

Are We Prepared for the Inevitable? A Survey on Defining and Managing Failure in Face Transplantation

Z-Hye Lee, MD*
 Christopher D. Lopez, BA*†
 Natalie M. Plana, BA*
 Arthur L. Caplan, PhD‡
 Eduardo D. Rodriguez,
 MD, DDS*

Background: Facial transplantation (FT) experience has grown but success in this innovative and complex field has yet to be defined. The purpose of this study is to determine attitudes regarding the failures in FT and the appropriate management of these failures.

Methods: An anonymous, 20-question survey elicited opinions regarding FT failure management. This survey was administered to attendees of 2 FT-focused national meetings. Demographics included sex, age, and personal/institutional FT experience. Attitudes related to FT recipient education, definition of FT failure, and management of complications were gathered.

Results: Eighty of 271 attendees completed the survey (29.5%). Respondents were predominantly male (81.3%) and 50 years of age or younger (80.5%). Thirty-eight percent previously performed an FT and 53.8% were a part of an institution with a vascularized composite allotransplantation (VCA)-related Institutional Review Board (IRB). Respondents almost unanimously agreed it was “absolutely essential” to discuss possibility of FT failure (93.8%), mortality (91.1%), and treatment for chronic rejection (78.8%). However, uncertainty of failure rate existed, with 56.4% citing failure rate as unknown, 25.6% citing <25% and 18.0% citing >25%. 51.2% of those with direct FT experience lacked clear criteria for defining FT success or an institutional protocol for managing chronic rejection. 78.8% believed failed FT patients should be considered for retransplantation, but only about 25% cited functional concerns or esthetic dissatisfaction as appropriate indications.

Conclusion: There is a lack of consensus regarding definition of FT failure and rates mortality amongst experts. Even institutions with FT experience lack protocols for managing chronic rejection. Expert consensus and institutional regulations surrounding these issues are warranted. (*Plast Reconstr Surg Glob Open* 2019;7:e2055; doi: 10.1097/GOX.0000000000002055; Published online 16 May 2019.)

BACKGROUND

Since the first facial transplantation (FT) performed in 2005, the field has grown tremendously, with approximately forty transplants reported to date. Different institutions

From the *Hansjorg Wyss Department of Plastic Surgery, NYU Langone Health, New York, N.Y.; †Icahn School of Medicine at Mount Sinai, New York, N.Y.; and ‡Division of Medical Ethics, NYU Langone Health, New York, N.Y.

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have reported successful first results,^{1,2} and some experienced groups have openly shared long-term outcomes with a summary of the first decade of facial.³⁻⁷ However, inevitably with any new surgical techniques and innovations, complications have emerged, including renal and cardiovascular disease, development of severe infections and malignancies, psychological sequelae, and chronic allograft rejection that have resulted in patient demise.⁸⁻¹¹ Furthermore, a review by Sosin et al.⁷ noted a relative underreporting of these negative events, suggesting a critical need for expert consensus on failure criteria and appropriate management in the field of FT.

As the number of FT increases, so has the number of unprecedented, challenging clinical scenarios. The second face transplant patient treated by the Amiens, France, group was diagnosed with recurrent B-cell lymphoma and achieved remission, only to develop a virus-related

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tumor that needed immunosuppressive alterations, which ultimately resulted in chronic rejection.¹¹ Özkan and colleagues' fourth face transplant recipient developed squamous cell carcinoma, requiring therapy that led to severe infection and respiratory failure and subsequent adjustments in immunosuppressive regimen that eventually led to chronic rejection and allograft necrosis. This patient required allograft removal and ultimately suffered death, the first FT with this unfortunate outcome.⁸ Although these sequelae both evidently embody transplant failure, identifying specific points during their clinical course as markers of failure is difficult, in part due to limited reports available. It is therefore critical to encourage the transparent, nonselective reporting of adverse events, as other groups have yet to report the sequelae leading to patient death in the peer-reviewed literature, thus contributing to the paucity of data making it difficult to achieve consensus for the definition of face transplant failure.^{7,12-14}

This lack of consensus for defining failure has in turn made it difficult to establish guidelines for FT failure management. Recently, the first patient to receive a second face transplant was reported,¹⁵ suggesting that retransplantation is feasible for failed allografts in the correct setting of donor availability. However, because this report was shared through the media, esthetic and functional short-term outcomes have yet to be addressed, and questions remain for surgeons interested in adopting this approach. Furthermore, immunosuppression-related complications such as renal decline have been reported^{3,4} and are thought to be underreported.¹⁶ This suggests that any retransplantation approach will likely need to have systemic considerations. Despite these complex concerns, no algorithm for the management of FT failure has been offered, and in considering the complications that have already been reported, the need for expert consensus is warranted.

The purpose of this study is to determine perspectives regarding the failures in FT and the appropriate management of these failures amongst experts in the field.

METHODS

An anonymous, Institutional Review Board-approved 20-question survey was designed to capture opinions of FT failure and preferences for management of such failures (See figure, Supplemental Digital Content, which displays the administered VCA survey, <http://links.lww.com/PRSGO/B94>). This survey was administered on 2 separate occasions to all of the attendees of 2 FT-focused national conferences: the 2016 American Society of Reconstructive Transplantation (November 3–5, 2016) and the 2017 State of the Art: Facial Reconstruction and Transplantation (May 19–21, 2017). Survey distribution was limited to these 2 conferences to survey individuals with the most interest, and therefore by assumption knowledge, of the current state of FT. There were 112 and 159 attendees at each meeting, respectively, for a total of 271 participants. Demographic information including sex, age, and personal or institutional experience with FT was collected. Additional questions gathered perceptions of FT patient

selection, patient education and asked specific information of how FT failure should be defined and treated.

RESULTS

There were eighty attendees who completed the survey, for a response rate of 29.5% (Table 1). The respondents were predominantly male (81.3%) and 50 years of age or younger (31–40 years old = 61.0%, 41–50 years old = 19.5%). Over one-third of respondents had previously performed an FT (38.0%) and more than half of the respondents (53.8%) were part of an institution with an IRB for some type of vascularized composite allotransplantation; 16.2% of respondents were a critical member and directly involved in FTs in the past.

When considering preoperative counseling for candidates of FT, the respondents almost unanimously agreed that it was “absolutely essential” to discuss the possibility of failure (93.8%), the possibility of mortality (91.1%), and the treatment options for chronic rejection (78.8%) as shown in (Table 2). There was variability in what respondents believed was the failure rate with 56.4% citing the failure rate as unknown, 25.6% citing the failure rate as >25%, and 15.4% citing the failure rate as >50% (Fig. 1). When asked about what was considered the best indicator of failure among options that could all be considered failure, 40.7% cited death within 5 years as the best indicator, 37.3% cited poor esthetic result, 13.6% cited high number of rejections, and 8.5% cited lack of facial muscle function

Table 1. Demographics and Experience With Face VCA

	No. respondents (%)
Total	80
Sex	
Male	65 (81.3)
Female	15 (18.8)
Age	
31–40	47 (61.0)
41–50	15 (19.5)
51–60	9 (11.7)
61–70	6 (7.8)
Performed face transplant	
Yes	30 (38.0)
No	50 (62.0)
Affiliated institution has VCA IRB	
Yes	43 (53.8)
No	37 (46.3)
No. face VCA performed	
0	67 (83.8)
1	10 (12.8)
2	1 (1.3)
3	2 (2.6)

Table 2. How Important Respondents Felt It Was to Discuss the Following Topics Before Face VCA

	Potential for failure (%)	Mortality risk (%)	Potential for chronic rejection (%)
Absolutely essential	75 (93.8)	72 (91.1)	64 (80.0)
Very important	3 (3.8)	6 (7.6)	12 (15.0)
Important	1 (1.3)	1 (1.3)	4 (5.0)
Somewhat important	1 (1.3)	0	0
Not important	0	0	0

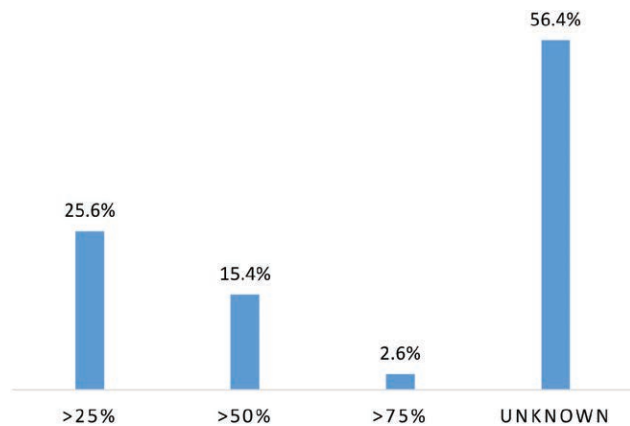


Fig. 1. What the respondents would counsel as the rate of failure to face VCA candidates.

(Fig. 2). Regarding mortality, 44.7% of respondents stated that the 5-year mortality was unknown, 28.9% stated the 5-year mortality as 10%, 19.7% stated the 5-year mortality rate as 5%, and 6.6% stated the 5-year mortality rate as 1% (Fig. 3).

Among those with direct experience with FT, the majority did not have clear criteria for defining the success

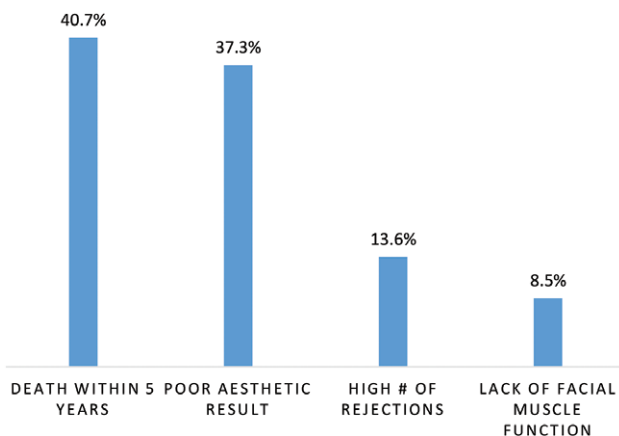


Fig. 2. What the respondents considered as the best indicator of failure.

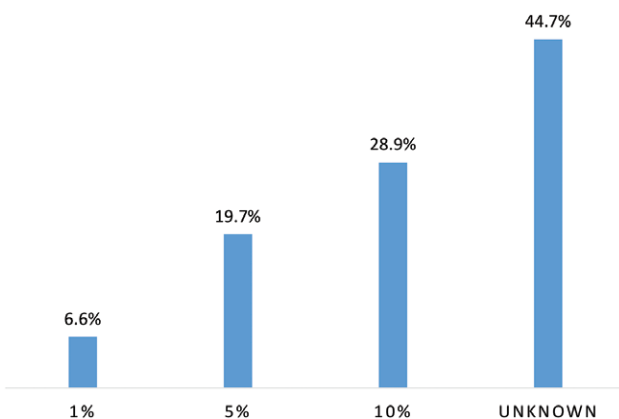


Fig. 3. What respondents would counsel as the rate of 5-year mortality to face VCA candidates.

Table 3. Attitudes Specifically for Respondents Who Have Been a Part of At Least One Face VCA (n = 30)

	No. respondents (%)
Do you have a specific protocol for defining the success of a face transplant?	
Yes	14 (46.7)
No	16 (53.3)
Does your institution have a specific protocol for managing chronic rejection in face transplant patients?	
Yes	14 (46.7)
No	16 (53.3)

of FT (51.2%) or have an institutional protocol for managing chronic rejection (51.2%), as shown in (Table 3). Finally, most respondents (78.8%) believed that a patient with a failed FT should be considered for another transplant. However, the indications for second transplant were not clear, as only about one quarter each stated functional concerns (25.3%) or esthetic dissatisfaction (25.6%) as appropriate indications for a second face transplant.

A subgroup for responders 50 years or older was analyzed to determine the role experience played in survey responses. Fifteen surveys were completed by individuals at least 50 years of age. Of these responses, 53.3% had previously performed a face transplant, including one respondent who performed 2 face transplants, and 2 respondents who had performed 3 face transplants. All respondents except for 2 said that discussing the possibility of failure was essential, one said that it was very important, and one said it was important. When it came to discussing mortality, 46.7% of respondents in this subgroup said that the face transplant failure rate was unknown, 30% said that the failure rate was >25%, and 20% said that it was >50%. When discussing the best indicator for FT failure, 40% believed that 5-year mortality was the best indicator, 20% did not respond, and 13.3% believed it should be patient dissatisfaction with esthetic outcome. Finally, 46.7% did not have clear criteria for FT success. Overall, results did not vary significantly between overall survey responses and the more experienced subgroup.

DISCUSSION

Consensus for the definitions of success and failure in FT and the definitive management protocol for failure has yet to be established. This survey assessed the perspectives and knowledge of leaders in the field to gain understanding of the variations in current opinions on how to evaluate outcomes for this emerging reconstructive option. While most survey respondents involved in FT agree that it is important to discuss failure and mortality with transplant candidates, there is uncertainty and inconsistency with respect to the definitions and rates of failure, and protocols for management of long-term complications such as chronic rejection appear to be lacking. The fact that over 60% of survey responders were under the age of 40, 50% were from institutions without an IRB and

attended FT meetings suggest that this cohort likely has early or exploratory interest in FT. While the presumed lack of experience from this group may contribute to the lack of consensus seen in the survey, it also highlights the importance of proposing a definition for FT failure for guidance. Based on the survey results, we propose that both mortality at 5 years postoperatively and poor esthetic outcome contribute to the as of yet still undecided definition of FT failure.

The lack of transparent FT outcomes in the peer-reviewed literature has contributed to misinformation even among the most experienced. Despite almost 40% of respondents having personal experience in performing an FT, over half replied that the current failure rate is unknown, and almost half stated that the 5-year mortality rate was also unknown. This can be attributed to the lack of peer-reviewed reporting of long-term outcomes.^{12–14,17} There are several potential reasons for underreporting. It is possible that some surgeons are hesitant to share negative outcomes with the general public; the VCA community should promote transparent disclosure of all clinical outcomes including adverse events. Groups may also hold off on immediate reporting to ensure patient stability after successful transplantation. Most importantly, outcomes may be kept private out of a patient's wishes for privacy. This is controversial because patient wishes should be kept as the highest of priorities, but advancements in a field that is still in its infancy depends on open sharing of data.

More than half of survey responders stated that they did not have an institutional protocol to address chronic rejection. This finding may be due to differences in the manifestation of chronic rejection in FT recipients, given that the first chronic rejection in this group presented differently compared with the rejections seen in long-term vascularized composite hand allotransplant cohorts.¹⁸ Although hand transplant chronic rejection has presented with anticipated changes such as intimal hyperplasia of both large and small vessels,^{19,20} Petruzzo and colleagues¹¹ reported focal lesions in facial arteries that were difficult to interpret, whereas dermal capillaries demonstrated sclerotic vessel walls and reduced lumen size. In addition, the current understanding and advances regarding chronic rejection is largely derived from the solid organ transplantation literature and further basic science research is needed to study this phenomenon in VCA. For example, the presence of donor-specific antibodies followed by complement activation has been described in the renal chronic rejection pathway,²¹ but anti-HLA antibodies were only transiently reported in the first chronic face transplant rejection, and no CD4 vascular deposits were reported at all.¹¹ As our understanding of the immunologic biology behind chronic rejection evolves in VCA, it is critical to incorporate these findings into future treatment protocols to aid in the management of chronic face transplant rejections.

It is also important to assess factors that affect FT recipients pre and posttransplant to improve outcomes and to mitigate any potential risk factors for failure.²² A systematic review from 1998 to 2012 by Zhu and col-

leagues²² reported a 20% failure rate in FT. Criteria for FT failure included graft failure, patient death from transplant-related disease, or graft survival with patient request for removal due to either mental or social stress. Statistically significant associations included questionable indications for FT, and inadequate documentation of psychosocial screening, adequate social support systems, and institutional review and team management resources.²² In our study, of the 30 respondents who had been a part of an FT previously, fewer than half (46.7%) of them endorsed an institutional protocol for managing chronic rejection. In the future, surgeons should ensure that specific regulations regarding management of permanent rejection and graft failure are in place before an FT is performed.

In conclusion, failure, mortality, and management in the field of FT remain elusive. As the FT patient cohort increases and long-term outcomes begin to emerge, expert consensus surrounding definitions of the success or a failure of face transplant and institutional protocols for management of failures is strongly needed.

Eduardo D. Rodriguez, MD, DDS

Hansjörg Wyss Department of Plastic Surgery
NYU Langone Health 305 East 33rd Street
New York, NY 10016
E-mail: Eduardo.Rodriguez@nyumc.org

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