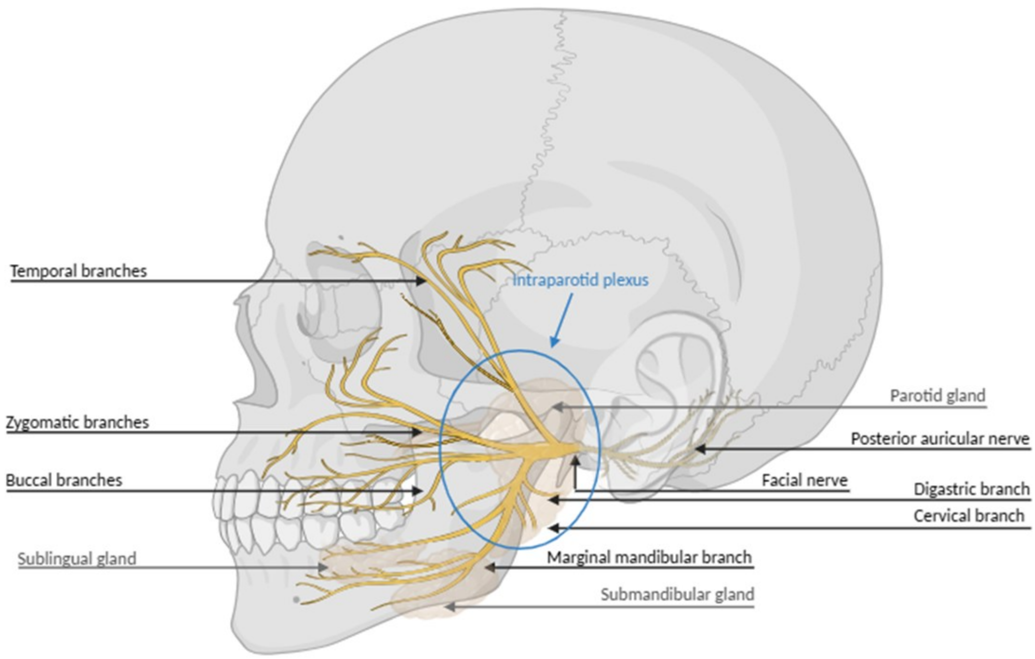

Figure 9. Facial nerve (CN VII) and salivary glands
Illustration created by the author with BioRender.com. Based on references from (30)

4.1.5.3 The hypoglossal nerve (CN XII)

The hypoglossal nerve is a somatic efferent nerve which innervates almost all intrinsic and extrinsic tongue muscles and therefore regulates the majority of tongue movements (45). It originates from the medulla and exits the cranial fossa via the hypoglossal canal. Subsequently, it continues extracranially, navigating between the internal jugular vein, the internal carotid artery, and the external carotid artery, until it reaches the trignonum caroticum (45). Ventral fibers of C1 and C2 briefly join the nerve along a short segment of its pathway to innervate the neck muscles (30,45). As it courses inferiorly from the neck through the submandibular triangle, the hypoglossal nerve reaches the floor of the oral cavity, supplying motor innervation to the muscles of the tongue (45).

4.2 Neck

The neck is the part that connects the head to the trunk and is bounded cranially by the lower edge of the mandible, tip of the mastoid process and the occipital bone, and caudally by the sternum via the clavicle, the acromion and the spinous process of the 7th cervical vertebra (29,30). It houses several organs and connecting elements, and serves as a passageway for neurovascular structures (48). In facial transplantation especially the anterior portions and soft tissues may be relevant as they form an aesthetic unit with the lowermost portions of the chin and mandible. Furthermore, vascular anastomoses for face transplants are commonly performed at neck level due to the larger vessel diameters.

4.2.1 Regions and Cervical Fasciae

The neck can be segmented into an anterior, lateral, sternocleidomastoid and posterior region, which can be further subdivided into additional triangles to facilitate anatomical orientation (30,50).

Table 5. Anatomical regions of the neck
Based on references from (30,50)

Region	Triangle	Content
Anterior region	Submandibular triangle	Submandibular lymph nodes Submandibular gland Parotid gland Hypoglossal nerve
	Carotid triangle	Carotid bifurcation Carotid body Hypoglossal nerve
	Muscular triangle	Thyroid gland Larynx Trachea Esophagus
	Submental triangle	Lymph nodes
Lateral region		Lymph nodes Accessory nerve Cervical plexus Brachial plexus
Sternocleidomastoid region		Sternocleidomastoid muscle Carotid artery Internal jugular vein Vagus nerve Jugular lymph nodes
Posterior region		Neck muscles Trigonum arteriae vertebralis

Beneath the skin lies the superficial cervical fascia which encompasses the platysma muscle and the external and anterior jugular veins. Deeper to the superficial cervical fascia are three successive layers of deep cervical fascia. The investing layer encases the entire neck and divides to envelop the sternocleidomastoid and trapezius muscles (50). The carotid sheath encircles neurovascular structures, including the common carotid artery, internal jugular vein, and vagus nerve (30).

4.2.2 Neck Muscles

The neck muscles contain different muscle groups namely the superficial, suprahyoid, infrahyoid, prevertrebral and lateral neck muscles (30). Only the muscles anatomically and functionally relevant for FT are discussed below.

The platysma is a wide flat sheet-like muscle plate extending across much of the anterior and lateral surfaces of the neck (51). The absence of facial envelope around the platysma and its intimate connection to the overlying skin into which it partially inserts, makes surgical dissection more challenging (30). Moreover, its superficial position and potentially thin appearance necessitates careful consideration of the neurovascular structures situated immediately beneath, such as the external and anterior jugular veins (26). The size of the platysma can also be attached to the perioral muscles enhancing their actions and contributing to facial expressions reflecting emotions like surprise, fear or disgust (51).

The sternocleidomastoid muscle is a key anatomical landmark for orientation during surgical procedures (52). It has its origins at the sternal manubrium and the medial clavicle and inserts at the mastoid process of the temporal bone and the superior nuchal line of the occipital bone. Its function includes tilting, rotating and extending the head (30).

The group of suprahyoid muscles is made up of the digastric muscle, geniohyoid muscle, mylohyoid muscle and stylohyoid muscle (30). The origin refers to the first part of the muscle, while the insertion refers to the second part (53). Along with surrounding tissues, they constitute the floor of the mouth, whereby the actual muscle bridge between the rami of the mandible is primarily formed by the mylohyoid muscles, also known as the oral diaphragm (30). The suprahyoid muscles play a crucial role in mastication, deglutition, and phonation (53).

The interaction of the infrahyoid muscles namely the sternohyoid, sternothyroid, thyrohyoid and omohyoid muscle contributes to swallowing and phonation (54). The omohyoid muscle performs an additional role owing to its anatomical relationship with the neurovascular bundle. By maintaining patency of the internal jugular vein, it facilitates venous drainage from the cranial region (29,30).

5 Indications

The primary indication for FT is severe facial trauma resulting in skin damage and substantial tissue loss in central midface units, along with major damage and disruption to important anatomical features such as the nose, lips, and eyelids (55–57). This is chiefly attributable to the total absence of the orbicularis oris and/or orbicularis oculi muscles (57). Out of the performed face transplants, 34 of the patients underwent the procedure to address severe facial disfigurement brought on by craniofacial injuries, caused by burns (thermal, electrical, chemical), animal attacks, machinery or ballistic trauma (11,58,59). It has also been performed on individuals who had substantial facial neurofibromas or significant facial deformity following cancer removal (55). Benign neoplasms should not inherently disqualify candidates for FT (57). Also patients with gangrenous stomatitis, vascular or lymphatic malformations should be evaluated as potential candidates (60). FT is not indicated after malignant tumour resection and past medical history of malignancy due to the higher risk of reappearance in the context of lifelong immunosuppression (55).

Conventional methods, multiple reconstructive procedures and even highly advanced super-microsurgical techniques can deliver a satisfactory functional and usually aesthetic result, but their effectiveness is limited to a certain extent of the injury (55,56). Difficulties may arise especially if there is complete damage of orbicularis oculi and/or orbicularis oris muscle and not enough residual muscle for restoration (55). In particular, those central facial structures, such as the nose, lips and eyelids, which are essential for function and appearance, are usually difficult to reconstruct using autologous techniques (1,14,61). In most cases, it is a functional indication, as those affected are limited in basic functions such as speaking, swallowing, breathing, seeing and smelling (55,60). For instance, circumstances like loss of nasal structure, upper airway obstruction, scarring, tongue atrophy and reduced mobility makes them dependent on permanent tracheostomies and gastrostomies (55,62). Therefore FT may be regarded as a first-line therapeutic option prior to conventional methods (57).

In addition to the functional indications, the alleviation of chronic pain and the achievement of a facial appearance deemed socially normative, therefore improving quality of life, are critical factors supporting the decision to proceed with a face transplant (62).

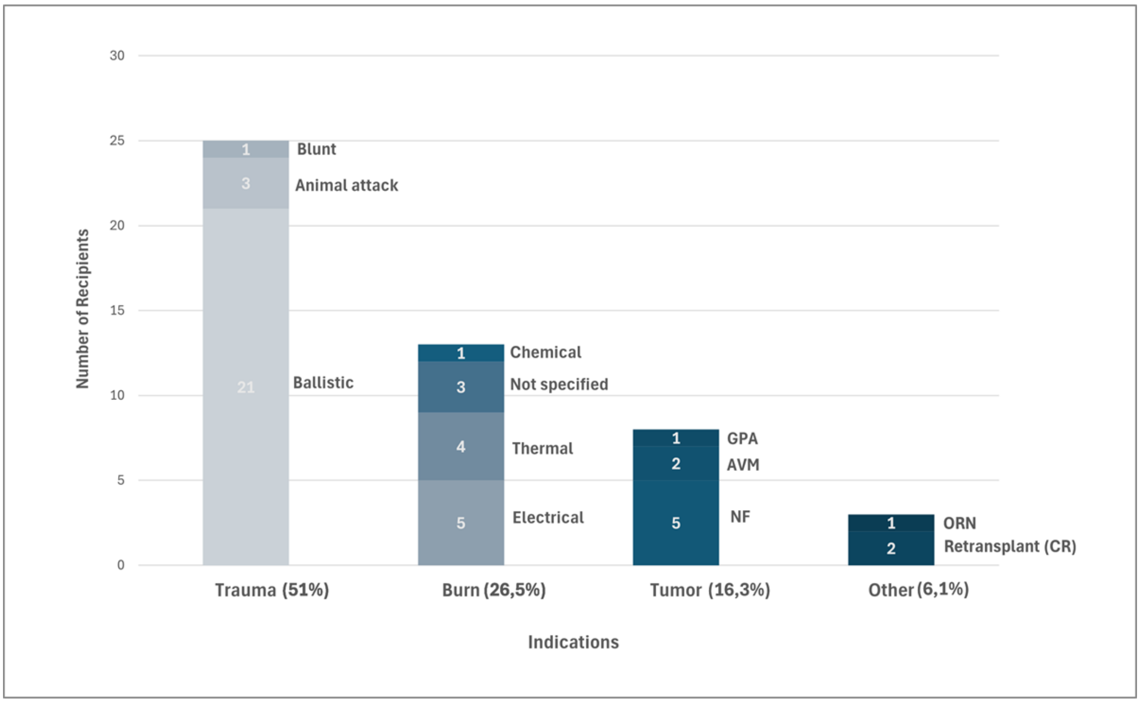

Figure 10. Distribution of indications among 49 reported FTs
Based on references from (12,13) **Abbr**.: NF: Neurofibromatosis; AVM: Ateriovenous Malformation; GPA: Granulomatosis with Polyangiitis; CR: Chronic Rejection; ORN: Osteoradionecrosis

6 Requirements

6.1 Permission, Logistic Considerations and Clinical Framework

It is usually necessary to obtain prior authorization from the review board of the institution or equivalent organization performing the transplant (63,64). The protocol approval process can be time-consuming and challenging due to legislation, regulations and socio-cultural constraints, depending on the country. Therefore, adequate time should be allocated in advance (64).

An operation of this magnitude necessitates an institution capable of assembling a multidisciplinary team with comprehensive expertise in the field, along with access to the necessary organizational structure, medical equipment and facilities (13). FT programs must be capable of delivering a comprehensive, long-term follow-up that integrates both clinical management and psychological care (57).

For the surgical procedure itself its required that the surgeons have sufficient technical and practical expertise in the fields of reconstructive microsurgery, otolaryngology surgery and craniofacial surgery. Given that the procedure typically entails the concurrent removal of multiple organs, it is imperative to have a highly trained transplant team available to ensure seamless execution and optimal outcomes (64). The responsible personnel should conduct a functionality check of surgical technologies and tools prior to procedure and ensure they are well-versed in their operation to guarantee smooth performance. As this leads to a high density of personnel, it is necessary to devise a plan beforehand to strategically position team members from various disciplines and the equipment within the operating room (13). Therefore key logistical processes related to facial transplantation were standardized in some institutions (65). Moreover, the institution should incorporate salvage contingency protocols into its plan to address the remote possibility oft graft failure (57).

6.2 Recipient Selection

Potential facial transplant candidates must undergo a thorough assessment by multidisciplinary experts (1). The following professional groups and medical specialties may be perioperatively and/or long-term involved in this process: organ procurement organization, hospital administration, reconstructive surgeons, transplant specialists, anaesthesiologists, radiologists, immunologists, infectiologists, dermatopathologist, dentists, dietitian, neurologists, psychologist, psychiatrists, mental health and social work professionals, physical therapist and speech therapists, and rehab centre (1,57,63,66). There must be a consensus among all these specialists, because a well-established support network is critical to success (1,66). There are different approaches to this but most programmes act under elaborated clinical research protocols which got permitted by a national ethics committee, an institutional review board or a local equivalent (67). Transplant centres have developed different concepts including inclusion and exclusion criteria for selecting the ‘ideal patient’ or recipient, but no globally endorsed standard has emerged so far (57).

At all transplant centres, a special focus was placed on the high validity of psychiatric screenings of potential candidates to uncover pertinent mental health disorders (1,57). Conditions such as severe depression, psychosis, cognitive impairments, and behavioural disorders present a contraindication due to potential challenges in postoperative management and patient cooperation (56,67). Especially since the worlds first hand transplant recipient and the worlds second facial transplant recipient both failed to follow the prescribed therapeutic measures due to non-compliance, the importance of meticulous psychological screening has become evident (67). The decision to choose patients with self-inflicted ballistic injuries is regarded by numerous teams as contentious (68).

The home environment and social support needs to be assessed in advance by multidisciplinary team members and should be reliable and well-established (57). Securing consent from caregivers guarantees that the individual undergoing treatment possesses a suitable support network and well-informed partner available throughout the entire process (57,57,63). It is advisable to involve local care facilities close to home to ensure that post-operative care is available (68). Engagement of the social support network at the earliest feasible point in the pathway is recommended (57). In Lantieris et. all open prospective study from 2016 it was mandatory that each recipient had to undergo a 5 year follow-up (66).

Patients should get comprehensive education on the potential risks and advantages associated with face transplantation, and thereafter be empowered to make autonomous decisions as the primary decision-makers (56). All nontransplant reconstructive methods should be thoroughly discussed, as well as patients expectations and personal definitions of “success” (57).

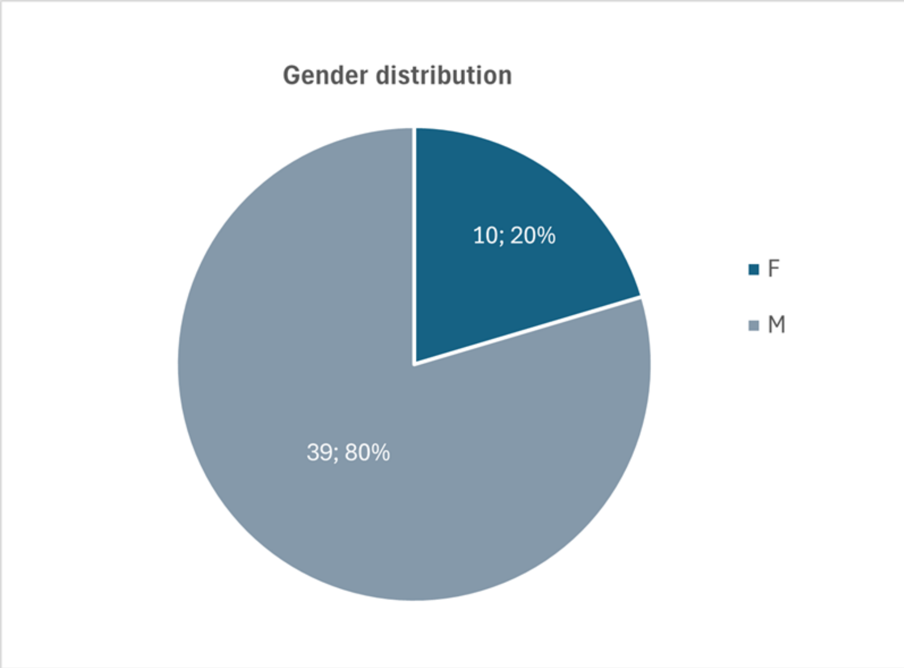

Figure 11. Patient characteristics: Gender distribution

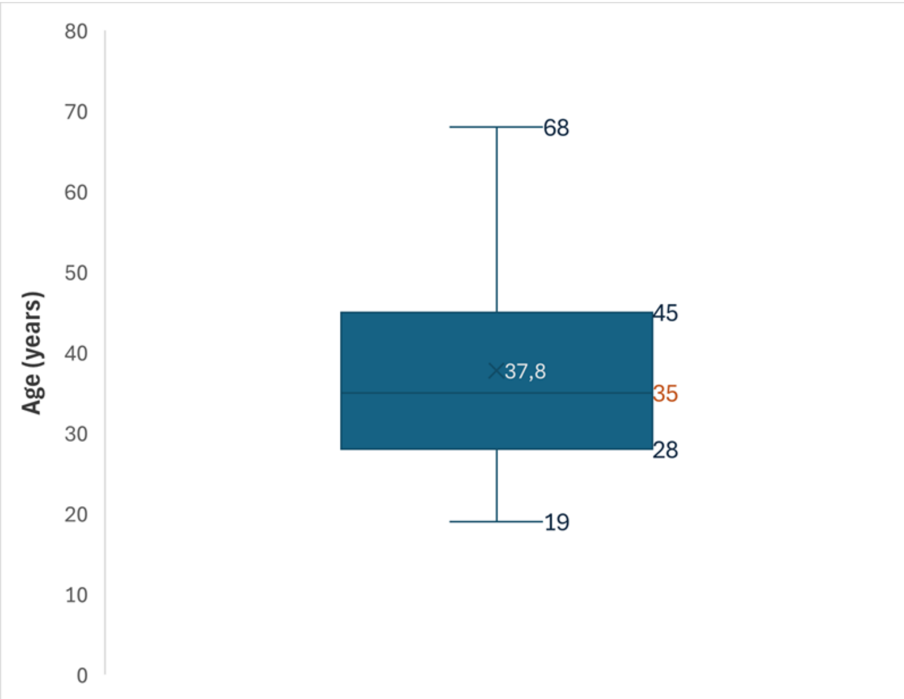

Figure 12. Patient characteristics: Age distribution

6.3 Donor Selection

A successful VCA also necessitates meticulous donor selection for achieving optimal compatibility (69). In general it is important to choose the best matching donor regarding immunologic, serologic and cephalometric points, as well as concordant sex, ethnicity, hair and skin color and similar body mass index (64,70,71). Regarding age, the acceptable margin should not exceed a deviation of plus or minus ten years (60). Donor selection in facial VCA therefore is more demanding than in solid organ transplantation which consequently leads to longer waiting times for recipients (1,70). Available data concerning actual waiting times are sparse, rendering the estimation of wait times for prospective recipients challenging (70).

7 Pretransplant Preparation

7.1 Clinical and Immunological Assessment

A thorough clinical and biological assessment must be performed. This includes panel reactive antibody screening (70), human leukocyte antigen (HLA) typing, T- and B-cell crossmatching, and serological testing for various viral pathogens like CMV, HIV, hepatitis B and C, herpes and EBV (60). The transplantation team must carefully review the past medical records regarding blood transfusions or cadaveric skin grafts. Screening for HLA is essential for identifying presensitized patients (56). Furthermore, investigation for infectious foci should be conducted through bacteriological examinations and evaluations in dentistry, otorhinolaryngology, and pulmonology. Due to the immunosuppressive effects of anti-rejection therapy, untreated infections could severely compromise the patient's health (55).

7.2 Cadaveric Simulation

As FT is not a routine procedure, it is advisable to carry out transplant simulations beforehand using cadaver models, especially at centers that are still inexperienced in this operation (72). By engaging in a series of cadaveric dissections surgeons gain proficiency in harvesting crucial anatomical elements such as major arteries and veins, nerves, salivary and lacrimal glands, soft tissues and ligaments. The utilization of cadaveric simulated transplantations facilitates the assessment of the feasibility and optimal timing for facial flap procurement, and aids in strategizing and delineating the sequence of steps required in the clinical context (63,64).

Some institutions have developed a training model for cadaveric transplants and carried out research procurements on brain-dead donors before final implementation (65,72,73). In the course of this, face restoration, virtual surgical planning, intraoperative perfusion angiography and nerve stimulation can already be integrated, uncovering unexpected perioperative difficulties (72). This allows further optimizing of the surgical plan and execution, leading to more reliable outcomes (13). Simulations serve as essential tools for familiarizing personnel with detailed plans and procedures, enhancing teamwork, practicing various approaches, and clarifying individual responsibilities (4,65). This preparatory measure allows for the identification of planning weaknesses and resource gaps within a controlled environment, thereby enabling further optimization of the surgical plan and execution, ultimately leading to more reliable outcomes (13).

7.3 Imaging and Virtual Planning

Particularly in the field of imaging, three-dimensional visualization methods in combination with computer-aided planning software have led to immense progress in the surgical approach and graft design (13,72). For computerized surgical planning (CSP), a three-dimensional craniofacial CT Scan can be taken of the donor and recipient (65). Feeding the scan data into a surgical operation planning software serves as a personalized patient-centered reconstructive approach and enables the creation of customized incision lines, as well as fixation points (74). Leveraging computer-aided design and manufacturing (CAD/CAM) workflows, this technique facilitates 3D printing of sterilizable, patient-specific cutting guides for intraoperative use (75). It also can be utilized to construct a 3D model of the defect, which serves as a useful intraoperative tool for evaluating the extent and depth of the graft procurements. This model enhances surgical precision by providing a detailed anatomical representation, facilitating meticulous planning and execution of the procedure (64). Especially in terms of skeletal segment procurement it ensures further refinement of an accurate and coordinated osteotomy of donor and recipient (63,68). When the maxilla and/or the mandible are included in the transplant, achieving proper occlusion is particularly difficult in cases of size mismatch. Additionally, accurate three-dimensional anatomical alignment of the donor midface onto the recipient's skull base is highly demanding and unattainable without virtual guidance (71). Another recent innovation in this field is computer-assisted intraoperative real-time navigation, which enables the integration and adaptation of the surgical plan created before the procedure in real time (59).

The most critical aspect of the procedure is the vascular anastomoses (39). In order to obtain an overview of the blood circulation, the anatomical vascular configuration and possible variants, it is advisable to conduct a preoperative CT angiography and in certain circumstances conventional angiography (55,68). Since the inception of facial transplantation, the optimal vascular approach for ensuring graft viability has been a topic of ongoing debate (76). Continuous communication between surgeons and radiologists is essential to preoperatively identify optimal target arteries, evaluate potential anastomoses and understand the three-dimensional relationships between vessels and other anatomical structures. Common recipient candidates exhibit highly intricate vascular anatomies resulting from severe injury and/or numerous previous attempts at reconstruction; hence, each procedure is custom-tailored based on the candidate's specific defects and vascular anatomy (39,56). This variability underscores the necessity of meticulous preoperative mapping based on the angiosome concept to ensure reliable microvascular anastomoses and minimize the risk of venous congestion and thrombosis, which are among the most frequent complications in microsurgical procedures (39). Although a single venous anastomosis may suffice to perfuse the facial tissues, typically two venous anastomoses are employed as a standard practice to uphold adequate outflow. By excluding vessels with unfavorable anatomical characteristics from anastomoses, the risk of vascular anastomotic complications can be significantly mitigated (39).

7.4 Face Restoration

To ensure the dignified return of the donor's body, there a multiple modern methods, employing diverse materials and molding techniques to craft masks that aim to restore the preoperative appearance as closely as possible (55,68).

One approach involves the use of alginate to create a mask and a reverse representation of the donor's facial features. Using this method, an orthodontic technician or anaplastologist creates a mask by casting it from acrylic resin and then enhances it with make-up using a photo from the donor as reference (77). After the graft is removed, the surgeon supervises the application of the mask to the donors face (55).

Another more recent approach is the use of three-dimensional printing on the basis of 3D images which can already be produced preoperatively. In this way, anaplastologists and invasive facial impressions are not required, reducing the risk of iatrogenic injury to the transplant (68). Studies have shown that a greater donor resemblance can be achieved with three-dimensional masks than with conventional methods (78). The manufacturing process entails a significant time investment spanning several hours. As such, it is crucial to strategize its execution efficiently and deliberately incorporate it into the transplantation schedule with meticulous consideration (77).

Emerging digital technologies, including improved image capture, manufacturing techniques and materials, offer promising potential for remotely producing facial prosthetics with enhanced precision, particularly in cases where full-face coverage is needed (77). Preserving the donor's facial identity through the use of facial prosthetics should be considered a moral imperative in the practice of facial transplantation, irrespective of the specific techniques employed. By acknowledging the prospect of conducting end-of-life ceremonies, the restoration of facial resemblance has facilitated an enhanced receptivity among donor families towards the donation process (57,78).

8 Surgical Procedure

Despite previous instances of successful FT performed immediately after injury, the ideal timing for conducting the procedure following an injury remains uncertain, particularly in light of donor shortages and stringent matching criteria (1,79). The conventional approach of initially treating the wounds with autologous therapy methods is currently still favoured (68). Due to unpredictable donor waiting times, it is also necessary to fully utilise these measures to achieve the best possible function and aesthetics. These can include skeletal stabilization, soft-tissue coverage, osteotomies, tendon repositioning, titanium implants for orbital floor reconstruction, tracheostomy and percutaneous gastrostomy (68). Nonetheless if feasible FT should be viewed as a primary treatment strategy when conventional methods are unlikely to succeed due to extensive defects (57).

8.1 Operation on the Donor – Graft Harvest

To keep the time of graft ischemia as low as possible, the operation on the donor and recipient commence simultaneously in adjoining operating rooms (68). In recipients with a history of multiple conventional surgeries and therefore an elevated risk of fibrosis, the procedure should be initiated earlier to accommodate the increased technical complexity and to ensure an adequate intraoperative time buffer (62). To uphold seamless communication within operating theatres and adherence to the predetermined surgical checklist, it is advisable to designate an additional individual, such as a member of the research team, for this specific task (63). One potential strategy involves positioning a primary surgeon along with an assistant surgeon on each side of the face, so that four surgeons are involved in the graft procurement (21). It is advisable to prioritize facial harvesting over other organ retrieval procedures, particularly when the donor still exhibits favourable hemodynamic conditions (66). This precautionary measure aims to mitigate potential adverse impacts on allograft vessels resulting from elevated catecholamine levels (57). During the organ retrieval process, catecholamines are often administered to sustain optimal blood perfusion, with dosages tailored according to the recipient's clinical status (55). If hemodynamic instability occurs, priority must shift to organ retrieval, and facial allograft harvest should be aborted or deferred (57).

Incision lines, vessel and nerve dissection, as well as the removal of soft tissue, muscles and bones is individually adapted depending on the extent of the recipient defect. The various institutions each have their own individual approaches and have differed accordingly in the sequence of the operational steps (21,62). Interinstitutional, the face harvesting process itself is often standardized and designed to be repeatable and executable irrespective of the recipient (66). Nevertheless, the standardised protocols must be constantly developed further as practical experience is gained and adapted to the individual needs of the recipient on a case-by-case basis (21).

To ensure that the face can be reached without restriction, the first step is to remove all face-associated tubes and perform a tracheostomy (55,57,64). Depending on the chosen restoration method a facial cast is then produced as already described above (72).

8.1.1 Neck Preparation

Right and left neck dissection is performed, starting the first skin incision for instance superior to the tracheostomy and being extended laterally to the posterior margin of the sternocleidomastoid muscle. Subsequently, the subplatysmal flap is raised and dissection around the anterior and external jugular veins is performed circumferentially (62,68). The retrograde approach, as well as transecting the posterior belly of the digastric muscle and the hypoglossal nerve, facilitates optimal exposure and the localization of the internal jugular vein and common carotid artery (62,68). This allows detection of the facial vein and the lingual and facial arteries (62). Vessel identification is facilitated by affixing vessel loops (64). Initially, it was presumed that bilateral facial and superficial temporal arteries were essential to ensure adequate perfusion in a full facial transplantation. Consequently, this approach necessitated the inclusion of the donor's parotid gland. However, it has now been shown that the bilateral facial arteries are sufficient as sole graft providers (21). If the upper jaw and/or zygoma is included in the transplantation, cadaveric studies found it necessary to encompass the internal maxillary artery along with both external carotid arteries, thereby guaranteeing sufficient perfusion across the entirety of the flap (39,80). All arteries are then carefully dissected following the natural direction of blood flow (64).

Opting for one or multiple feeding and draining vascular pedicles, depends on the anatomical consideration, without necessitating symmetry between sides. (56). Suitable arterial vessels for this purpose include the external carotid artery and facial artery (81,82). Correspondingly, appropriate venous vessels comprise the facial vein and external jugular vein (62,82). Neck dissection also contains the harvesting of lymph nodes and either preservation or removal of the submandibular gland (13,83). The hyoid bone, along with the floor-of-mouth muscles and tongue segments may also be incorporated into the allograft (83). Special attention is required to avoid injuring the facial artery, given its close anatomical proximity to the submandibular gland (21).

8.1.2 Facial Dissection

With the aid of a previously prepared silicate template of the recipient defect, the graft to be removed from the donor can be outlined with brilliant green (64). Marking lines are drawn for better orientation and precise realisation of the incision (68). A local anaesthetic containing epinephrine can be injected superficially along the incision site and the cheeks to minimise bleeding and enable facial nerve dissection (64,82). Then coronal face-lift incisions extending to the preauricular region are performed, followed by a sub-SMAS dissection towards the supraorbital rim, subsequently merging into a subperiosteal layer. The two branches of the frontal nerve (supraorbital and supratrochlear nerve) are located at their bony exit points. The surrounding bone is carefully sculpted with an osteotome to ensure an adequate nerve length is preserved (21).

Various techniques have been described for eyelid reconstruction, with the volume of tissue harvested tailored to the recipient's residual anatomy. Consequently, severing the donor's levator and orbicularis oris muscles may be indicated (21,83). In many cases, a conjunctival incision is employed as detailed below under "Orbital Reconstruction" (72). The canthal ligaments are then exposed at their bony attachments, allowing the facial graft to be carefully dissected through the deep soft tissue layer down to the lower orbital margin, thereby maintaining the full thickness of both eyelids (21).

For a partial face transplant, the incision lines can start at the root of the nose and run subciliary over to the preauricular folds (68). From there on they are extended to anterior aspect of the parotid gland, the neck, and supraclavicular to the jugulum (62,68).

8.1.3 Facial Nerve Dissection

Superior to the parotid gland, traversed by the facial nerve pathway, dissection of a skin flap is conducted until reaching the depth of the masseteric fascia (13). Facial nerve functionality testing, detection and individual tagging of zygomatic, buccal and marginal mandibular branches is performed on both sides using intraoperative stimulation (64,68). Identification of the marginal mandibular branch is carried out during submandibular gland removal and facial nerve trunk detection is performed by raising the back areas of the parotid glands (64). If the parotid gland is excluded from the transplant, the parotid duct is ligated (21). The next step is transecting the nerve trunk at its most proximal segment (62).

8.1.4 Osteotomies Preparation

In preparation for osteotomies, infraorbital incisions are extended to the medial orbital rim and the anterior maxilla, in a deep dissection level for preserving the angular arteries and maintaining their blood supply (21). The infraorbital nerves are transected at their most proximal points within the orbits and retracted towards the skin (82). Also the inferior alveolar nerves should be meticulously preserved in maximal length (62).

For intraoral mucosal resurfacing a cut is made within the oral cavity at the soft palate that reaches from the retromolar trigone to the floor of the mouth, following the mucosal edges of the mandibular ramus. It extends upwards to the posterior soft palate, with careful consideration to protecting the buccal and palatal mucosae (62,82). Beneath the buccal fat pad, the buccal nerve is identified and carefully dissected (21,83). To guarantee a tension-free intraoral closure, the donor incisions are planned to incorporate broad soft tissue cuffs at the levels of the soft palate and floor of the mouth (62). Conserving bony-musculocutaneus complexes as well as the buccal and sub-orbicularis fat compartments can help prevent soft-tissue sagging and enhance a more natural facial silhouette (71).

8.1.5 Osteotomies

By utilizing a previously generated three-dimensional print of the recipient's osseous defect, the bony segment can be tailored to fit more precisely (65). With the use of prefabricated cutting guides, BSSO and Le Fort III Osteotomies are carried out (23,68,72,83). To ensure proper alignment in the center of the face, the nasal bone pyramid is detached with a curved osteotome and included in the allograft, enabling the anterior mobilization of the midfacial segment (21). If the maxillary artery is not included as a vascular pedicle within the allograft, the external carotid arteries can be ligated superior to the origin of the facial artery to control potential bleeding during Le Fort III Osteotomies (82).

The graft is elevated in a cranial-to-caudal direction below the piriform aperture, and in a lateral-to-medial trajectory approaching the modiolus. Before releasing the caudal portion of the graft, the vascular pedicles are carefully identified and preserved (21).

8.1.6 Graft Perfusion and Ischemia Time

An Indocyanine Green Angiography (ICGA) is then conducted to monitor graft perfusion objectively prior to separating the vascular pedicles (65). The pure dissection time can vary depending on the extent (partial face transplant, full face transplant) and usually take up to 12 or more hours (62,68,72). If other organs have been designated for removal, solid organ procurement is now performed and a heparin infusion is administered (68). Facial allograft ischemia time should be kept as low as possible and begins with cutting the vascular pedicles, followed by back table preparation and graft infusion with University of Winsconsin (UW) solution (62,68,72,83). The UW solution is the most widely utilized medium for abdominal organ preservation, designed to maintain graft viability during the interval between organ retrieval and implantation. During this ischemic period, when perfusion with oxygen and nutrients is interrupted, the graft is inherently vulnerable to ischema reperfusion injury (IRI). The accepted standard for mitigating IRI involves hypothermic storage and transport following thorough flushing with a cold preservation solution, containing osmotic and oncotic buffering agents(84,85). Currently, there is no definitive threshold for acceptable ischemia duration (57). Since the muscles in the allograft are the most sensitive structure, a maximum ischaemia time and reperfusion within 4 hours cold ischaemia time is recommended (21,57). At the end of the donor operation, the preformed facial restoration mask is applied (55,83).

Table 6. Composition and Functional Components of the UW Preservation Solution
Based on references from (84)

Functional category	Representative component(s)
Osmotic	Raffinose/Lactobionate
Buffer	PO4
Oncotic	Hydroxyethyl starch (HES)
Na^+	Low
K^+	High
Antioxidant/IRI Protection	Adenosine, Glutathione, Allopurinol

8.2 Operation on the Recipient

As mentioned before it is advisable to establish a tracheostomy prior to the transplant procedure, if not already in situ, to gain full access to the operating field (63,83). The operation is performed under general anaesthesia via tracheostomy tube and it is recommended that two main surgeons and one assistant surgeon are placed on each side of the patient, who is positioned supine. At this stage, induction immunosuppressive therapy may be initiated (21). The initial recipient débridement which mirrors the donor's procurement, comprises neck dissection, facial dissection, facial nerve dissection, osteotomy preparation, BSSO and osteotomies. However, the dissection process may necessitate variations in the sequence of steps and can be performed in a reverse way (62).

The common and external carotid arteries, as well as the internal and external jugular veins, along with their respective branching vessels, are meticulously dissected in a circumferential manner. Facial nerve branches and sensory nerves (supraortbital, infraorbital, inferior alveolar and mental nerves) should be protected and severed as far as feasable (68,72,82). The parotid duct should be retained (68). In cases where recipient muscles (for instance orbicularis oris) are retained, attention must be directed towards preserving the innervating nerve branches (62).

A conventional BSSO approach is utilized to expose the mandibles, using intraoral incisions that extend anteriorly along to the parotid ducts, towards the maxillary dentition and hard palate. These incisions are shaped to include broad soft tissue margins. Dissection beneath the mucosa and periosteum progresses distally to separate the connection between the hard and soft palate. The insertions of the masseter muscles proximal to the osteotomy sites remain undisturbed (62). Subsequently, Le Fort III Osteotomies are executed using predesigned cutting guides (68).

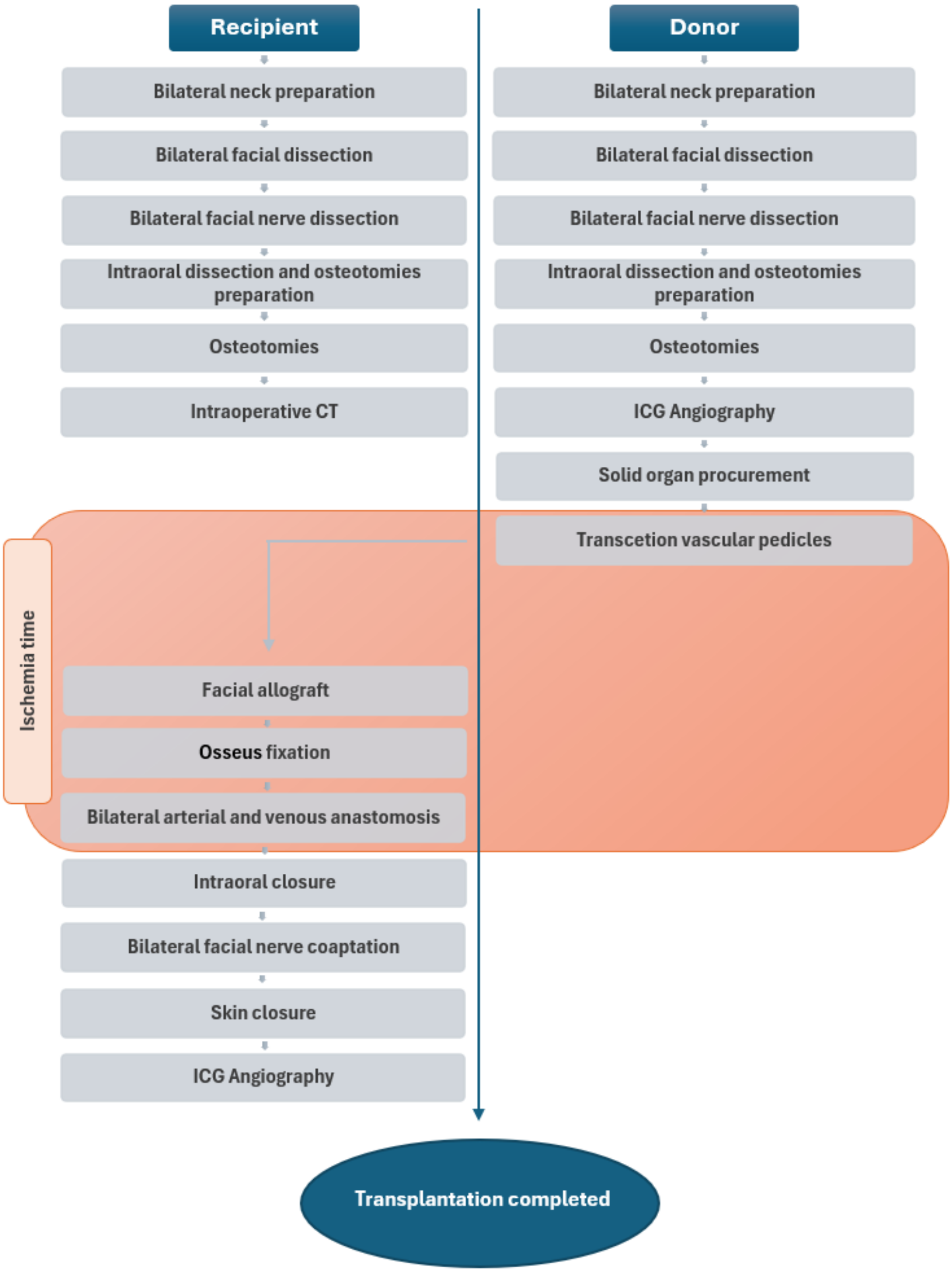

Figure 13. Schematic timeline of a representative FT scenario visualized by the author
Based on references from (68)

8.2.1 Osseus fixation

As soon as the facial allograft is in the operating room, the bilateral osseus fixation can be done CT-guided (62). Positioning and securing the bony elements before performing vascular anastomosis prevents the vascular pedicles from kinking and ensures a stable operating field (13). Real-time navigation ensures precise placement of the allograft skeletal segments by comparing the planned positioning with the actual placement. Various approaches were employed to achieve stable bony fixation across patients. A common approach for rigid fixation is using miniplates for the zygoma and bicortical positional lag screws for the mandible to ensure firm cohesion and effective stability (62,68). Nasal bone fixation may involve simple methods such as titanium plate fixation or more complex approaches utilizing modular midface plating systems (21). The incorporation of calvarial segments can be utilized to mitigate the risk of postoperative brow ptosis (63).

8.2.2 Vascular Anastomosis

Ischaemia period ends with completion of the vascular anastomosis on one side and clinical signs of graft perfusion. Subsequently, the anastomosis on the contralateral side is performed (23,68). As described above, this step and the number of anastomoses depend on the extent and the vascular situation. The following vessels can be considered for arterial anastomoses: common carotid artery, external carotid artery, and facial artery (23,62,68). Consideration should be given to including the maxillary artery to mitigate the risk of palatal hypoperfusion (76). In procedures involving allografts that encompass the upper face and scalp, it may be necessary to incorporate the superficial temporal arteries, utilizing the external carotid artery as the primary source vessel (39). The recipient’s and donor’s internal jugular veins are typically used for end-to-side venous anastomoses, yet the following vessels can also be used: external jugular vein, anterior jugular vein, facial vein (13,23,62).

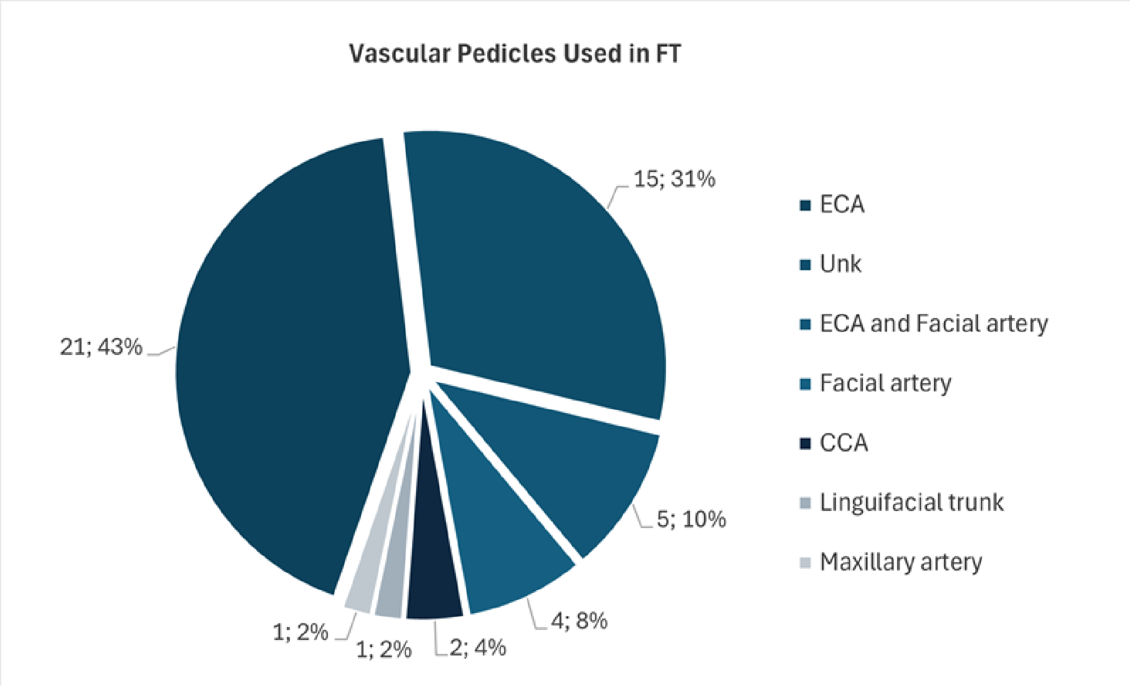

Figure 14. Vascular pedicles used in FT
(n=49) **Abbr.:** ECA: External Carotid Artery; Unk: Unknown; CCA: Common Carotid Artery

Ensuring precision for the delicate suturing and therefore optimizing success of the vascular connections, these anastomoses are conducted under the microscope and may be performed with the aid of microvascular coupling devices (13,62). Surgical strategizing intricately assesses and aligns the caliber and length of both recipient and donor vessels. When these parameters exhibit a high degree of compatibility, the option of conducting end-to-end anastomoses emerges, characterized by its simplicity and reduced blood flow disturbance (39). However, instances often necessitate alternative techniques, like arterial end-to-side (63), sleeve and „fishmouth“ anastomoses, particularly in cases marked by substantial disparities in vessel diameter, which elevate the technical complexity of anastomoses and the dependability of the resultant conduit. Additionally, abrupt changes in vessel caliber are discouraged due to their propensity to induce turbulence and foster platelet aggregation (86). ICGA may be performed at this stage to evaluate graft perfusion (62).

8.2.3 Nerve Coaptation

Bilateral coaptation of all nerves incorporated into the allograft is then carried out (23,68). The supraorbital nerve, infraorbital nerve, alveolar nerve and the branches of the facial nerve (zygomatic, buccal and marginal mandibular branch) are sutured as a primary, tensions-free, end-to-end neurorrhaphy (62,68,72). To verify intact muscular function electrical stimulation of the facial nerve branches may be conducted (72). For full face transplants, the coaptation is done at the facial nerve trunk. In cases of partial transplant, the coaptation of the facial nerve is performed either at the lower or higher branch of the first division (66). It is advisable to conduct nerve coaptation in a distal location close to the target muscles to mitigate the potential for involuntary contraction of facial muscles (21,83). Whenever feasible, sensory nerve coaptation should be performed (13).

It can be necessary to use nerve grafts as a bridge to close potential gaps between recipients and donors anatomic structures. Hypoglossal nerve, vagus nerve, thoracadorsal nerve, and greater auricular nerve of the donor have been used for motor nerve graft (21–23).

8.2.4 Oral Reconstruction

The intraoral reconstruction is achieved by mucosa and muscle repair. Great emphasis is placed on repairing the muscles that are essential for the swallowing process. This includes the mylohyoid and infrahyoid muscles. A dental splint build prior can be inserted and stable occlusion is generated through jaw screws (68). In cases of pharyngeal constriction, the hyoid bone can be advanced anteriorly via a bone anchor suture affixed to the mandible (62). Residual soft tissue is contoured to create a tension-free junction at the nasal and intraoral mucosa (63).

8.2.5 Orbital Reconstruction and Eye Transplant

Physiological intercanthal width can be accomplished using titanium barbed sutures affixed to screws placed within the orbit (68). For orbital floor reconstruction implants made out of porous polyethylene can be used (23). A transconjunctival incision enables preservation of the donor’s eyelid skin, the tarsal plates and orbicularis oculi muscles (72). Meticulous preservation of motor nerves and periorbital structures, as well as meticulously repositioning the eyelid skin, can maintain eyelid mobility and blink reflex, as well as minimize the risk of ectropium and eyelid retraction (71). Precise rearrangement of orbicularis muscles can also be achieved through subciliary incisions (68). Strategic planning of osteotomy lines allows for preservation of the lateral canthi and maintenance of medial canthal tendon continuity with the naso-orbitoehtmoidal segment. Customized coronal osteotomies in the nasofrontal region are designed to safeguard both the medial canthal structures and the lacrimal drainage system (73).

Following extensive preclinical work in ocular transplantation, encompassing animal models and cadaveric simulations, the first combined eye and face allotransplantation was performed in 2023 (2,87,88). This pioneering experimental procedure poses formidable microsurgical challenges to minimize retinal ischemia and maintain structural and neural integrity of the optic nerve. The donor's allograft incorporated a long anterior branch of the superficial temporal artery and its accompanying vein for the anastomosis to establish vascular inflow and outflow. This is necessary because facial allografts are conventionally perfused via pedicles of the external carotid artery and its branches, whereas the ophthalmic artery derives from the intracranial circulation. Next, the donor's cranial vault and orbital cavity were carefully opened under preservation of periocular and facial soft tissue. They were prepared to expose the ophthalmic artery and veins, the internal carotid artery, and both the motor and optic nerves. The latter was transected at the level of the optic chiasm. The ophthalmic vessels were subsequently anastomosed to the previously harvested superficial temporal vessels at their respective origins, resulting in a total warm ischemia time of 25 minutes. Face transplantation was then carried out as described, with addition of orbital debridement and epineural coaptation of the recipient's optic nerve. This anastomosis remained patent intra- and postoperatively, and at one year post-transplant the globe was viable, although without light perception, corneal sensitivity or extraocular motility (2).

8.2.6 Soft Tissue and Skin Closure

To generate an aesthetically pleasing and symmetrical appearance, soft tissue should be carefully repositioned orientated to the recipient to maintain contour and anatomical integrity (21). Reattaching soft tissue to the periosteum of the zygomatic bones reduces ptosis and enhances facial aesthetics. Surplus skin can be excised, with incisions strategically placing within the patient's natural wrinkles (68). Residual neck and preauricular skin can be retained to enable biopsies, accommodate swelling and minimize suture-line tension post-transplantation (83). The transplantation concludes with skin closure and a final examination of graft perfusion using ICGA (73).

Such a lengthy medical procedure is highly haemorrhagic and scheduled to take up to 30 hours in total (73,83). It is to be expected that the recipient will require several units of packed red blood cells and platelet concentrates, as well as fresh frozen plasma and albumin (68,83).

8.3 Secondary Procedures

Numerous teams have performed secondary revision, as they may be necessary as an elective procedure for aesthetic reasons or unexpected functional corrections (4,66). They can highly vary in timepoints of need and have been categorized by Diep et. al in Soft-tissue Revisions, Craniofacial Skeleton and Dental Revisions, Oronasal Cavity and Salivary Glands Revisions, Ocular Revisions and Additional Revisions (89). Also a retransplantation falls under a secondary procedure and is recognized as a viable treatment option in the case of graft failure or allograft loss (57).

Soft-tissue revisions are most common and often required due to volume loss, laxity, gravitational droop and atrophy, therefore procedures like excess skin and fat removal, blepharoplasty, canthopexy, brow lift and scar revisions are performed (4,66,89).

Craniofacial Skeleton and Dental Revisions persist highly prevalent and should be directed by cephalometric analysis and bone healing (90). They include Le Fort Osteotomy advancements, malocclusion correction, dental restoration, orthodontic braces and elastics treatment (4,62,66). Also TMJ-related coronoidectomy or condylectomy, ossointegrated implants and donor teeth extraction may be required (89).

Oronasal Cavitiy Revisions mainly involved procedures due to wound healing disorders, as detailed in a following section, and had to be performed primarily in cases of transplants involving the mandible and the maxilla (89). To manage complications such as salivary leakage and sialocele formation, interventions including botulinum toxin injections, duct stenting and glandular drainage are frequently employed (83,89)

9 Posttransplant Care

9.1 Immunosuppressive Therapy and Infection Prophylaxis

To date, no standardized immunosuppressive protocol has been established. However, individual institutions have developed their own center-specific protocols based on clinical experience and interdisciplinary collaboration with immunologist and transplant specialists (1,23,63,68). These regimens are largely modelled after protocols used in solid organ transplantation (3).

Induction therapy is typically initiated intraoperatively to ensure potent immunosuppression during the critical early postoperative phase, when rejection risk is at its peak (3,63). Agents such as tacrolimus, MMF, rATG, rituximab (anti-CD20), alemtuzumab (anti CD-52) and corticosteroids have been employed in varying combinations, tailored to each patient by the respective clinical teams (1,23,63,68,83).

For maintenance therapy, although dosage and timing of administration varied, the teams mostly used the immunosuppression protocol for kidney transplants: a steroid taper, mycophenolate mofetil and tacrolimus (1,60,63). Although skin and mucosa are more immunogenic than solid organs, VCA immunosuppression is still largely based on solid organ transplantation protocols. Recent findings indicate that the mucosa could be particularly susceptible to rejection, underscoring the need for VCA-specific regimens. Current research focuses on tolerance induction through more targeted treatment options of the patient's immune system (3). Plasmapheresis with albumin exchange and extracorporeal photopheresis was additionally employed as part of the therapeutic regimen (63,66).

During postoperative period, standard antimicrobial prophylactic regimen against opportunistic infections is administered, comprising antibiotics (e.g. trimethoprim-sulfamethoxazole), antiviral (e.g. ganciclovir, valganciclovir, acyclovir) and antifungal (e.g. fluconazole, anidulafungin) drugs (62,63,71).

9.2 Clinical Assessment and Rejection Monitoring

A clinical assessment in predefined intervals is necessary to monitor progress and identify possible complications at an early stage (66,68). It should contain important blood values (liver, pancreas, kidney), immunosuppressants plasma concentrations, serologic screening for viral infections, donor specific antibodies test (63), electromyography and imaging (CT, MRI), as well as skin and mucosa biopsies. The latter was conducted in a Canadian transplant aftercare program on a weekly basis until postoperative week 24, followed by intervals of every 2 to 3 weeks through week 44 (62). Clinical inspection should be carried out in detail so that signs of rejection, such as erythema and oedema, which are typical in early stages after transplantation, are noticed (66). Particularly areas that are difficult to visualize but prone to complications, such as intraoral sites, should be carefully examined post-transplant (89,91).

9.3 Functional Therapy

Speech therapy, physical exercises to improve range of motion and sensory re-education should be incorporated into the rehabilitation program and be performed daily for the first few weeks (23,66). It should also include functional evaluation of mastication, olfaction, swallowing and facial expression (23).

9.4 Psychological and Psychiatric Support

Therapeutic support should not be limited to physical needs, but should also contain psychological factors such as anxiety, depression, self-esteem and perception of quality of life. Various instruments such as rating scales, assessment tools and questionnaires can be used for this purpose (23). In the postoperative course, it may be necessary to adjust psychiatric care and continued emphasis should be placed on sustaining patient engagement with social workers and mental health professionals (83).

10 Complications

10.1 Skeletal and Dental Complications

Major adverse events have been documented with bone-including facial transplants (90). Favorable outcomes of initial face transplants prompted the addition of the maxilla and mandible. This inclusion can lead to skeletal deformity, malocclusion, dental and periodontal diseases, bone infections and tongue retroposition, often requiring corrective secondary surgery and teeth extraction (62,90,91). Therefore careful attention to the donor and recipient's skeletal size matching, bone healing processes, and the long-term condition of the dentition needs to be placed (90). It may be necessary to use palatal and occlusal splints during the first few months after the operation (62).

10.2 Impaired Wound Healing

Difficulties like wound dehiscence, necrosis and fistula formation have been reported despite sufficient perfusion and carefully executed tissue closure, emphasizing the issue of wound healing when faced with immunosuppressive therapy (89). These complications often occur intraorally, as floor-of-mouth dehiscence and fistulas at the hard and soft palate (68,83,90). The latter could be the result of poor blood flow and sole graft supply through the facial artery at that transition zone. Especially when transplanting Le Fort III segments it could be necessary to include the maxillary artery to avoid these complications. Cadaveric studies suggest that through adjusting the Le Fort III osteotomies the maxillary artery can be preserved thereby enhancing arterial supply to the palate (76). The inclusion of salivary glands has been linked to a high incidence of postoperative complications. Sialocele formation may promote local tissue autolysis, delay wound healing, facilitate fistula development, and thereby increase risk of infection (24).

10.3 Graft Rejection

Among all complications, graft rejection is the most prevalent (3). Despite considerable variations in induction and maintenance procedures, the vast majority of face transplant recipients have as predicted gone through one or more episodes of acute rejection, with varied degrees of clinical and histopathological severity (62,92). Most rejection episodes were histopathologically categorized as Banff grade II or III (3). Usually rejection can be easily controlled through escalated systemic immunosuppressive measures or intravenous immunoglobulin (56,66), however it may be challenging to detect without histopathological confirmation due to the absence of clinical manifestations (62). Ensuring precise identification of acute rejection is essential, since unwarranted administration of immunologic treatments can elevate the patient's risk for infection and cancer (92). It should be mentioned that acute cell-mediated rejection episodes usually do not result in functional or severe cosmetic damage, yet skin hyperpigmentation has been observed (66).

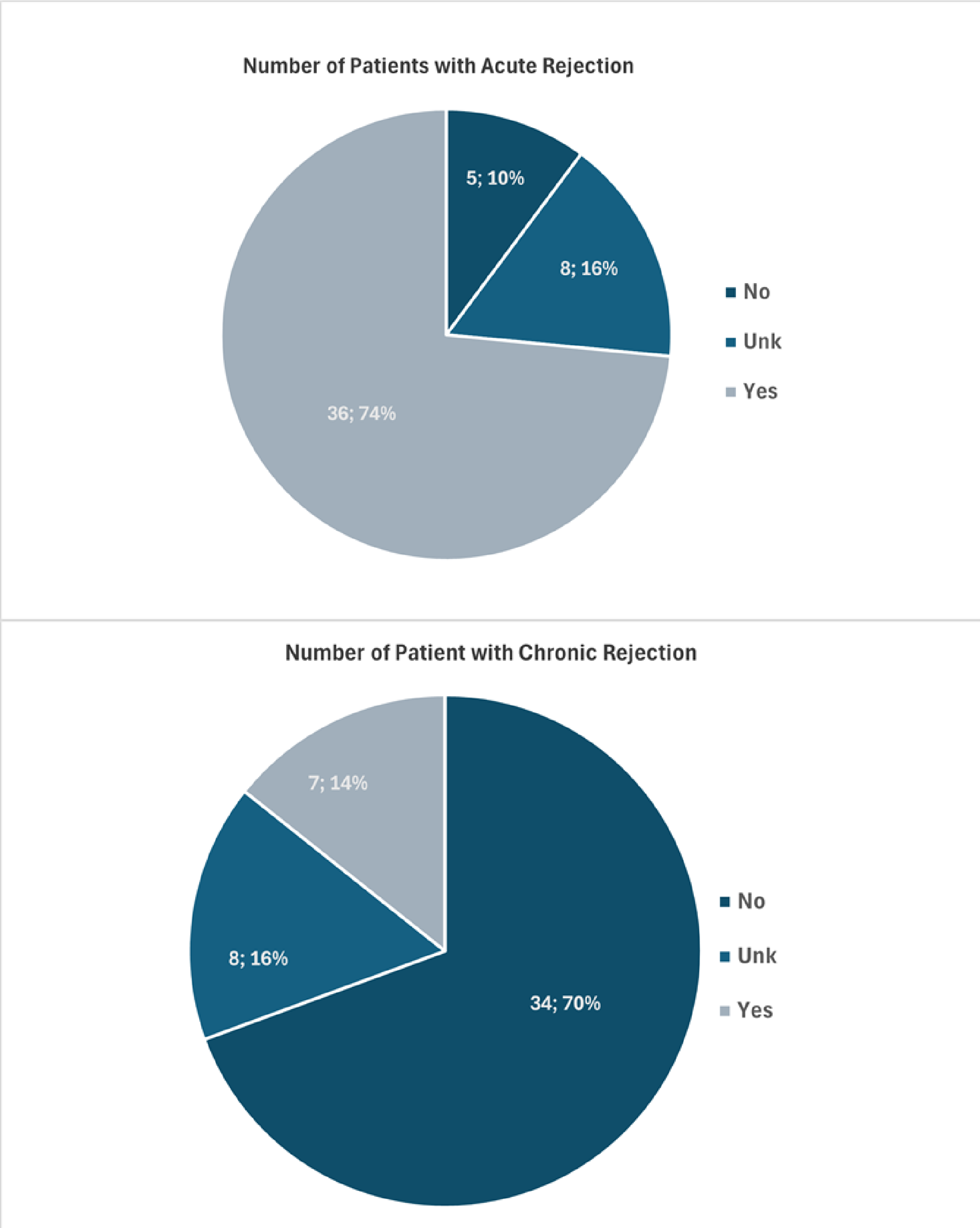

Figure 15. Rejection status in FT recipients
(n=49) Based on references from (12)

10.4 Complications associated with Immunosuppression

The biggest challenge in FT and other skin-containing VCAs is definitely the health concerns associated with life-long high-dose immunosuppressive medication (1). This posttransplant therapy is associated with various metabolic complications such as renal insufficiency and acute kidney injury (tacrolimus toxicity), therefore various groups now focus on reducing the use of nephrotoxic immunosuppressive agents in order to mitigate renal injury (4,66). Furthermore it is closely associated with diabetes, malignancy, avascular necrosis and (opportunistic) infections (56,60,62).

Systemic and local post-transplant infections occur frequently, with viral pathogens being the most common, followed by bacterial and fungal causes (3). Infections were caused by pathogens such as CMV, HPV, HSV, *Pseudomonas spp*. and others (66). Among others they included ventilator associated pneumoniae, *clostridium difficile* colitis, CMV-oesophagitis, dacryocystitis and cutaneous mucormycosis (62).

While infections and metabolic issues are frequently reported after FT, severe complications such as malignancies and fatal outcomes are likely underestimated. The deaths of at least seven recipients have been reported, attributed to various causes including the occurrence of malignancies such as lymphoma and EBV-related tumours, systemic infections and respiratory failure, and in one case suicide (3,4). A 2024 international consensus statement proposed criteria for defining FT failure. These include (1) permanent graft decline caused by surgical complications, immune mediated rejection or non-immune vasculopathy, (2) explanation necessitated by systemic complications or malignancy, (3) death attributable to immunosuppression-related toxicity, and (4) mortality resulting from otherwise “avoidable” external factors such as suicide or non-adherence (57).

11 Outcomes

Published results to date have generally initially shown promising functional and cosmetic benefits, with notable improvements in motor and sensory recovery as well as essential face functions (56). However, the extent of improvement varied widely amongst patients ranging from minimal gains to substantial and clearly observable functional recovery (62). Developing a validated outcome metric is particularly challenging given the low number of procedures performed. So far, only a few long-term outcome studies have been made public (67,93). For defining proven processes for facial transplantation, based on researched evidence, it is necessary that all teams publish their long-term outcomes (67).

11.1 Sensate, Motor and Functional Recovery

Facial muscular movement expressing emotions plays a pivotal role in the substantial recuperation post-facial transplantation, significantly influencing the patient's quality of life (94). Presently, there exists no standardized assessment approach for evaluating muscle recuperation and functional outcomes subsequent to facial transplantation (93). So far, methods such as manual muscle testing according to Daniels and Worthingham and facial surface electromyography have been utilized (95–97). This allowed for objective verifying of successful motor muscle activation (83,96). However, a multicenter international study conducted by Dorante et al. in 2023 introduced an innovative approach employing AI-controlled software to quantitatively analyse facial expressions in face transplant recipients non-invasively and objectively. The findings revealed a median motor recovery rate of 36.7% post-transplantation. Furthermore, it was observed that distal facial nerve coaptation led to superior motor function recuperation in comparison to coaptation of other nerve branches (93).

Functional and motor outcomes proved highly individual among patients, with frequent issues such as incomplete oral closure, swallowing difficulties and impaired speech (66,68). Nonetheless, in several cases patients were still able to achieve intelligible speech and oral intake, thereby eliminating the need for enteral nutrition via jejunostomy (66,68,83). Even if signs of motor regeneration appear after just a few months, facial expressions like smiling can be severely restricted (62,68).

Regarding respiratory and phonation rehabilitation, face transplants have exhibited remarkable progress, enabling patients to perform typical functions such as speech, breathing and blowing (56,83,96). In line with these functional improvements, a tracheostomy was no longer required (66,68).

Sensory reinnervation may take several months to occur and shows considerable variability among patients, ranging from near-complete satisfactory facial touch sensation to partial or insufficient recovery (62,83,96).

11.2 Aesthetic Outcome

Aesthetic outcomes have also been reported to vary, reflecting the inherent subjectivity of their evaluation and the difficulty of establishing objective criteria (83). An innovative strategy employs artificial intelligence algorithms, serving as an objective means of outcome assessment. Knoedler et al. applied the CAARISMA ® ARMM (AI Research Metrics Model) to evaluate aesthetic results in 14 facial transplant recipients. The Facial Youthfulness Index (FYI), Facial Aesthetic Index (FAI) and Skin Quality Index (SQI) were compared pre- and postoperatively, with all indices demonstrating postoperative improvement associated with enhanced aesthetic appearance (98).

11.3 Psychological Aspects and Quality of Life

Psychosocial outcomes can be assessed using measures such as health-related quality of life, sense of identity, degree of social reintegration and resumption of employment (57). Recipients may encounter identity-related challenges stemming from the anticipated changes brought about by the transplantation procedure (56). So far the patients have expressed overall satisfaction with their new facial appearance, which has subsequently facilitated the restoration of social relationships (62,66,83). Psychological enhancements have been noteworthy, facilitating the reintegration of patients into broader societal contexts, including social networks and professional environments (56,96). To obtain a comparison of the quality of life pre- and postoperatively, validated questionnaires such as the *15 Dimensions of Health-Related Quality of Life Questionnaire* (15D), the *European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Head and Neck Module 35 (*EORTC QLQ-H&N35) and Facial Disability Index can be employed to evaluate physical, psychological and social function. In this context, an increase in quality of life was mostly observed (2,62,66,83).

Nonetheless, one-year follow-up assessments also revealed reports of worsening mental health, deteriorating physical health, as well as pain and discomfort in some cases, particulary during episodes of acute rejection (96). It has been found that recipients who have undergone face transplantation, due to self-inflicted injuries, and have previously already struggled with mental illness, had a less pronounced psychological benefit and a worse compliance (66,67,99).

12 Conclusion and Future Directions

While some argue that facial deformities do not warrant the risks associated with high-risk immunosuppressive treatment, patients experiencing major functional impairments may contend that the disfigurements significantly diminish their quality of life (60). The integration of multidisciplinary knowledge and advances in procedural and immunologic techniques allows for the successful reconstruction of cases once considered unsalvageable (63). Technological and logistical advancements have significantly propelled progress in the field, so that a facial transplant procedure can be employed as a feasible solution for addressing significant facial deformities in selected patients (13). It presents a source of newfound optimism for individuals afflicted by severe consequences stemming from irreversible facial injuries, particularly when conventional reconstructive methods have reached their limits or have failed to achieve the desired reconstructive objectives. A multitude of treatment options are extensively documented, yet frequently pose significant challenges and may fall short of attaining an optimal outcome (72). Patients with complex traumas are likely to benefit from expanding therapeutic approaches and improved well-being, driven by active research, modern innovations and measures to improve clear reporting and broader applicability (100).

Great emphasis should be placed on improving functional and aesthetic outcomes and standardizing perioperative management, as the feasibility of the procedure has long been established (66,72). A structured and standardized assessment protocol for facial transplantation candidates should be developed by a multidisciplinary team to ensure clinical and psychosocial suitability (57). A significant challenge still lies in devising reconstructive strategies tailored to individual patients, given the wide variation in facial defects among potential candidates. This variability, coupled with the limited number of procedures performed thus far, has hindered the standardization of surgical face transplantation techniques (65). Establishing and executing standardized approaches is crucial for ensuring patient safety, enhancing quality, and achieving consistent outcomes in intricate surgical procedures (13). In addition, after a detailed risk-benefit assessment, facial transplantation should be considered as a primary treatment option if the extent of the defect suggests that traditional reconstructive methods would likely result in unsatisfactory outcomes (57).

Although complex transplant procedures are now technically feasible and improving in form and function, long-term success will depend on better understanding immune interactions. In addition to standardised assessments and surgical procedures, a uniform protocol and research regarding life-long immunosuppressive therapy should be implemented (3). This should also include protocols to assess graft rejection, including biopsy schedule, vascular evaluation and measurement of serum antibody titers (57).

In order to be able to determine and evaluate the long-term risk-benefit ratio and therefore the legitimacy of face transplants, great importance must be attached to systematic and complete follow-up studies with predefined primary and safety endpoints after future procedures (66). Therefore it is also critical to scrutinize the prevailing emphasis on surgical benchmarks, as this overlooks patient-reported self-perception and psychosocial outcomes essential for a fully comprehensive evaluation (101). Therefore improved effort in collection and reporting of data, preferably through the establishment of an international data registry, after face transplantations is needed. Detailed patient-focused narratives that illuminate post-transplant experiences, challenges and social-support dynamics should also be included (57).

A variety of factors determine and complicate the feasibility of facial transplantation, including the medical institution and equipment, multidisciplinary collaboration, administration, the ethical and legal basis typical of the country, social values and norms. Through collaborative efforts and transparent knowledge sharing, a paradigm shift in facial reconstruction can be achieved, offering renewed hope to patients with no other alternatives (56).

13 References

1. Rifkin WJ, David JA, Plana NM, Kantar RS, Diaz-Siso JR, Gelb BE, et al. Achievements and Challenges in Facial Transplantation. Ann Surg. 2018 Aug;268(2):260–70.

2. Ceradini DJ, Tran DL, Dedania VS, Gelb BE, Cohen OD, Flores RL, et al. Combined Whole Eye and Face Transplant. JAMA. 2024 Nov 12;332(18):1551–8.

3. Huelsboemer L, Boroumand S, Kochen A, Dony A, Moscarelli J, Hauc SC, et al. Immunosuppressive strategies in face and hand transplantation: a comprehensive systematic review of current therapy regimens and outcomes. Front Transplant. 2024 Mar 6;3:1366243.

4. Sosin M, Rodriguez ED. The Face Transplantation Update: 2016. Plast Reconstr Surg. 2016 Jun;137(6):1841–50.

5. Hernandez JA, Miller J, Oleck NC, Porras-Fimbres D, Wainright J, Laurie K, et al. OPTN/SRTR 2020 Annual Data Report: VCA. Am J Transplant. 2022 Mar 1;22:623–47.

6. Alberti FB, Hoyle V. Face Transplants: An International History. J Hist Med Allied Sci. 2021 Jun 28;76(3):319–45.

7. In your face. New Sci. 1998 Jan 23;157(2123):18.

8. Morris PJ, Bradley JA, Doyal L, Earley M, Hagan P, Milling M, et al. Facial transplantation: a working party report from the Royal College of Surgeons of England: Transplantation. 2004 Feb;77(3):330–8.

9. Clark J. Face transplants technically possible, but "very hazardous." CMAJ. 2004 Feb 3;170(3):323.

10. Barker JH, Furr A, Cunningham M, Grossi F, Vasilic D, Storey B, et al. Investigation of Risk Acceptance in Facial Transplantation. Plast Reconstr Surg. 2006 Sep;118(3):663–70.

11. Ramly EP, Kantar RS, Diaz-Siso JR, Alfonso AR, Shetye PR, Rodriguez ED. Outcomes After Tooth-Bearing Maxillomandibular Facial Transplantation: Insights and Lessons Learned. J Oral Maxillofac Surg. 2019 Oct;77(10):2085–103.

12. Hadjiandreou M, Pafitanis G, Butler P. Outcomes in facial transplantation - a systematic review. Br J Oral Maxillofac Surg [Internet]. 2024 Jun;62(5). Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b53t0b66.han.medunigraz.at/38637216/

13. Kantar RS, Alfonso AR, Diep GK, Berman ZP, Rifkin WJ, Diaz-Siso JR, et al. Facial Transplantation: Principles and Evolving Concepts. Plast Reconstr Surg. 2021 Jun;147(6):1022e.

14. Mohan R, Borsuk DE, Dorafshar AH, Wang HD, Bojovic B, Christy MR, et al. Aesthetic and Functional Facial Transplantation: A Classification System and Treatment Algorithm. Plast Reconstr Surg. 2014 Feb;133(2):386–97.

15. Glazier AK. Regulatory oversight in the United States of vascularized composite allografts. Transpl Int. 2016 Jun;29(6):682–5.

16. Rahmel A. Vascularized Composite Allografts: Procurement, Allocation, and Implementation. Curr Transplant Rep. 2014 Sep;1(3):173–82.

17. Thuong M, Petruzzo P, Landin L, Mahillo B, Kay S, Testelin S, et al. Vascularized composite allotransplantation – a Council of Europe position paper. Transpl Int. 2019 Mar;32(3):233–40.

18. U.S. Department of Health and Human Services. Organ Procurement and Transplantation Network, Final Rule: 42 CFR § 121.2 Definitions. Code Fed Regul Title 42 Public Health. 2014 Jul;§ 121.2.

19. European Parliament, Council of the European Union. Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation. Off Jorunal Eur Union. 2010;14–29.

20. Barret JP, Serracanta J. LeFort I osteotomy and secondary procedures in full-face transplant patients. J Plast Reconstr Aesthet Surg. 2013 May;66(5):723–5.

21. Pomahac B, Pribaz JJ, Bueno EM, Sisk GC, Diaz-Siso JR, Chandawarkar A, et al. Novel Surgical Technique for Full Face Transplantation. Plast Reconstr Surg. 2012 Sep;130(3):549–55.

22. Alam DS, Papay F, Djohan R, Bernard S, Lohman R, Gordon CR, et al. The Technical and Anatomical Aspects of the World's First Near-Total Human Face and Maxilla Transplant. Arch Facial Plast Surg. 2009 Dec;11(6).

23. Siemionow M, Papay F, Alam D, Bernard S, Djohan R, Gordon C, et al. Near-total human face transplantation for a severely disfigured patient in the USA. The Lancet. 2009 Jul;374(9685):203–9.

24. Frautschi R, Rampazzo A, Bernard S, Djohan R, Papay F, Gharb BB. Management of the Salivary Glands and Facial Nerve in Face Transplantation. Plast Reconstr Surg. 2016 Jun;137(6):1887–97.

25. Holtmann H, Hackenberg B, Wilhelm SB, Handschel J. BASICS Oral and Maxillofacial Surgery with Plastic Operations in the Head and Neck Region. 3rd ed. Munich: Elsevier; 2024. 118 p.

26. Watanabe K, Shoja MM, Loukas M, Tubbs SR, Tubbs RS. Anatomy for Plastic Surgery of the Face, Head and Neck. Stuttgart: Thieme; 2016. 226 p.

27. Hohman MH, Patel BC, Waseem M. Le Fort Fractures. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Aug 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK526060/

28. Monson LA. Bilateral Sagittal Split Osteotomy. Semin Plast Surg. 2013 Aug;27(3):145–8.

29. Sobotta J, Paulsen F, Waschke J. Sobotta - Atlas of Human Anatomy, Vol.3: Head, Neck and Neuroanatomy. 17th ed. Munich: Elsevier; 2023. 118 p.

30. Schünke M, Schulte, Erik, Stefan, Cristian. Head, Neck, and Neuroanatomy. 2nd edition. Stuttgart: Thieme; 2016. 555 p. (Atlas of anatomy).

31. Jain P, Rathee M. Anatomy, Head and Neck, Orbicularis Oris Muscle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545169/

32. Pessino K, Patel J, Patel BC. Anatomy, Head and Neck; Frontalis Muscle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557752/

33. Tong J, Lopez MJ, Fakoya AO, Patel BC. Anatomy, Head and Neck: Orbicularis Oculi Muscle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK441907/

34. Piccinin MA, Zito PM. Anatomy, Head and Neck, Lips. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507900/

35. Szymanski A, Geiger Z. Anatomy, Head and Neck, Ear. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470359/

36. Basit H, Tariq MA, Siccardi MA. Anatomy, Head and Neck, Mastication Muscles. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541027/

37. Nguyen JD, Duong H. Anatomy, Head and Neck, Anterior: Common Carotid Arteries. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK546613/

38. Platzer W, Shiozawa-Bayer T. Color Atlas of Human Anatomy, Vol. 1: Locomotor System. 8th ed. Stuttgart: Thieme; 2022. 484 p. (Taschenatlas Anatomie).

39. Soga S, Pomahac B, Wake N, Schultz K, Prior RF, Kumamaru K, et al. CT Angiography for Surgical Planning in Face Transplantation Candidates. Am J Neuroradiol. 2013 Oct;34(10):1873–81.

40. Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. Plast Reconstr Surg. 2000 Jun;105(7):2287–313.

41. Fakoya AO, Nessel TA, Downs BW. Anatomy, Head and Neck: Facial Artery. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Apr 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK536932/

42. Rivard AB, Kortz MW, Burns B. Anatomy, Head and Neck: Internal Jugular Vein. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK513258/

43. Bechmann S, Rahman S, Kashyap V. Anatomy, Head and Neck, External Jugular Veins. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538222/

44. Nguyen JD, Duong H. Anatomy, Head and Neck: Face. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551530/

45. Kim SY, Naqvi IA. Neuroanatomy, Cranial Nerve 12 (Hypoglossal). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK532869/

46. Shafique S, Das JM. Anatomy, Head and Neck, Maxillary Nerve. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK542277/

47. Fagan SE, Roy W. Anatomy, Head and Neck, Lingual Nerve. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK546652/

48. Ghatak RN, Helwany M, Ginglen JG. Anatomy, Head and Neck, Mandibular Nerve. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507820/

49. Seneviratne SO, Patel BC. Facial Nerve Anatomy and Clinical Applications. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554569/

50. Roesch ZK, Tadi P. Anatomy, Head and Neck, Neck. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK542313/

51. Hoerter JE, Patel BC. Anatomy, Head and Neck, Platysma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545294/

52. Bordoni B, Jozsa F, Varacallo M. Anatomy, Head and Neck, Sternocleidomastoid Muscle. StatPearls [Internet]. 2023 Apr 4 [cited 2025 Jul 6]; Available from: https://www.statpearls.com/point-of-care/32320

53. Khan YS, Fakoya AO, Bordoni B. Anatomy, Head and Neck: Suprahyoid Muscle. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK546710/

54. Mnatsakanian A, Khalili YA. Anatomy, Head and Neck, Thyroid Muscles. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2025 Jul 7]. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK541063/ /

55. La Padula S, Pensato R, Pizza C, Coiante E, Roccaro G, Longo B, et al. Face Transplant: Indications, Outcomes, and Ethical Issues—Where Do We Stand? J Clin Med. 2022 Sep 28;11(19):5750.

56. Eun SC. Facial Transplantation Surgery Introduction. J Korean Med Sci. 2015 Jun;30(6):669–72.

57. Longo B, Alberti FB, Pomahac B, Pribaz JJ, Meningaud JP, Lengelé B, et al. International consensus recommendations on face transplantation: A 2-step Delphi study. Am J Transplant. 2024 Jan;24(1):104–14.

58. Kantar RS, Alfonso AR, Ramly EP, Diaz-Siso JR, Jacoby A, Sosin M, et al. Incidence of Preventable Nonfatal Craniofacial Injuries and Implications for Facial Transplantation: J Craniofac Surg. 2019 Oct;30(7):2023–5.

59. Shah A, Chinta S, Rodriguez ED. Computerized Surgical Planning in Face Transplantation. Semin Plast Surg. 2024 May 27;38(3):242–52.

60. Hui-Chou HG, Nam AJ, Rodriguez ED. Clinical Facial Composite Tissue Allotransplantation: A Review of the First Four Global Experiences and Future Implications: Plast Reconstr Surg. 2010 Feb;125(2):538–46.

61. Gottlieb L, Agarwal S. Autologous Alternatives to Facial Transplantation. J Reconstr Microsurg. 2012 Jan;28(01):49–62.

62. Govshievich A, Saleh E, Boghossian E, Collette S, Desy D, Dufresne S, et al. Face Transplant: Current Update and First Canadian Experience. Plast Reconstr Surg. 2021 May;147(5):1177–88.

63. Ramly EP, Alfonso AR, Berman ZP, Diep GK, Bass JL, Catalano LWI, et al. The First Successful Combined Full Face and Bilateral Hand Transplant. Plast Reconstr Surg. 2022 Aug;150(2):414.

64. Siemionow M, Ozturk C. Donor Operation for Face Transplantation. J Reconstr Microsurg. 2012 Jan;28(01):35–42.

65. Kantar RS, Rifkin WJ, Diaz-Siso JR, Bernstein GL, Rodriguez ED. Quality Improvement in Facial Transplantation: Standard Approach for Novel Procedures. Plast Reconstr Surg Glob Open. 2018 Jan 23;6(1):e1653.

66. Lantieri L, Grimbert P, Ortonne N, Suberbielle C, Bories D, Gil-Vernet S, et al. Face transplant: long-term follow-up and results of a prospective open study. The Lancet. 2016 Oct;388(10052):1398–407.

67. Diaz-Siso JR, Rodriguez ED. Facial transplantation: knowledge arrives, questions remain. The Lancet. 2016 Oct;388(10052):1355–6.

68. Kantar RS, Ceradini DJ, Gelb BE, Levine JP, Staffenberg DA, Saadeh PB, et al. Facial Transplantation for an Irreparable Central and Lower Face Injury: A Modernized Approach to a Classic Challenge. Plast Reconstr Surg. 2019 Aug;144(2):264e–83e.

69. Pomahac B, Pribaz J, Eriksson E, Bueno EM, Diaz-Siso JR, Rybicki FJ, et al. Three Patients with Full Facial Transplantation. N Engl J Med. 2012 Feb 23;366(8):715–22.

70. Kauke M, Haug V, Obed D, Diehm Y, Tchiloemba B, Safi AF, et al. Donor and Recipient Matching in Facial Vascularized Composite Allotransplantation: A Closer Look at the Donor Pool. Plast Reconstr Surg. 2021 Jul;148(1):194.

71. Dorafshar AH, Bojovic B, Christy MR, Borsuk DE, Iliff NT, Brown EN, et al. Total Face, Double Jaw, and Tongue Transplantation: An Evolutionary Concept. Plast Reconstr Surg. 2013 Feb;131(2):241–51.

72. Sosin M, Ceradini DJ, Levine JP, Hazen A, Staffenberg DA, Saadeh PB, 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 Jul;138(1):205–19.

73. Sosin M, Ceradini DJ, Hazen A, Sweeney NG, Brecht LE, Levine JP, et al. Total Face, Eyelids, Ears, Scalp, and Skeletal Subunit Transplant Research Procurement: A Translational Simulation Model. Plast Reconstr Surg. 2016 May;137(5):845e–54e.

74. Brown EN, Dorafshar AH, Bojovic B, Christy MR, Borsuk DE, Kelley TN, et al. Total face, double jaw, and tongue transplant simulation: a cadaveric study using computer-assisted techniques. Plast Reconstr Surg. 2012 Oct;130(4):815–23.

75. Ramly EP, Kantar RS, Diaz-Siso JR, Alfonso AR, Rodriguez ED. Computerized Approach to Facial Transplantation: Evolution and Application in 3 Consecutive Face Transplants. Plast Reconstr Surg Glob Open. 2019 Aug 19;7(8):e2379.

76. Bassiri Gharb B, Frautschi RS, Halasa BC, Doumit GD, Djohan RS, Bernard SL, et al. Watershed Areas in Face Transplantation. Plast Reconstr Surg. 2017 Mar;139(3):711–21.

77. Grant GT, Liacouras P, Santiago GF, Garcia JR, Al Rakan M, Murphy R, et al. Restoration of the Donor Face After Facial Allotransplantation. Ann Plast Surg. 2014 Jun;72(6):720–4.

78. Cammarata MJ, Wake N, Kantar RS, Maroutsis M, Rifkin WJ, Hazen A, et al. Three-Dimensional Analysis of Donor Masks for Facial Transplantation. Plast Reconstr Surg. 2019 Jun;143(6):1290e.

79. Maciejewski A, Krakowczyk Ł, Szymczyk C, Wierzgoń J, Grajek M, Dobrut M, et al. The First Immediate Face Transplant in the World. Ann Surg. 2016 Mar;263(3):e36–9.

80. Banks ND, Hui-Chou HG, Tripathi S, Collins BJ, Stanwix MG, Nam AJ, et al. An Anatomical Study of External Carotid Artery Vascular Territories in Face and Midface Flaps for Transplantation: Plast Reconstr Surg. 2009 Jun;123(6):1677–87.

81. Prabhu V, Plana NM, Hagiwara M, Diaz-Siso JR, Lui YW, Davis AJ, et al. Preoperative Imaging for Facial Transplant: A Guide for Radiologists. RadioGraphics. 2019 Jul;39(4):1098–107.

82. Pomahac B, Lengele B, Ridgway EB, Matros E, Andrews BT, Cooper JS, et al. Vascular Considerations in Composite Midfacial Allotransplantation: Plast Reconstr Surg. 2010 Feb;125(2):517–22.

83. Lassus P, Lindford A, Vuola J, Bäck L, Suominen S, Mesimäki K, et al. The Helsinki Face Transplantation: Surgical aspects and 1-year outcome. J Plast Reconstr Aesthet Surg. 2018 Feb;71(2):132–9.

84. Micó-Carnero M, Zaouali MA, Rojano-Alfonso C, Maroto-Serrat C, Abdennebi HB, Peralta C. A Potential Route to Reduce Ischemia/Reperfusion Injury in Organ Preservation. Cells. 2022 Sep 5;11(17):2763.

85. Tripathy S, Das SK. Strategies for organ preservation: Current prospective and challenges. Cell Biol Int. 2023 Mar;47(3):532–40.

86. López-Monjardin H, de la Peña-Salcedo JA. Techniques for management of size discrepancies in microvascular anastomosis. Microsurgery. 2000;20(4):162–6.

87. Zor F, Polat M, Kulahci Y, Sahin H, Aral AM, Erbas VE, et al. Demonstration of technical feasibility and viability of whole eye transplantation in a rodent model. J Plast Reconstr Aesthet Surg. 2019 Oct;72(10):1640–50.

88. Bravo MG, Granoff MD, Johnson AR, Lee BT. Development of a New Large-Animal Model for Composite Face and Whole-Eye Transplantation: A Novel Application for Anatomical Mapping Using Indocyanine Green and Liquid Latex. Plast Reconstr Surg. 2020 Jan;145(1):67e–75e.

89. 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 Aug;8(8):e3042.

90. Coombs DM, Bassiri Gharb B, Tuncer FB, Djohan RS, Gastman BR, Bernard SL, et al. Skeletal and Dental Outcomes after Facial Allotransplantation: The Cleveland Clinic Experience and Systematic Review of the Literature. Plast Reconstr Surg. 2022 Apr;149(4):945.

91. Knoedler L, Kauke-Navarro M, Knoedler S, Niederegger T, Hofmann E, Heiland M, et al. Oral health and rehabilitation in face transplant recipients - a systematic review. Clin Oral Investig. 2025 Jan 6;29(1):47.

92. Jacoby A, Cohen O, Gelb BE, Ceradini DJ, Rodriguez ED. Vascularized Composite Allotransplantation and Immunobiology: The Next Frontier. Plast Reconstr Surg. 2021 Jun;147(6):1092e.

93. Dorante MI, Wang AT, Kollar B, Perry BJ, Ertosun MG, Lindford AJ, et al. Facial Expression after Face Transplant: An International Face Transplant Cohort Comparison. Plast Reconstr Surg. 2023 Aug;152(2):315e.

94. Aycart MA, Kiwanuka H, Krezdorn N, Alhefzi M, Bueno EM, Pomahac B, et al. Quality of Life after Face Transplantation: Outcomes, Assessment Tools, and Future Directions. Plast Reconstr Surg. 2017 Jan;139(1):194–203.

95. Topçu Ç, Uysal H, Özkan Ö, Özkan Ö, Polat Ö, Bedeloğlu M, et al. Assessment of Emotional Expressions after Full-Face Transplantation. Neural Plast. 2017;2017:1–7.

96. Kiwanuka H, Aycart MA, Gitlin DF, Devine E, Perry BJ, Win TS, et al. The role of face transplantation in the self-inflicted gunshot wound. J Plast Reconstr Aesthet Surg. 2016 Dec;69(12):1636–47.

97. Tasigiorgos S, Kollar B, Turk M, Perry B, Alhefzi M, Kiwanuka H, et al. Five-Year Follow-up after Face Transplantation. N Engl J Med. 2019 Jun 27;380(26):2579–81.

98. Knoedler L, Hoch CC, Knoedler S, Klimitz FJ, Schaschinger T, Niederegger T, et al. Objectifying aesthetic outcomes following face transplantation - the AI research metrics model (CAARISMA ® ARMM). J Stomatol Oral Maxillofac Surg. 2025 Feb 12;126(6):102277.

99. Siemionow M, Cwykiel J, Ozturk C. Facial transplantation: facing the limits, planning the future. Lancet. 2017 Dec;390(10114):2197–9.

100. Horen SR, Lopez J, Dorafshar AH. Facial Transplantation. Facial Plast Surg FPS. 2021 Aug;37(4):528–35.

101. Bound Alberti F, Weins D, Weins AB. Listening to face transplant patients and caregivers: How medical humanities approaches redefine surgical "success." Med Humanit. 2025 Feb 24;51(1):154–60.

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